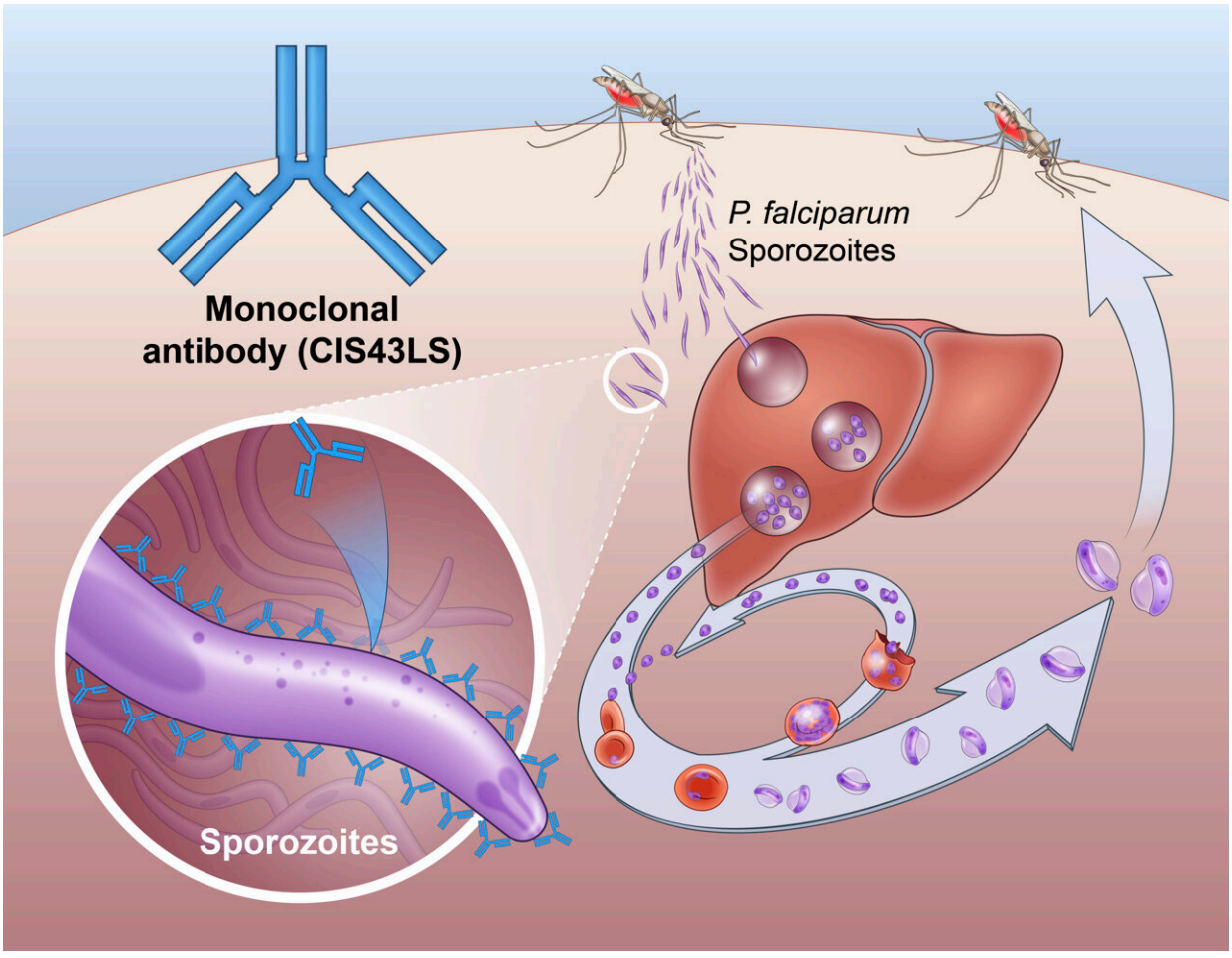
Monoclonal antibody prevents malaria infection in African adults

October 31 2022



An antibody drug called CIS43LS prevents malaria infection by interrupting the lifecycle of the Plasmodium falciparum parasite. The antibody binds to and neutralizes sporozoites, the stage of the parasite transmitted from mosquitos to humans. Credit: NIH

One dose of an antibody drug safely protected healthy, non-pregnant adults from malaria infection during an intense six-month malaria season in Mali, Africa, a National Institutes of Health clinical trial has found. The antibody was up to 88.2% effective at preventing infection over a 24-week period, demonstrating for the first time that a monoclonal antibody can prevent malaria infection in an endemic region. These findings were published today in *The New England Journal of Medicine* and presented at the American Society of Tropical Medicine & Hygiene 2022 Annual Meeting in Seattle.

