Indian Academy of Pediatrics (IAP)

nRICH

Newer **R**esearch and recommendations **I**n **C**hild **H**ealth

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UNDER THE AUSPICES OF THE IAP ACTION PLAN 2023

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Dear fellow IAPans,

nRICH

Newer **R**esearch and recommendations **I**n **C**hild **H**ealth-aims to bring you the abstracts of some of the breakthrough developments in pediatrics, carefully selected from reputed journals published worldwide.

Expert commentaries will evaluate the importance and relevance of the article and discuss its application in Indian settings. nRICH will cover all the different subspecialities of pediatrics from neonatology, gastroenterology, hematology, adolescent medicine, allergy and immunology, to urology, neurology,vaccinology etc. Each issue will begin with a concise abstract and will represent the main points and ideas found in the originals. It will then be followed by the thoughtful and erudite commentary of Indian experts from various subspecialties who will give an insight on way to read and analyze these articles.

I'm sure students, practitioners and all those interested in knowing about the latest research and recommendations in child health will be immensely benefitted by this endeavor which will be published online on every Monday.

Happy reading!

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Three-year Efficacy and Safety of Takeda's Dengue Vaccine Candidate (TAK-003)

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BASED ON ARTICLE

Luis Rivera, Shibadas Biswal, Xavier Sáez-Llorens, et al. Clinical Infectious Diseases 24 August 2022

ABSTRACT

Background: Takeda's live attenuated tetravalent dengue vaccine candidate (TAK-003) is under evaluation in a long-term clinical trial across 8 dengue-endemic countries. Previously, they have reported its efficacy and safety in both seronegative and seropositive participants after 18 months and 2 years follow up. This exploratory analysis provides an update with cumulative three-year data.

Methods: Healthy 4–16-year-olds (n = 20,099) were randomized 2:1 to receive TAK-003 or placebo (0, 3-month schedule). The protocol included baseline serostatus testing of all participants and detection of all symptomatic dengue throughout the trial with a serotype specific reverse transcriptase-polymerase chain reaction.

Results: Cumulative efficacy after 3 years was 62.0% (95% CI, 56.6–66.7) against virologically confirmed dengue (VCD) and 83.6% (76.8–88.4) against hospitalized VCD. Efficacy was 54.3% (41.9–64.1) against VCD and 77.1% (58.6–87.3) against hospitalized VCD in baseline seronegatives, and 65.0% (58.9–70.1) against VCD and 86.0% (78.4–91.0) against hospitalized VCD in baseline seropositives. Efficacy against VCD during the third year declined to 44.7% (32.5–54.7), whereas efficacy against hospitalized VCD was sustained at 70.8% (49.6–83.0). Rates of serious adverse events were 2.9% in TAK-003 group and 3.5% in placebo group during the ongoing long-term follow-up (i.e., second half of the 3 years following vaccination), but none were related. No important safety risks were identified.

Conclusions: TAK-003 was efficacious against symptomatic dengue over 3 years. Efficacy declined over time but remained robust against hospitalized dengue. A booster dose evaluation is planned.

Commentary

In 2019 WHO has notified Dengue in its list of top ten global health concerns with estimated 3.9 billion people being at risk of infection with dengue viruses in 129 countries, of which 70% is in Asia.

CYD-TDV (Dengvaxia-Sanofi) was the first dengue vaccine to be licensed in Mexico in December 2015 for use in individuals 9-45 years of age living in endemic areas, and later licensed in 20 other countries. CYD-TDV is a live recombinant tetravalent dengue vaccine, given as a 3-dose series on a 0/6/12-month schedule. This vaccine performed differently in seropositive versus seronegative individuals and was high among baseline seropositive participants ≥9 years of age: 76% (95%CI: 63.9, to 84.0), but much lower among baseline seronegative participants: 38.8% (95%CI: –0.9 to 62.9%) in the first 25 months after the first dose of vaccine. Also, there was an increased risk of hospitalization and severe dengue in seronegative individuals starting about 30 months after the first dose, probably due to ADE.

