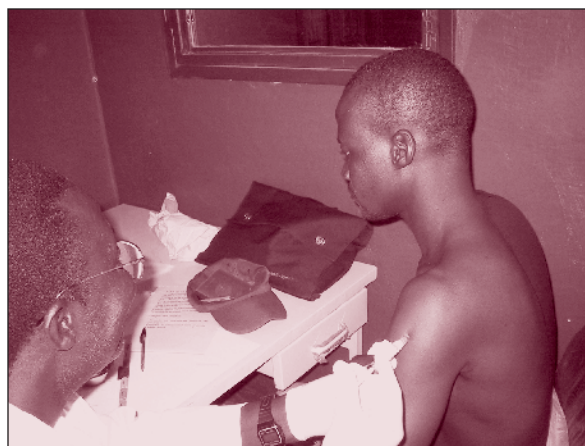


MALARIA

Malaria, a serious disease caused by parasites of the genus *Plasmodium* and transmitted by mosquitoes, continues to pose a tremendous public health burden for people living in the tropics, particularly in Africa. Globally, malaria causes more than 1 million deaths each year and continues to be the most important tropical parasitic disease in terms of annual mortality.⁴² Approximately 80 percent of malaria deaths worldwide occur in Africa south of the Sahara, with the majority of deaths occurring in children aged 5 years and younger.⁴³ Unfortunately, malaria parasites have developed a variety of mechanisms to resist the action of antimalarial drugs and to evade host immune responses, and the mosquitoes responsible for transmission of malaria parasites have similarly developed resistance to insecticides. Together, these factors make the sustained control of malaria technically very challenging.

Malaria research at the NIH dates back to the 1930s, when malaria was still a major public health problem in the United States. NIAID maintains a broad malaria research portfolio that includes parasite biology, pathogenesis, drug development, vaccine development, epidemiology, and vector biology. NIAID-funded malaria research is conducted by scientists at institutions throughout the United States, including NIAID intramural laboratories, and overseas.

NIAID's intramural malaria vaccine research program is centered in the Malaria Vaccine Development Branch (MVDB). The MVDB collaborates with investigators within the United States and throughout the world, as well as with the extramural NIH malaria program and a variety of funding organizations such as the U.S. Agency for International Development and the Malaria Vaccine Initiative at the Program for Appropriate Technology in Health (PATH). The MVDB has produced multiple vaccine components using the quality control practices required for manufacturing clinical materials.



Malaria Vaccine. First volunteer in NIAID-supported malaria vaccine trial in Mali.

Two of these have been combined into a vaccine called AMA1-C1, which was well tolerated in a phase I trial in U.S. adults and further tested in a phase I study in adults in Mali, marking the first time that MVDB products have been tested in a malaria endemic area. MVDB researchers are working to improve the immunogenicity of this formulation and to broaden the reactivity of anti-AMA1 antibody response. In addition, they have completed the preclinical studies for two other vaccine candidates and have initiated a phase I clinical trial in U.S. adults as a prelude to anticipated future studies in an endemic area in African children who desperately need a malarial vaccine to reduce disease and death. A vaccine trial for efficacy will be performed in African children, the target population who most need the vaccine. The MVDB is also developing vaccines aimed at eliminating *Plasmodium falciparum* and *Plasmodium vivax* from regions of Asia and Latin America.

Intramural investigators also are conducting basic studies aimed at providing fundamental biological information for the development of diagnostics, therapeutics, and other control measures against the disease. For example, Division of Intramural Research scientists are using the malaria parasite genome databases and microarray analysis to identify genes that might be involved in drug resistance and parasite sexual development.

Identifying these genes is an important step in developing measures to interrupt parasite transmission, and will provide critical information for drug and vaccine development.

In 2005, NIAID researchers advanced understanding of the factors that affect the severity of malaria through their discovery of the mechanism by which hemoglobin C protects children from severe and fatal complications of *P. falciparum* malaria. Along with a team of international collaborators, they found that hemoglobin C alters red blood cells so that the malaria parasites have trouble placing a protein called PfEMP-1 in knob-like protrusions at the cell surface. This makes the cells less able to adhere to blood vessels, which causes the inflammation and circulatory obstruction seen in severe disease. Other hemoglobin variants, such as the sickle-cell mutation, might protect against malaria by a similar mechanism. These findings suggest that interventions affecting the display of this protein could reduce the impact of malaria.

