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SYSTEMATIC REVIEW OF DENGUE VACCINE EFFICACY

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Abstract

Background: *Dengue fever belongs to the arboviruses which are the genus Flavivirus (family Flaviridae) and is transmitted through female mosquitoes that carry the dengue virus. There are four serotypes of dengue fever, namely DENV−1, DENV−2, DENV−3, and DENV−4. The number of cases of dengue fever infection is estimated at 390 million spread across 128 countries. Although globally, only 3.2 million cases were reported to WHO in 2015. There are many challenges in developing a safe and effective dengue fever vaccine. Infection with one of the four dengue virus serotypes has been shown to provide long-term protection against homotypic reinfection, but protection against secondary heterotypic infection is only temporary.*

The aim: *This study aims to show about dengue vaccine efficacy.*

Methods: *By comparing itself to the standards set by the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, this study was able to show that it met all of the requirements. So, the experts were able to make sure that the study was as up-to-date as it was possible to be. For this search approach, publications that came out between 2013 and 2023 were taken into account. Several different online reference sources, like Pubmed and SagePub, were used to do this. It was decided not to take into account review pieces, works that had already been published, or works that were only half done.*

Result: *In the PubMed database, the results of our search brought up 83 articles, whereas the results of our search on SagePub brought up 147 articles. The results of the search conducted for the last year of 2013 yielded a total 79 articles for PubMed and 90 articles for SagePub. The result from title screening, a total 31 articles for PubMed and 24 articles for SagePub. In the end, we compiled a total of 7 papers. We included five research that met the criteria.*

Conclusion: *Dengue vaccines can be produced with live attenuated chimeric recombinant viruses, live attenuated viruses, inactivated viruses, recombinant proteins and mRNA vaccines. Each of these vaccines has good efficacy in terms of protection against dengue virus.*

Keyword: *Dengue fever, dengue vaccine, dengue virus*

INTRODUCTION

Dengue fever is a common arboviral disease in humans. About 2.5 billion people in the world are at risk of contracting this disease. The impact of the dengue fever epidemic on more than 100 countries. Every year, an estimated 390 million infections occur in the world, of which 96 million have clinical manifestations. This includes approximately 250,000 cases manifested by dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). The global incidence of DHF/DSS has increased more than 500 times in recent years.[1]

Dengue fever is caused by infection with one of four serotypes of dengue virus (DENV). This viral disease is transmitted by mosquitoes and is a major public health problem. Clinical manifestations of DENV infection range from asymptomatic infection or mild flu-like syndrome, also known as dengue fever (DF), to the more severe and life-threatening forms, dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). An estimated 390 million DENV infections occur annually worldwide, and 50-200 million of these are true cases (symptomatic infections, including those not detected by reporting systems). Data from 76 countries show there has been a substantial increase in the incidence of dengue, with the number of real cases more than doubling every decade between 1990 and 2013, with the highest incidence of infection reported in Asian countries.[2]

Vaccination is one of the important public health developments today and has played a role in reducing the burden of various infectious diseases. Dengue fever causes millions of symptomatic cases each year and has a major impact on public health and the economy. Developing a dengue vaccine is fraught with challenges due to the complexity of formulating the vaccine against 4 serotypes (DENV-1, DENV-2, DENV-3, and DENV-4) and evaluating it in large field studies over several years to demonstrate durable protection and assess scale-up. risk of dengue fever or severe dengue fever in vaccinated and unvaccinated individuals following wild-type infection (i.e. disease progression). In contrast to other diseases that can be prevented by vaccines, there is no correlation between immunity and protection (CoP) against dengue fever. The last decade has shown progress in the field of dengue vaccine development under license from Dengvaxia (Sanofi Pasteur). However, the vaccine is associated with an increased risk of severe disease or hospitalization in recipients who have never had dengue fever, necessitating pre-vaccination screening to only vaccinate those with evidence of past infection.[3]

