Dengue Vaccines: An Update

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Abstract

Dengvaxia is a live recombinant tetravalent dengue vaccine, licensed from December 2015 for individuals from endemic area in the age-group of 9–45 years. This update gives the recent recommendations for dengue vaccination and also provides information on the newer dengue vaccines in the pipeline.

Keywords: Chimeric vaccine, Dengvaxia, Newer dengue vaccine.

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Dengvaxia™ (CYD-TDV), the only licensed dengue vaccine, is a live recombinant vaccine containing all the four dengue serotypes and was developed by Sanofi Pasteur. It is recommended to be administered as a 3-dose schedule of 0–6–12 months schedule. Dengvaxia was licensed in the end of 2015. It is now used in the endemic regions of 19 countries in persons aged between 9 years and 45 years of age. In some countries, it is licensed in persons aged 9–60 years. In Philippines and Brazil, it has been introduced in two subnational programs covering over 1 million individuals.[1]

Dengvaxia is a mixture of chimeric vaccine viruses of DEN 1, DEN 2, DEN 3, and DEN 4. The vaccine is based on the backbone of the yellow fever virus from which the genes encoding prM and E proteins have been replaced with the corresponding genes of the 4 dengue virus strains.

Dengvaxia was licensed following two large clinical trials, the CYD14 and CYD 15, conducted in five Asian and Latin American countries, respectively.[2–4]

In the combined phase 3 trials, which included over 30,000 participants in the age-group of 2–16 years, the pooled vaccine efficacy at 12 months after the last dose was 59.2% against laboratory confirmed dengue and 79.1% against severe dengue. The infecting serotype, age, and serostatus influenced the vaccine efficacy.[3,4]

In the phase 3 trials, hospitalization rates due to dengue and severe dengue cases were increased in those receiving Dengvaxia® in the third year after the first dose, mainly in those aged 2–5 years but up to 9 years age. In the CYD 14 trial, analysis of year 3 data revealed that the relative risk (RR) of hospitalization in the 2–5-year age-group was 7.45 [95% confidence interval (CI) 1.15–313.8].[3,4] In a *post hoc* analysis of year 3 data from all three trials (CYD14, CYD15, and CYD57), it was found that the RR for children >9 years for hospitalized dengue was 0.50 (95% CI 0.29–0.86) while in children under 9 years of age, the RR was 1.58 (95% CI 0.83–3.02).[5] Prevaccination baseline blood samples for assessment of serostatus prior to vaccination were available in only 13% of the trial participants.

Based on these findings, the vaccine was licensed for the age-group 9–45 years only in areas where the seroprevalence exceeded 70%.[5]

In November 2017, using a newly devised test that could differentiate antibodies against NS1 antigen induced by the vaccine and that induced by natural infection, blood samples from all participants obtained in the 13th month, one month after the third dose, were reanalyzed to assess serostatus prior to vaccination.

Trial participants who were found to be seronegative prior to vaccination had a significantly higher risk of more severe dengue and hospitalizations from dengue compared to unvaccinated participants, irrespective of the age at time of vaccination. While protection was similar in the first 2 years, the risk was maximum in year 3, declined subsequently, but persisted till 5 years of follow-up.

In the symptomatic virologically confirmed dengue (VCD) cohort, in the 25 months after dose 1 in 2–16-year-olds, the vaccine efficacy (VE) was 72% (58–82) in those seropositive vs 32% (–9–58) in those seronegative. The RR of hospitalized dengue comparing vaccinated to controls in the 66 months after dose 1 in 2–16-year-olds was 0.29 (0.21–0.42) in those seropositive and 1.65 (1.04–2.61) in those seronegative. The RR of severe VCD comparing vaccinated to controls in the 66 months after dose 1 in 2–16-year-olds was 0.28 (0.15–0.52) in those seropositive and 3.00 (1.10–8.15) in those seronegative.

