A Candidate Dengue Vaccine Walks a Tightrope

EDITORIALS

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The most advanced candidate vaccine against dengue viruses, called CYD-TDV, is progressing toward potential registration and review by the World Health Organization (WHO) in 2016. CYD-TDV is a formulation of four chimeric yellow fever 17D vaccine viruses, each one engineered to express the surface envelope and prM (membrane) proteins from one of the four serotypes of dengue virus. The surface envelope protein is a target of virus-neutralizing antibodies. The safety and efficacy of CYD-TDV after the administration of three doses over a 12-month period was recently measured in two pediatric phase 3 trials in Latin America[1] and Southeast Asia.[2] The short-term safety profile was encouragingly benign. However, the efficacy profile during 25 months of disease surveillance was complex. The most striking benefit to vaccinees was a large reduction (by 67 to 80%) in dengue hospitalizations. On the other hand, efficacy against any disease caused by serotype 2 viruses ranged from 35 to 50% and was lower still for vaccine recipients who were seronegative at baseline (i.e., those with no serologic evidence of previous dengue virus infection).

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 (CYD14 and CYD15) 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 subgroup 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 vaccinees 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 explain this increased epidemiologic risk. Indeed, the possibility of vaccine-mediated 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 profile. Prudently, the investigators are continuing disease surveillance in all trial participants to address these safety and efficacy concerns.

What do these findings mean for CYD-TDV and its potential future role in dengue control? The new evidence from years 3 and 4 of hospital surveillance indicates that children between the ages of 9 and 16 years continue to benefit, probably because CYD-TDV evokes pan-serotype immunity in many recipients who have had a previous natural infection. Longer-term efficacy results

will inform the need for booster doses, if any, in this age group. The benefits for children younger than 9 years of age are less clear, and more data will be needed to understand the risk–benefit profile of CYD-TDV in this age group. If countries in which dengue is endemic were to license CYD-TDV for children 9 years of age or older, then policymakers in each setting would subsequently need to make decisions on the cost and benefit of programmatic vaccination. In places in which a sizable fraction of the case burden occurs in children younger than 9 years of age, this decision will be a complex one. Moreover, in low-transmission settings, seroprevalence surveys might be needed to identify the most appropriate age range for vaccination — and this may change over time.

What are the implications of these findings for the dengue vaccine field? The CYD-TDV trials have been superbly conducted and are hugely informative; they have delivered major insights into disease burden, clinical epidemiology, and immunity. They have also highlighted knowledge gaps, since we still lack definitive immune correlates of protection or vaccine-associated disease risk. A lesson from these trials, and from our understanding of the natural history of dengue epidemiology, is that partial, waning immunity is a particularly unwelcome outcome after vaccination. Live vaccines need to be sufficiently potent in their infectiousness and replicative capacity to initiate immunity in both unexposed recipients and those with partial immunity. Dengue human challenge studies might help in the down-selection of second-generation candidate vaccines[5] before large phase 2–3 trials are conducted. The bumpy road to a vaccine-based solution for dengue continues.

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

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Monoclonal Antibodies in Multiple Myeloma Come of Age

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Multiple myeloma is a cancer of plasma cells that has an estimated incidence of 26,850 new patients in 2015 in the United States.[1] In the past few years, dramatic progress has been made in the treatment of this disease. New classes of drugs, including proteasome inhibitors (e.g., bortezomib and carfilzomib) and immunomodulatory agents (e.g., lenalidomide and pomalidomide), have improved response rates and survival significantly, and it now appears that immunotherapy is likely to lead to even greater advances.

Results regarding the use of daratumumab, an antibody directed against CD38, in patients with relapsed, refractory multiple myeloma are now reported in the *Journal*.[2] Earlier this year, a phase 3 trial that targeted signaling lymphocytic activation molecule F7 (SLAMF7) with a monoclonal antibody, elotuzumab, showed encouraging results.[3] The latest data provide convincing evidence that targeting CD38 is very effective in the treatment of advanced multiple myeloma. We may finally be at the threshold of having several monoclonal antibody–based treatments approved for the treatment of myeloma.

Daratumumab is a human IgG1 antibody that targets CD38, a 46-kD type II transmembrane glycoprotein that is abundantly expressed on malignant plasma cells. This antibody was granted a breakthrough-therapy designation by the Food and Drug Administration for patients