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EFFECTIVENESS AND SAFETY OF CYD-TDV VACCINE IN CHILDREN

Sonny Edbert[1], Hotimah Masdan Salim[2*]
Universitas Surabaya[1],Universitas Nahdlatul Ulama Surabaya[2]
**Corresponding Author* : dr.hotimah@unusa.ac.id

ABSTRACT
Dengue virus is classified as an arbovirus and its incidence rate continues to grow, especially in children in the last few years recorded by WHO. In the absence of specific therapy to treat dengue, prevention with vaccination is the right choice, especially for Asia and endemic regions such as Indonesia. Until now, the vaccine for dengue is only available in one commercial formulation (CYD-TDV) which has been licensed and developed by Sanofi Pasteur. The purpose of this study is to determine the effectiveness and safety of the CYD-TDV vaccine for children in endemic areas. The method used in this study is a literature search. Conducted meta-analyses and systematic reviews published between 2017 and 2020 identified in MEDLINE, especially in children based on inclusion and exclusion criteria. The findings obtained are Immunogenicity in the test group vaccinated with CYD-TDV was higher than the control group and side effects between two groups were not significant. So it can be concluded CYD-TDV vaccine is effective and safe for children's in endemic areas. This conclusion is the basis for further vaccine development, especially for Asian regions, such as Indonesia.

Keywords: *CYD-TDV Vaccine, Dengue Disease, Dengue Virus*

ABSTRAK
Virus dengue tergolong arbovirus dan angka kejadiannya terus meningkat terutama pada anak-anak dalam beberapa tahun terakhir yang tercatat oleh WHO. Dengan belum adanya terapi khusus untuk mengobati DBD, pencegahan dengan vaksinasi merupakan pilihan yang tepat terutama untuk Asia dan daerah endemik seperti Indonesia. Hingga saat ini, vaksin demam berdarah hanya tersedia dalam satu formulasi komersial (CYD-TDV) yang telah dilisensikan dan dikembangkan oleh Sanofi Pasteur. Tujuan dari penelitian ini adalah untuk mengetahui efektivitas dan keamanan vaksin CYD-TDV untuk anak di daerah endemik. Metode yang digunakan dalam penelitian ini adalah pencarian literatur. Dilakukan meta-analisis dan tinjauan sistematis yang diterbitkan antara 2017 dan 2020 yang diidentifikasi di MEDLINE, terutama pada anak-anak berdasarkan kriteria inklusi dan eksklusi. Temuan yang diperoleh adalah Imunogenisitas pada kelompok uji yang divaksinasi CYD-TDV lebih tinggi daripada kelompok kontrol dan efek samping antara kedua kelompok tidak signifikan. Sehingga dapat disimpulkan vaksin CYD-TDV efektif dan aman untuk anak di daerah endemik. Kesimpulan ini menjadi dasar pengembangan vaksin lebih lanjut, khususnya untuk kawasan Asia, seperti Indonesia.

Kata kunci: Penyakit DBD, Vaksin CYD-TDV, Virus DBD

INTRODUCTION

Disease is an infectious disease spread primarily by the bite of an infected female mosquito of the species Aedes aegypti, though Aedes albopictus is also a vector. This mosquito-borne illness has recently spread rapidly across the WHO region, especially in the tropics, where rainfall, temperature, and rapid urbanization all play a role in determining the relative risk of infection (World Health Organization, 2015).

The four DENV serotypes (DENV1, DENV2, DENV3, and DENV4) each have their own unique phylogenetic and antigenic characteristics and are caused by different strains of the Dengue virus (DENV). Bhatt et al. (2013) estimated that "there were about 390 million (95% CI 284 to 528) dengue infections occurring per year, of which 96 million were clinically manifest. Recovery from infection by a single dengue serotype provides lifelong immunity to

that serotype". Based on research conducted by Rosa et al. (2019), "Severe dengue fever is the leading cause of death among children in Southeast Asian and Latin American countries".

Viral infection can be asymptomatic. In contrast to what occurs in adults, the onset of dengue infection can go undetected in children. Children infected with dengue fever usually get worse suddenly, preventing the identification of warning signs. Godói et al. (2017) explain that "the annual costs of dengue fever ranged from US $ 13.5 million in Nicaragua to US $ 56 million in Malaysia from 2010 to 2013".

