

The Immunogenicity and Safety of CYD-Tetravalent Dengue Vaccine (CYD-TDV) in Children and Adolescents: A Systematic Review

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ABSTRAK

Tujuan: menilai imunogenisitas dan keamanan CYD-tetravalent dengue vaccine (CYD-TDV) pada anak. **Metode:** pencarian literatur dilakukan pada beberapa database. Studi randomized controlled trials pada anak yang divaksinasi dengan CYD-TDV dipilih berdasarkan kriteria inklusi dan eksklusi. Data yang diperoleh dari studi tersebut mencakup keamanan, serta imunogenisitas, dalam kaitannya dengan Geometric Mean Titres (GMT) dari antibodi. **Hasil:** enam percobaan klinis dipilih berdasarkan kriteria yang telah ditentukan. Angka GMT diperoleh menggunakan 50% Plaque Reduction Neutralization Test (PRNT), sedangkan keamanan diuji secara semi-kuantitatif berdasarkan penilaian efek samping. Pengolahan data lebih lanjut dilakukan untuk membandingkan hasil dari berbagai studi. Imunogenisitas pada kelompok yang divaksinasi dengan CYD-TDV lebih tinggi dibanding kelompok kontrol. Hasil dari semua studi menunjukkan bahwa vaksin cukup aman, efek samping yang berat tidak terkait dengan vaksin yang diberikan. **Kesimpulan:** vaksin CYD-TDV efektif dan aman untuk pasien pada daerah endemik. Kesimpulan ini merupakan dasar untuk pengembangan vaksin lebih lanjut, serta penelitian skala besar untuk menguji kemampuan vaksin ini dalam mengurangi prevalensi dengue, serta implementasinya pada negara-negara endemik, seperti Indonesia.

Kata kunci: dengue, imunogenisitas, keamanan, CYD-tetravalent dengue vaccine, vaksin.

ABSTRACT

Aim: to assess the immunogenicity and safety of CYD-tetravalent dengue vaccine (CYD-TDV) in children. **Methods:** comprehensive literature searches were conducted on various databases. Randomized-controlled trials on children with CYD-TDV as intervention were selected based on inclusion and exclusion criteria. Data extracted from selected trials included safety of vaccine and immunogenicity in terms of Geometric Mean Titres (GMT) of antibodies. **Results:** six clinical trials were selected based on preset criteria. GMT values were obtained using 50% Plaque Reduction Neutralization Test (PRNT) and safety was semi-quantitatively assessed based on adverse effects. Additional data processing was done to obtain a better understanding on the trends among the studies. The results showed that the groups vaccinated with CYD-TDV showed higher immunogenicity against dengue virus antigens than the control groups. Safety results were satisfactory in all trials, and most severe side effects were unrelated to the vaccine. **Conclusion:** CYD-TDV is both effective and safe for patients in endemic regions. This gives promise for further development and large-scale research on this vaccine to assess its efficacy in decreasing dengue prevalence, and its pervasive implementation in endemic countries, such as Indonesia.

Keywords: dengue, immunogenicity, safety, CYD-TDV, vaccine.

INTRODUCTION

Dengue disease is caused by one of the four serotypes of dengue virus, namely DENV-1, DENV-2, DENV-3, and DENV-4. The transmission of the four serotypes is arthropod-borne, with the main vector being the mosquito *Aedes aegypti*. Most of the infections of dengue virus are asymptomatic, but infections can also cause diseases ranging from a mild fever to a shock syndrome, which can be lethal. Even though infection with one serotype provides immunity against it for life, disease can subsequently be caused again by other serotypes in later life.¹ In recent decades, the incidence of dengue has increased dramatically across the world. An epidemiological study estimates that 3.9 billion people from 128 countries are at risk of infection with dengue viruses.² One recent estimate reports that there are 390 million dengue infections per year, of which 96 million cases progress to manifest clinically.³

Currently, vector control has been the main strategy in managing dengue. According to WHO, countries should adopt an integrated management approach to vector control in order to optimize the use of resources, efficacy, cost effectiveness, ecological safety and sustainability.⁴ Current control measures target different stages of development of *A. aegypti*.⁵ For example, in Indonesia, dengue prevention is carried out through both vector control and early warning system.⁶ Vector control includes source reduction and elimination of adult mosquitos. The source reduction program is commonly known as “3M – *Menguras, Menutup dan Mengubur*” which means to drain, to close and to bury potential breeding sites of dengue. Additional methods include the utilization of larvacide powder, and controlling lighting and ventilation in the house.⁷

Despite all the existing vector control measures, the global spread of the disease still persists.⁴ This calls for a more urgent need to introduce a vaccine into the prevention scheme. When integrated with the current vector control, a safe, efficacious and cost-effective vaccine has the potential to significantly improve dengue prevention.

