EFFECTIVENESS AND SAFETY OF CYD-TDV VACCINE IN CHILDREN

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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. Hasil penelitian ini menunjukkan bahwa vaksin CYD-TDV memiliki tingkat imunogenisitas yang lebih tinggi pada kelompok uji yang divaksinasi dibandingkan dengan kelompok kontrol. Imunogenisitas yang lebih tinggi ini menunjukkan bahwa vaksin mampu merangsang sistem kekebalan tubuh untuk menghasilkan respons yang kuat terhadap infeksi virus yang ditargetkan. Selain itu, temuan bahwa tidak terdapat perbedaan signifikan dalam efek samping antara kedua kelompok menunjukkan bahwa vaksin CYD-TDV aman untuk digunakan. Keamanan vaksin adalah hal yang sangat penting dalam upaya pencegahan penyakit, terutama dalam populasi anak-anak yang rentan terhadap efek samping dan komplikasi yang mungkin timbul akibat imunisasi. Temuan ini memberikan keyakinan tambahan bahwa vaksin ini dapat diandalkan dalam program imunisasi anak di daerah endemik. Kesimpulan bahwa vaksin CYD-TDV efektif dan aman memiliki implikasi penting dalam pengembangan vaksin lebih lanjut, terutama untuk kawasan Asia seperti Indonesia.

Kata Kunci: penyakit DBD, vaksin CYD-TDV, virus DBD

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 results of this study showed that the CYD-TDV vaccine had a higher level of immunogenicity in the vaccinated test group compared to the control group. This higher immunogenicity indicates that the vaccine is able to stimulate the immune system to produce a strong response against the targeted viral infection. In addition, the finding that there was no significant difference in adverse events between the two groups suggests that the CYD-TDV vaccine is safe to use. Vaccine safety is of paramount importance in disease prevention efforts, especially in the pediatric population who are vulnerable to adverse effects and complications that may arise from immunization. These findings provide additional confidence that these vaccines can be relied upon in childhood immunization programs in endemic areas. The conclusion that the CYD-TDV vaccine is effective

and safe has important implications for further vaccine development, especially for Asian regions such as Indonesia.

Keywords: *CYD-TDV vaccine, dengue disease, dengue virus*

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 (Bhatt et al., 2013). 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" (Rosa et al., 2019).

Viral infection can be asymptomatic. In contrast to what occurs in adults, the onset of dengue infection can go undetected in children (Agamasi & Darmawan, 2022). 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" (Godói et al., 2017).

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" (da Silveira et al., 2019).

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).(Deen, 2004)

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 (World Health Organization, 2016).

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 (Rosa et al., 2019).

An analysis that included participants of all ages showed a decrease in the number of hospitalized VCD cases in vaccinated participants (Arredondo-García et al., 2018). Among vaccinated children aged 9-16 years, the overall decrease in hospitalized VCD was 68%, and this trend remained consistent over time, although there was a slight decrease in years 3 and 4. There was also an overall reduction in clinically severe VCD hospitalizations. While more cases occurred in the CYD-TDV group during years 3 and 4 compared to years 1 and 2, the control group experienced fewer cases in years 3 and 4. The overall benefit-risk ratio remained positive. Vaccinated participants aged <9 years had lower rates of VCD hospitalization in years 1 and 2 compared to the control group. However, during year 3, an imbalance of hospitalized VCD cases was observed among vaccinated participants compared to unvaccinated participants, which was not observed in those aged 9 years. In year 4, the point estimate of the relative risk (RR) was lower than in year 3 for those aged <9 years. A similar trend was observed for clinically severe VCD hospitalizations in 9-year-old participants, with a lower RR in year 4 compared to year 3. The cumulative RR for years 1 to 4 for clinically severe hospitalized VCD in children aged <9 years was 1.029. Data collected from an additional 2-year follow-up (years 5 and 6) will provide insight into the imbalance observed in year 3 among younger children (Arredondo-García et al., 2018).

Previous study (Dayan et al., 2020) demonstrated that CYD-TDV provided protection against VCD in 9-year-old dengue seropositive participants, starting from the first dose and lasting up to M25. Vaccine efficacy of approximately 80% was observed between doses 2 and 3 in seropositive participants aged 6-8 and 9 years. For seropositive participants aged 2-5 years, vaccine efficacy was evident at an interval of 13 months after the third dose. However, the point estimate of vaccine efficacy in seropositive participants aged 2-5 years tended to be lower in comparison to seropositive participants in older age groups. Notably, efficacy could not be demonstrated between doses 1 and 2, as well as between doses 2 and 3, as the lower limit of the 95% confidence interval (CI) crossed the zero value. Furthermore, vaccine efficacy could not be established in seronegative participants at any time point, irrespective of age. The estimates exhibited a general lack of precision, with all lower bounds of the 95% CIs crossing the zero value.

