

Questions and Answers on Dengue Vaccines: Phase III study of CYD-TDV in Latin America

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What is the current status of dengue vaccine development?

There is a significant and growing public health need for effective preventive interventions against dengue.¹ No licensed dengue vaccine is currently available. A safe, effective and affordable dengue vaccine would represent a major advance for the control of the disease and could be an important tool for reaching the WHO goal of reducing dengue morbidity by at least 25% and mortality by at least 50% by 2020.² There are several candidates currently under clinical development. The vaccine candidate currently at the most advanced clinical development stage is a live attenuated tetravalent dengue vaccine developed by Sanofi Pasteur (CYD-TDV). The results of a phase III trial of CYD-TDV in Latin America were recently published.³

What were the main objectives of the phase III study of CYD-TDV in Latin America?

The primary objectives of the phase III study were to assess the safety and efficacy of CYD-TDV in preventing dengue disease for one year after completion of the vaccination schedule of three doses given 6 months apart. Additional objectives included the evaluation of immunogenicity. The study population consisted of 20,869 children aged 9 to 16 years in five countries in the Latin America region: Brazil, Colombia, Honduras, Mexico, and Puerto Rico (US). The study protocol includes a hospital-based follow-up period of four additional years, which is currently ongoing.

What conclusions can be drawn from the results of this phase III study in Latin America and how do the results compare with the phase III trial conducted in Asia?

WHO was advised on the interpretation of phase III trial results by a technical advisory group of experts.⁴ The results reported represent the second of two phase III studies conducted by Sanofi Pasteur to evaluate the efficacy of the CYD-TDV dengue vaccine candidate against clinical dengue disease. The results of the first phase III trial conducted in Asia have previously been reported⁵.

The primary efficacy analysis, as defined in the protocol for the trial, was based on the number of dengue cases of any serotype in vaccinated and control subjects, during a one year observation period from 28 days after the 3rd dose. In this period, 397 cases of virologically-confirmed dengue were diagnosed. The primary endpoint was met in this trial. Overall, vaccine efficacy against all dengue serotypes combined in this period (the per-protocol (PP) analysis) was estimated as 60.8% (95% CI 52.0, 68.0). There was statistically significant protection demonstrated for each of the four serotypes, but the level of protection varied between serotypes. Serotype specific efficacies were secondary trial endpoints: vaccine efficacy against DENV1 was 50.3% (95% CI 29.1, 65.2), against DENV2 was 42.3% (95% CI 14.0, 61.1), against DENV3 was 74.0% (95% CI 61.9, 82.4), and against DENV4 was 77.7% (95% CI 60.2, 88.0). Similar estimates of efficacy to the PP estimates were obtained when the analysis was based on all 662 dengue cases occurring at any time after the first dose of vaccine (the intention to treat (ITT) analysis).

In an exploratory analysis (ITT population), based on a subset of the trial population for which blood samples were collected before the first vaccine dose, vaccine efficacy was higher in those participants who had measurable antibodies (geometric mean titers ≥ 10) to one or more dengue serotypes at baseline as measured by the PRNT₅₀ neutralization assay: the vaccine efficacy was 83.7% (95% CI 62.2, 93.7) in seropositive participants, and 43.2% (95% CI -61.5, 80.0) in seronegative participants.

The findings from this trial in Latin America are consistent with those seen in the trial conducted in Asia. In the trial conducted in Latin America, the vaccine efficacy against severe dengue was estimated to be 95.0% (95% CI 64.9, 99.9; ITT analysis), which is also consistent with the results from the trial in Asia, but the total number of severe cases in the two trials was relatively small.

There was no evidence of an increase in serious adverse events in the trial, which included follow up for 13 months after the three-dose series, consistent with the safety results from the trial in Asia. This large trial provides further reassurance of the safety of CYD-TDV in the first 13 months following the primary vaccine series.

As with all new vaccines, it is unknown how long the measured protection against dengue will last. Prolonged monitoring in both Asian and Latin American trials, as well as post-licensure studies, will be needed to measure long-term safety and efficacy, including whether there is any waning of protection over time.

Were there any unexpected findings in the two trials?

There were two features of the phase III trial results that were not expected.

Firstly, the efficacy of the vaccine was found to be higher in those who had serological evidence of previous exposure to dengue. Pre-vaccination blood samples were only taken from a sample of participants and the number of children with no evidence of previous dengue exposure was relatively small, but there was not statistically significant evidence of a protective effect of the vaccine in this group (i.e., the 95% confidence interval included a vaccine efficacy of 0%). Whether or not vaccine efficacy is confined to those with a prior dengue infection will require further studies.

Secondly, vaccine efficacy estimates for the PP and ITT analyses were very similar. This raises the question of whether or not 3 doses of the vaccine are required to provide lasting protection in endemic settings. Because nearly all participants in the trial received all 3 doses of the vaccine (over 95%), the follow-up period after one dose, and after two doses, was effectively only 6 months and longer term protection after less than 3 doses could not be evaluated. This also will require further investigation in post-licensure studies.

What are the plans for a WHO position on use of dengue vaccines?

The WHO Strategic Advisory Group of Experts (SAGE)⁹ on immunization will advise WHO on any recommended use of dengue vaccines. Key issues to consider include parameters around programmatic suitability, including dose scheduling. A formal WHO assessment of public health utility and any recommendations for use will only be issued following licensure of the vaccine by a functional National Regulatory Authority (NRA).

References

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² World Health Organization (2012). Global Strategy for dengue prevention and control, 2012–2020. Accessible online at <http://www.who.int/denguecontrol/9789241504034/en/>

³ Vilar L, et al. Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children and adolescents in aged 9 to 16 years in Latin America. NEJM. 2014 (published online November 3)

⁴ WHO Technical Advisory Group on Dengue Vaccines in Late Stage Development. Further information at http://www.who.int/vaccine_research/committees/dengue_tag/en/index.html

⁵ Capeding MR, et al. Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial. Lancet. 2014 Jul 10.

⁶ Sabchareon A, et al. Protective efficacy of the recombinant, live-attenuated, CYD tetravalent dengue vaccine in Thai schoolchildren: a randomised, controlled phase 2b trial. Lancet. 2012 Nov 3;380(9853):1559-67.

⁷ World Health Organization. Questions and Answers on Dengue Vaccines: Phase IIb study of CYD-TDV. Accessible online at http://www.who.int/immunization/research/committees/WHO_dengue_vaccine_QA_september2012.pdf?ua=1.

⁸ World Health Organization. Questions and Answers on Dengue Vaccines: Phase III study of CYD-TDV. Accessible online at http://www.who.int/immunization/research/development/WHO_dengue_vaccine_QA_July2014.pdf

⁹ WHO Strategic Advisory Group of Experts (SAGE) on Immunization. Further information at <http://www.who.int/immunization/policy/sage/en/>