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Whole-parasite malaria vaccine shows promise in clinical trial

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For the first time, a malaria vaccine that uses the entire malaria parasite has proven safe and shown promise to produce a strong immune response in a clinical trial, according to a new study co-authored by researchers at the University of Maryland School of Medicine Center for Vaccine Development. The vaccine is unique in that it employs the entire malaria parasite, while most experimental malaria vaccines consist of just one or at most a few proteins found in the parasite. Researchers found that the vaccine— the first whole parasite vaccine to be approved by the U.S. Food & Drug Administration for clinical trials — could provide unprecedented immune responses against malaria when administered intravenously. The study was published online in the journal *Science* this week.

"This is the first whole organism malaria vaccine ever produced," says Kirsten Lyke, M.D., associate professor of medicine and a research scientist at the Center for Vaccine Development at the University of Maryland School of Medicine. Dr. Lyke was one of three lead authors and two senior authors on the study, along with colleagues from the U.S. Military Malaria Vaccine Program at the Naval Medical Research Center, the Vaccine Research Center at the National Institutes of Health (NIH), and the Rockville-based biotechnology firm Sanaria, Inc., which developed and manufactured the vaccine.

"No vaccine has completely protected against malaria in a challenge trial, in which vaccinated volunteers are subjected to the bite of an infected mosquito to measure their immunity," says Dr. Lyke. "This vaccine

showed strong promise. We hope that with further study it could help revolutionize the field and prevent death and illness from malaria worldwide, and be used to eliminate malaria from certain areas."

Though malaria has been largely eliminated in much of the developed world, it is still a widespread threat in warm, tropical areas where infected mosquitoes thrive, such as Africa. Malaria, caused by a parasite transmitted through the bite of an infected mosquito, kills nearly one million people and infects 300 million annually worldwide. The condition can be treated with anti-parasite drugs, but can have fatal consequences for vulnerable patients who have no immunity to the disease. Children under the age of five succumb at high rates to the neurological and cardiac effects of malaria, particularly in Africa.

Researchers found that the vaccine produced a partial protective response in the 80 volunteers who were immunized subcutaneously, or under the skin, by traditional needle and syringe in the trial at the Center for Vaccine Development in Baltimore. However, this response was significantly less than the 80 percent to 90 percent protective immunity the research team is intent on achieving. Researchers suspected that administering the vaccine more directly into the bloodstream, accelerating its path to the liver, might produce an even stronger response. Further study conducted by collaborating authors from the Vaccine Research Center at the NIH found that administering the vaccine intravenously produced a very high level of immune response in animal subjects.

"Our hope is that we can optimize the delivery of this vaccine to prevent and eliminate malaria on a global level," says Dr. Lyke. She and her colleagues are already at work designing new studies to find the best way to administer the vaccine.

Scientists consider a whole parasite vaccine to be the "holy grail" of

malaria vaccine research. Such a vaccine is believed to be more capable of broadly protecting people against the scores of varying strains of malaria. Historically, vaccines are comprised of various proteins found in the virus or, in the case of malaria, the parasite. Recombinant vaccines — those comprised of various components of the parasite — often are narrowly protective against just certain strains. Whole parasite vaccines have seemed unattainable because of the many challenges of large-scale production and preservation of whole parasites, which can only be produced by infecting mosquitoes with malaria-infected blood. Using mosquitoes raised in aseptic conditions, Sanaria Inc. developed a unique large-scale production and cryopreservation process, allowing the parasite to be frozen, shipped to remote locations and safely thawed.

Dr. Lyke collaborated with fellow University of Maryland School of Medicine scientists including Matthew B. Laurens, M.D., M.P.H., assistant professor of pediatrics and medicine, and Christopher Plowe, M.D., professor of medicine, epidemiology and public health and microbiology and immunology and leader of the Malaria Group at the School of Medicine. Dr. Plowe is also a Doris Duke Distinguished Clinical Scientist and an investigator at the Howard Hughes Medical Institute. Robert Edelman, M.D., clinical professor of medicine and pediatrics at the School of Medicine, also contributed to the paper. The group co-authored the study with colleagues from the Howard Hughes Medical Institute, the Walter Reed Army Institute of Research, the PATH Malaria Vaccine Initiative and the biotechnology firm Protein Potential LLC.

The parasite used in the vaccine is a sporozoite, an early life-cycle stage of the parasite Plasmodium falciparum, the most dangerous type of malaria parasite. The sporozoite is carried in the salivary glands of a mosquito, where it infects a human through the mosquito's bite. The sporozoites used in the vaccine were rendered harmless when Sanaria's manufacturing team administered radiation to the mosquitoes carrying

the parasites. The radiation leaves the sporozoites incapable of reproducing and incapable of causing malaria once the human is bitten. Instead, the sporozoite is intended to stimulate the body's immune response, creating immunity to malaria.

Previous studies have shown that the bites of infected, irradiated mosquitoes have the ability to immunize humans against malaria. In fact, previous trials pioneered at the University of Maryland School of Medicine and the U.S. Navy almost 40 years ago showed that 90 percent of humans bitten by at least 1,000 irradiated malaria-carrying mosquitoes did not contract malaria from the bites of ordinary malaria-infected mosquitoes. However, the bite of a mosquito — essentially using a mosquito as a syringe and needle — is not a practical method of administering a vaccine to large groups of people. Sanaria's large-scale production and cryopreservation process creates the potential for the vaccine to be administered globally.

"The University of Maryland School of Medicine and its Center for Vaccine Development have a world-leading malaria research program with a prominent global presence, including in remote areas of Africa where malaria rates are at their worst," says E. Albert Reece, M.D., Ph.D., M.B.A., vice president for medical affairs for the University of Maryland and John Z. and Akiko K. Bowers Distinguished Professor and dean, University of Maryland School of Medicine. "This research is the culmination of decades of study in this field, and brings hope to the millions of people worldwide who face daily threat of malaria."

The study included 98 adult volunteers, 18 of whom served as control volunteers. As a Phase I trial, the study's focus was to establish that the vaccine was safe and well tolerated. The results have guided the design of the next study, a Phase II clinical trial in which scientists will administer the vaccine intravenously to human volunteers and measure immunity to determine the effectiveness of Sanaria's vaccine. Scientists

have traditionally regarded intravenous delivery as an impractical strategy for large-scale global immunization, but Dr. Lyke said the researchers will evaluate its potential in future studies. Other possibilities for administering the vaccine might include novel microneedle injection devices. If these studies continue to show promise, the next step would be to test the whole parasite vaccine's ability to prevent malaria in people naturally exposed to malaria.

"We would love to test this vaccine in Mali," says Dr. Plowe, who leads the Malaria Section at the University of Maryland School of Medicine and has led several malaria vaccine trials in Mali, West Africa. There, his team found that highly variant malaria parasites are difficult to prevent with single-strain, single-protein vaccines. "That will be the real test — does this vaccine have enough immunological firepower to protect against all the different strains circulating in the field, not just the strain the vaccine is based upon? If the whole parasite doesn't work, I don't know what will — this is the best chance we've got."

Provided by University of Maryland Medical Center