Several dengue vaccines have been developed in the past. However, the one that has shown

most promise is the CYD-TDV (Trade name: Dengvaxia), which is a Tetravalent Dengue Vaccine developed by Sanofi Pasteur. This is a live-attenuated chimeric vaccine that contains all four dengue virus antigens (DENV 1-4) with a yellow fever backbone. WHO recommends the introduction of this vaccine in areas where there is a high burden of dengue disease.⁸ As of April 2016, CYD-TDV has been licensed only in Mexico, Brazil, El Salvador, Paraguay, and the Philippines.⁹ Nevertheless, due the novelty of this vaccine, more evidence on its safety and efficacy is required before it can be widely approved. This review aims to discuss whether the CYD-TDV is a viable preventive measure for Dengue through a systematic review by assessing its efficacy (in terms of immunogenicity) and safety (in terms of reactogenicity).

METHODS

Search Strategies

A comprehensive literature search was conducted in October 2016 using the databases PubMed, The Cochrane Library, Scopus, ProQuest, EBSCOhost, and Science Direct. The combinations of terms used for the search included “Tetravalent Dengue Vaccine”, “CYD-TDV”, “children”, and “immunogenicity”. Where applicable and available, appropriate advance search techniques were applied to narrow the search.

Selection of Trials

Inclusion and exclusion criteria were set prior to selection of trials. The inclusion criteria used to select the studies for this article are based on the PICOS formula. The population included in this study are healthy subjects aged between 2 to 18 years old. The intervention used in all trials must be a 3-dose regimen of CYD-TDV. Studies must also have a group of patients receiving placebo as control for comparison. The outcomes measured are humoral immunogenicity and safety of CYD-TDV. Study designs included in this review are all randomized-control trials.

Studies that mixed subjects of all age groups in the same treatment group, or studies that did not measure the baseline characteristics of patients were excluded.

Data Extraction

For each selected trial, information about study design and data for immunogenicity (hence efficacy) and safety of CYD-TDV will be extracted. Study design includes population characteristics (age, region, sample size, baseline seropositivity - Baseline seropositivity refers to the percentage of the population that has antibody titers ≥ 10 1/dil for any one of the four dengue serologies (measured using Plaque Reduction Neutralization Test)), intervention, control, and outcome measurements. Immunogenicity is measured by using data of Geometric Mean Titers of neutralizing antibodies against DENV 1, DENV 2, DENV 3, and DENV 4 at baseline and after each dose of CYD-TDV and control. Safety is evaluated by the authors' reports on adverse reactions and safety profile of CYD-TDV as compared to control injections.

Quality Assessment

The quality of included studies was assessed using "Quality Assessment of Controlled Intervention Studies"¹⁰ developed by The National Heart, Lung, and Blood Institute (NHLBI) and Research Triangle Institute International Jointly. It includes 14 criteria that need to be assessed, which refer to the internal validity of each of the included studies based on their methodology. All of the criteria were scored with either yes, no, Cannot Determine (CD), or Not Applicable (NA). A "yes" was given one point, whereas a "no" was given a score of 0.

No standard for a good, moderate, or poor study was given. Hence, a study obtaining a score of 11/14 or higher was defined as a good quality study, meanwhile studies receiving a score of 7/14 or less were defined as poor studies. A score between 7 and 11 out of 14 was defined as moderate.

Two reviewers (RA, OEY) independently analyzed the included studies based on the quality assessment criteria. If the ratings differed, the articles were discussed until a common consensus was reached.

RESULTS

The search terms were applied to all of the 6 search engines and databases mentioned earlier.

Titles and abstracts were screened and relevant titles were selected. After removal of duplicates, a total of 61 studies were obtained from the database search. Initial screening of abstracts against eligibility criteria excluded 41 studies. A further 14 trials were excluded after reading full text articles as they did not have a viable study design based on preset inclusion and exclusion criteria. The comprehensive data on the study selection process can be seen in **Figure 1**.

The six clinical trials selected in this systematic review were conducted by Dayan, et al. (2013),¹¹ Amar-Singh, et al. (2013),¹² Lanata, et al (2012),¹³ Sabchareon, et al (2012),¹⁴ Villar, et al (2013),¹⁵ and Leo, et al (2012).¹⁶

Quality of the Included Studies

Quality assessment (as seen in the table in the appendix) showed that all 6 studies were defined as good quality studies. The results of the quality assessment done for all included studies reflects any possibilities of bias or other weaknesses in the study designs. In the study conducted by Leo et al.¹⁶, there was only single blinding. This is because the placebo used for the 2nd and 3rd doses included an intramuscular Hepatitis A vaccine (as described under "Study Designs and Characteristics"), whereas CYD-TDV is administered subcutaneously. Hence, the investigators could differentiate between the control and intervention groups based on the route of delivery. This could be a possible source of bias.