Developing an effective vaccine against the four DENV serotypes is an important strategy in controlling dengue fever. Flavivirus monotype vaccines, such as yellow fever, Japanese encephalitis, have an efficacy of 95% and are used as a reference in the development of dengue fever vaccines. Since the 1970s, several techniques have been applied to produce vaccines capable of inducing immunity against four virus serotypes. Several vaccine candidates have been developed using live attenuated viruses, inactivated viruses, and DNA vaccines. The tetravalent dengue fever vaccine (CYD-TDV) from Sanofi Pasteur, Dengvaxia®, contains four recombinant viruses engineered with DENV1–4 and the capsid protein of the Yellow Fever vaccine virus (YF-17D) which is attenuated. CYD-TDV is the first vaccine to be licensed for the prevention of dengue fever. As of October 2016, 11 countries have granted regulatory approval for Dengvaxia®, for example Mexico, Philippines, Brazil, El Salvador, Costa Rica, Paraguay, Guatemala, Peru, Indonesia, Thailand and Singapore.[4,5]

The vaccine is indicated for individuals living in endemic areas and between 9 and 45 years of age, in contrast to Paraguay which extends the upper limit to people aged 60 years. The capacity of a vaccine to produce an immune response is influenced by many factors including age, presence of underlying disease, immune status, and previous exposure to the same or similar substances (seropositivity). In endemic areas, presensitization may induce an immune response prior to vaccination, as may occur with CYD-TDV. In Phase III trials, vaccination showed lower efficacy in seronegative individuals, suggesting that the vaccine expanded existing immunity rather than efficiently boosting new protective immunity.[4,6]

Recombinant, live, attenuated, tetravalent dengue vaccine (CYD TDV, Dengvaxia; Sanofi Pasteur) is licensed for the prevention of dengue fever in individuals previously exposed to dengue fever in more than 20 countries. In the first phase 2b CYD-TDV efficacy study (CYD23, NCT00842530), conducted in children aged 4-11 years in one province in Thailand, high efficacy (VE) vaccine against dengue virus serotype (DENV)-1 was reported. , -3 and -4 (62-90%), while the VE against DENV-2 infection was very low (3.5%). In the CYD TDV phase 3 study (CYD14, NCT01373281; CYD15, NCT01374516) strong efficacy against all four serotypes was seen in a total population of participants aged 2–16 years with and without prior dengue infection. Further analysis of CYD14 and CYD15 data in participants classified as seropositive at baseline also demonstrated strong efficacy against all four serotypes in those aged 9-16 years.[7,8]

METHODS

Protocol

By following the rules provided by Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020, the author of this study made certain that it was up to par with the requirements. This is done to ensure that the conclusions drawn from the inquiry are accurate.

Criteria for Eligibility

For the purpose of this literature review, we compare and contrast of dengue vaccine efficacy. It is possible to accomplish this by researching or investigating the efficacy of dengue vaccine. As the primary purpose of this piece of writing, demonstrating the relevance of the program that have been identified will take place throughout its entirety.

In order for researchers to take part in the study, it was necessary for them to fulfil the following requirements: 1) The paper needs to be written in English, and it needs to determine the efficacy of dengue vaccine. In order for the manuscript to be considered for publication, it needs to meet both of these requirements. 2) The studied papers include several that

were published after 2013, but before the time period that this systematic review deems to be relevant. Examples of studies that are not permitted include editorials, submissions that do not have a DOI, review articles that have already been published, and entries that are essentially identical to journal papers that have already been published.

Search Strategy

We used "Dengue vaccine efficacy"; "the efficacy of dengue vaccine" as keywords.The search for studies to be included in the systematic review was carried out using the PubMed and SagePub databases by inputting the words: *((("dengue"[MeSH Subheading] OR "dengue fever"[All Fields] OR "dengue vaccine"[All Fields]) AND ("dengue vaccine efficacy"[All Fields] OR "dengue virus"[All Fields]) AND ("the efficacy of dengue vaccine"[MeSH Terms] OR ("prevalence of dengue fever"[All Fields]) OR ("dengue fever in Indonesia"[All Fields]) AND "the impact of dengue vaccine"[All Fields]) OR ("prevalence of dengue"[All Fields]) OR ("prevalence dengue fever in Indonesia"[All Fields]) OR ("dengue vaccine in Indonesia"[All Fields]) AND "the prevention program of dengue fever"[All Fields])) AND ("the prevention program of dengue virus"[All Fields]))* used in searching the literature.