Through its extramural malaria research program, NIAID also supports extensive research on malaria vaccines conducted by researchers from academia and industry. The Institute currently funds multiple studies aimed at developing vaccines against different stages of the malaria parasite and has conducted clinical trials of the most promising candidates in the United States and abroad. These research efforts represent a critical component of NIAID's Research Plan for Malaria Vaccine Development, which is designed to accelerate research leading to the development of malaria vaccines. Under a contract with Science Applications International Corporation, NIAID established a capability to undertake targeted research essential to translating basic research concepts into prototype vaccine products for clinical evaluation. Recent activities included process development for production of novel candidate vaccines, production and qualification of critical reagents for quality control of new candidate vaccines, and preclinical safety

evaluation of promising candidate vaccines prior to entry into clinical trials. Reagents were also provided to the Malaria Research and Reference Reagent Resource, which will make them available to the international malaria research community.

NIAID has undertaken a phase I trial of a novel candidate malaria vaccine at the University of Maryland Center for Vaccine Development. This vaccine was developed with grant support from the Small Business Innovation Research Program administered at NIAID, with additional support and collaboration from the Malaria Vaccine Initiative at PATH. Results of this trial are expected to be available late 2006. Additional clinical trials of promising vaccine candidates are planned through NIAID's Vaccine and Treatment Evaluation Units.

A key component of NIAID's Research Plan for Malaria Vaccine Development has been the establishment of research centers in malaria-endemic areas that can support epidemiological and clinical research relevant to malaria, as well as conduct clinical trials. In collaboration with the Walter Reed Army Institute of Research, the University of Maryland Center for Vaccine Development, and the University of Bamako (in Mali), NIAID has now completed two trials of novel candidate malaria vaccines in Mali. Additional clinical trials of candidate malaria vaccines are scheduled for Mali and Ghana in 2006.

Identification, validation, and evaluation of new antimalarial therapies remain NIAID priority activities. In 2004, NIAID issued a renewal of the Tropical Diseases Research Units (TDRU) program. The objective of the TDRU program is to support translational research leading to the discovery and preclinical development of new drugs and vector control methods to reduce or eliminate morbidity and mortality resulting from parasitic infection. One of the three new awards made under this program

focuses on development of novel antimalarials. The Challenge Grants and Partnerships Program has funded requests for applications for collaborations with private companies for the development of new compounds and strategies for malaria treatment and mosquito control. These initiatives currently support studies aimed at the screening and validation of novel classes of anti-mosquito candidates, exploring the use of larval control strategies in certain areas in Africa, mitigating insecticide resistance, and developing new environmentally safe insecticides to kill mosquitoes. NIAID also supported a phase I clinical trial of a chloroquine analog effective against chloroquine resistant *P. falciparum*, as well as investigator-initiated research on preclinical development and evaluation of novel compounds. The Institute also supports preclinical and clinical studies of combination therapies for malaria, especially those including artesunate, and works with other groups (such as the U.S. Food and Drug Administration and the nonprofit organization, Medicines for Malaria Venture) to develop a consensus on the design of clinical trials of artemisinin-containing antimalarial drug regimens.

Clinical research capacity continues to be strengthened in overseas sites in Africa with support through the “Malaria Vaccines: Clinical Research and Trial Sites in Endemic Areas” contract and through grants awarded through the International Collaborations in Infectious Disease Research program. Research staff members continue to participate in training in epidemiology, bioethics, good clinical practice, good laboratory practice, and financial

management. Clinical facilities, research and clinical safety laboratories, and satellite Internet connectivity have been established or expanded.

NIAID also continues to participate in the Federal Malaria Vaccine Coordinating Committee and provides support to the Multilateral Initiative on Malaria and the World Health Organization Special Programme for Research and Training in Tropical Diseases Task Force to advance malaria research and research capacity-strengthening activities at African institutions. Moreover, NIAID participates in the Malaria Vaccine Advisory Committee established at the World Health Organization Initiative for Vaccine Research and in the External Scientific Advisory Committee of the Medicines for Malaria Venture, a public-private partnership that fosters the accelerated development of new antimalarial compounds. In addition, NIAID has worked with the European Commission, the European Malaria Vaccine Initiative, and the European-Developing Countries Clinical Trial Partnership to coordinate product development and clinical trial activities in vaccines and drugs.

In addition to the targeted activities listed above, malaria-related research and training activities are supported under a number of other programs, such as the TDRUs, International Centers for Tropical Diseases Research Network, U.S.–Japan Cooperative Medical Science Program, Indo–U.S. Vaccine Action Program, and Clinical Research and Training Opportunities. Additional information is available at www.niaid.nih.gov/ictdr/tдру.htm.