Other than this, because of the long time period of the regimen (6 months for 3 doses), none of the studies could control exposure of subjects to dengue antigens outside of the study (ex: from the environment). Such exposure could be immunogenic independent of the effects of the vaccine, hence acting as a potential confounding factor. However, this is insignificant due to the large sample size of the trials.

Other than these, all studies fulfilled the criteria in the quality assessment tool, and hence had good internal validity.

Study Designs and Characteristics

Table 1 provides the summary of the study design of all of the included studies. All of the studies applied a similar study design, and

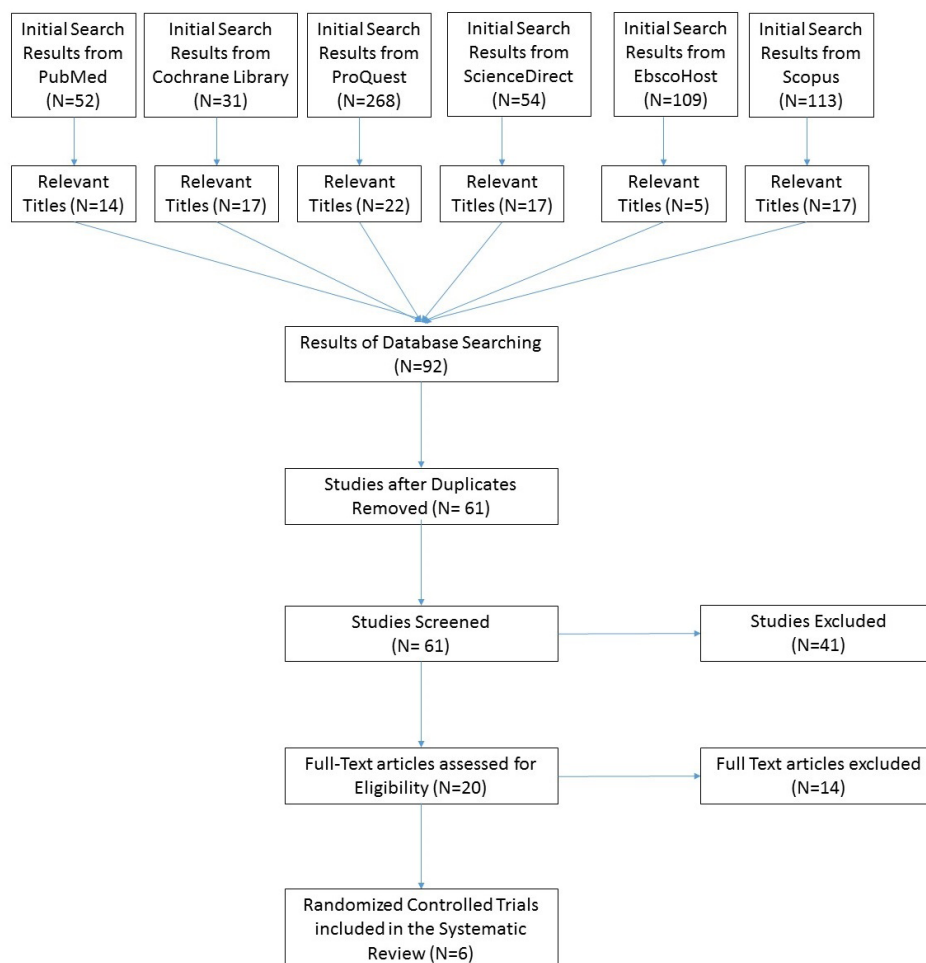


Figure 1. Flow chart of search strategy

hence can be compared reliably. There are some differences in the control group of the studies, as some use 0.9% NaCl and others use other vaccines. However, we consider that this does not significantly affect the results as none of the control vaccines contain antigens of Dengue Virus. The study conducted by Leo et al.¹⁶ separated the data for different age groups, hence the data will be presented separately in tables and charts.

Study Outcome: Efficacy of Intervention

The efficacy of CYD-TDV was primarily measured by analyzing the immunogenicity of the interventions, indicated by the geometric mean titers (GMT) of neutralizing antibodies (antibody titer) against each of the four antigens (DENV-1, DENV-2, DENV-3, DENV-4). The GMT represents the average antibody titer in a population of people.

Plaque reduction neutralization test (PRNT) was used to quantify the titer of antibodies in all trials. The data is represented in **Figure 2**.