In light of the evidence on the long-term safety issue in seronegative individuals, balanced against the documented efficacy and safety in seropositive individuals, SAGE carefully considered two strategies: population seroprevalence criteria versus pre-vaccination screening. This strategy is not practical in a large setting. Also, a reduced efficacy in younger age group and a prolong schedule (three doses over 12 months) is a big deterrent for a mass programme.

There remains an urgent need for a dengue vaccine which can be used broadly without any pre-screening to confirm prior dengue infection. Takeda's dengue vaccine candidate (TAK-003), a recombinant tetravalent dengue vaccine based on a DENV-2 backbone. It is under evaluation in an ongoing long-term efficacy clinical trial in 8 dengue endemic countries. This paper present cumulative data after 3 years of follow up.

A total of 20,071 of 20,099 randomized participants received the first dose of TAK-003 or placebo between September 2016 and March 2017, and 94.6% completed 3 years of follow-up after the second dose).

All 4 serotypes were identified in Asia, whereas only DENV-1 or DENV-2 were identified in Latin America. At the study level, DENV-1 was the most common (39%) and DENV-4 the least common (3.4%) serotype. In the placebo group, hospitalization rates were 16.3% (32/196) for DENV-1, 41.9% (75/179) for DENV-2, 14.4% (16/111) for DENV-3, and 17.6% (3/17) for DENV-4. Hospitalization rates also varied among the trial countries (placebo group data: Latin America, from 2.5% [1/40] in Panama to 20% [4/20] in Nicaragua; Asia, from 9.4% [17/181] in the Philippines to 68% in Sri Lanka [68/100]). In a year-by-year comparison, the highest number of VCD cases in the placebo group were reported during year 3.

For the first time, a positive lower bound of the 95% CI (16.0–81.6) was observed, with a VE of 60.7% against DENV-4 in baseline seropositives. In baseline seronegatives, TAK-003 was efficacious against DENV-1 (VE 43.5%; 21.5–59.3) and DENV-2 (91.9%; 83.6–96.0), but no efficacy was observed against DENV-3 (−23.4%; −125.3 to 32.4). Only 10 DENV-4 cases were reported in baseline

seronegatives, most of which occurred in the latter part of the study, precluding a robust interpretation.

Overall, VE against dengue haemorrhagic fever (DHF) and Dengue Case Severity Adjudication Committee (DCAC) defined severe dengue was 65.4% (19.0–85.2) and 70.2% (−24.7 to 92.9), respectively).

Seven deaths were reported (5 in TAK-003 recipients; 2 in placebo recipients) and SAEs were reported by 2.9% of TAK-003 recipients and 3.5% of placebo recipients in the first half of part 3. None of the deaths or SAEs were considered related to the study vaccine.

A booster dose may have the potential to reverse some of the observed waning efficacy. Data from a phase 2 study that evaluated different dosing schedules (single dose, 0- and 3-month, and 0- and 12-month) showed considerable boosting of titres in baseline seronegatives when the second dose was administered at 12 months, whereas the second dose at 3 months largely improved vaccine responders. Although GMTs were similar between schedules in the longer term, a potential booster effect on antibody specificity or affinity maturation and its related efficacy is plausible. In the current study, a booster is planned to be administered approximately 4 years after the second dose, which was the earliest operationally feasible time. Subsequently, there will be follow-up over 25 months.

Overall, this phase 3 study demonstrates that TAK-003 was efficacious against symptomatic dengue in children and adolescents in a varied epidemiological setting across 8 dengue-endemic countries. Efficacy, which was variable by serotype, declined over time but remained durable against hospitalized dengue. These data support the utility of TAK-003 in dengue control.

An exploratory data after 4.5 years of follow up was presented as a poster in the International Congress on Military Medicine, in Brussels in Sept 2022. It stated that the vaccine prevented 84% of hospitalised dengue cases and 61% of symptomatic dengue cases, with no important safety risks identified, in the overall population including both seropositive and seronegative individuals through four and a half years (54 months) after vaccination.

The vaccine has been launched in Indonesia for age group 9-45 years and approved by EU on 8 December 2022 for ages 4 plus with no upper age limit specified.

Abbreviations: CI, confidence interval; DHF, dengue haemorrhagic fever; NE, non-estimable; VCD, virologically confirmed dengue; DCAC, Dengue Case Adjudication Committee; WHO, World Health Organization.

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