The correlation between high Geometric Mean Titres (GMT) in seropositive individuals and the effectiveness of CYD-TDV has been established (Moodie et al., 2018). The vaccine efficacy findings in this study were substantiated by the immunogenicity results. Remarkably high vaccine efficacy was observed starting from the first dose in 9-year-old seropositive participants, and from the second dose in participants aged 6-8 years. This phenomenon can be partly attributed to the

priming of pre-existing dengue antibodies resulting from previous natural infections. Subsequently, 1 or 2 doses of CYD-TDV led to an elevation in neutralizing antibodies of adequate 'quality' (e.g., enhanced neutralization potency and avidity) and quantity, thereby conferring protection against dengue (Patel et al., 2017; Valdés et al., 2019).

In a study conducted by Ismaila et al. (2021), the initial seroprevalence among the study participants ranged from 50 percent to 80 percent. In terms of CYD-TDV vaccine safety, injection site reactions (pain, swelling, erythema) exhibited relative risks (RR) with a 95% confidence interval (CI) of 0.46-1.76. Additionally, systemic reactions (fever, headache, myalgia) were also observed, with RR at a 95% CI of 0.89-1.81, within the participant group. Among the four reviewed studies, three reported instances of severe adverse events experienced by participants, with RR at a 95% CI of 0.92-2.11. In terms of immunogenicity, notable Geometric Mean Titre (GMT) values were reported for DENV-2 at 67.8 (95% CI 64.8-70.8), DENV-3 at 73.1 (95% CI 69.9-76.3), and DENV-4 at 65 (95% CI 62-67.9). Although slightly lower values were reported, these findings remained consistent with other published studies on the immunogenicity of CYD-TDV against DENV serotypes. This comprehensive review suggests that the use of CYD-TDV could be contemplated in the Asian context, albeit with certain reservations, and adherence to prevailing safety recommendations (Ismaila et al., 2021).

The pooled vaccine efficacy (VE), determined through a per-protocol analysis in two trials, was found to be 59.2% in the year following the assessment, with variability observed across serotypes, age at vaccination, and baseline serostatus (Kariyawasam et al., 2023). VEs were notably higher among children who exhibited seropositivity at baseline in comparison to those who started as seronegative. This disparity was most pronounced in the seronegative group, which also experienced the highest risk of dengue hospitalization (7.45 [95% confidence interval (CI): 1.15, 313.80]), particularly evident among vaccinated children aged 2-5 years in the CYD14 trial (Yang et al., 2018).

Due to the increased vulnerability of the 2-5 year age group to vascular permeability and antibody-dependent enhancement (ADE), the CYD15 trial focused its recruitment on participants aged 9 years and above (Yang et al., 2018). In the seronegative group, the VE was determined to be 38.1%, primarily influenced by observations related to DENV4 (Yang et al., 2018). Conversely, within the seropositive group, the overall VE was notably higher at 78.2%, with the most robust VE seen against DENV3 and DENV4 (89.9% and 75.4%, respectively), as opposed to DENV1 and DENV2 (70.2% and 67.9%, respectively). Furthermore, a trend emerged suggesting greater effectiveness within older age groups, especially those aged 9 years or older (Yang et al., 2018).

A subsequent post-hoc retrospective analysis of long-term safety data revealed an elevated risk of severe dengue among individuals who were seronegative at baseline. Serostatus, indicating prior dengue infection, plays a pivotal role in this context (Sridhar et al., 2018). This increased risk among seronegative subjects became noticeable approximately 30 months after the initial dose administration. A plausible hypothesis suggests that CYD-TDV might induce an immune response to dengue in seronegative individuals, potentially heightening their susceptibility to more severe disease. This scenario mirrors the phenomenon observed in natural secondary dengue infections (Annelies Wilder-Smith et al., 2019).

