

Experimental Respiratory Syncytial Virus Vaccine Prompts Antibody Surge

Structure-based candidate designed by NIAID scientists shows promise in early study.

August 5, 2019 By National Institute of Allergy and Infectious Diseases

A novel experimental vaccine against respiratory syncytial virus (RSV), a leading cause of severe respiratory illness in the very young and the old, has shown early promise in a Phase 1 clinical trial.

The candidate, DS-Cav1, was engineered and developed by researchers at the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, who were guided by their atomic-level understanding of the shape of an RSV protein. An interim analysis of study data showed that one dose of the investigational vaccine prompted large increases in RSV-neutralizing antibodies that were sustained for several months. The findings are [reported in Science](#).

First described in 1956 as a cause of infant pneumonia, the health burden of RSV has long been underappreciated. In fact, the virus is an important contributor to serious illness worldwide and causes as many as 118,000 deaths annually among young children. In the United States each year, RSV infections account for approximately 57,000 hospitalizations and 2 million outpatient clinic visits among children younger than five years old, according to the Centers for Disease Control and Prevention. Among people older than 65, RSV is estimated to cause 14,000 annual deaths in the United States. Globally, a recent large study led by the International Vaccine Access Center found that the virus was responsible for 31% of all cases of severe pneumonia requiring hospitalization in young children in seven low- and middle-income countries.

“A vaccine to prevent RSV is a long-sought goal that has eluded us for decades,” said NIAID Director Anthony S. Fauci, M.D. “The early results of this trial suggest that this structure-based strategy for developing an RSV vaccine may bring that goal within reach.”

The development of DS-Cav1 was spearheaded by NIAID Vaccine Research Center (VRC) scientists Barney S. Graham, MD, PhD, and Peter D. Kwong, PhD, along with Jason McLellan, PhD, a former postdoctoral researcher at VRC who is now at the University of Texas at Austin. Dr. Graham has studied RSV for many years and notes that previous candidate RSV vaccines made with traditional techniques, such as by inactivating the whole virus or by making subunit vaccines without attention to protein conformation, have failed.

“In retrospect,” said Dr. Graham, “many of these failures can be explained by the loss of neutralization-sensitive sites on the fusion glycoprotein that RSV uses to enter cells and begin the infection process. This protein undergoes spontaneous rearrangement and, if not stabilized, the key vaccine targets are lost.”

Structural biology techniques now permit researchers to visualize in minute detail areas of viral proteins, called epitopes, recognized by the immune system. Over several years, Drs. Graham and Kwong and their colleagues have used structural information to develop a candidate RSV vaccine that could stimulate neutralizing antibodies. To do this, they first determined the atomic-level structure of a surface protein, fusion (F) glycoprotein, in its rearranged postfusion and functional prefusion states. The prefusion state displays the epitopes best able to elicit strong-binding neutralizing antibodies, but those epitopes are lost once the F protein changes into the irreversible postfusion shape.

Next, the VRC scientists used structural engineering techniques to stabilize F protein in its prefusion shape. In 2013 they tested several versions as a vaccine in both mice and nonhuman primates. These protein variants elicited high levels of neutralizing antibodies and protected the animals against RSV infection. The most promising, DS-Cav1, was selected for clinical evaluation and subsequently manufactured for clinical testing by the VRC.

“The ability of our multidisciplinary teams to rapidly take a laboratory-based discovery into human clinical testing is one of the unique features of our center,” said VRC Director, John R. Mascola, MD.

The Science report is an interim analysis of data from the first 40 healthy adult volunteers enrolled in the trial, which began in the NIH Clinical Center [in 2017](#). Volunteers received a dose of either 50 or 150 micrograms (μg) of investigational vaccine. Half the volunteers received vaccine with an alum adjuvant (a compound commonly added to vaccines to boost the body’s immune response) and half received unadjuvanted vaccine.

After four weeks, levels of RSV-neutralizing antibodies in those who received 50 μg of vaccine (with or without alum) had increased sevenfold over the levels present prior to vaccination. A single dose of 150 μg without alum boosted neutralizing antibody levels 12-fold, while alum-adjuvanted vaccine at that dose prompted a 15-fold surge in neutralizing antibodies. The vaccine-induced antibody levels greatly exceed those seen following natural RSV infection in human challenge trials (where healthy volunteers are exposed to pathogens under carefully controlled conditions in order to observe the course of infection), when neutralizing antibody levels merely triple over those present before infection.

At 12 weeks after vaccination, neutralizing antibodies remained five- to tenfold above baseline levels in all vaccine dosage groups, the interim analysis showed.

“Compared to previous RSV subunit vaccines, the DS-Cav1 vaccine candidate elicits neutralizing antibodies with a superior functional profile, providing the basis for the next steps in developing an effective vaccine against RSV,” said Dr. Graham. “The clinical data from this trial demonstrate the

feasibility of using information about viral protein structure to rationally design vaccines and represents an important step toward a future of precision vaccines,” he added.

Additional information about the Phase 1 trial of DS-Cav1, VRC 317, is available at clinicaltrials.gov by using the trial identifier [NCT03049488](https://clinicaltrials.gov/ct2/show/study/NCT03049488). Final results of the trial are expected next year.

This [news release](#) was published by the National Institute of Allergy and Infectious Diseases on August 1, 2019.

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