The data is extracted for GMTs of antibodies against each antigen at baseline, after dose 2, and after dose 3 of both test and control groups in all 6 trials (except for the study by Leo et al.¹⁶ which only presented data for immunogenicity at baseline and post-dose 3).

In order to improve the analysis of the trend, the fold increase in GMTs from baseline to post-dose three were calculated for all 4 antigens in all studies for both test and control groups. This data can be seen in **Figure 3**.

We also collected data for the peak of GMT values in test groups of all trials. This represents the highest GMT value recorded for the test groups for all serology tests either at baseline, after dose 2, or after dose 3. These results would

Table 1. The summary of experimental designs of the six studies

Study	Population	Intervention	Control	Outcome Measures
Dayan, et al (2013) ¹¹	Age: 9-16 Participants: 150 Mean Age: 12.7 Country: Brazil Baseline Seropositivity: 69% in test group 71% in control group	Three doses of CYD-TDV at 0, 6, and 12 months Enrollment and Dropout: 100 enrolled, 89 completed	Three doses of NaCl 0.9% at 0, 6, and 12 months Enrollment and Dropout: 50 enrolled, 46 completed	Efficacy: Immunogenicity against DENV 1-4 measured at baseline and 28 days after each dose using PRNT50 and calculation of GMT Safety: Unsolicited systemic reaction, solicited injection site reactions, solicited systemic reactions, and Serious Adverse Effects (SAEs) were recorded
Amar-Singh, et al (2013) ¹²	Age: 2-11 Participants: 250 Mean Age: 6.4 Country: Malaysia Baseline Seropositivity: 44.9% in test group 48% in control group	Three doses of CYD-TDV at 0, 6, and 12 months Enrollment and Dropout: 199 enrolled, 196 completed	Three doses of placebo at 0, 6, and 12 months Enrollment and Dropout: 51 enrolled, 50 completed	Efficacy: Immunogenicity against DENV 1-4 measured at baseline and 28 days after dose 2 and 3 using PRNT50 and calculation of GMT Safety: Unsolicited systemic reaction, solicited injection site reactions, solicited systemic reactions, and Serious Adverse Effects (SAEs) were recorded
Lanata, et al (2012) ¹³	Age: 2-11 Participants: 300 Mean Age: 6.29 Country: Peru Baseline Seropositivity: 37.2% in test group 48.5% in control group	Three doses of CYD-TDV at 0, 6, and 12 months Enrollment and Dropout: 200 enrolled, 186 completed	Two doses of placebo at 0 and 6 months, pneumococc. vaccine at month 12 Enrollment and Dropout: 100 enrolled, 90 completed	Efficacy Immunogenicity against DENV 1-4 measured at baseline and 28 days after dose 2 and 3 using PRNT50 and calculation of GMT Safety: Unsolicited systemic reaction, solicited injection site reactions, solicited systemic reactions, and Serious Adverse Effects (SAEs) were recorded
Sabchareon et al (2012) ¹⁴	Age: 4-11 Participants: 296 Mean Age: 8.21 Country: Thailand Baseline Seropositivity: 70% in test group 68% in control group	Three doses of CYD-TDV at 0, 6, and 12 months Enrollment and Dropout: 197 enrolled, 95 completed	Three doses of NaCl 0.9% at 0, 6, and 12 months Enrollment and Dropout: 99 enrolled, 48 completed	Efficacy: Immunogenicity against DENV 1-4 measured at baseline and 28 days after each dose using PRNT50 and calculation of GMT Safety: Unsolicited systemic reaction, solicited injection site reactions, solicited systemic reactions, and Serious Adverse Effects (SAEs) were recorded
Villar, et al (2013) ¹⁵	Age: 9-16 Participants: 600 Mean Age: 12.56 Region: Latin America Baseline Seropositivity: 75.1% in test group 77.9% in control group	Three doses of CYD-TDV at 0, 6, and 12 months Enrollment and Dropout: 401 enrolled, 364 completed	Two doses of NaCl 0.9% at 0 and 6 months, and a dose of DPT at 12 months Enrollment and Dropout: 199 enrolled, 180 completed	Efficacy: Immunogenicity against DENV 1-4 measured at baseline and 28 days after each dose using PRNT50 and calculation of GMT Safety: Unsolicited systemic reaction, solicited injection site reactions, solicited systemic reactions, and Serious Adverse Effects (SAEs) were recorded
Leo, et al (2013) ¹⁶	Age: 2-45 (results were separated for all age groups, & data for ages 2-17 was extracted) Participants: 316 (2-11 y.o) 187 (12-17 y.o) Country: Singapore Baseline Seropositivity: 16.6% in test group 20.8% in control group	Three doses of CYD-TDV at 0, 6, and 12 months Enrollment: 236 enrolled (2-11 y.o) 141 enrolled (12-17 y.o) 93% pts completed the trial	One dose of NaCl 0.9% at 0 months, followed by two doses of either Hep-A or Influenza vaccines at months 6 and 12 (based on age) Enrollment: 80 enrolled (2-11 y.o) 46 enrolled (12-17 y.o) 92% pts completed the trial	Efficacy: Immunogenicity against DENV 1-4 measured at baseline and 28 days after third dose using PRNT50 and calculation of GMT Safety: Unsolicited systemic reaction, solicited injection site reactions, solicited systemic reactions, and Serious Adverse Effects (SAEs) were recorded