Data Retrieval

After reading the abstracts and titles of each study, the authors conducted an examination to determine whether the study met the inclusion criteria or not. The author then selects and chooses previous research that will be used as a source for the articles to be made. After looking at a number of different studies, all of which seemed to show the same trend, the following conclusions were drawn. All submissions must be written in English and cannot be viewed anywhere else.

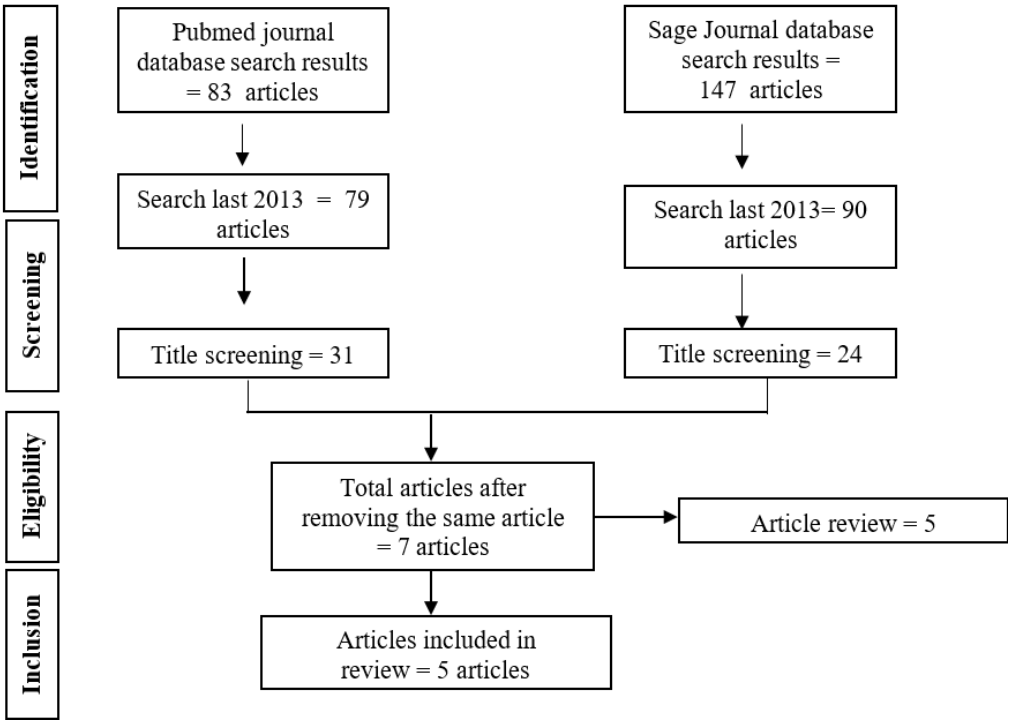

Figure 1. Article search flowchart

Only those papers that were able to satisfy all of the inclusion criteria were taken into consideration for the systematic review. This reduces the number of results to only those that are pertinent to the search. We do not take into consideration the conclusions of any study that does not satisfy our requirements. After this, the findings of the research will be analysed in great detail. The following pieces of information were uncovered as a result of the inquiry that was carried out for the purpose of this study: names, authors, publication dates, location, study activities, and parameters.