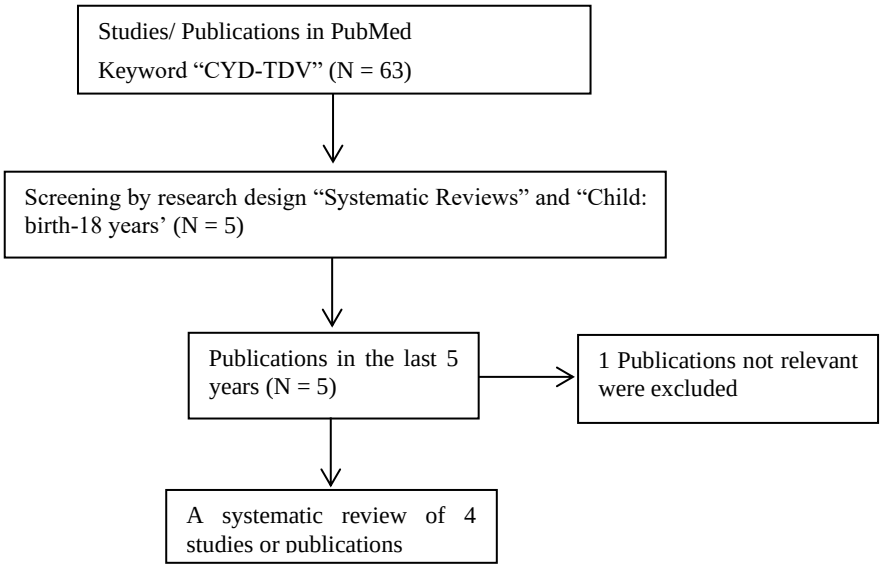
The subsequent infection involving the primary wild-type dengue virus could manifest as a 'secondary-like' dengue disease. Notably, the dengue non-structural protein (NS) is absent in the Sanofi dengue chimeric vaccine. Given that NS1 might possess properties akin to toxins, capable of disturbing endothelial glycocalyx through both inflammation-dependent and independent pathways (Beatty et al., 2015; Glasner et al., 2017; Modhiran et al., 2015; Puerta-Guardo et al.,

2016), the omission of NS1 in CYD-TDV may also contribute to the vaccine's restricted performance (Annelies Wilder-Smith, 2020).

The public health applicability of CYD-TDV is limited to seropositive individuals. Consequently, the ongoing need for implementation research pertains to the establishment of pre-vaccination screening procedures, particularly for specific settings like schools, to enable the rollout of CYD-TDV in national or subnational programs (A Wilder-Smith et al., 2019). In light of the aforementioned contextual background, the primary objective of this study is to assess the effectiveness and safety of the CYD-TDV vaccine among children residing in endemic areas.

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 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."	"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."
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	Systematic Review and Meta Analysis	To evaluate efficacy, immunogenicity and safety of	"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	"CYD-TDV is considered safe and able to partially protect children and adolescents against

tetravalent dengue vaccine (CYD-TDV) in children aged 2–17 years: systematic review and meta-analysis”	CYD-TDV in the prevention of dengue in children aged 2–17 years.	vaccine was 51% for dengue virus type-1 (DENV1) (RR 0.49 (0.39 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 advers”.	four serotypes of DENV for a 1-year period. Despite this, research should priorities improvements in vaccine efficacy, thus 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.

Godói et al. (2017) conducted a systematic review that comprehensively synthesized high-quality research findings pertaining to the safety of the CYD-TDV (Denvaxia®) vaccine against dengue virus infection. The outcomes presented robust evidence of the vaccine's noteworthy global efficacy, showcasing efficacy rates of up to 60% among volunteers under 16 years of age. Furthermore, an analysis of immunogenicity within the adult population suggests promising prospects for this vaccine to yield a favorable impact once it enters the market. However, the ongoing evaluation of CYD-TDV's efficacy and safety remains of paramount importance, particularly considering the substantial prevalence of infection and the severe manifestations of dengue disease in endemic regions (Godói et al., 2017).

The findings of this systematic review underscore the critical significance of stringent adherence by pharmaceutical companies and researchers to meticulous technical protocols throughout all phases of clinical trials. Such diligence is imperative to provide robust data that can guide health authorities in their decisions regarding the integration of these vaccine technologies into the healthcare system. Furthermore, the review accentuates the pressing need for the development of vaccines that not only demonstrate safety and efficacy but are also financially accessible to all strata of society. The ultimate objective is to preemptively curtail the potential rapid propagation of dengue fever, particularly in regions where dengue virus infection poses a substantial and persistent public health challenge. To this end, collaborative endeavors among the pharmaceutical industry, researchers, and global health authorities assume paramount importance.