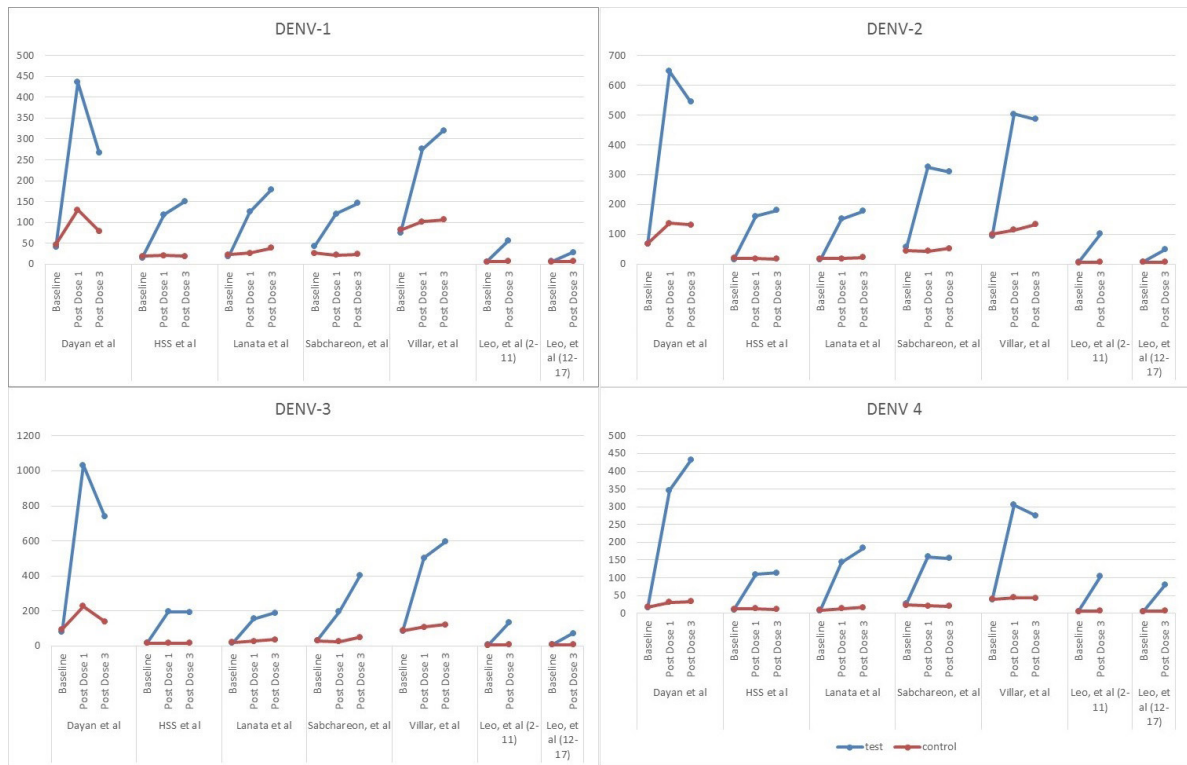


Figure 2. Geometric mean titers (1/dil) of neutralizing antibodies against DENV 1-4 in test and control groups

