

Tetravalent Dengue Vaccine for Children

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SUMMARY

In this phase-3 efficacy trial of a tetravalent dengue vaccine in five Latin American countries, 20,869 healthy children between the ages of 9 and 16 years were randomly assigned in a 2:1 ratio to receive three injections of recombinant, live attenuated, tetravalent dengue vaccine (CYD-TDV) or placebo at months 0, 6, and 12 under blinded conditions, and followed for 25 months. The primary outcome was vaccine efficacy against symptomatic, virologically-confirmed dengue occurring more than 28 days after the third injection. At baseline, 79.4% of an immunogenicity subgroup of 1944 children had seropositive status for one or more dengue serotypes. In the per-protocol population, there were 176 dengue cases (with 11,793 person-years at risk) in the vaccine group and 221 dengue cases (with 5,809 person-years at risk) in the control group, for a vaccine efficacy of 60.8% (95% CI 52.0%, 68.0%). Serotype-specific vaccine efficacy was 50.3% for serotype 1, 42.3% for serotype 2, 74.0% for serotype 3 and 77.7% for serotype 4. Among the severe confirmed dengue cases, 1 of 12 was in the vaccine group, for an intention-to-treat vaccine efficacy of 95.5%. Vaccine efficacy against hospitalization for dengue was 80.3%. The authors concluded that CYD-TDV dengue vaccine was efficacious against virologically-confirmed dengue infection, including severe disease.

COMMENTARIES

Evidence-based Medicine Viewpoint

Relevance: Dengue is a common and serious infection in many parts of the world, including India [1]. An effective vaccine against dengue is eagerly awaited. This randomized controlled trial (RCT) of a tetravalent dengue vaccine, conducted in five South American countries [2], suggests progress towards a safe and effective vaccine. It also provides an excellent opportunity to learn about well-conducted RCTs, and vaccine trials in particular.

Critical appraisal: A detailed critical appraisal is presented in **Table I**. Most of the criteria for a trial with low risk of bias are fulfilled.

Extendibility: The data in this RCT can be extrapolated to similar epidemiologic settings in terms of disease endemicity, burden of infection, and affected population group. Prior to initiating a similar trial in India (which is highly likely given the trends of new vaccine trials in recent years), an estimation of burden of disease, age-specific infection rate, hospitalization rate, mortality rate, and complication rate of dengue should be calculated (at least in the areas believed to have significant burden). The lack of efficacy among sero-negative individuals and slightly higher local adverse reactions also advocate in favour of further evaluation of efficacy and safety.

This trial has shown efficacy of the vaccine against dengue serotype 2, unlike the previous trial of the same vaccine in Asian countries [3]. This could have implications for India as serotype 2 predominated in the major outbreak of 1998. However, the 2003 outbreak was mainly with serotype 3 [4], whereas a study from Uttar Pradesh noted serotype 2 to be predominant during 2009 to 2012 [5]. In contrast, molecular analysis suggests that serotype 3 is also prevalent [6]. Currently, it is believed that all four serotypes are circulating, suggesting the need for pan-serotype efficacy [4,7].

Conclusions: Although there are some concerns regarding safety and efficacy, this well-designed RCT raises hope that a safe and efficacious dengue vaccine can be available in the near future.

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TABLE I: CRITICAL APPRAISAL OF THE TRIAL

