Questions and Answers on Dengue Vaccines: Efficacy and longer-term safety of CYD-TDV

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What is the current status of dengue vaccine development?
There is a growing public health need for effective preventive interventions against dengue, a disease caused by four viruses, termed serotypes 1-4. 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. The vaccine candidate at the most advanced clinical development stage is a live recombinant tetravalent dengue vaccine developed by Sanofi Pasteur (CYD-TDV), which has been evaluated in Phase III clinical trials as a 3-dose series, on a 0/6/12 month schedule, and has been submitted for registration in several endemic countries. Additional dengue vaccine candidates are in clinical development, with two candidates (developed by Butantan and Takeda) expected to begin Phase III trials.

What is being reported in the integrated analysis and interim long-term follow up of the CYD-TDV trials?
A recently published report provides pooled vaccine efficacy over the first 25 months for the two Phase III trials (CYD14 in Asia and CYD15 in Latin America), as well as interim results from long-term follow up of hospitalized and severe dengue cases from these trials and from a smaller Phase Ib study in Thailand (CYD23/57). Individual results from these trials have previously been published. Together, these trials included over 35,000 participants aged 2 to 16 years: ages at first vaccination were 2 to 14 years in CYD14, 9 to 16 years in CYD15, and 4 to 11 years in CYD23/57. In each of these trials, participants were randomized to vaccine and placebo in a 2:1 ratio. The study protocols included an active phase of follow-up for one year after the last dose of vaccine in the series (25 months from dose 1) and include a hospital-based follow-up period of four additional years, which is ongoing. The available long-term follow up data reported are for a duration of three years post-dose 1 in CYD14 and CYD15, and four years post-dose 1 in CYD23/57. Data are presented for all children included in the trials, as well as post-hoc analyses restricted to those aged 2-8 years and 9-16 years.

What conclusions can be drawn from the integrated vaccine efficacy analyses?
The protocol-defined primary efficacy analysis of the trials was based on the number of virologically-confirmed dengue (VCD) cases of any dengue virus serotype in vaccinated and control subjects, during a one year observation period from 28 days after the 3rd vaccine dose. Vaccine efficacy against dengue of any one of the four serotypes in this time period (the per-protocol (PP) analysis) was 59.2% (95% CI 52.3%, 65.0%) in the two Phase III trials combined. In the pooled analysis from dose 1 (“intention to treat” (ITT) analysis) the vaccine efficacy was higher against serotypes 3 and 4 (71.6% and 76.9%, respectively) than against serotypes 1 and 2 (54.7% and 43.0%, respectively), with the lower confidence bound above zero for all serotypes. Pooled vaccine efficacy against severe dengue during this time period was 79.1% (95% CI 60.0%, 89.0%).

Within the randomized subset of participants for whom pre-vaccination blood samples were collected, pooled vaccine efficacy against VCD in those seropositive for a prior exposure to dengue virus was 78.2% (95% CI 65.4%, 86.3%), while in those seronegative at baseline it was 38.1% (95% CI 3.4%, 62.9%). In a post-hoc analysis in those ≥9 years of age, vaccine efficacy in those seronegative at baseline was 52.5% (95% CI 5.9%, 76.1%). Overall pooled vaccine efficacy amongst all participants aged 9 years or over was 65.6% (95% CI 60.7%, 69.9%), and in participants aged <9 years it was 44% (95% CI 31.6%, 55.0%).