Quality Assessment and Data Synthesis

Each author did their own study on the research that was included in the publication's title and abstract before making a decision about which publications to explore further. The next step will be to evaluate all of the articles that are suitable for inclusion in the review because they match the criteria set forth for that purpose in the review. After that, we'll determine which articles to include in the review depending on the findings that we've uncovered. This criteria is utilised in the process of selecting papers for further assessment. in order to simplify the process as much as feasible when selecting papers to evaluate. Which earlier investigations were carried out, and what elements of those studies made it appropriate to include them in the review, are being discussed here.

RESULT

In the PubMed database, the results of our search brought up 83 articles, whereas the results of our search on SagePub brought up 147 articles. The results of the search conducted for the last year of 2013 yielded a total 79 articles for PubMed

and 90 articles for SagePub. The result from title screening, a total 31 articles for PubMed and 24 articles for SagePub. In the end, we compiled a total of 7 papers. We included five research that met the criteria.

Godoi *et al* (2017)[4] showed that of the 895 titles screened, the abstracts of 321 records were assessed, and of these, 89 full-text studies were assessed for eligibility. Six Phase II and three Phase III randomized clinical trials were included. From a search on ClinicalTrials.gov, including one ongoing trial in a Phase II trial for CYD-TDV. Three Phase III trials evaluated CYD-TDV. All studies were conducted in endemic areas of Latin America or Southeast Asia. A total of 34,631 volunteers participated in the Phase II-III CYD-TDV trial (CYD-TDV, n = 23,193; control, n = 11,438). The trial implemented randomization ratios of 2:1, 3:1 and 4:1. The vaccination schedule consists of three doses at 6 month intervals. The control group of Phase II trials consists of a combination of placebo (one or two doses) and another vaccine (e.g. pneumococcal polysaccharide, meningococcal polysaccharide) (one or two doses). All Phase III studies were placebo controlled. As a group, the Phase II trial evaluated adolescents and adults (2–45 years), while the Phase III trial was conducted only in children and adolescents (2–17 years). 6% of participants did not complete the CYD-TDV vaccination schedule in the Phase II trial. Two Phase III trials reported loss to follow-up (0.8% on CYD-TDV). The main reason for treatment loss is voluntary discontinuation of treatment, not due to adverse events. This vaccine is approved for individuals between the ages of 9–45 and 9–60 years. There is one ongoing study, a Phase II randomized control trial (NCT01943305) evaluating CYD and conducted in Singapore with 90 volunteers (aged 18-45 years), expected to be completed by the end of 2016. This study was funded by Sanofi Pasteur and the Medical School of Singapore, in cooperation with the Singapore General Hospital.

Reynales *et al* (2020)[8] showed In a posthoc case-cohort study, 959 participants (645 in the CYD-TDV group and 314 in the control group) from Colombia were part of a subcohort for analysis based on dengue serostatus at baseline. The proportion of participants in this subcohort who were dengue seropositive at baseline was similar in the CYD-TDV group and the control group (91.5% in the CYD-TDV group and 92.0% in the control group). During the active phase (years 1–2), 2,798 febrile episodes were reported in the CYD-TDV group compared with 1,486 in the control group. During the hospital phase (years 3-6), acute blood samples of fever cases were collected for 74 episodes. During SEP (years 4–6), a total of 862 febrile episodes were reported, 568 in the CYD-TDV group and 621 in the control group. During the active phase, VE for symptomatic VCD due to any of the 4 serotypes, regardless of dengue serostatus at baseline, was 67.5% (95% CI: 58.3–74.7) and remained the same during SEP, 64 , 5% (95% CI: 3.0–87.6). In terms of safety, 15.0% (977/6495) of participants in the CYD-TDV group experienced at least 1 SAE and 16.2% (527/3245) in the control group during the entire study, the majority of SAEs being due to infectious diseases. There were 29 deaths (20 in the CYD-TDV group and 9 in the control group). None of the deaths and few SAEs were related to CYD-TDV (respiratory, chest, and mediastinal disorders, and asthma); the deaths were caused by traffic accidents (n = 9), violence (i.e., gunshot wounds, stabbings, homicides) (n = 8), intentional self-poisoning and exposure to chemicals and other unspecified hazardous substances (n = 3) , deliberate self-harm by hanging (n = 2), death due to falling from a roof (n = 1), renal failure due to systemic peri-nuclear antineutrophil cytoplasmic antibodies vasculitis due to autoimmune etiology (n = 1), intracranial hemorrhage secondary to rupture aneurysm (n = 1), autoimmune encephalitis due to antibodies to the N-methyl-D-aspartate receptor (n = 1), unattended death (corpse found in the forest after disappearance) (n = 1), acute respiratory failure (n = 1) and septic shock due to chest compression trauma (n = 1).

