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Candidate dengue vaccine shows promise in early-stage trial

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A candidate dengue vaccine developed by scientists at the National Institutes of Health (NIH) has been found to be safe and to stimulate a strong immune response in most vaccine recipients, according to results from an early-stage clinical trial sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), part of the NIH. The trial results were published online on January 17 in the *Journal of Infectious Diseases*.

Dengue fever, prevalent in many tropical and subtropical regions of the world, is caused by any of four related viruses—DENV-1, DENV-2, DENV-3 and DENV-4 —that are transmitted to humans by Aedes mosquitoes. The World Health Organization estimates that every year, 50 million to 100 million cases of dengue occur worldwide, resulting in 500,000 hospitalizations of patients with severe disease, many of them in children.

Infection with one dengue virus results in immunity to that specific virus but not to the other three. Research shows that the likelihood of severe disease increases when a person is subsequently infected with a different dengue virus. This observation suggests that the ideal dengue vaccine would be tetravalent—that is, protective against all four dengue viruses.

"The global burden of dengue is enormous—and it is growing," said NIAID director Anthony S. Fauci, M.D. "We are cautiously optimistic about these recent clinical trial results with this candidate tetravalent vaccine developed at NIAID; however, much more work still needs to be

done."

The Phase I clinical trial, launched in July 2010 and led by principal investigator Anna Durbin, M.D., at Johns Hopkins Bloomberg School of Public Health in Baltimore, tested a single dose of each of four versions of the investigational dengue vaccine TetraVax-DV. The vaccine was developed by scientists in NIAID's Laboratory of Infectious Diseases. It is a live, attenuated vaccine, which means that the viruses it contains are weakened enough such that they do not cause illness but still can induce an immune response. Each of the four vaccines tested included different mixtures of components designed to protect against all four dengue viruses.

The Phase I study was conducted in Baltimore; Burlington, Vt.; and Washington, D.C. The final study analysis included 112 healthy men and women ages 18 to 50 years who had not previously been exposed to dengue or related viruses such as West Nile virus and yellow fever virus.

Participants were randomized into four groups. In each group, 20 volunteers received a single 0.5-milliliter subcutaneous (under the skin) injection of one of the tetravalent candidate vaccine combinations, and eight others received placebo. All were monitored for immediate adverse reactions for at least 30 minutes after vaccination, and subsequently took their body temperatures three times daily for 16 days to check for possible adverse reactions. Participants also received a physical exam every other day up to Study Day 16, and then again on study days 21, 28, 42 and 180, when blood tests were also performed.

The researchers found that all four candidate vaccine combinations induced antibody responses against each of the dengue viruses. However, one vaccine combination, TV003, appeared to induce the most balanced antibody response against the dengue viruses. A single dose of TV003 resulted in an antibody response to all four dengue viruses in 45 percent

of participants and against three of the four viruses in an additional 45 percent. Overall, an immune response to at least three viruses was seen in 90 percent of vaccinees given TV003.

"What is promising about TV003 is that it elicited solid antibody responses after just one dose," explained Stephen Whitehead, Ph.D., of NIAID's Laboratory of Infectious Diseases, who led the development of the vaccine candidates. "Other vaccines in development require two or three injections at higher doses to achieve similar results."

All four candidate tetravalent vaccines were found to be safe, and no participants experienced fever or dengue-like illness after vaccination. The most common side effect was a faint rash (in 64 percent of vaccinees and none of the placebo recipients) consisting of small, non-painful bumps on the arms and torso that resolved within five to seven days. The presence of the rash appeared to correlate with being white and having a stronger immune response to vaccination, according to the researchers. Ninety percent of white vaccinees experienced a vaccine-related rash while only 35 percent of African-American vaccinees developed a rash. Further, 97 percent of white vaccine recipients (42 of 43) developed antibodies to at least three of the dengue viruses, compared with 60 percent of African-American vaccine recipients (22 of 37). It is unclear what caused this difference, but previous studies of severe dengue outbreaks in Brazil, Cuba and Haiti suggest that black people may have some inherent protection from dengue infection. Alternatively, unknown factors may have resulted in a weaker antibody response to the vaccine among African-American participants. Additional research to evaluate racial differences in dengue infection and antibody response rates to dengue vaccines is needed, the authors wrote.

"The results of this Phase I dengue vaccine study look very promising, and NIAID scientists and their partners are pursuing further

development of TV003," said Kathryn Zoon, Ph.D., director of NIAID's Division of Intramural Research. The researchers are conducting studies to further evaluate the vaccine's safety and ability to stimulate an immune response in healthy volunteers and in people who have been infected previously by dengue or related viruses.

TV003's inexpensive production cost—less than $1 per dose—is critical to its potential use in developing countries, noted Dr. Whitehead. Manufacturers in Brazil, India and Vietnam—countries where dengue is prevalent – have licensed the vaccine technology for production and further evaluation. Phase II trials to evaluate the safety of TV003 and its capacity to create an immune response will begin soon in Brazil and Thailand.

Provided by NIH/National Institute of Allergy and Infectious Diseases