What conclusions can be drawn from the interim analysis of longer-term safety?
Based on available data for the full three years post-dose 1 and all ages combined, there is a cumulative benefit of CYD-TDV against hospitalized and severe dengue. While efficacy was reported against hospitalized and severe dengue in Years 1 and 2 post-dose 1, an excess of cases of hospitalized and severe dengue cases in those receiving CYD-TDV was seen in Year 3 in some subgroups, although it is based on
relatively small numbers of cases. The excess was mostly observed in those vaccinated aged 2-5 years in CYD14 in Asia, for which the relative risk of hospitalized dengue in vaccinees was 7.45 (95% CI 1.15, 313.80) in Year 3, based on 15 cases in the CYD-TDV group and 1 case in the control group. An elevated risk during Year 3 was also seen in CYD57 in the youngest age group (RR=2.44 amongst participants vaccinated at 4-5 years of age, not statistically significant), but not during Year 4. No safety signals were reported in the older age groups. The clinical severity of hospitalized cases was similar in the CYD-TDV and control groups. In the post-hoc analysis of participants 9 years of age or older, the relative risk of hospitalized dengue in Year 3 was 0.50 (95% CI 0.29, 0.86) across the three trials, and was 1.58 (95% CI 0.83, 3.02) in participants less than 9 years of age in CYD14 and CYD23/57, the two trials that included participants <9 years.

In Year 3 of CYD14, there were 11 severe cases in the CYD-TDV group compared to 1 in the control group; 8 of these were among participants aged less than 9 years (participants were randomized to vaccine and placebo in a 2:1 ratio). In Year 3 of CYD15, there were 3 severe cases in the CYD-TDV group compared to 5 in the control group. In Year 3 of CYD23/57, there were 4 hospitalized severe cases in the CYD-TDV group and none in the control group; all of these cases were among participants aged less than 9 years. Most cases of severe disease were dengue haemorrhagic fever (DHF) Grade I or II.

WHO interpretation
This analysis provides important information on the safety and efficacy of the most advanced dengue vaccine candidate. Vaccine efficacy estimates in the two years post-dose 1 were consistent and encouraging in both Phase III trials for the variety of outcomes measured. In the combined and stratified analyses, vaccine efficacy varied by serotype, age at vaccination and serostatus prior to vaccination. The finding of increased risk of hospitalized and severe dengue among vaccinated participants in the younger age group in CYD14 is of concern. The mechanism for this apparent excess risk among those vaccinated is currently unexplained, although there are a number of hypotheses. While differences in the relative risk of hospitalized or severe disease among those vaccinated are associated with age, other factors such as serostatus at baseline may be as, or more, important. The potential increased risk of hospitalized or severe dengue among some vaccinees should be further investigated.

What are the implications for CYD-TDV, including potential future licensure and use?
There are now two large pivotal Phase III trials that continue to provide important data to understand the performance of CYD-TDV. A number of National Regulatory Authorities (NRAs) in countries endemic for dengue have received an application for licensure of CYD-TDV. NRAs will make their own assessment of the safety and efficacy of CYD-TDV and the risk/benefit for their epidemiological context.

The WHO Strategic Advisory Group of Experts (SAGE)6,7 on Immunization is currently reviewing the evidence and will advise WHO (likely in April 2016) on recommended use of a dengue vaccine. Main considerations include vaccine safety, vaccine efficacy, disease burden, programmatic suitability, including dose scheduling, and cost-effectiveness. Formal WHO guidance on public health use will only be issued following licensure of the vaccine by a functional NRA meeting certain criteria as assessed by WHO and the SAGE assessment.

What are the implications for future vaccine candidates?
Until there is a better understanding of the relationship between vaccine-induced immune response, individual attributes, and disease risk, it is unknown whether similar safety and efficacy profiles would be seen with other candidate dengue vaccines, none of which have yet been evaluated in Phase III trials. Clinical trials of future dengue vaccine candidates will also need to carefully monitor efficacy and safety over time among different subsets of the trial population. Continued efforts for dengue vaccine development are needed to address the growing burden of dengue globally.

WHO was advised on the interpretation of the integrated analysis and interim longer-term safety results by a technical advisory group of experts on dengue vaccines’ and the Global Advisory Committee on Vaccine Safety.8
References
http://www.who.int/denguecontrol/9789241504034/en/
8 WHO Global Advisory Committee on Vaccine Safety. Further information at http://www.who.int/vaccine_safety/committee/en/