EDITORIALS

# Three Dengue Vaccines — What Now?

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In 2019, the four serotypes of the mosquito-borne dengue virus (DENV) caused an estimated 56 million cases of disease and 5000 to 40,000 deaths in a global swath of tropical and near-tropical countries, defying control and motivating the development of vaccines.[1] Outcomes of clinical trials of dengue vaccines are necessarily governed by the biologic and immunologic behavior of DENV in humans. Initial infection with any DENV serotype in persons who have not previously been infected with DENV typically results in at most mild-to-moderate febrile illnesses of short duration. These initial infections provide lifelong protection against reinfection with the same immunologic DENV serotype. Second heterotypic dengue infections occur in 12 sequences (e.g., DENV-1 then DENV-2, DENV-2 then DENV-3, etc.). Second infections are responsible for much of the spectrum of severe dengue illnesses worldwide. Severe dengue disease occurs only in rare cases during a third or fourth DENV infection. It is this two-infection protective immune status that fuels the development of dengue vaccines.

There is a red flag, however: when multi-DENV IgG antibodies are transferred to fetuses through the placenta, DENV infections in the newborns are prevented for weeks to months. However, when antibodies are catabolized to non-protective levels, these infants may have antibody-enhanced DENV infections that result in severe disease, hospitalization, and death.[2] Non-neutralizing DENV IgG antibodies, whether acquired through infection or vaccine, are a universal risk factor for severe dengue among persons who do not have protective immunity. Unfortunately, there are no agreed-upon serologic criteria that identify protective immunity in persons who are thought to have had two or more DENV infections. This lack of an identified protective factor makes clinical trials of tetravalent dengue vaccines important learning experiences.

Nearly 50 years have passed since development of a tetravalent dengue vaccine was initiated at the Walter Reed Army Institute of Research. Since then, three fundamental discoveries have challenged the design of a dengue vaccine: antibody-dependent enhancement, the protective role of cellular immunity,[3] and the direct pathogenicity of dengue nonstructural protein 1 (NS1).[4] In order to provide a high level of protection, dengue vaccines should present a full array of structural and nonstructural antigens (including NS1) of all four DENV serotypes.

Efficacy trials involving three tetravalent dengue vaccines have been completed. Dengvaxia (Sanofi) is a yellow fever virus–derived vaccine integrated chimerically with the structural regions of the four DENV serotypes. The large, well-designed, multicountry clinical trial of three doses of Dengvaxia provided unexpected but informative results. Tetravalent neutralizing antibodies developed in nearly all vaccinees in the trial. Vaccinated seronegative participants had unexpected breakthrough DENV infections, including severe disease, with some cases leading to hospitalization for illness characterized by vascular permeability. Vaccinated seropositive participants were protected against breakthrough DENV illnesses.[5] The two-dose dengue vaccine, TAK-003, also known as Qdenga (Takeda), contains live, attenuated DENV-2 plus DENV-2 chimeras of the structural regions of DENV-1, DENV-3, and DENV-4. In clinical trials, there was one unequivocally positive outcome: vaccinated seronegative

participants and seropositive participants were highly protected against DENV-2 disease. A serious limitation was the absence of DEN-4 infections. Moderate protection against DENV-1 disease was found in both seronegative participants and seropositive participants, and a suggestion of a higher frequency of hospitalization for DENV-3 disease among vaccinated seronegative participants.[6]

In this issue of the *Journal*, Kallás et al.[7] report the findings from their phase 3 trial of a single administration of Butantan-DV (Instituto Butantan), a tetravalent vaccine developed in a National Institute of Allergy and Infectious Diseases laboratory.[8] Between February 2016 and July 2019, one dose of Butantan-DV, containing full-length attenuated DENV-1, DENV-3, and DENV-4 plus a DENV-2–DENV-4 chimera, was administered to 10,259 children and adults at 16 sites in five geographical regions of Brazil; placebo was administered to 5976 children and adults. Vaccine efficacy against overt mild DENV-1 dengue disease was 96.8% and 85.6% among seropositive participants and seronegative participants, respectively, with modest efficacy against overt DENV-2 disease among 83.7% and 57.9%, respectively. On the basis of protection against DENV that was shown during preclinical testing of the analogous TV003 formulation developed by the National Institutes of Health, it was expected that a single dose of Butantan-DV would provide protective immunity against all four DENV serotypes.[9] The absence of cases of DENV-3 and DENV-4 undoubtedly is attributable to the introduction of Zika virus (ZIKV) to Brazil in 2015. The number of ZIKV infections exploded to epidemic proportions and was followed in both 2017 and 2018 by an 80% reduction in total dengue cases and deaths. Among the 270 participants who received vaccine or placebo in the current trial and in whom clinical dengue illnesses developed during the trial, none were severely ill or hospitalized. This is in stark contrast to the frequency of severe dengue or hospitalization of vaccinees and controls in clinical trials of Dengvaxia and TAK-003. ZIKV, a flavivirus, behaves antigenically like a fifth DENV. A person with monotypic DENV immunity who has been infected with ZIKV converts to the immune status of a person who has been infected with two DENV serotypes,[10] and there should be an unusually high prevalence of the antibody patterns associated with two DENV serotypes in the prevaccination serum samples of these persons. This possibility should be studied.

What now? The World Health Organization Strategic Advisory Group of Experts on Immunization (SAGE) has recommended that persons 9 years of age or older with evidence of at least one previous DENV infection receive three doses of Dengvaxia. SAGE is considering recommending that persons 6 to 16 years of age in countries where DENV is highly endemic receive two doses of TAK-003 without restriction. Given the realities of the dimensions of the dengue pandemic in the 20th and 21st centuries, a highly effective, one-dose, tetravalent vaccine remains in high demand. Butantan-DV clinical trials should continue and, if possible, be expanded.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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