By fostering a collective approach, these stakeholders can design effective and sustainable solutions that effectively address the multifaceted challenges posed by dengue disease (Godói et al., 2017).

In another study conducted by Rosa et al. (2019), three randomized controlled trials (RCTs) were undertaken to evaluate the effectiveness of the CYD-TDV vaccine. These trials collectively encompassed 31,128 participants, with 20,841 subjects in the test group and 10,287 subjects in the control group. The overall effect estimate for CYD-TDV was 0.40 (Relative Risk (RR) 0.40, 95% Confidence Interval (CI) 0.30 to 0.54), signifying an efficacy of 60% for the vaccine.

Systemic side effects were reported more frequently in the test group, affecting 37.8% of participants, compared to 33.2% in the control group. Notably, the most common local side effect was pain at the injection site, experienced by 33.1% of those administered CYD-TDV and 29.3% of those given a placebo. No statistically significant disparities were observed between the two groups, apart from this effect. However, a notable limitation of this study was the presence of unclear or incomplete data (Rosa et al., 2019). For instance, two RCTs examining immunogenicity were excluded from the meta-analysis due to their publication of only pooled Geometric Mean Titres (GMTs) for the four DENV serotypes, thus precluding a statistical analysis based on individual viral serotypes.

In another study, only the incidence of febrile episodes was documented for both study groups, with no comprehensive response provided to address this concern. The authors communicated their inability to furnish additional data. Additionally, the study faced limitations in conducting a long-term analysis as the participants of the chosen clinical efficacy trial were monitored for just one year following the administration of the third vaccine dose. A thorough and long-term analysis, aligning with World Health Organization (WHO) recommendations, is imperative to comprehensively assess vaccine effects, ensuring that vaccination-induced immune responses do not render individuals more susceptible to severe disease, nor escalate the risk of severe disease over time. Such events could arise due to vaccine-induced declines in antibody levels, as measured by GMT, in individuals whose natural immunity has not concurrently heightened.

Among the 1932 studies identified in the surveyed database by da Silveira et al. (2019), a total of seven studies were meticulously chosen for subsequent analysis. The trials encompassed populations ranging from 150 to 20,869 subjects, with participants spanning an age range of 2 to 45 years. The outcomes of this analysis notably revealed that the tested vaccines exhibited efficacy against serotypes 3 and 4, yet demonstrated ineffectiveness against serotypes 1 and 2. This crucial finding underscores the vaccines' capacity to confer substantial protection against specific viral variants, particularly serotypes 3 and 4, while their protective efficacy against serotypes 1 and 2 remained comparatively diminished. Moreover, a notable trend emerged in which vaccine effectiveness appeared to be heightened in individuals who displayed seropositivity at baseline, especially among those aged 9 years. This observation underscores the significance of acknowledging the heightened immune response within this demographic, adding an important dimension to the overall understanding of vaccine efficacy (da Silveira et al., 2019).

Nevertheless, the conclusions drawn from the study by da Silveira et al. (2019) highlight a trend of diminished vaccine effectiveness within the age group of children aged 2 to 5 years. However, even in light of these observations, this study amplifies the paramount importance of vaccination as a pivotal strategy in the realm of infectious disease prevention. These findings substantiate the rationale for introducing vaccination within age groups below 9 years, underlining the critical need for continuous efforts aimed at enhancing vaccine effectiveness. This endeavor

assumes a particular significance, especially in safeguarding the pediatric population from infectious diseases (da Silveira et al., 2019).

In a broader perspective, this study unequivocally affirms the enduring significance of vaccination as a pivotal instrument in the concerted endeavor to curb the proliferation of infectious diseases. The implications drawn from this analysis unequivocally emphasize the necessity of allocating resources toward continued research and development endeavors aimed at enhancing vaccine efficacy, with particular emphasis on shielding younger and more susceptible age cohorts. A comprehensive comprehension of immune responses, coupled with a nuanced understanding of distinct population characteristics, holds the potential to pave the way for the creation of more efficacious vaccines. Such advancements could potentially furnish a broader shield of protection against a spectrum of infectious diseases, heralding a promising trajectory for the future of disease prevention (da Silveira et al., 2019).

