

FEBRUARY 04, 2010

New Vaccine Shows Promise Against Malaria in Early-Stage Study

The Life cycle of Malaria Part 1: Human Host When a malaria-carrying mosquito bites a human host, the malaria parasite enters the bloodstream, multiplies in the liver cells, and is then released back into the bloodstream, where it infects and destroys red blood cells.

A new vaccine tested in 100 West African children triggers the immune system to produce antibodies against the malaria parasite at levels normally seen only in adults who have strong resistance to the disease.

“We may have achieved our goal of producing with a vaccine a level of immunity that normally takes many years to develop,” said Christopher V. Plowe, a Howard Hughes Medical Institute (HHMI) investigator at the University of Maryland School of Medicine in Baltimore.

Based on its safety and strong immune response, Plowe and his collaborators are now testing the vaccine in 400 children to see whether it is effective in protecting them against malaria. The results will be submitted for publication later this year.

Plowe and a group of U.S. and Belgian collaborators from the Walter Reed Army Institute of Research, USAID and GlaxoSmithKline Biologicals have been developing and testing the vaccine with a large team of researchers led by Professors Ogobara K. Doumbo and Mahamadou A. Thera at the University of Bamako in Mali. The results of their phase I randomized controlled trial were published online in the February 4, 2010, issue of *PLoS ONE*, a journal of the Public Library of Science.

"The antibody levels that the vaccinated children achieved were as high or higher than those measured in adults whose lifelong exposure to malaria protects them against the disease."

- Christopher V. Plowe

The malaria parasite, *Plasmodium falciparum*, is transmitted to humans by infected mosquitoes. When the mosquito bites, the parasite enters a person's bloodstream and migrates to the liver. Inside liver cells, the parasite multiplies and takes on a new form, called a merozoite, which is capable of infecting red blood cells. The clinical symptoms of malaria -- typically chills and fever -- occur as the merozoites burst from infected blood cells to infect other red blood cells and repeat the cycle.

Children in countries where malaria is endemic are particularly susceptible to the disease because they have not built up the levels of immunity found in adults who live in the same regions. More than 300 million cases of malaria occur each year, leading to more than one million deaths. More than 80 percent of those deaths occur among African children younger than age five. No approved vaccine is available to protect against the disease. Medications are available to treat malaria, but resistance to these drugs is a common problem that is worsening.

Plowe and his colleagues tested a vaccine that targets a molecule on the malaria parasite known as apical membrane antigen 1 (AMA1). The molecule sits on the surface of the merozoite form of the parasite and helps it invade red blood cells. The human immune system recognizes the presence of AMA1 molecules and generates antibodies that prevent invasion of red blood cells by the merozoites. But the body generates antibodies only after repeated exposure to malaria. If researchers could develop a vaccine that primes the immune system to recognize AMA1 before malaria infection occurs, it would be a major advance in the effort to control and eventually eradicate the disease.

In the trial, 100 healthy Malian children received either the vaccine or, as a control, a rabies vaccine. Some of the children experienced temporary pain and swelling at the site of the injections, but the effects were generally "well-tolerated," according to Plowe.

Prior to receiving the vaccine, the children in the trial had only low levels of antibodies against AMA1 in their blood. Those antibody levels increased more than 100-fold in the children receiving the malaria vaccine and remained high during a year of follow-up blood tests. "The antibody levels

that the vaccinated children achieved were as high or higher than those measured in adults whose lifelong exposure to malaria protects them against the disease,” said Plowe.

The study was funded by the National Institute of Allergy and Infectious Diseases and the United States Agency for International Development. The vaccine was invented and manufactured by the Walter Reed Army Institute of Research and formulated with an adjuvant -- a compound that boosts the immune response to the vaccine -- from GlaxoSmithKline Biologicals.

Based on its safety profile and strong immune response, Plowe and his U.S. and Malian collaborators are now testing the vaccine in 400 children. The results of the larger trial will shed light on a key uncertainty surrounding malaria vaccines. The AMA1 molecule occurs in many different forms both within Africa and around the world, and a vaccine against some forms of the molecule may not protect against other forms. “We want to know whether this vaccine, which is based on a single strain of the malaria parasite, can protect against the diverse array of wild parasites,” said Plowe.

Even if one vaccine does not protect against all strains of the parasite, a combination of vaccines could improve protection, Plowe adds. “If our next trial shows even partial protection, it would open the possibility that this vaccine can be combined with other vaccines to produce a next-generation, multi-component vaccine that is broadly protective,” said Plowe.