NIH dengue vaccine leaps into phase 3 studies

An investigational dengue vaccine developed by scientists at the National Institutes of Health (NIH), in Bethesda, Maryland, entered large-scale phase 3 efficacy trials in Brazil on February 22 following a small human challenge trial conducted in the US. A single dose of the dengue vaccine TV003 fully protected 21 vaccinated volunteers against infection in a virus challenge study, whereas 20 unvaccinated controls all developed an infection. "The challenge study looks very good, very promising," says Annelies Wilder-Smith, director of the Global Health and Vaccinology Program at Lee Kong Chian School of Medicine in Singapore. But, she noted, the study size was relatively small, and only a single, attenuated challenge virus was used.

Anna Durbin, associate professor at the Center for Immunization Research at the Johns Hopkins Bloomberg School of Public Health (in Baltimore, Maryland), who led the trial, and her team reported the results on March 16 (*Sci. Transl. Med.* **8**, 330ra36, 2016). The 21 dengue-naive individuals who received a single dose of TV003 were challenged six months later with a dengue virus type 2 (DEN-2) strain. Vaccinated participants were all protected from the challenge virus, including 12 who exhibited "sterilizing immunity," Durbin says, meaning that the virus was effectively blocked from even entering the body. In contrast, all 20 participants in the placebo group developed viremia.

Brazil's Butantan Institute in Sao Paulo will manufacture the dengue vaccine for the phase 3 studies at its own premises.

Dengue virus infects some 390 million individuals worldwide annually, according to the World Health Organization. The infection is transmitted by the *Aedes aegypti* mosquito, also a vector for the Zika, yellow fever, and chikungunya viruses. As many as 3.9 billion people are at risk for the disease, which is caused by any of four related, but distinct, flavivirus serotypes (DEN-1–DEN-4). Initial infection with any dengue serotype typically is asymptomatic or results in mild disease. But a subsequent infection with a second serotype can produce severe disease, hospitalization, and even death. Antibodies from the primary infection seem to facilitate the secondary infection, a process called antibody-dependent enhancement. As a result, dengue vaccines are tetravalent, targeting all four serotypes at once.

The first vaccine to enter late-stage clinical trials was Dengvaxia (ChimeriVax-dengue, CYD-TDV), developed over two decades by Sanofi Pasteur of Lyon, France. It is a chimeric tetravalent three-dose vaccine composed of four recombinant, live, attenuated viruses. Each uses the 17D yellow fever virus as replicative backbone to carry genes encoding structural proteins from one of the four dengue virus serotypes. The vaccine was safe and induced neutralizing antibodies against all serotypes, but results from the trials were disappointing (*Nat. Biotechnol.* **32**, 605–606, 2014). The vaccine offers only incomplete protection, with 58%, 47%, 74%, and 83% efficacy against DEN-1, DEN-2, DEN-3, and DEN-4, respectively (*N. Engl. J. Med.* **37**, 1195–1206, 2015). In addition, it was effective in those who were dengue seropositive at baseline and in children over 9 years old. But children aged 2–5 were five times more likely than unvaccinated children to be hospitalized within three years of vaccination because of dengue fever, says Scott Halstead of the Uniformed Services University of the Health Sciences in Bethesda, Maryland, who recently analyzed the Sanofi Pasteur phase 3 data (*Vaccine* **34**, 1643–1647, 2016).

Dengvaxia, Halstead says, seems to protect people who have been infected once and thus are at risk of severe disease. But, conversely, it puts people who were susceptible to a first infection at risk of severe disease. Even so, the vaccine is approved in Mexico (*Nat. Biotechnol.* **24**, 8, 2016), the Philippines, and Brazil.

The TV003 vaccine, developed by a group of scientists from the NIH's National Institute of Allergy and Infectious Disease (NIAID) led by Stephen Whitehead, is a mixture of four live, attenuated recombinant candidate viruses. These were obtained by targeted mutagenesis of the noncoding regions in the native dengue virus, rather than inserted into the 17D yellow fever virus background, and express both structural and nonstructural viral proteins.

The components were tested individually over the course of a decade and then combined into multiple tetravalent formulations, which were assessed and selected prior to large-scale clinical trials. The challenge virus is a genetically modified version of a DEN-2 serotype isolated by Whitehead and colleagues in the Kingdom of Tonga in 1974.

Of the recent results, Whitehead says he is certainly excited but also, ironically, "a little bummed out" by the across-the-board success. Normally, a few participants don't respond to a vaccine, and by comparing responders and nonresponders, researchers can identify "immunological correlates" of protection, such as neutralizing antibody titer. The vaccine induces a strong antibody and cellular $CD8^+$ T cell response and a high level of protection. "Everybody was protected, so that makes it more difficult [to find those markers]," says Whitehead. The team is now developing a human challenge model using a modified DEN-3 virus. Osaka, Japan–based Takeda's vaccine, a chimeric construct built in a DEN-2 backbone, is scheduled to enter phase 3 trials this year.

In Brazil, the newly launched multicenter phase 3 trial expects to enroll some 17,000 participants at 14 endemic locations. The Butantan Institute in Sao Paulo, a nonprofit producer of immunological products for Brazil, licensed the vaccine technology and will be coordinating the placebo-controlled trials as well as producing the vaccine at its facilities. So far, around 100 participants have been recruited and vaccinated, says Alexander Precioso, director of Butantan's Clinical Trials and Pharmacovigilance Division. Precioso expects to vaccinate all participants within a year and collect sufficient data to apply for approval within three years. "We are working with the goal of making it available in 2018," he says.

But it will take years for the long-term efficacy of TV003 to be clear, Whitehead says, and booster injections may well be needed to ensure long-term protection. In the meantime, his team is hard at work building a live, attenuated Zika virus vaccine, which Whitehead hopes to incorporate into TV003 to create a pentavalent cocktail. A phase 1 trial of the Zika virus component could begin in late 2016, he says.

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