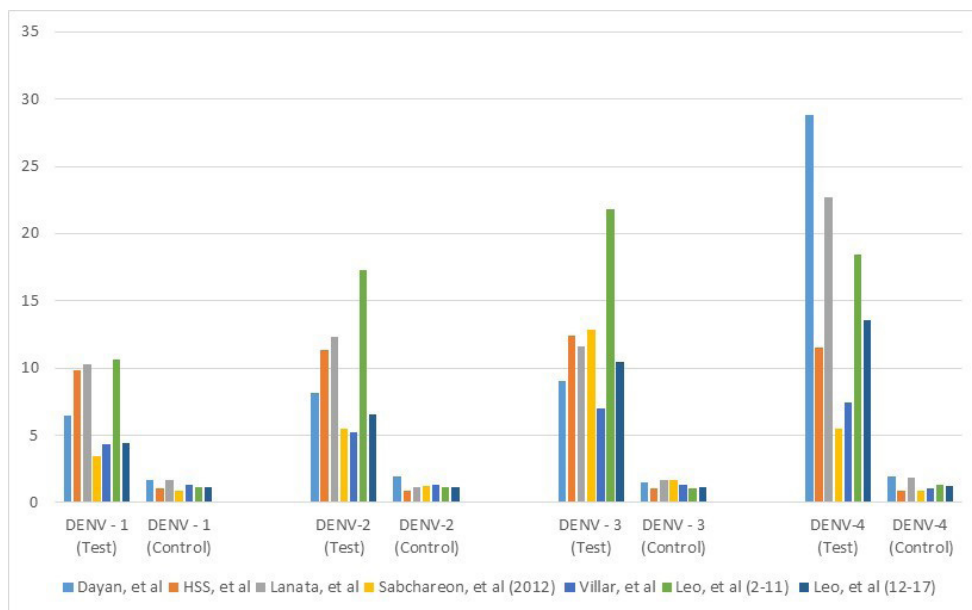


Figure 3. Fold increase in geometric mean titers of each serotype from baseline to the end of third dose

help us to compare immune responses against CYD-TDV in different trials. This data can be seen in **Figure 4**.

Study Outcome: Safety of Intervention

All of the studies collected data for unsolicited systemic reactions, solicited injection-site

reactions, solicited systemic reactions, and severe adverse effects. Additionally, any immediate AEs that occurred within 30 minutes of injections were observed (except for Lanata et al.¹³).

Solicited injection-site reactions include erythema, swelling, and pain, among others,

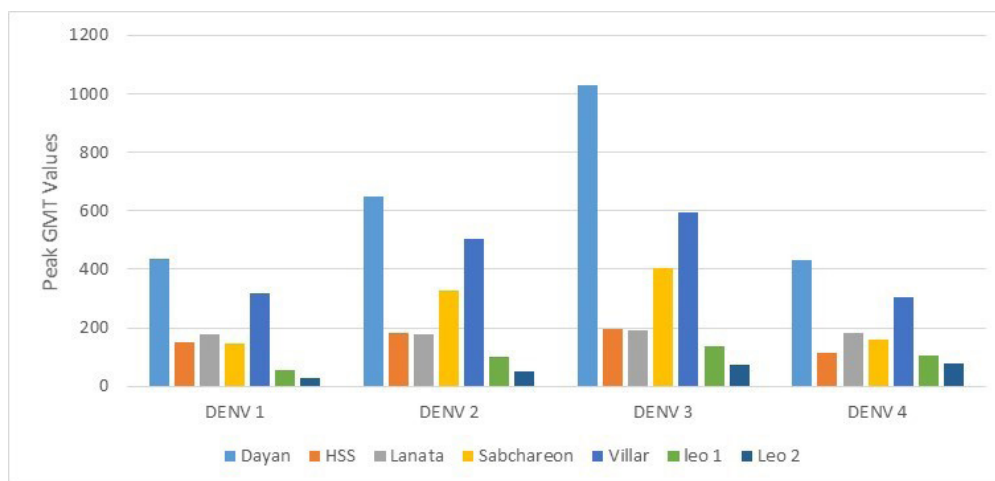


Figure 4. The peak of GMT values (1/dil) in test groups of all trials

and were observed for up to 7 days after the injections in all trials. Solicited systemic reactions are systemic reactions which are expected from the injections, and include fever, headache, malaise, myalgia, and myasthenia, and were observed for up to 14 days after injections. Unsolicited systemic reactions are any systemic reactions in response to the vaccine that are not expected, and were observed for up to 28 days after each injection in all trials. Severe adverse effects were any serious illnesses or reactions contracted during the course of the trial that needed hospitalization. This included symptomatic dengue disease. All of the trials graded solicited and unsolicited reactions from 1-3. The data for safety of the vaccine is presented semi-quantitatively in **Table 2**.

DISCUSSION

Immunogenicity in trials was analyzed by fold increase of Geometric Mean Titer from baseline to post dose 3 (**Figure 3**). The fold increase of all antibody titers in patients injected with CYD-TDV vaccine is larger when compared to control groups in all trials. For example, in Amar-Singh et al.¹², the antibody titer against DENV3 increased 12.37 fold in test group and only 1.03 in control group. This trend is seen across all trials for antibodies against all 4 antigens. This is attributed to the tetravalent nature of this vaccine, which is capable of inducing a humoral immune response for all four

serotypes of the dengue virus. This indicates that the CYD-TDV is more effective in eliciting a protective immune response against the dengue infection.