Table 1. The litelature include in this study

Author	Origin	Method	Sample Size	Result
Godoi *et al.*, 2017[4]	Brazil	Meta-analysis and systematic review	10 studies	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.
Reynales *et al.*, 2020[8]	Columbia	Posthoc case–cohort study	9740 respondents	During the active phase of the trial in Colombia, the efficacy of CYD-TDV was 67.5% [95% confidence interval (CI): 58.3–74.7] against symptomatic VCD due to any serotype from injection 1 (month 0) to 25 months postinjection 1. Over 6 years, the RR across all 4 serotypes was 0.166 (95% CI: 0.09–0.29) in hospitalized VCD patients and 0.154 (95% CI: 0.04–0.50) in patients with severe hospitalized VCD.
Moodie *et al.*, 2018[9]	America	Case cohort	2848 vaccine, 1574 placebo	For each trial and serotype, vaccinees with higher month 13 titer to the serotype had significantly lower risk of VCD with that serotype (hazard ratios, 0.19–0.43 per 10-fold increase). Moreover, for each trial, vaccinees with higher month 13 average titer to the 4 serotypes had significantly higher VE against VCD of any serotype (P < .001).
Plennevaux *et al.*, 2018[10]	America	Randomized controlled trial	≥31000 children aged 2–16 years across 10 countries in Asia	There were 1284 VCD episodes (575 and 709 in the CYD-TDV and placebo groups, respectively) and 17673 other febrile episodes (11668 and 6005, respectively). Compared with VCD, the sensitivity and specificity of probable dengue definition were 93.1% and 77.2%,

			and Latin America.	respectively. Overall positive and negative predictive values were 22.9% and 99.5%, respectively, reflecting the much lower probability of correctly confirming probable dengue in a population including a vaccinated cohort. Vaccination-induced bias toward false-positive diagnosis was more pronounced among individuals seronegative at baseline.
Savarino *et al.*, 2022[11]	America	A retrospective analysis of phase 3 efficacy trials	3983 participants	Of 3983 participants in the immunogenicity subsets of the efficacy trials CYD14 and CYD15, 3962 had complete dengue reference test results enabling baseline serostatus classification and 3833 had sufficient serum samples remaining for evaluation with the OnSite IgG RDT. Of the samples tested, 2486 (64·9%) of 3833 were OnSite IgG RDT-positive. In participants aged 2–16 years who were OnSite IgG RDT-positive, vaccine efficacy was 84·1% (95% CI 71·6–91·1) against symptomatic VCD, and 69·2% (38·8–84·5) against hospitalisation with VCD, with similar findings in those aged 6 years or older and those aged 9 years or older. The OnSite IgG RDT showed very high sensitivity (91·1%, 89·9–92·1) and high specificity (92·8%, 91·2–94·2) in participants aged 2–16 years, with significantly higher specificity in those aged 9 years or older (96·6%, 94·9–97·8).

