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

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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 The vaccine candidate currently at the most advanced clinical development stage is a live attenuated tetravalent dengue vaccine developed by Sanofi Pasteur (CYD-TDV), which is under evaluation in phase III clinical studies. At least five other dengue vaccine candidates are also in clinical development: two other live attenuated vaccines (by Takeda and the U.S. National Institutes of Health/Butantan); an inactivated vaccine (by GlaxoSmithKline/Biomanguinhos/WRAIR); a subunit vaccine (by Merck); and a DNA vaccine (by the U.S. Naval Medical Research Center).

What are the main objectives of the phase III study of CYD-TDV in Asia?³
The primary objective of the phase III study was 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 vaccine safety and immunogenicity. The study population consisted of 10,275 children aged 2 to 14 years in five countries in the Asia-Pacific region: Indonesia, Malaysia, the Philippines, Thailand, and Vietnam. The first results of this study are described in a recent publication.³ 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 Asia?³
WHO was advised on the interpretation of phase III trial results by a technical advisory group of experts.⁴ The results reported represent the first of two phase III studies conducted by Sanofi Pasteur to evaluate the efficacy of the CYD dengue vaccine candidate against clinical dengue disease.

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 vaccine dose. In this period, 250 cases of virologically-confirmed dengue were diagnosed. The primary endpoint was met in this trial. Vaccine efficacy against dengue of any one of the four dengue virus (DENV) serotypes in this period (the per-protocol (PP) analysis) was estimated as 57% (95% CI 44, 66). Vaccine efficacy for each of the four serotypes, a secondary trial endpoint, was variable and for serotype 2 was not statistically significant: vaccine efficacy against DENV1 was 50% (95% CI 25, 67), against DENV2 was 35% (95% CI -9, 61), against DENV3 was 78% (95% CI 53, 91), and against DENV4 was 75% (95% CI 54, 87). Similar estimates of efficacy to the PP estimates were obtained when the analysis was based on all 595 dengue cases occurring at any time after the first dose of vaccine (the intention to treat (ITT) analysis).

In an exploratory analysis (ITT population) vaccine efficacy was higher in those vaccinated at older ages: 74% (95% CI 59, 84) in participants aged 12-14 years, 60% (95% CI 49, 68) in participants aged 6-11 years, and 34% (95% CI 12, 50) in participants aged 2-5 years. The study population did not include children younger than 2 or older than 14 years of age. In a further exploratory analysis,
an additional finding was that vaccinated children were found to be at reduced risk of severe disease (based on a definition by an independent data monitoring committee) with a PP vaccine efficacy of 81% (95% CI 43, 95). The total number of severe cases observed in the trial was 32, so this observation will need to be interpreted with some caution and confirmed in future studies.

There were no signals of an increase in serious adverse events in the trial during the two years following the administration of vaccine. This large trial provides further reassurance of the safety of CYD-TDV in the first 12 months following the primary vaccine series.

The results from this trial are encouraging, and as this was the first ever phase III trial of a candidate dengue vaccine, represent a significant advance for the field of dengue vaccine research. A fuller assessment of the efficacy of the CYD-TDV vaccine will be possible when the results of the ongoing phase III trial in Latin America with the same vaccine become available later in 2014.

Prolonged monitoring in both trials will be needed to measure long-term safety and efficacy.

**How do these results relate to the phase IIb results published in 2012?**

In a phase IIb study of 4,002 Thai children, the reported vaccine efficacy result for the PP analysis was 30% (95% CI: -13% to 57%) and was not statistically significant, in contrast to the results from the Phase III trial. WHO provided a Q&A at the time these results were published. The results of the phase IIb study are overall consistent with the results of this much larger phase III study in multiple sites and epidemiological settings in Asia. The larger sample size of the phase III trial allows for additional precision in the efficacy estimates. The phase III trial again showed that the vaccine efficacy against DENV2 has a tendency to be lower than for the other three serotypes. The differing overall vaccine efficacy estimate (30% in the phase IIb trial, during which DENV2 was the predominant circulating serotype, and 57% in the phase III trial, in which DENV2 was responsible for a smaller proportion of dengue cases) are not significantly different and may also be explained in part by the different distribution of circulating DENV serotypes at the trial sites in one trial compared to the other.

**What are the implications for ongoing Phase III studies and potential future licensure?**

WHO awaits the results of the second phase III trial in Latin America. These additional data will be critical to better understand the performance of the CYD-TDV vaccine and for considering the potential for this vaccine among integrated strategies for dengue prevention.

The WHO Strategic Advisory Group of Experts (SAGE) on immunization will advise WHO on any recommended use of dengue vaccines. A formal WHO assessment of the public health utility of a dengue vaccine and any recommendations for use will only be issued following licensure of the vaccine by a functional National Regulatory Authority (NRA).

**References**


