Delivering safe dengue vaccines

Unique antigenic and biological attributes of the four dengue viruses create serious pathogenic problems for humans. An initial dengue virus infection can result in a short-duration, mild-to-moderate febrile illness followed by an immune response that provides lifetime protection against clinically overt homotypic virus re-infection. The IgG antibodies raised can interact with a second infecting dengue virus to produce intrinsic antibody-dependent enhancement, the process by which dengue viruses IgG immune complexes suppress intracellular antiviral defenses.[1,2] Antibody-dependent enhancement generates increased production of the dengue virus's non-structural protein, NS1, an endothelial toxin that circulates to cause vascular permeability and other abnormalities contributing to severe, sometimes fatal, dengue.[3] Unfortunately, the mechanisms of immune protection against dengue virus infection, in particular, the contributions of cellular immunity are not fully understood.[4] The four different dengue viruses result in pathogenic second infections in 12 different infection sequences. Regretfully, new pathogenic sequences of dengue virus infection have been discovered: Sanofi Pasteur's DENGVAXIA vaccine followed by infection with any of the four dengue viruses, and—possibly—Takeda's QDENGA vaccine followed by infection with dengue virus 3.[5,6]

What makes sensitisation to severe secondary dengue infections by tetravalent dengue vaccines possible? DENGVAXIA contains structural but no non-structural genes for any dengue virus. Thanks to the large datasets generated by Sanofi Pasteur's efficacy trials, humans who are seronegative and given three doses of DENGVAXIA were seen to develop neutralising antibodies to all four dengue viruses but little protection against infection or disease. 5 years after vaccination, in a 10% sample, among the 512 children who were vaccinated and seronegative, aged 2–16 years, 187 were hospitalised (ie, treated within hospital) with dengue viruses 1–4 infections. Among the 272 children who received placebos, only 53 were hospitalised.[5] Using the attack rate unvaccinated – attack rate vaccinated / attack rate unvaccinated × 100 formula, this generates a negative vaccine efficacy of 18%. Fortunately, individuals immune to one or more dengue viruses when vaccinated were protected from breakthrough dengue virus infections and disease. This is good news, as dengue virus mono-immunes contribute importantly to those at risk of severe dengue.

In Takeda's recent 4–5-year QDENGA efficacy report (February, 2024),[6] of 3174 patients who were vaccinated and seronegative aged 4–16 years, 11 were hospitalised with dengue virus 3 infections, while among 1832 patients who were seronegative and given placebos only three were hospitalised.[6] This generates a negative efficacy of 11·6%, similar to that of the Sanofi vaccine. The major difference between the two studies is the small scale of Takeda clinical dengue virus 3 cases. Overt dengue virus 4 infections were also rare.

The Strategic Advisory Group of Experts on Immunization's recent recommendation for the use of QDENGA is that in dengue virus-endemic countries in settings of high transmission, vaccines should be given to children aged 6–16 years regardless of serostatus.[7] Citing an absence of a statistically significant number of severe dengue 3 infections in patients vaccinated with QDENGA who are seronegative, the report noted Takeda's plans to conduct an extensive "post-authorization effectiveness study… to assess the impact of TAK-003 against hospitalized dengue. The planned trial size and locations are intended to overcome limitations in the pivotal licensure study so that the impact of TAK-003 on severe/hospitalized cases due to DENV3 [dengue virus 3] and DENV4 may be evaluated. The study will be a multi-country, multisite nested case–control study with a cohort of 70 000 participants for whom the baseline serostatus will be determined".[7]

Immense global populations of *Aedes aegypti* supporting the circulation of the four dengue viruses, reinforce the need for vaccines to contain dengue transmission. Because there is no explicit model of a safe and effective tetravalent protective dengue virus vaccine, commercial manufacturers have relied on empirical products. Why not use clinical trial data to better understand the correlates of dengue vaccine success or failure? Notably, DENGVAXIA lacked dengue virus non-structural genes. Surprisingly, QDENGA is expected to provide protection when three of its dengue virus constructs lack non-structural antigens. The vaccine does contain a classical, protective live-attenuated dengue virus 2. Should wider clinical testing of candidate dengue vaccines that contain all four dengue viruses structural and non-structural proteins not be looked and promoted? Perhaps, there should be wider testing of the National Institutes of Health dengue vaccine—a product composed of three live attenuated dengue viruses, missing only an attenuated dengue virus 2.[8]

I declare no competing interests.

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