Moodie *et al* (2019)[9] denotes the number of study participants with neutralization data. With controls and dengue cases specified in Methods, month 13 titers were measured from n = 1,879 controls (1,275 vaccine, 604 placebo) in CYD14 and n = 1,884 controls (1,275 vaccine, 609 placebo) in CYD15. Month 13 titers were measured from n = 244 cases occurring after month 13 to month 25 (115 vaccine, 129 placebo) in CYD14 and n = 415 cases (183 vaccine, 232 placebo) in CYD15, representing 99, 6% and 99.8% of total DENV-Any Cases. Because month 0 samples were collected only for the immunogenicity subset, month 0 neutralization responses were available for 99.7% of controls but only n = 52 (21.3%) cases at CYD14 and n = 36 (8.7%) cases at CYD15. Of 2123 (2299) participants with 13th month neutralization data on CYD14 (CYD15), 99.6% (99.4%) received all three immunizations.

Plennevaux *et al* (2018)[10] showed There were 18957 episodes of fever experienced by 10272 participants: 6848 CYD-TDV and 3424 placebo recipients. Acute blood samples were obtained for 17765 (93.7%) episodes, and convalescent samples for 18489 (97.5%) episodes. There were 1,284 VCD episodes and 17,673 other fever episodes. Twenty-eight episodes without an acute serum sample for virological testing were included in other febrile episodes. In the immunogenicity subset, there were 145 VCD episodes and 2646 other febrile episodes. Of the remaining 39 episodes, 5 (11.4%) of the 5 participants experienced an increase in PRNT titer before each episode, indicating the potential for previous asymptomatic dengue infection during the study. No further increase in PRNT titer occurred after this asymptomatic episode. Therefore, the serologic profile observed for this episode may be due to an asymptomatic infection. Twenty-eight (63.6%) of the other episodes in 17 participants (1 participant had 7 febrile episodes, 4 of them before the VCD episode and 3 after) had acute and/or convalescent IgM-positive samples but no improvement was observed. between acute and cured. Except for 1 episode (a JE-seropositive participant), all episodes had IgG-negative acute and convalescent samples, and none of the final 27 episodes had elevated PRNT. Overall, this episode did not have a serological profile or PRNT associated with VCD. Therefore, this episode was most likely caused by the variability of detection in the IgM ELISA. The last 6 episodes (13.6%) in 6 participants had positive IgM samples and PRNT titers increased after the episode for 1 serotype. Of these, 2 people experienced an increase in IgM between acute and recovery periods and 1 of them had positive IgG, which was consistent with the VCD profile. These last two episodes suggest potential symptoms of dengue fever, but previous asymptomatic infection cannot be ruled out as no PRNT data are available for these episodes.

Savarino *et al* (2022)[11]savrinos demonstrated vaccine efficacy against symptomatic VCD was 84 1% (95% CI 71 6–91 1) in all participants with Onsite IgG RDT test results (overall population, aged 2–16 years). Estimates of vaccine efficacy that are similar to the overall population were obtained for participants aged 9 years or older and those aged 6 years and older; for those younger than 9 years, vaccine efficacy was numerically lower than that of the population as a whole, albeit with a wider and overlapping CI. Vaccine efficacy against hospitalization with VCD in participants with positive IgG RDTs in Place aged 2–16 years was 69·2% (38·8 to 84·5), and the rates were similar between the different age groups. Consistent with other efficacy results, vaccine efficacy against severe VCD in participants with a positive IgG In Place RDT test aged 2–16 years was 73 3% (−6 8 to 93 3); however, the lack of events results in a CI of 95%, the lower bound exceeding zero. Vaccine efficacy against severe VCD is similar in different age groups. Estimates of the efficacy of these vaccines were similar between the studies; however, the lack of severe VCD events in CYD15 precludes assessing vaccine efficacy.