Background	The authors have mentioned the importance of dengue and its public health significance, and suggested a need for vaccine. However, there is no data on burden of disease or mortality. Results of a previous similar trial conducted in Asian countries suggested that the vaccine could be efficacious.
Hypothesis	Although a clearly defined hypothesis in the PICO format is not presented, it is possible to infer that the aim was to evaluate efficacy and safety (<i>O=Outcomes</i>) of a candidate live attenuated tetravalent dengue vaccine (<i>I=Intervention</i>) compared against Placebo (<i>C=Comparator</i>), over a period of 2 years (<i>T=time-frame</i>) among 9-16 year-old children living in five dengue-endemic South American countries (<i>P=Population</i>), through a RCT (<i>S=Study Design</i>).
Setting	The setting for this RCT is described as the community residing in dengue-endemic municipalities. Although details of dengue epidemiology and age-specific burden are not provided, there is scope for generalizability of the results to other similar settings.
Participants	Healthy children in the age group 9-16 years were included. Although the enrolment procedure is not explicitly presented in the publication, these are recorded in the protocol available in the public domain. However a flow-chart depicting eligible participants, recruited participants, analyzed participants and reasons for missing participants, has not been presented. The mean age, gender distribution and pre-trial sero-positivity rates against the four dengue serotypes are similar in the two arms of the trial. However, no other baseline characteristics are described.
Interventions	The intervention (dengue vaccine) and comparator (normal saline placebo) administered to the participants are well-described, including the two preparations, storage conditions, dosage, site and route of administration.
Outcomes	Primary and secondary outcomes have been clearly defined. The primary outcome was efficacy against dengue (any severity, any serotype) occurring over a period of one year, starting from one month after the third vaccine dose. Secondary outcomes were measures of efficacy against specific serotypes, severe disease, dengue hemorrhagic fever, and hospitalization. In a sub-group of 10% participants, the investigators evaluated safety (in terms of serious adverse events and death within 28 days of vaccination, post vaccination local and systemic reactions, and all-cause mortality) and immunogenicity (antibodies against dengue virus serotypes).
Sample size	A detailed calculation of sample size along with assumptions used has been presented. The investigators were able to achieve nearly 100% enrolment as per the sample size calculation.
Randomization	A random sequence generated by a computer program was used, with block sizes of 6. The sequence was stratified by age of participants (9-11, 12-16 y, and study site).
Allocation concealment	Allocation to groups as per the random sequence was done through an interactive voice response system (IVRS) or web-response platform.
Blinding (masking)	It is stated that the investigator team, children in the study and their parents, as well as the study sponsor were unaware of the allocations. However, detailed procedures used for blinding, and measures to confirm efficacy of these procedures is not described. It is presumed that personnel evaluating outcomes of efficacy, safety and immunogenicity were part of the investigator team, and hence blinded.
Statistical methods	The investigators have provided details of how vaccine efficacy was calculated in terms of the probability of disease in the two arms. The methods used are similar to other vaccine trials. The primary outcome was evaluated per protocol (i.e in those who received the interventions as intended); however intention-to-treat (ITT) analysis wherein children who received even one dose of intervention, is also reported.
Incomplete outcome reporting	The data in the published version of the manuscript does not present absolute numbers for outcomes, except the primary outcome. Most of these are available in the supplementary tables available for the Journal website. Overall, there does not appear to be incomplete reporting.
Selective outcome reporting	The authors have reported all the proposed outcomes.

