Human clinical trial of NIH-developed dengue vaccine begins

9 August 2010

After more than a decade of development at the National Institutes of Health, a vaccine to prevent infection by the mosquito-borne dengue virus has begun human clinical testing. The vaccine was developed by scientists at the National Institute of Allergy and Infectious Diseases (NIAID) and is undergoing clinical study at the Johns Hopkins Bloomberg School of Public Health in Baltimore.

About 2.5 billion people in more than 100 countries worldwide live in areas where they are at risk of dengue infection. "This is an important milestone for NIAID's intramural scientists in the development of a model dengue vaccine, which could potentially have a major impact in preventing dengue," says NIAID Director Anthony S. Fauci, M.D. "With increasing infection rates and disease severity around the world and the discovery of dengue in parts of Florida, finding a way to prevent dengue infection is an important priority."

Dr. Fauci is co-author of a 2008 commentary in the *Journal of the American Medical Association* that raised awareness of dengue as an emerging infectious disease.

Dengue fever is caused by any of four related viruses - DENV-1, DENV-2, DENV-3 and DENV-4 - which are transmitted to humans by Aedes mosquitoes. Dengue virus is prevalent in the tropical and subtropical regions of the world and each year infects about 50 million to100 million people. It accounts for 25,000 deaths annually, most of them in children.

Most people infected with dengue virus experience no symptoms at all or only a mild fever. Others develop flu-like symptoms, headache, and joint and muscle pain. A smaller portion of those infected experience the more severe dengue hemorrhagic fever/shock syndrome (DHF/DSS), which can cause high fever, pain, bleeding, a drop in blood pressure, and, in some cases, coma or death.

There is no vaccine to prevent dengue infection or drug treatment for those who become infected. Current treatment recommendations include bed rest, drinking fluids, and taking medicine to reduce fever. The only way to prevent infection is to avoid being bitten by Aedes mosquitoes. These mosquitoes are most active during the day and thrive in urban environments, two factors that make them difficult to avoid.

"Controlling the mosquito vector can work, but it is very expensive and difficult to sustain," says Anna Durbin, M.D., who is leading the study at Johns Hopkins. "In the long run, vaccination would be a more efficient and cost-effective approach."

The new vaccine is tetravalent, meaning that it is designed to protect against all four dengue viruses, also called serotypes. This is especially important because of the way the immune system responds. A person who develops antibodies against one serotype of dengue virus is protected against only that specific serotype. To be fully protected against the four forms of dengue, a person must have antibodies against all four serotypes of the virus. However, having some antibodies to dengue may be worse than having none: Someone who has antibodies against only one or a few of the virus serotypes is actually at higher risk of developing the severe form of the disease upon infection by another serotype. But a person who is immune to all four serotypes cannot be reinfected, and, therefore, is less likely to develop DHF/DSS.

Development of the vaccine was led by Stephen S. Whitehead, Ph.D., and Brian Murphy, M.D., of NIAID's Laboratory of Infectious Diseases. The researchers started by testing seven monovalent vaccines, each of which is designed to protect against a single dengue serotype.

"Our overall strategy was to identify the best individual candidate for each serotype, based on safety and ability to induce an immune response,

and to then combine those into a tetravalent vaccine," explains Dr. Whitehead. To optimize the immune response to each dengue serotype, the researchers are testing three different candidate combinations of the four monovalent vaccines.

In this Phase I trial, study volunteers who have never been exposed to dengue were randomly assigned to receive one of the candidate tetravalent vaccine formulations or a placebo. The candidate vaccines are live-attenuated, or created by making the live virus harmless or less virulent.

Evaluation of a second candidate combination vaccine has been initiated at the University of Vermont in Burlington, and trials of the third candidate will begin shortly thereafter at Johns Hopkins. These early clinical trials are designed to test the vaccine's safety and ability to stimulate immune responses in healthy adults ages 18 to 50. After a baseline assessment, participants will receive one dose of the assigned vaccine or placebo. At follow-up study visits over the next six months, the researchers will assess their health and dengue symptoms and collect blood and urine samples for analysis. After determining which tetravalent vaccine is most promising, the researchers will test that candidate in a trial in a new group of volunteers in Brazil, where dengue has become highly prevalent.

The next stage of testing, a Phase II trial, will involve more participants and will test for differences in preliminary signs of effectiveness between people who have been exposed to dengue and those who have not, as well as the need for a booster shot within a few months of the initial vaccination. "If everything goes well after that stage, we hope to start the final phase of human testing in three to four years," says Dr. Durbin.

More information: clinicaltrials.gov/ct2/show/NC … erm=dengue&state1=NA %3AUS%3AMD&rank=11

Provided by NIH/National Institute of Allergy and Infectious Diseases