Systematic Review

Systematic review of Dengue Vaccines (CYD-TDV and TAK-003) in children: efficacy, immunogenicity, safety and challenges

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ABSTRACT

Background: Vaccination has emerged as a promising strategy for dengue prevention, with several vaccines undergoing clinical evaluation. This systematic review is aimed to synthesize the current literature on the efficacy, immunogenicity, and safety of dengue vaccines, particularly CYD-TDV (Dengvaxia®) and TAK-003 (Qdenga®) in children.

Methods: PRISMA guidelines were used to guide standard processes for data extraction during a systematic literature search. To find pertinent research published, electronic databases such as PubMed, Medline, Embase, and the Cochrane Library were searched up to 2024. Observational studies, randomized controlled trials, meta-analyses and systematic reviews, focused on children (<18 years of age) were considered eligible for inclusion. The CYD-TDV vaccination and TAK-003 were evaluated for their overall and serotype-specific effectiveness.

Results: Key findings regarding vaccine efficacy, immunogenicity, and safety in children are summarized in this review. CYD-TDV, despite its efficacy in dengue-experienced individuals, long term safety data demonstrated that this vaccine increased the risk of more severe symptoms upon dengue infection in individuals who were dengue-naive and in children <9 years of age. TAK-003 has shown promising results, with an overall efficacy in preventing symptomatic dengue in children and adolescents.

Conclusion: Dengue vaccines represent a promising tool for dengue prevention in children. While vaccine efficacy and safety issues remain, ongoing research and innovation hold promise for the safer and more effective dengue vaccines development.

Keywords: Dengue vaccine, children, systematic review, efficacy, immunogenicity, safety, challenges

INTRODUCTION

Dengue fever poses a significant global health challenge, particularly in tropical and subtropical regions, caused by dengue virus (DENV). Amongst those affected, children bear a disproportionate burden of dengue-related morbidity and mortality [1]. There has been a notable increase in dengue cases during the previous 50 years, marked by outbreaks of escalating frequency and scale. The regions most severely affected by this trend, according to the World Health Organization (WHO), are the Americas, the Western Pacific and South-East Asia [2].

Vaccination has emerged as a key intervention to prevent dengue-related illness and reduce

disease burden. Clinical trials have been done on efficacy and safety outcomes of various developed dengue vaccines [3]. This systematic review is aimed to evaluate the present evidence on dengue vaccines, efficacy, immunogenicity, and safety of dengue vaccines particularly CYD-TDV (Dengvaxia®) and TAK-003 (Qdenga®) in children.

METHODS

PRISMA guidelines were used to guide standard processes for data extraction during a systematic literature search. To find pertinent research published, electronic databases such as PubMed, Medline, Embase, and the Cochrane Library were searched up to 2024.

The search string included keywords related to 'dengue vaccines' OR "CYD-TDV" 'Dengvaxia' OR 'TAK-003' OR 'DENVax-TDV' OR 'Qdenga' AND 'efficacy AND 'immunogenicity' AND 'safety'. Observational studies, randomized controlled trials, meta-analyses and systematic reviews, focused on children (<18 years of age) were considered eligible for inclusion. Studies were excluded if they did not focus on children or did not report relevant outcomes related to dengue vaccine efficacy, immunogenicity or safety. Two reviewers independently evaluated the bias risk in the selected trials, taking into account factors such as participant blinding, investigator blinding, and outcome assessor blinding, as these are associated with bias risk.

The CYD-TDV vaccination and TAK-003 were evaluated for their overall and serotype-specific effectiveness. By assessing each DENV serotype's geometric mean titers (GMTs) at predetermined intervals following the last vaccination dose and comparing GMTs between the intervention and control groups, immunogenicity was evaluated. The 50% plaque reduction neutralization test (PRNT50) was used to calculate GMTs. Adverse events (AEs) were recorded; these included vaccine-related AEs, severe AEs (SAEs), and local and/or systemic AEs.

Two independent reviewers performed data extraction to resolve discrepancies through consensus. PROSPERO is a worldwide database that included prospective registered systematic reviews in the field of health care, and registration for this study has been applied for. (Figure I)

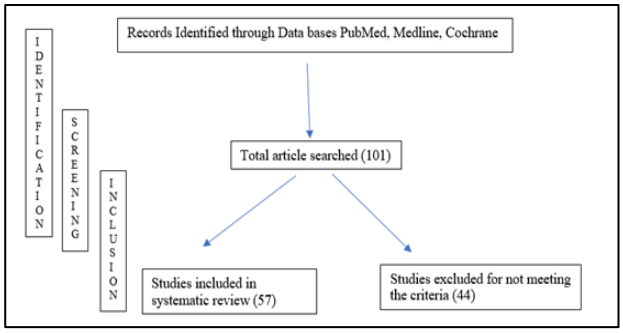

Figure I: Flow chart according to PRISMA guidelines

RESULTS

The systematic review identified 57 studies that met the inclusion criteria. Out of searched studies, 44 were excluded as those did not meet inclusion criteria. Key findings regarding dengue vaccine development, efficacy, immunogenicity and safety in children are summarized below.

