Dengue Vaccine Development: An Update

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**Abstract**

Dengue is a growing global problem that urgently needs to be addressed. We now have a robust pipeline with several promising dengue vaccine candidates, all using different approaches. The only vaccine to have completed Phase 3 trials is the CYD-TDV vaccine sponsored by Sanofi Pasteur. CYD-TDV is a formulation of four chimeras, each one engineered to express the envelope and pre-membrane proteins from one of the four serotypes of DENV. Pooled efficacy and safety results of CYD-TDV from phase 3 trials conducted in over 30,000 children aged 2-16 years in 10 countries (5 in Asia, and 5 in Latin America) were recently published. These trials have shown this vaccine to be complex: efficacy varied widely depending on serotype, baseline flavivirus priming status (i.e., prior DENV infection status) and age. Protection against serotypes 3 and 4 was good, but marginal against serotype 1 and poor against serotype 2. Absence of prior DENV infection was associated with low efficacy. Higher age had an overall beneficial impact on efficacy: among individuals aged 9 to 16 years, efficacy against virologically confirmed DENV infection regardless of severity and serotype was higher (66%) than in those below 9 years (44%). Efficacy against severe dengue and hospitalization was also higher (93% and 81%, respectively) in individuals aged 9 years or older; compared with 45% and 56% in children younger than 9 years. However, long-term safety follow up showed a safety signal in the third year of the Asian Phase 3 trial in those younger than 9 years, which was much more pronounced in the very youngest children 2-5 years old who had an almost eight-fold increase in hospitalizations among vaccinees compared to the control group. Given the higher efficacy and better benefit/risk profile for individuals aged 9 years and above, Sanofi Pasteur now seeks licensure with an indication in children from 9 years of age and above. Eliciting the reasons for the imbalanced efficacy results and the safety signal is now a subject of intense research. Many lessons can be learnt from the CYD-TDV vaccine, including the urgent need to identify an immune correlate, the role of T-cell immunity, and the role of non-structural proteins in the immune response. Alternative live attenuated dengue vaccines are now also approaching Phase 3 trials and may overcome some of the problems observed with CYD-TDV.

**Selected Publications for Reference**