Agarwal et al. (2017) conducted a systematic review that delved into the efficacy of the CYD-TDV (Dengvaxia) vaccine within a pediatric demographic spanning 2 to 18 years of age. Within this study, six distinct clinical trials involving children were subjected to intervention, entailing administration of three doses of CYD-TDV over a six-month period. To assess the vaccine's immunogenicity, the study scrutinized the elevation of Geometric Mean Titer (GMT) levels of antibodies from their baseline measurements to post the third dose administration. The findings unveiled an intriguing trend: post the second dose, antibody titers reached their zenith, yet the third dose did not elicit a significant increase. This intriguing pattern suggests that the CYD-TDV vaccine's immunogenicity may peak after the second dose, implying that two doses could potentially be more efficacious than the third. Nonetheless, the significance of the third dose endures, particularly for individuals initially lacking antibodies to flaviviruses. In this context, the inclusion of a third dose within a vaccination strategy retains its relevance. The third dose notably enhances GMT levels specifically in those who are seronegative to flaviviruses. This observation underscores the pivotal role of the third dose for individuals without prior flavivirus exposure, even if a comparable effect is not observed among those who are already seropositive (Agarwal et al., 2017).

The administration of the third dose of the vaccine has yielded promising outcomes, particularly among individuals lacking prior exposure to flaviviruses. Notably, in instances where the patient was previously seronegative for flaviviruses, the third dose has demonstrated notable effectiveness. These findings advocate for a standardized three-dose regimen as a viable immunization strategy. It is important to acknowledge that assessing antigen seropositivity prior to vaccine administration remains a challenge, given the current impracticality of preemptively determining this status. Despite this limitation, the commendable success of the third dose among patients previously seronegative to the virus underscores the potential advantages of adopting a three-dose protocol to enhance the overall efficacy of immunization.

Moreover, the insights gleaned from this review lend support to the continued development and widespread utilization of CYD-TDV, commonly known as Dengvaxia. This complements existing vector control methods and offers a robust strategy for curtailing dengue disease among children and adolescents. By integrating CYD-TDV into established vaccination programs, the incidence of dengue infection can be notably reduced in regions bearing a high disease burden (Agarwal et al., 2017).

The fundamental objective underlying the development of the CYD-TDV vaccine, Dengvaxia, is to thwart the onset of dengue fever symptoms that stem from the dengue virus itself (Agarwal et al., 2017). Notably transmitted by Aedes mosquitoes, the dengue virus can instigate

manifestations such as fever, joint discomfort, and, in severe cases, escalate to more critical forms like dengue fever and dengue shock syndrome. The vaccine's core design revolves around eliciting a robust immune response within the body upon exposure to the dengue virus, thereby effectively thwarting the development of disease in individuals at risk (Agarwal et al., 2017).

Thorough and systematic testing, with a focus on children, has been conducted to assess the effectiveness and safety of the CYD-TDV vaccine. The culmination of these analyses underscores both its efficacy and safety, thereby signaling the vaccine's significant potential in curbing the incidence of dengue disease within the pediatric population. Measuring the vaccine's effectiveness entails evaluating the reduction in both the number of cases and the severity of dengue disease among those who receive the vaccine. Beyond efficacy, vaccine safety stands as a pivotal consideration in the contemplation of widespread vaccination initiatives.

The triumphant outcomes associated with CYD-TDV pave the way for further avenues of exploration and protracted research. Bolstered by the favorable results from efficacy and safety analyses, more comprehensive investigations involving larger cohorts and extending over extended durations are essential. Such endeavors are geared towards scrutinizing the vaccine's prolonged efficacy in reducing dengue prevalence in a more nuanced manner. These protracted studies are poised to offer deeper insights into the vaccine's mode of action and its overarching impact on the immunized population.

Moreover, the initial seropositivity level to the dengue virus holds substantial implications for the immune response elicited by CYD-TDV. Particularly in regions endemic to dengue, like Latin America, higher seropositivity levels may signify a more robust immune reaction to the vaccine. This heightened response is attributed to prior dengue virus exposure, which primes the immune system for a more effective reaction to the vaccine. The baseline seropositivity level can potentially influence the extent of protection furnished by the vaccine, serving as a pivotal element in the formulation of an optimized vaccination program.

Consideration of the regional context and the level of dengue endemicity holds significant importance in this analysis. Regions with a high risk of dengue, such as Latin America and Indonesia, stand to gain substantial benefits from the adoption of the CYD-TDV vaccine. This vaccine possesses the potential to substantially alleviate the burden of dengue disease within these areas, emerging as a pivotal component of a comprehensive disease prevention strategy. Overall, this analysis underscores the indispensability of the CYD-TDV vaccine within dengue prevention endeavors, highlighting avenues for further research and outlining its impact across diverse geographical landscapes.