Spectrum of Development of Dengue vaccines

Creating an inexpensive, secure, and efficient dengue vaccine covering all four dengue virus serotypes (DENV 1, DENV 2, DENV 3, DENV 4) would represent a substantial step forward in managing the illness. Research has explored a wide range of approaches for DENV vaccine development, such as inactivated and live-attenuated virus vaccines, DNA vaccines, subunit-based vaccines, nucleic acid-based vaccines, chimeric and viral-vectored vaccines [4].

Sanofi Pasteur created the first tetravalent DENV vaccine, CYD-TDV, which was first licensed by a number of dengue-endemic nations [5]. Other significant candidates for live-attenuated virus vaccines presently conducting phase III clinical studies are TAK-003 (DENVax-TDV) from Takeda and TetraVax TV003/TV005 from the National Institutes of Health (NIH). TV003/TV005 is a combination formulation of four attenuated wild-type DENV serotypes, whereas CYD-TDV consists of a chimeric-attenuated DENV2 strain that expresses the "pre-membrane protein" (prM-E) proteins of the other serotypes. Although phase II studies for these vaccinations have yielded encouraging results, protective effects over time data are currently unavailable [6,7, 8].

Efficacy

Among the assessed clinical trials, the majority of trials consistently demonstrated the effectiveness of both TAK-003 and CYD-TDV vaccines in averting dengue fever due to all 4 serotypes of the den-

gue virus. [9-23] Depending on how they were prepared, these vaccinations had varying degree of efficacy. Eleven confirmed cases of children who received the dengue vaccination in clinical trials were able to successfully trigger an immunological response, especially in terms of producing antibodies [24-34] The CYD-TDV vaccine was proved to be more efficient against DENV-4 (77%—RR "0.23" (95% CI "0.15-0.34"), p<0.00001), according to a serotype-specific effectiveness study. On the other hand, CYD-TDV lessened the impact of DENV-2 (34%—RR "0.66" (95% CI "0.50-0.86"), p<0.002) [35,36,37] In first 25 months of phase 3 trials, the prevention of symptomatic virologically confirmed illness (VCD) of any severity was less effective than the prevention of hospitalization for dengue and severe dengue [38]. For individuals ≥9 years, the corresponding effectiveness estimations against severe dengue were 79.1% and 93.2% respectively. The effectiveness for symptomatic VCD of any severity in persons aged 2-8 years was more "70.1%" in initially seropositive people and "14.4%" in initially seronegative trial participants [39].

TAK-003 is well tolerated, able to generate humoral responses against serotypes 1-4, sustain long-term antibody levels, and induce cross-reactivity and multifunctional T-cell-mediated responses, according to phase 1 and phase 2 studies. TAK-003 is presently being evaluated in extensive phase 3 efficacy research comprising children ages 4 to 16 years, with dosage schedules of 0 and 3 months. In those who were seronegative before to immunization, efficacy differed between serotypes, with DENV-2 showing the greatest efficacy [40]. TAK-003, on the other hand, showed long-term safety and effectiveness for all four DENV serotypes in persons who had previously been exposed to dengue, as well as for DENV-1 and DENV-2 in people who had never had dengue [41].

Immunogenicity

Of the studies which were analyzed, seven studies examined the immune response of CYD-TDV in children, whereas the other four looked into the immunogenicity of the TAK-003 vaccine. [25,27,28,30,31,33,34]. These investigations showed that giving children CYD-TDV in a three-dose regimen produced a strong humoral reaction for all 4 DENV serotypes [24,26,29,32] On the other hand, the Takeda vaccine demonstrated good immunogenicity against each of the four dengue serotypes in the four experiments. Following administration of the CYD-TDV vaccination, individuals who were seropositive (i.e., previously infected with dengue) exhibited elevated levels of neutralizing antibodies identifiable by PRNT50 for each dengue serotype compared to vaccine recipients who were seronegative at baseline. The geometric mean titers (GMTs) for baseline seropositive persons (703, 860, 762, and 306) and baseline seronegative individuals (35, 105, 94, and 90) for serotypes 1, 2, 3, and 4 were recorded for participants aged nine years or older following dose 3 [42].

During the 3-year follow-up period, seropositive subjects aged ≥9 had GMTs that were greater than those aged <9. GMTs seemed to be equally high in those who tested positive for the vaccination after two doses as they were after three [43]. Amongst patients who were seronegative at baseline and received TAK-003, GMTs from the last three time points (9, 15, and 27 months) showed a general declining trend of DENV-2 GMTs over time, while DENV-1, 3 and 4 GMTs in TAK-003 recipients stayed comparatively stable [40, 41].