Another trend common to test groups in all trials is that the antibody titers reached high levels after dose 2, but the subsequent dose (dose 3) failed to increase it further substantially. This presents as a plateau-shaped pattern in **Figure 2**. In Amar-Singh et al,¹² the GMT for DENV 1 antibody increased from 15.3 at baseline, to 119.0 post dose 2, which is an increase of 103.7. However, at the end of dose 3, the GMT only reached 151.0, which is a meagre increase of 32.0 from post dose 2. This trend is consistent in all trials, as seen in **Figure 2**.

This plateau pattern implies that 2 doses of CYD-TDV vaccine are more immunogenic, hence more effective, than the third dose. However, the three dose regimen is still supported. Observations from some trials^{12, 13, 15} stated that the third dose significantly increased GMT levels in patients who were flavivirus seronegative at baseline, but not in patients who were flavivirus-seropositive at baseline. This means that the third dose is still effective for previously flavivirus seronegative patients. Moreover, in a clinical setting, it is impractical to assess antigen seropositivity before vaccine administration. Therefore, it is still most efficient to standardize a three dose regimen for this vaccination.

Table 2. Safety and reactivity of the CYD-TDV as compared to control in the 6 trials

Study	Severe adverse effects	Solicited injection site AEs	Solicited Systemic AEs	Unsolicited AEs	Overall Comments
Dayan, et al (2013) ¹¹	6 Severe Adverse reactions in CYD-TDV and 5 adverse reactions in control groups; none considered to be related to the intervention	Pain was the most common injection-site side effect (40-41% patients in both groups). Most solicited injection site AEs were low grade and transient	Headache was the most common solicited systemic AE (61% patients in test; 51% patients in placebo). Most solicited systemic AEs were low grade and transient	No difference in occurrence of unsolicited systemic AEs in test and control groups. Unsolicited AEs were not related to the interventions / control studied.	In general, the vaccine was well tolerated and did not cause any severe adverse effects
Amar-Singh, et al (2013) ¹²	5.5% patients in test groups and 11.8% patients in placebo group experienced SAEs; All were unrelated to treatment (except for one case in Placebo group)	89.4% and 94.1% patients in test and placebo groups respectively experienced solicited reactions (both injection site and systemic). Injection site reactions included pain, erythema and swelling, whereas systemic reactions included malaise and headaches among others. These were reported frequently but at Grade 1 intensity and were transient		About half (53.8% CYD-TDV and 49% Placebo) experienced unsolicited AEs, these were unrelated to vaccine	In general, the vaccine had a satisfactory safety profile and was well tolerated
Lanata, et al (2012) ¹³	2 SAEs were reported in the test group, and 5 were reported in the placebo group. None of them were considered to be related to the vaccine/ intervention and all continued the study	Injection-site reactions were similar in test and placebo groups in terms of incidence	Solicited systemic reactions such as fever, malaise, and headaches occurred in comparable rates in both placebo and test groups, and were of low grade.	Unsolicited adverse effects were considered unrelated to the injections (Upper respiratory tract infections, gastrointestinal disorders, etc)	The vaccine had a good safety profile and was well tolerated in general
Sabchareon, et al (2012) ¹⁴	No severe adverse effects were vaccine related in test group, but one was in placebo group	Injection site reactions occurred in 61.6% patients in test groups, and in 63.2% of patients in control group	Solicited systemic side effects such as malaise and fever occurred in 77.7% of patients in test group, and 74.3% patients in control group, but were mostly low grade and transient	Unsolicited Adverse effects occurred at similar effects in both groups (45% of patients in vaccine group, 47% of the patients in control group)	The vaccine was well tolerated and there were no SAEs related to the vaccine in a two year follow up
Villar, et al (2013) ¹⁵	10 (2.5%) patients in study group, and 15(7.5%) patients in control group experienced SAEs, none of which were considered vaccine related	32% CYD TDV group and 27% Placebo group experienced solicited injection site reaction (mild or moderate severity)	58% CYD-TDV group and 54% Placebo group experienced solicited systemic reaction (mild or moderate severity)	-	Favorable safety profile, with vaccine being well tolerated
Leo, et al (2013) ¹⁶	1(0.3%) discontinuation after AE in the control group and 3(0.3%) for AEs related to vaccination in the CYD-TDV group: Fever, rash, and worsening cervical spondylosis	55% patients in the CYD-TDV group and 67% in control group had solicited injection-site reactions after vaccination	More solicited systemic reactions reported after first CYD-TDV vaccination (45.9%) than after the placebo control (37.0%). Headache, myalgia, and malaise most frequently reported solicited systemic reactions, followed by fever and asthenia	Unsolicited AEs were reported by 17.0% of participants in the CYD-TDV group and 20.7%, most frequent of which were infections and infestations of upper respiratory tract infections, which were considered not related to vaccination	Relatively safe overall profile in terms of reactivity and AEs

Finally, we also observed that the magnitude of immune response in test groups is different between studies, as some studies show more robust immune responses than others. We can compare the strength of immune responses in each study by comparing the peak antibody titers (GMT) recorded (**Figure 4**). In all 4 serologies, the highest and second highest peaks were achieved by Dayan, et al.¹¹ and Villar, et al.¹⁵ respectively.

