Researchers begin trial of Shigella vaccine candidates

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Researchers have launched an early-stage human clinical trial of two related candidate vaccines to prevent infection with *Shigella*, bacteria that are a significant cause of diarrheal illness, particularly among children. The Phase I clinical trial, funded by the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, will evaluate the vaccines for safety and their ability to induce immune responses among 90 healthy adults ages 18 to 45 years. The trial is being conducted at the Cincinnati Children's Hospital Medical Center, one of the eight NIAID-funded Vaccine and Treatment Evaluation Units in the United States.

Shigella infection, called shigellosis, is an intestinal disease spread via contact with infected feces, by consumption of contaminated food or water or by contact with a contaminated surface. Symptoms include diarrhea, abdominal pain, fever, nausea and vomiting. In healthy adults, the infection generally clears on its own in five to seven days, but if left untreated, can lead to hospitalization or death, especially among young children and adults with weakened immune systems.

According to the World Health Organization, shigellosis causes roughly 90 million cases of severe disease each year and 108,000 deaths, most of which occur in the developing world and affect children under 5 years of age. In the United States, 14,000 shigellosis cases are reported annually, with most cases occurring among children ages 1 to 4 years.

Antibiotics are the standard treatment for patients with shigellosis, but

drug-resistant strains of the bacterium are becoming more common.

"It seems that *Shigella* bacteria know our immune system better than we do," said William Alexander, Ph.D., a program officer in NIAID's Enteric and Hepatic Diseases Branch, Division of Microbiology and Infectious Diseases. "They've become very good at evading the human immune response and causing significant illness, so developing vaccines and better treatments is critical."

Led by principal investigator Robert W. Frenck, Jr., M.D., director of clinical medicine at Cincinnati Children's, the new clinical trial will evaluate two related candidate vaccines, known as WRSs2 and WRSs3, which have been found to be safe and effective when tested in guinea pigs and nonhuman primates. Both target *Shigella* sonnei, one of the bacteria's four subtypes and the cause of most shigellosis outbreaks in developed and newly industrialized countries. Though neither candidate vaccine has been tested in humans, a precursor to both, known as WRSs1, was found to be safe and generated an immune response in small human trials in the United States and Israel. This early work was supported by NIAID, the U.S. Department of Defense and the Walter Reed Army Institute of Research. All three versions of the vaccine were developed by researchers at the Walter Reed institute.

WRSs2 and WRSs3 are live, attenuated vaccines, which means that the bacteria they contain are weakened such that they do not cause illness but still can induce an immune response. The weakened versions of S. sonnei used in WRSs2 and WRSs3 cannot spread between human cells, limiting their ability to cause disease. They are designed to improve upon WRSs1 by reducing the mild diarrhea associated with that vaccine in some patients. In addition, WRSs3 is designed to reduce the fever that accompanied some WRSs1 vaccinations.

After undergoing informed consent, study participants will be split into

10 groups of eight participants each, with each group receiving an increasing dose of WRSs2 or WRSs3. The remaining 10 participants will receive placebo. All doses will be given orally and will be preceded with a sodium bicarbonate (baking soda) suspension to neutralize stomach acid, which prevents the bacteria in the vaccine from being killed too quickly. Immediately after vaccination, participants will be admitted to inpatient care. Eight days later, or sooner if serious shigellosis symptoms occur, participants will begin a course of antibiotics until they pass two consecutive stools that test negative for S. sonnei. During the hospital stay, which can last up to 13 days, participants will be closely monitored and receive physical exams several times daily. Once discharged, participants are expected to collect and supply a stool sample at follow-up physical exams on study days 14, 28 and 56.

More information: Additional information about the clinical trial is available at www.ClinicalTrials.gov under the identifier NCT01336699.

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