The outcomes of this study carry noteworthy theoretical and practical implications for the domains of vaccine development and dengue control. On a theoretical level, this study robustly affirms the efficacy of the CYD-TDV (Denvaxia®) vaccine against dengue virus infection, furnishing compelling evidence of the pivotal role that this vaccine technology plays in diminishing the prevalence and symptoms associated with dengue disease. Moreover, the study effectively draws attention to variations in immunogenicity contingent upon the dengue virus serotypes, thus pointing towards the imperative of devising vaccines that can incite potent immune responses against varying virus serotypes to enhance the efficacy of disease prevention strategies. Concurrently, the study sheds light on the potential disparities in CYD-TDV vaccine efficacy based on age and baseline seropositivity status. This underscores the need to systematically account for these variables during the planning and assessment phases of immunization programs and evaluations of vaccine effectiveness.

The comprehensive review focusing on adherence to technical protocols in clinical trials underscores the pressing need for precise and consistent research methodologies, ensuring the acquisition of dependable data to inform decisions pertaining to vaccine development and utilization. In practical terms, the primary implication of this study lies in the seamless integration of the CYD-TDV vaccine into established vaccination programs, with a particular emphasis on targeting children and adolescents residing in endemic regions. This strategic move is anticipated to substantially curtail the incidence of dengue disease and its associated impact on public health.

Moreover, this study strongly accentuates the significance of immunizing vulnerable groups, stratified by both age and baseline seropositivity status, with the overarching aim of bolstering the efficacy of disease prevention endeavors. Additional practical implications encompass the imperative for continued research and innovation to enhance the effectiveness, safety, and long-term potency of the CYD-TDV vaccine. Concurrently, fostering closer collaboration among the pharmaceutical industry, researchers, health authorities, and the global community is crucial to design pragmatic and affordable solutions aimed at combatting dengue.

Enhancing public awareness and education regarding the critical importance of vaccination and preventive measures emerges as a pivotal practical implication underscored by this study. This endeavor holds the potential to significantly mitigate disease transmission and alleviate its ramifications. Thus, the outcomes of this study extend invaluable guidance for the development of health policies, planning of immunization programs, and the orchestration of disease prevention initiatives within endemic regions. The collective effort is aimed at effectively addressing the formidable challenges associated with dengue virus infection.

Overall, the findings of this study furnish compelling evidence of the potency and promise held by CYD-TDV as a potent vaccine against dengue virus infection. Notwithstanding, the study acknowledges the existence of data limitations and the variability in immunological responses, underscoring the continued imperative for ongoing research and advancement. Collaborative endeavors between researchers, the pharmaceutical industry, and health authorities are pivotal in surmounting the challenges posed by dengue, particularly within endemic areas. Thus, this review instills optimism regarding the robust efficacy of this vaccine when applied within the Indonesian population.

CONCLUSION

Research results related to the CYD-TD Vaccine have demonstrated its effectiveness and immunogenic potential against the dengue virus. However, there are still several aspects that need consideration for further development. One of the primary concerns is extending the vaccine's efficacy to encompass all four serotypes of DENV1-4. While this vaccine has shown success against multiple serotypes, additional research is necessary to ensure that the protection it offers applies equally to all dengue virus serotypes.

Furthermore, it is crucial to highlight the safety aspects of the vaccine, especially for children under 9 years of age. Although the CYD-TD Vaccine shows promise in providing protection, further research should prioritize confirming its safety for this younger and vulnerable age group. In the pursuit of a more optimized vaccine, it is also essential to factor in potential side effects and immune reactions that may arise from vaccine administration. Conducting long-term studies will be essential for gaining a comprehensive understanding of the lasting impact of CYD-TD vaccination on the vaccinated population.

Vaccine development must also address the duration of protection offered by these vaccines. Long-term studies will facilitate an assessment of the CYD-TD vaccine's capacity to sustain immunity against the dengue virus over an extended period. While the CYD-TD vaccine holds promise for safeguarding against dengue disease, achieving the "ideal" vaccine – one that effectively combats all DENV serotypes and is safe for all age groups – necessitates further research efforts that encompass innovations in vaccinology and foster interdisciplinary collaborations.

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