A possible explanation for this is that the populations in these studies had high baseline DENV seropositivities (**Table 1**). High baseline seropositivity rates imply that a large portion of the population selected in these trials have had previous exposure to dengue virus. The baseline seropositivity in the test group of Dayan et al.¹¹ and Villar et al.¹⁵ was 69% and 75.1%, respectively. This is much higher than the values reported by Leo et al (16.6%),¹⁶ Amar-Singh et al.¹² (44.9%), and Lanata et al.¹³ (37.2%), all of whom had a relatively low peak antibody titer for all serologies. In previously seropositive patients, the dengue vaccine would elicit a secondary, instead of a primary, immune response. This explains the more enhanced peak GMT levels found in Dayan et al.¹¹ and Villar, et al.¹⁵

From the safety and reactogenicity reports in all trials (**Table 2**), CYD-TDV vaccine is well tolerated and has a relatively good safety profile. As reported, all solicited injection-site or systemic adverse effects were similar in both test and control groups in all trials. Systemic and injection-site adverse effects were generally described as low grade in all trials. Unsolicited systemic adverse reactions occurred in similar rates between test and control groups in all studies, but were generally described to be unrelated to the injections.

The safety profile of the tested CYD-TDV is similar to that of other vaccines commonly used. The study by Villar et al.¹⁵ used DPT as the injection in control group (**Table 1**). From **Table 2**, we see that in this study, the rate of incidence of adverse effects is similar both in test and control groups, which implies that the safety profile of the CYD-TDV is similar to that of the DPT vaccine. The control groups of

studies by Lanata, et al.¹³ and Leo et al.¹⁶ also used alternative vaccines. Hence, the similarities in the data for reactogenicity in control and test groups of these studies also implies a similar safety profile between the CYD-TDV and the vaccine they used for their control group.

Severe adverse effects were reported in all trials. However, they occurred in similar rates between control and test groups. The incidence of severe adverse effects is not unexpected as the trials lasted for a year in all studies, and SAEs were recorded throughout the trial period. In all of the trials except for Leo, et al.¹⁶, none of the cases of severe adverse effects were considered to be related to the vaccine in test groups. Three patients (0.3%) from Leo et al.¹⁶ study experienced relatively severe AEs (fever, rash and worsening of cervical spondylosis related to vaccination) such that they had to be withdrawn from the study.

Limitations of the Study

The efficacy measured in this systematic review is based solely on the induction of the immune system due to the dengue vaccine, which is expected to protect the subjects from the virus in the future. However, this systematic review does not provide concrete evidence on the long term efficacy of the vaccine. Several studies have been started on the long term efficacy of the vaccine, but they are still on-going as of July 2016.⁸

Future Research and Applications

The main purpose of developing the CYD-TDV is to prevent the onset of symptomatic dengue disease. Since this systematic review shows that the CYD-TDV was effective and safe in children, therefore, it opens possibilities for further exploration of this vaccine in large-scale long term studies to assess its long-term efficacy in decreasing the prevalence of symptomatic dengue disease.

Additionally, from the discussion, it is seen that the high baseline dengue seropositivity rates in populations of Dayan et al.¹¹ and Villar et al.¹⁵ expressed a stronger immune response to the CYD-TDV. It is plausible that this high baseline seropositivity is attributed to the fact that these studies were conducted in the highly

endemic regions of Latin America. Indonesia is also considered to be a highly endemic region for dengue virus. Hence, this review gives promise for high efficacy of this vaccine when applied in Indonesian populations.

CONCLUSION

In conclusion, this systematic review confirms that the efficacy (in terms of immunogenicity) and overall safety profile (in terms of reactogenicity) of CYD-TDV are satisfactory. Furthermore, this review supports the continued development and widespread use of CYD-TDV, in addition to current vector control methods, for the prevention of dengue disease in children and adolescents. CYD-TDV may be integrated into current vaccination programs to reduce incidence of dengue infections in areas with high burden of disease.

CONFLICT OF INTEREST

The authors of this systematic review article state that they have no conflicts of interest, and no affiliation or connection to or with any entity or organization which may raise a question of bias in the discussion and conclusion of this article.

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