The annual number of DHF cases reported to WHO has been rising steadily over the past decade. The average annual number of cases rose to 1.656.870 between 2000 and 2008, which is more than three and a half times the number of cases recorded between 1990 and 1999 (479.848 instances). As of 2008, 69 nations in the Southeast Asia, Western Pacific, and United States WHO area reported cases of dengue fever. Between 2001 and 2004, the number of places where dengue fever is transmitted or has re-emerged increased in Bhutan, Nepal, Timor-Leste, Hawaii (USA), the Galapagos Islands (Ecuador), Easter Island (Chile), and the Special Administrative Region of Hong Kong and Macao (China). There were nine dengue fever outbreaks in northern Queensland, Australia, between 2005 and 2008 (World Health Organization, 2012).

The average annual rate of dengue cases in Indonesia has risen dramatically over the past half-century, from 0,05 cases per 100.000 people in 1968 to 77,96 cases per 100.000 people in 2016; the epidemic peaked for six consecutive years (1968, 1973, 1988, 1998, 2009, and 2016) (Harapan et al., 2019).

Considering that there is currently no cure for dengue fever, it is prudent to take measures to prevent infection, particularly through vector control. According to WHO cited by da Silveira et al. (2019), "the dengue vaccine must protect against all four serotypes, given as a single dose, have long-term immunity and have no serious side effects".

Research on developing a vaccine that would provide coverage against the four different virus serotypes has been ongoing since the 1970s. Live attenuated viral vaccines, attenuated virus vaccines, and DNA vaccines are only a few of the vaccine candidates that have been created. Dengvaxia®, a tetravalent dengue vaccine developed by Sanofi Pasteur, combines four modified recombinant viruses that protect against dengue infections caused by DENV1 through DENV4 and the capsid protein from an attenuated yellow fever vaccine virus (YF-17D).

The first vaccination to gain approval was CYD-TDV. Dengvaxia® has received regulatory approval in 11 countries as of October 2016, including Mexico, the Philippines, Brazil, El Salvador, Costa Rica, Paraguay, Guatemala, Peru, Indonesia, Thailand, and Singapore. In endemic regions, people between the ages of 9 and 45 are encouraged to get vaccinated.

According to research Rosa et al. (2019), "The effectiveness of CYD-TDV needs to be evaluated exclusively in individuals, especially those under the age of 18 years because dengue infection has different clinical manifestations in children, which can influence the assessment of vaccine effectiveness and there are changes that have been observed in the epidemiological pattern of dengue fever in Brazil, which characterized by the occurrence of cases classified as severe and a proportional increase in cases especially in children". Therefore, an effective and safe vaccine is needed for child protection.

METHOD

Research searches using MEDLINE (accessed via PubMed - from 2017 to 2020). The population in this study were children aged 2-18 years. The intervention was a 6-month 3-dose CYD-TDV regimen. The humoral immunogenicity and safety of CYD-TDV were evaluated,

and a control group of patients received a placebo. Both meta-analysis and systematic reviews were used in the research that formed the basis of this synthesis.

