First controlled malaria infection trial in Africa paves way for drug and vaccine development

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An international research team today reports the first-ever clinical trial demonstrating controlled malaria infection in an African nation in the modern era. The study, published online in the *American Journal of Tropical Medicine and Hygiene* (*AJTMH*) represents a significant milestone in the search for new malaria drugs and vaccines.

The study establishes that in controlled laboratory conditions in Africa, a new product containing frozen, preserved whole sporozoites, an infectious stage of the malarial parasite *Plasmodium falciparum*, can be used with a syringe to infect volunteers with malaria safely, providing a critical step in malaria research and development. Infected volunteers are later treated for malaria. The clinical trial is also the first of a novel malaria product to be financially supported by the government of Tanzania, through the Tanzania Commission for Science and Technology.

"We are extremely excited by the good results of this malaria challenge test, which opens up unprecedented opportunity for evaluation of new malaria drugs and vaccines in Africa," said Salim Abdullah, PhD, principal investigator of the study and Chief Executive Director of the Ifakara Health Institute (IHI) Bagamoyo Research and Training Centre, Bagamoyo, Tanzania, where the study took place.

Africa suffers the highest burden of malaria deaths in the world. An

estimated 90 percent of the 660,000 annual malaria deaths occur in sub-Saharan Africa, according to the World Health Organization.

The research became possible through a breakthrough technical innovation a decade in the making. Scientists, led by Stephen L. Hoffman, MD, chief executive and scientific officer of the US company Sanaria Inc., in Rockville, Maryland—and a past president of the American Society of Tropical Medicine and Hygiene—developed technology to grow the sporozoites in mosquitoes in the laboratory and then package them in a purified, aseptic form acceptable for human clinical trials. Prior to this innovation, the ability to test or "challenge" a vaccine's effectiveness required deliberately infecting vaccinated volunteers with malaria by exposing them to live infective mosquito bites in a specially constructed insectary. Few such malaria insectaries exist, and due to the resources needed, these are limited to a handful in the United States and Europe, far from the countries where malaria takes its toll.

This clinical trial established, in a controlled laboratory setting, that injecting the skin of volunteers with cryopreserved, aseptic parasites, which were harvested from mosquito salivary glands in compliance with U.S. and international regulatory standards, can safely and effectively infect adult volunteers with *P. falciparum* malaria in a malaria-endemic country.

The procedures used to infect the mosquitoes of the genus Anopheles with parasites cultured in the laboratory require high-security facilities, making such challenge trials logistically difficult and expensive. Building such a facility within Africa would have been prohibitive due to the risk of introducing a new species of mosquito, since the one used in malaria challenge studies globally is not native to Africa. By avoiding live mosquitoes, the research team avoided public health concerns about new mosquito introduction.

"This innovation is a game-changer for malaria research and development in Africa," said Hoffman. "This is about making available within Africa the same research tools to study malaria that we have in the USA and Europe. The IHI has now established that they can be equal partners with any clinical trial center anywhere in the world to do these first-in-humans, Phase 1 types of trials."

In an editorial accompanying the study's publication, a malaria vaccine researcher at Griffith University in Australia, Michael Good, MD, PhD, stated these benefits. "By challenging an individual in early-stage trials with a defined number of parasites of a specific laboratory strain in a controlled clinical environment, it is possible to derive more meaningful data and significantly reduce trial costs, thus facilitating product development," he said.

Good also said that there may be work still to be done to further optimize this approach to inducing malaria infection in humans, noting that sporozoites administered by mosquito bites appear to be significantly more infective than cryopreserved ones via syringe. He points toward intravenous injections as an alternate strategy to explore. "However," he concludes, "the technological significance of these developments to date cannot be overstated."

Methodology

In the current study, which took place between February and August 2012, the researchers recruited a group of 30 highly educated Tanzanian men, residents of Dar es Salaam, who had minimal exposure to malaria during the previous five years. The study was double-blind to eliminate bias from scientists and participants about which persons were administered PfSPZ Challenge and which were administered a harmless saline solution.

The scientists compared the infection rate to that of a similar group of Dutch volunteers who participated in a similar study in the Netherlands in 2011. After about two weeks, all but two of the 23 Tanzanian volunteers injected with live sporozoites developed active infections, a rate similar to the Dutch volunteers. Once active infection was established, volunteers were immediately treated for malaria and cleared of parasites. None of the volunteers developed serious side effects related to the study. Mild side effects included low-grade fever, headaches and fatigue.

"For Ifakara Health Institute, this collaboration has opened up new possibilities for attracting international product development partners while increasing our own national capacity to conduct even more sophisticated clinical studies and laboratory research," said Abdullah. In addition, he added, research groups in other African nations are already getting involved, with one additional PfSPZ Challenge study completed in Kenya and others being planned.

"This is a real step forward for developing a vaccine against malaria—which has killed more human beings throughout history than any other single cause, " said Christopher Plowe, MD, MPH, professor of medicine at the University of Maryland, president-elect of the American Society of Tropical Medicine and Hygiene, and one of the study authors. "The ability to safely administer malaria parasites by injection rather than by mosquito bite makes it possible to test new malaria vaccines as well as drugs anywhere in the world. This is exactly the kind of new tool needed to eliminate malaria that is made possible by public-private partnerships and the continued investment in science and innovation by the U.S. and other partners."

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