Safety

After CYD-TDV immunization, adverse reactions, both local and systemic, are similar to those observed with previous live attenuated vaccines. For people between the ages of 9 and 60, safety data from many clinical studies using the ultimate composition and vaccination frequency were merged between prevalent and non-prevalent areas [44]. It was noted that 66.5% of CYD-TDV users reported very mild systemic responses, as opposed to 59% of control participants. The most common mild systemic effects that were reported were headache (more than 50%), malaise (more than 40%), and myalgia (more than 40%). Individuals aged 9–17 exhibited the highest prevalence of third-grade solicited systemic responses, whereas children aged 2–8 years experienced fever (4.4%) more frequently, while 49.6% of CYD-TDV users reported solicited injection-site responses, as opposed to 36.5% of control subjects.

Table 1: Summary of efficacy, immunogenicity and safety

Vaccine (Reference)	Efficacy	Serotype specific efficacy	Immunogenicity	Common Side effects
Dengvaxia®(CYD-TDV) (48,49,50)	25–59%	DENV-4 > DENV-3 > DENV-1 > DENV-2	CD8+ respond principally to NS3, mostly DENV-4-neutralizing antibodies	Limitation on age; elevated risk of severe dengue in seronegative individuals; high effectiveness and safety in seropositive individuals; elevated hospitalisation rates among immunisation recipients
DEN-Vax/TAK003/TDV (40,41,51, 52,53)	73.3–85.3%	DENV-2 > DENV-1 > DENV-4	Antibodies effective against all 4 serotypes	Teens and children accept it well; Several phase I and II clinical studies have shown that it is immunogenic, well-tolerated, and independent of participant age or serostatus; Unknown safety profile
TetraVax-DV-V003/TV005 (50,54,55,56)	Not yet released	DENV-4 > DENV-3 > DENV-1 > DENV-2	Rhesus macaque strong neutralizing antibodies	well tolerated single dosage; balanced immunological response; effective when administered as a single dose; minor rash as an adverse reaction
TDEN LAV (57)	Not yet released	Not yet released	Not yet released	Discontinued
TDENV PIV (58)	Not yet released	Not yet released	Not yet released	No current data, well tolerated, and immunogenic in naïve and seropositive individuals. No chance of reactivation and a balanced immune system

Between those who were vaccinated against dengue and those who were not, there was no discernible variation in the incidence of major adverse effects. Neurotropic and viscerotropic disorders are uncommon but dangerous side effects linked to immunization against yellow fever (YF) and they usually manifest soon after vaccination. Unless they occur within eight days of vaccine administration, no cases of neurotropic or viscerotropic disease associated with the YF part of CYD-TDV have been reported in the study group thus far [45].

Vaccinated seronegative people were shown to have a greater incidence of leakage of plasma and serious thrombocytopenia (platelet count <50x109 per litre) than unvaccinated seronegative participants in the trial. Those who were seronegative after vaccination showed comparable clinical signs of severe dengue to those who were seropositive but had not received vaccination. There have been no recorded dengue-related fatalities, and all afflicted youngsters have recovered [46,47]. Subjects in the TAK-003 and control groups had 2.0% and 2.3% of serious adverse events (SAEs), respectively. None of these SAEs were found to be connected to the study's methods or the investigational product [40,41].

Challenges to DENV vaccine development

The capacity of a dengue vaccine to offer protection against each of the four antigenically diverse DENV serotypes while maintaining uniform protection levels against each is essential for the vaccine's successful development. The production of equal amounts of neutralizing antibodies for every serotype in a vaccination might result in adverse events (AEs), which makes developing a viable DENV vaccine extremely difficult [59]. Regarding the methods by which antibody responses are elicited following dengue vaccination,

many important aspects are yet unsolved. Research into cell-mediated immunity has been a focus of dengue vaccine studies, in addition to T-cell responses [60].

However, due to their basic heterogeneity, it is difficult to create a consistent standard for assessing protective correlates across various dengue vaccinations. It is challenging to identify suitable correlations for protection against DENV infection due to this variability in dengue vaccines [61].

Dengue Vaccination; Strengthening the Public Health Initiatives in Pakistan

In Pakistan, dengue control efforts have primarily concentrated on reducing the population of Aedes mosquitoes. However, substantial cross border movement of people influences dengue transmission dynamics. With the evolving nature of the disease, global travel, climate change, and rapid urbanization that promotes mosquito breeding, might be inadequate to prevent dengue outbreaks. This is evident by the increasing frequency of dengue outbreaks in Pakistan since 2011. To strengthen these efforts, introducing a dengue vaccination program is crucial for reducing both the incidence and severity of dengue infections, thereby easing the burden on the healthcare system and improving the public health outcomes [62].

CONCLUSION

Dengue vaccines represent a promising tool for dengue prevention in children. While vaccine efficacy and safety issues remain, ongoing research and innovation hold promise for the safer and more effective dengue vaccines development. Future directions for exploration and development include optimizing vaccine formulations, dosing schedules, and implementation strategies to maximize vaccine impact and decrease morbidity and mortality in children due to dengue across the globe

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