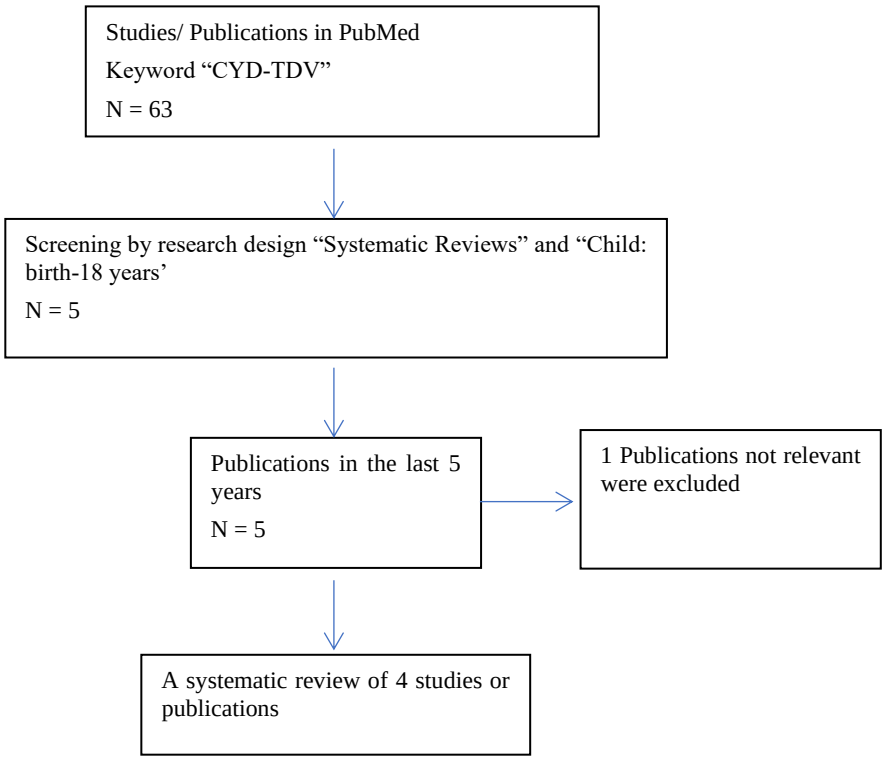

Figure 1. Theoretical framework

RESULTS

The results encompass four systematic reviews and meta-analyses focusing on the CYD-Tetravalent Dengue Vaccine (CYD-TDV) and its efficacy, immunogenicity, and safety across various populations. These comprehensive studies collectively offer valuable insights into the vaccine's performance and its potential in combatting dengue virus infections. The key findings from each study are as follows:

Table 1. Previous research

Study	Design	Aim	Result	Conclusion
Agarwal et al. (2017): "The Immunogenicity and Safety of CYD-Tetravalent Dengue Vaccine (CYD-TDV) in Children and Adolescents: A Systematic Review"	Systematic Review	to assess the immunogenicity and safety of CYD-tetravalent dengue vaccine (CYD-TDV) in children	"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	"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."

			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."	
da Silveira et al. (2019): "Systematic review of dengue vaccine efficacy"	Systematic review	To evaluate the efficacy of Dengue vaccine (CYD-TDV)	"Seven clinical trials were included, with a total of 36,371 participants (66,511 person-years) between the ages of 2 and 45 years. The meta-analysis using the random-effects model estimated the efficacy of the vaccine at 44%, with a range from 25 to 59% and high heterogeneity (I2 = 80.1%). The serotype-stratified meta-analysis was homogeneous, except for serotype 2, with the heterogeneity of 64.5%. Most of the vaccinated individuals had previous immunity for at least one serotype, which generated safety concerns in individuals without previous immunity"	"Compared with other commercially available vaccines, the dengue vaccine showed poor efficacy"
Godói et al. (2017): "CYD-TDV dengue vaccine: systematic review and meta-analysis of efficacy, immunogenicity and safety"	Systematic Review and Meta Analysis	Summarize all available evidence on the immunogenicity, efficacy and safety of the CYD-TDV dengue vaccine	"The best and worst immunogenicity results were for DENV4 and DENV1, respectively. Vaccine efficacy of 60% was derived from studies with participants aged 2–16 years old, with DENV4 and DENV2 presenting the best and worst results, respectively. Erythema and swelling were more frequent with CYD-TDV. No differences were detected for systemic adverse events".	"CYD-TDV showed moderate efficacy in children and adolescents. From the immunogenicity results in adults, we can expect satisfactory efficacy from vaccination in this population".
Rosa et al. (2019): "Efficacy, immunogenicity and safety of a recombinant tetravalent dengue vaccine (CYD-TDV) in children aged 2–17 years:	Systematic Review and Meta Analysis	To evaluate efficacy, immunogenicity and safety of CYD-TDV in the prevention of dengue in children aged 2–17 years.	"Nine studies involving 34 248 participants were included. The overall efficacy of CYD-TDV was 60% (RR 0.40 (0.30 to 0.54)). Serotype-specific efficacy of the vaccine was 51% for dengue virus type-1 (DENV1) (RR 0.49 (0.39	"CYD-TDV is considered safe and able to partially protect children and adolescents against four serotypes of DENV for a 1-year period. Despite this, research should priorities improvements in vaccine efficacy, thus