Salient Results	Per-protocol vaccine efficacy: 60.8% (CI 52.0%, 68.0%) ITT vaccine efficacy: 64.7% (CI 58.7%, 69.8%) Efficacy against hospitalization: 80.3% (CI 64.7%, 89.5%) Efficacy against severe dengue after three doses: 91.7% (CI 31.4%, 99.8%) Efficacy against DHF after three doses: 90.0% (CI 10.7%, 99.8%) ITT vaccine efficacy against serotype 1: 54.8% (CI 40.2%, 65.9%) ITT vaccine efficacy against serotype 2: 50.2% (CI 31.8%, 63.6%) ITT vaccine efficacy against serotype 3: 74.2% (CI 63.9%, 81.7%) ITT vaccine efficacy against serotype 4: 80.9% (CI 70.9%, 87.7%) <i>Sub-group analyses</i> Vaccine efficacy among sero-positive participants: 83.7% (CI 62.2%, 93.7%) Vaccine efficacy among sero-negative participants: 43.2% (CI -61.5%, 80.0%) <i>Safety analyses</i> Serious adverse events within 28 d of intervention: OR 1.01 (CI 0.69, 1.48) Death within 28 d of intervention: None in either group Local reactions (unsolicited): OR 1.50 (CI 0.40, 5.55) Local reactions (solicited): OR 1.40 (CI 1.16, 1.70) Systemic reaction (unsolicited): OR 1.75 (CI 0.36, 8.43) Systemic reaction (solicited): OR 0.95 (CI 0.78, 1.17) Systemic non-serious adverse event (unsolicited): OR 1.03 (CI 0.85, 1.24)
Interpretation of results in terms of public health significance	The tetravalent vaccine has significantly better efficacy than placebo. However, evidence of this benefit disappears among sero-negative persons wherein the efficacy is comparable to placebo. The vaccine safety in terms of local and systemic reactions appears comparable to placebo. However, solicited local reactions are more frequent with vaccine than placebo.
Overall impression	<i>Validity:</i> Well-designed and well-conducted RCT with a low risk of bias. <i>Results:</i> Statistically and clinically meaningful results for almost all outcomes with caveats described above. <i>Applicability:</i> Detailed evaluation of local burden, age-specific burden, serotype burden, and sero-status of population is required before results can be generalized.

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Vaccinologist's Viewpoint

Dengue is global public health problem with about 2.5 billion (40% of world population) at risk. In addition to vector control measures, an effective and safe vaccine is required for reducing mortality and morbidity due to the disease. In this trial conducted in South America, recombinant live attenuated tetravalent dengue vaccine (CYD-TVD) has been studied in a large population with adequate follow up for clinical disease in an endemic area. Population studied were 9-16 years with 80% already seropositive. Since the disease occurs in all age groups, even children less than 9 years or earliest possible age when the vaccine is to be given should have

been studied. No definite immunological correlate of the vaccine is known and hence the strength of the study is a 25 month follow up for clinical disease to demonstrate efficacy of the vaccine. If the genotype included in the vaccine is similar to the circulating genotype, the efficacy of the vaccine can be considered as good; hence the need to know the circulating genotypes in the area before introduction of the vaccine [1]. Dengue infection has a wide range of clinical manifestations and severity. Heterotypic immunity is protective for some time but later leads to increases in severity of disease – a paradoxical challenge of the immunopathogenesis of dengue [2,3]. Hence, there is a need to include all circulating genotypes in the vaccine.

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Pediatrician's Viewpoint

Antibody-dependent enhancement and its role in severe dengue supports the necessity for tetravalent dengue vaccines that stimulate balanced immune responses to the four serotypes. Only one Chimeric Tetravalent vaccine has undergone Phase III trials so far with promising efficacy.

The authors in this article have used a recombinant, live, attenuated, tetravalent dengue vaccine (CYD-TDV) and reported an efficacy of 60.8% against symptomatic virologically-confirmed dengue, after a three-dose vaccination schedule among children between the ages of 9 and 16 years; an efficacy of 80.3% against hospitalization for dengue, and 95.5% against severe dengue were observed over the 25-month period. No safety concerns or evidence of more severe disease in breakthrough cases in the vaccine group over the 25-month surveillance period were observed by the authors. It is not known whether this favourable safety profile will be sustained through periods of waning immunity and successive dengue exposures remote from vaccination in endemic areas.

The efficacy results reported here are consistent with those of the similarly designed Asian trial [1]. The

observation of vaccine efficacy against hospitalization for dengue of 80.3% is encouraging from the public health point of view, particularly in the Indian context. Excellent safety and reactogenicity profiles in this study are reassuring. Vaccine immunogenicity was consistent as in the earlier Thailand study. This study and the Asian study provide a consistent picture of the efficacy and safety of this dengue vaccine after 25 months of active surveillance in 10 countries among different populations.

There is an urgent need for large, multicenter phase 3 trials to test investigational dengue vaccines in heterogeneous epidemiologic settings, and to obtain confirmatory data for serotype-specific efficacy.

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