Encouraging results but questions remain for dengue vaccine

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Dengue has expanded dramatically over the past several decades, with the four dengue virus serotypes (DENV-1–4) now co-circulating in most dengue-endemic regions.[1] A safe and efficacious vaccine will be a crucial element of comprehensive global prevention and control. In *The Lancet Infectious Diseases*, Xavier Sáez-Llorens and colleagues[2] report 18-month interim results from a phase 2 trial of a live attenuated tetravalent dengue vaccine candidate, TDV (Takeda, Osaka, Japan). TDV was administered in either one or two doses separated by 3 or 12 months in 1800 participants aged 2–17 years in three dengue-endemic countries: Dominican Republic, Panama, and Philippines. No safety issues were reported, and high neutralising antibody seroconversion rates were observed across all DENV serotypes. A minor increase in DENV-3 neutralising antibody levels was noted with two doses compared with one dose in dengue-seronegative participants. The incidence of virologically confirmed dengue virus infection was found to be significantly lower in TDV recipients (21 [1·3%] of 1596) than in the placebo group (nine [4·5%] of 198) during the 18-month study period, suggesting a potential clinical benefit of vaccination with TDV.

Currently, the only licensed dengue vaccine is CYD-TDV (Dengvaxia, Sanofi Pasteur, Lyon, France), which has been registered in many dengue-endemic countries. However, CYD-TDV has been implemented in public health programmes in only two countries to date as part of subnational programmes. Several factors might have contributed to this limited national uptake, such as concerns about the marginal benefit against some dengue serotypes (especially DENV-2), possible safety risks in vaccination of dengue-seronegative individuals, the exclusion of children younger than 9 years from the indication, and operational complexities regarding the introduction of the vaccine into only high-transmission settings as recommended by WHO.[3] Nevertheless, the experience with CYD-TDV has provided important lessons for next-generation dengue vaccine developers. Specific approaches are now known to be crucial in the assessment of next-generation vaccines, including investigation of serotype-specific differences in efficacy, the effect of baseline dengue serostatus on protection and risk, and the durability of protection beyond the period when short-term heterotypic protection (induced by an immunodominant serotype) can wane, leaving the recipient with only limited longer-term homotypic protection.[4] Additionally, the issue of possible vaccine-induced enhancement of disease in young children and seronegative individuals has been raised following the increased relative risk of being admitted to hospital with dengue, observed in children aged 2–5 years during the third year of the phase 3 trial of CYD-TDV in Asia, many of whom were seronegative before vaccination.[5] Further complicating the vaccine development process is the questionable adequacy of how immune responses to vaccination are measured (eg, by neutralising antibody) and whether these measures correlate with protection from disease.[6]

TDV differs from CYD-TDV most notably in that TDV uses attenuated DENV-2 as either a full-length strain (DENV-2) or chimeric backbone (DENV-1, DENV-3, and DENV-4), whereas CYD-TDV uses a yellow fever virus chimeric backbone for all four serotype components. This difference has the potential for TDV to induce better cellular immunity to DENV-2 because of the inclusion of DENV-2 non-structural proteins and their T-cell epitopes, and perhaps also cross-reactive cellular immunity to the other dengue serotypes.[7] However, similar to CYD-TDV, TDV is a live attenuated tetravalent vaccine, which can lead to imbalanced vaccine virus replication and immunodominance, particularly by the full-length DENV-2 component, potentially leading to variability in serotype-specific protection and short-term heterotypic immunity. To lessen this possibility, Takeda decreased the DENV-2 component in their TDV formulation by one log relative to the other serotypes for the current phase 2 trial.[8] The neutralising antibody responses are more balanced than in the phase 1 and 2 trials using the previous formulations.[8–10] However, since neutralising antibody responses might not correlate with clinical efficacy, whether this change in formulation ultimately makes a difference will only be answered by clinical endpoint trials.

Overall, the interim results from this phase 2 trial are encouraging. Of particular note, the decreased risk of virologically confirmed dengue virus infection in TDV-vaccinated individuals suggests TDV might offer some level of protection. However, the phase 2 trial

was designed to assess safety and immunogenicity, not protection. Therefore, the number of dengue cases and period of observation were not sufficient to make conclusions about the vaccine's efficacy. Efficacy as a function of age, serotype, and serostatus could not be assessed. Durability of protection and risk, along with the related issue of heterotypic versus homotypic immunity, also could not be assessed. Ultimately, the true test to see if Takeda's dengue vaccine candidate is substantially different from the licensed Sanofi Pasteur vaccine will be the multicountry phase 3 trial (NCT02747927) of TDV initiated in 2016. Those results, along with results from the phase 3 trial (NCT02406729) from the Instituto Butantan, São Paulo, Brazil, of their live attenuated tetravalent dengue vaccine candidate, co-developed with the US National Institutes of Health, are highly anticipated by the global scientific and public health communities.

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