systematic review and meta-analysis"	to 0.63)); 34% for DENV-2 (RR 0.66 (0.50 to 0.86)); 75% for DENV-3 (RR 0.25 (0.18 to 0.35)) and 77% for DENV-4 (RR 0.23 (0.15 to 0.34)). Overall immunogenicity (MD) of CYD-TDV was 225.13 (190.34 to 259.93). Serotype-specific immunogenicity was: DENV-1: 176.59 (123.36 to 229.83); DENV-2: 294.21 (181.98 to 406.45); DENV-3: 258.78 (146.72 to 370.84) and DENV-4: 189.35 (141.11 to 237.59). The most common adverse".	proving higher long-term protection against all virus serotypes".

DISCUSSION

Of the 895 titles surveyed by Godói et al. (2017), a total of 321 studies were assessed, and of these, 89 studies were deemed worthy of assessment. A total of 6 Phase II studies and 3 Phase III randomized clinical trials were included and 1 trial is ongoing in Phase II trials. Of the 27,355 subjects, two Phase III trials showed an overall vaccine effectiveness of 60%.

In a study of 1.600 children and adolescents, the immunogenicity responses varied in nature depending on the DENV serotype, with the greatest findings obtained from DENV3 and DENV4. Lower immunogenicity yield of 55% was seen for DENV1. With only a 43% success rate against DENV2, this is a major problem. According to long-term observational safety assessments, DENV1 and DENV2 infection accounted for the bulk of hospitalized cases. Although pain, GI issues, and infection were the most common adverse events, neither group experienced significantly more than the other.

In another study by Rosa et al. (2019), "three RCTs assessed the effectiveness of using the CYD-TDV vaccine, with a total of 31.128 participants analyzed (20841 subjects in the test group and 10287 subjects in the control group) obtained an overall estimate of the effect of CYD-TDV was 0,40 (RR 0.40 (95% CI 0.30 to 0.54))". With the results of the effectiveness of CYD-TDV by 60%. The most common systemic side effects experienced by the test group were 37,8% compared to 33,2% in the control group. Pain at the injection site was the most common local side effect, affecting 33,1% of those given CYD-TDV and 29,3% of those given a placebo, but otherwise there were no statistically significant differences between the two groups.

Of the 1932 studies identified in the database surveyed by da Silveira et al. (2019), seven were selected for analysis. The population of each trial ranged from 150-20.869 subjects, and ranged in age from 2 to 45 years. Results showed high effectiveness against serotypes 3 and 4 whereas serotypes 1 and 2 did not show vaccine protection because of insignificance and greater effectiveness at 9 years of age which was seropositive at baseline and actually low for children between 2 and 5 years. However, vaccination should be a preventive strategy, ideally effective for ages less than 9 years.

A systematic review by Agarwal et al. (2017) assessed 6 appropriate clinical trials with children aged 2-18 years and received intervention as a 3-dose CYD-TDV regimen for 6 months. Immunogenicity was analyzed by increasing the Geometric Mean Titer (GMT) from

baseline to the 3rd dose. Another common trend for the test arm across all trials was that antibody titer reached its highest level after dose 2, subsequent doses showing no substantial increase. This leads to the conclusion that two doses of the CYD-TDV vaccination are more immunogenic, and thus more effective, than a third dosage. Nonetheless, the three-dose strategy is still recommended because additional results from several trials indicate that a third dosage considerably enhances the GMT level in flavivirus-seronegative individuals, but not in flavivirus-seropositive patients.

However, the third dose is successful for patients who were flavivirus-seronegative previously. In addition, assessing antigen seropositivity prior to vaccine administration is impossible, therefore it is still possible to infer that standardizing a three-dose schedule for this immunization is effective.

CONCLUSION

The CYD-TD vaccine is proven to be effective and has immunogenic abilities against the dengue virus, but further research is needed to find a "perfect" vaccine that can be effective for all four DENV1-4 serotypes, and is safe in children under 9 years of age.

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