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Editorial

A Candidate Dengue Vaccine- Current Status

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The most advanced candidate vaccine against dengue viruses, called CYD-TDV, is progressing toward potential registration and reviewed by the World Health Organization (WHO) in 2016. CYD-TDV is a tetravalent, live attenuated, chimeric dengue vaccine in a Yellow fever 17D back bone developed by Sanofi Pasteur. The schedule that has been evaluated in phase III clinical trials included 3 doses of vaccine (at 0, 6 and 12 months). Results from 2 phase III trials in Asia[1] (CYD 14; 10275 children aged 2-14 years) and Latin America[2] (CYD 15; 20869 children aged 9-16 years) were published in 2014. Vaccine efficacy against symptomatic virologically confirmed dengue was estimated to be 56.5% and 60.8% respectively. Vaccine efficacy varied by serotype, serostatus at the time of receiving the first dose (measured by presence of neutralizing antibody against dengue), and severity of disease in both studies, and by age in the phase III study in Asia. The percentage of subjects with unsolicited non-serious adverse events, solicited systemic reactions, solicited injection site reactions, or solicited adverse reactions was slightly higher in the CYD vaccinated subjects compared to placebo recipients, but statistically not significant.

Hadinegoro et al. now provide in the Journal[3] updated efficacy results from the third year of hospital-based surveillance from two phase 3 trials (CYD 14 and CYD 15) and the third and fourth years of one phase 2b trial (CYD23/57). Most eye-catching is the suggestion that CYD-TDV vaccination was associated with an elevated risk of hospitalization for dengue among children younger than 9 years of age (but most markedly, among those 2 to 5 years of age) when they were naturally infected in the third year after vaccination, There is some comfort in the fact that CYD-TDV vaccination did not increase the frequency of genuinely severe, life-threatening complications (e.g., dengue shock syndrome). Whether the excess of hospitalized children younger than 9 years of age in the vaccine group during year 3 is the tip of the iceberg and reflects a higher incidence of symptomatic infections in this sub-group is unknown because surveillance in this period was hospital-based only. It's possible the results are chance findings. If not, a possible explanatory hypothesis is that age is a proxy for previous dengue infection and that CYD-TDV immunization of some young children elicits only transient antibody-mediated full or partial immunity. Subsequent waning of antibody titers predisposes vaccines to infection and clinical presentations for which hospitalization is indicated. Mechanistically, antibody-dependent enhancement of challenge virus infection, particularly by non-neutralizing vaccine-elicited antibodies, could ex0plain this increased epidemiologic risk. Indeed, the possibility of vaccine-medicated modification of disease risk (i.e., sensitization) is the basis for WHO recommendations for long-term follow-up of recipients of candidate vaccines.[4] A critical question is whether the elevated risk of hospitalization for dengue that was observed in young recipients of CYD-TDV is a short-term or long-term phenomenon, potentially, booster doses of vaccine might be used to break the disease-risk

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profile. Prudently, the investigators are continuing disease surveillance in all trial participants to address these safety and efficacy concerns.

Dengue vaccine introduction should be a part of comprehensive dengue control strategy, including well-executed and sustained vector control, evidence based best practices for clinical care for all patients with dengue illness. Countries should consider introduction of the dengue vaccine CYD-TDV only in geographic settings (national or sub-national) where epidemiological data indicate a high burden of disease. If CYD-TDV is introduced, it should be administered as a 3 dose series given on a 0/6/12 month schedule.[5] However, additional evidence is needed to determine whether simplified schedules may elicit equivalent or better protection.

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All corresponds to
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