DISCUSSION

Dengue fever is caused by four different serotypes of the dengue virus, where infection with any of the serotypes confers long-term immunity against the infected serotype. Dengue fever is transmitted through the bite of Aedes mosquitoes, especially Aedes aegeypti, which is the main vector in most countries, including Indonesia. When an infected mosquito bites a human, it causes a person to have the opportunity to contract dengue fever. Infected humans can then recover from

dengue fever and have cross-immunity for about six months. After that, they are again susceptible to other dengue serotypes. This process repeats itself and previously infected humans may be reinfected by other strains. Secondary infections can result in more dangerous forms of dengue fever, known as Dengue Hemorrhagic Fever (DHF) and Dengue Shock Syndrome (DSS) with a mortality rate of 20% if appropriate and immediate treatment is not provided. This is caused by the effect of antibody-dependent enhancement (ADE).[12–14]

There have been several attempts to produce a vaccine against DENV, including live attenuated chimeric recombinant virus, live attenuated virus, inactivated virus, recombinant protein and mRNA vaccines. Each vaccine prototype has different attenuation properties, efficacy and immunogenicity profiles.[15,16]

Sanofi Pasteur's Dengvaxia is the first and only commercially licensed dengue vaccine and is currently recommended and administered in 20 countries. The vaccine is a tetravalent formulation and comprises the Sanofi Pasteur yellow fever vaccine backbone (YFV 17D) with the PrM and E proteins from DENV replacing the PrM and E proteins from YFV 17D. As the first vaccine against DENV, Dengvaxia's clinical trials and field results have been closely monitored, with a particular focus on the possibility of ADEs. In a phase-III clinical trial, children under 9 years of age were vaccinated with a three-dose Dengvaxia regimen with doses given at 0, 6, and 12 month intervals. Vaccination efficacy was monitored by detecting symptoms of dengue infection at 25 months after vaccination 12 months. Dengvaxia gave efficacy results of 65.6% in children over 9 years of age and 44.6% in children under 9 years of age. In terms of hospitalization, children aged 9 years or more who were hospitalized were 80.75%, while children aged 9 years or younger who were hospitalized were 55.9%.[15,17]

Long-term trials of Dengvaxia in the first year showed that the efficacy of Dengvaxia against hospitalization was promising, with the major caveat that the results were highly dependent on DENV exposure serostatus as well as age at the time of the vaccine trial. Further research needs to be done to understand why the efficacy of Dengvaxia is reduced in subjects who were seronegative at the time of vaccination and why the risk of hospitalization is increased in children aged less than 9 years.[15]

The National Institute of Allergy and Infectious Diseases (NIAID) has been at the forefront of the development of live attenuated tetravalent vaccines (LATV) for more than 15 years. Given that partial immunity to DENV may increase the risk of more severe disease with subsequent infection, several monovalent and tetravalent DENV vaccines were evaluated to identify candidates with optimal safety, infectivity and immunogenicity profiles with the overall goal of developing LATV that can induce disease protection against all four serotypes. DENV with a single dose.[15]

TAK-003 (TDV) is a live attenuated tetravalent dengue vaccine produced by the pharmaceutical company Takeda and originally designed and manufactured by scientists at the US Division of Vector-Borne Diseases of the Centers for Disease Control and Prevention. The vaccine is based on attenuated viruses and chimeric viruses made using recombinant DNA technology. TAK-003 is based on live attenuated DENV-2 virus which provides the genetic backbone for all four vaccine viruses. The first recombinant vaccine candidate was produced by chimerizing the prM and E proteins of the DENV-1 16 007 virus to become the DENV2 PDK-53 virus. Various vaccine constructs are produced by combining different wild-type viruses with PDK-inactivated vaccine viruses.[15,18]

The cumulative efficacy values for vaccine recipients who were seronegative at baseline were 67 and 74.8% in seropositive individuals, respectively. Most importantly, the reduced efficacy against DENV-2, which is the backbone of TAK 003 cannot be discounted and suggests that TAK-003 may not fully mimic the protection afforded by natural infection. In addition, data from the second year showed that there was higher efficacy in children aged 6–11 years (60.6%) and children aged 12–16 years (71.2) when compared to children aged 4–5 years (24 .5%).[15]

CONCLUSION

Dengue vaccines can be produced with live attenuated chimeric recombinant viruses, live attenuated viruses, inactivated viruses, recombinant proteins and mRNA vaccines. Each of these vaccines has good efficacy in terms of protection against dengue virus.

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