In the dengue-seronegative participants aged 9–16 years, the cumulative incidence of hospitalization for VCD was 1.57% among vaccine recipients and 1.09% among controls, with a hazard ratio of 1.41 (95% CI, 0.74–2.68).[6]

Following availability of abovementioned data, the World Health Organization revised the recommendations for Dengvaxia, which was published in a position paper in September 2018.[7] The statement is as follows:

- Introduction of the dengue vaccine CYD-TDV should be considered only by those countries that can minimize the risk among seronegative individuals.

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- For countries considering vaccination as part of their dengue control program, prevaccination screening is the recommended strategy. Only persons with evidence of a past dengue infection (positive antibody test or laboratory confirmed dengue infection in the past) should be vaccinated
- If prevaccination screening is not feasible, mass vaccination could be considered in areas, where recent seroprevalence studies have revealed rates of at least 80% by age 9 years.

Newer Dengue Vaccines

As of end of 2018, there are 14 dengue vaccines in the pipeline, 3 in phase 1 trials, 1 in phase 2 trials, and 2 in phase 3 trials.[8]

Some of the promising vaccines in pipeline are:[9]

The Takeda vaccine is a DENV-DENV chimera, whereby the attenuated dengue strain DENV-2 PDK-53 protects against DENV-2, while the prM and E proteins of DENV-1, DENV-3, and DENV-4 inserted on to the backbone of the attenuated DEN-2, protects against DEN-1, DEN-3 and DEN-4.

The vaccine is being tested in a large multicenter phase III efficacy study in 8 countries in Asia and South America, involving approximately 20,000 children aged 4–16 years.[9]

The primary efficacy data from part 1 of this study was recently published.[10]

In the per-protocol analyses, vaccine efficacy against virologically confirmed dengue was 80.2% (95% CI, 73.3–85.3) and 95.4% (95% CI, 88.4–98.2) against dengue leading to hospitalization. The vaccine efficacy was 74.9% (95% CI, 57.0–85) in the 27.7% of the per-protocol population who were baseline negative.

VE against DEN 1 was 73.7% (74.5–87.6), DEN 2: 97.7% (92.7–99.3), DEN 3: 62.6% (43.3–75.4), and DEN 4: 63.2% (−64.6–91.8)

No significant differences were observed in the incidence of serious adverse events in the vaccine group and placebo group (3.1% and 3.8%, respectively).

TetraVax-DV (NIH) is a combination of four monovalent attenuated dengue viruses in which attenuation has been achieved by a deletions in the 30 nontranslated region (NTR) of the DENV genomes of the four monovalent vaccine viruses. A phase 3 efficacy trial in about 17,000 children, adolescent, and adults is being conducted in Brazil. Additional phase II trials, which are ongoing in Thailand, Taiwan, and Bangladesh, are scheduled to be completed in the next 1–2 years.[9]

TDENV-PIV: this is a tetravalent dengue-purified inactivated vaccine (TDENV-PIV). Two phase 1 studies in adults in the United States[11] and Peurto Rico[12] have demonstrated the immunogenicity and safety of this vaccine in different formulations and adjuvants. The encouraging results has resulted in progress to phase 2 trials.

TDENV-LAV: this is a tetravalent dengue live-attenuated vaccine that is being jointly developed by the Walter Reed Army Institute of Research (WRAIR), USA and GlaxoSmithKline (GSK). The phase I clinical trial in healthy volunteers in the age-group 18–42 years is expected to end in January 2022.[13]

The Indian vaccine producers Panacea Biotec, Serum Institute, and Biological E have received licenses for the clinical development and marketing of the dengue vaccine TetraVax-DV developed by the US NIH.[9]

Panacea Biotec has completed preclinical studies and is planning a phase I/II trial with 200 healthy volunteers in the age-group 2–60 years spread recruited from three sites in North and South India. This study aims to evaluate the safety, reactogenicity, and immunogenicity of one dose of TetraVax-DV.[9]

Serum Institute of India Limited is currently conducting preclinical toxicity studies on TetraVax-DV. Initial phase I testing is being planned. A 5-year follow-up is planned before seeking licensure.[9]

The status of development of the LAV from NIH, being developed by the Indian company, Biological E, is not available.[9]

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