"We need to expand the arsenal of available interventions to prevent malaria infection and accelerate efforts to eliminate the disease," said Anthony S. Fauci, M.D., director of the National Institute of Allergy and Infectious Diseases (NIAID), part of NIH. "These study results suggest that a monoclonal antibody could potentially complement other measures to protect travelers and vulnerable groups such as infants, children, and pregnant women from seasonal malaria and help eliminate malaria from defined geographical areas."

The trial was led by Peter D. Crompton, M.D., M.P.H., and Kassoum Kayentao, M.D., M.P.H., Ph.D. Dr. Crompton is chief of the Malaria Infection Biology and Immunity Section in the NIAID Laboratory of Immunogenetics, and Dr. Kayentao is a professor at the University of Sciences, Techniques and Technologies (USTTB) of Bamako, Mali.

An estimated 241 million cases of malaria occurred worldwide in 2020, according to the World Health Organization (WHO), resulting in an estimated 627,000 deaths, mostly in children in sub-Saharan Africa. These cases included more than 11 million pregnant women in Africa, resulting in an estimated 819,000 newborns with low birthweight and thus at increased risk for illness and death.

The only malaria vaccine currently recommended by WHO, called

RTS,S (Mosquirix), provides partial protection against clinical malaria during the early years of life when given to children aged 5 to 17 months in four doses over a 20-month period. Other drugs consisting of small chemical compounds that effectively prevent malaria infection are also available for infants and young children as well as travelers. The requirement for frequent dosing of these drugs can limit adherence, however, and the emergence of drug resistance may also limit their usefulness. Thus, there is an urgent need for new, fast-acting, infrequently-dosed interventions that safely provide strong protection against malaria infection.

Malaria is caused by Plasmodium parasites, which are transmitted to people through the bite of an infected mosquito. The mosquito injects the parasites in a form called sporozoites into the skin and bloodstream. These travel to the liver, where they mature and multiply. Then the mature parasite spreads throughout the body via the bloodstream to cause illness. P. falciparum is the Plasmodium species most likely to result in severe malaria infections, which—if not promptly treated—may lead to death.

The Phase 2 NIAID-USTTB trial evaluated the safety and efficacy of a one-time, intravenous infusion of a monoclonal antibody called CIS43LS. This antibody was previously shown to neutralize the sporozoites of P. falciparum in the skin and blood before they could infect liver cells. Researchers led by Robert A. Seder, M.D., isolated a naturally occurring form of this antibody from the blood of a volunteer who had received an investigational malaria vaccine, and then modified the antibody to extend the length of time it would remain in the bloodstream. Dr. Seder is the acting chief medical officer and acting associate director of the NIAID Vaccine Research Center (VRC) and chief of the VRC's Cellular Immunology Section.

The study team for the Phase 2 trial enrolled 369 healthy, non-pregnant

adults aged 18 to 55 years in the rural communities of Kalifabougou and Torodo in Mali, where intense P. falciparum transmission typically occurs from July through December each year.

The first part of the trial assessed the safety of three different doses of CIS43LS—5 milligrams per kilogram of body weight, 10 mg/kg and 40 mg/kg—administered by intravenous infusion in 18 study participants, with six participants per dose level. The study team followed these participants for 24 weeks and found the antibody infusions were safe and well-tolerated.

The second part of the trial assessed the efficacy of two different doses of CIS43LS compared to a placebo. Three hundred and thirty participants were assigned at random to receive either 10 mg/kg of the antibody, 40 mg/kg, or a placebo by intravenous infusion. No one knew who was assigned to which group until the end of the trial. The study team followed these individuals for 24 weeks, testing their blood for P. falciparum weekly for the first 28 days and every two weeks thereafter. Any participant who developed symptomatic malaria during the trial received standard treatment from the study team.

The investigators analyzed the efficacy of CIS43LS two ways. Based on the time to first P. falciparum infection over the 24-week study period, the high dose (40 mg/kg) of CIS43LS was 88.2% effective at preventing infection and the lower dose (10 mg/kg) was 75% effective. An analysis of the proportion of participants infected with P. falciparum at any time over the 24-week study period found the high dose was 76.7% at preventing infection and the lower dose was 54.2% effective.

"These first field results demonstrating that a monoclonal antibody safely provides high-level protection against intense malaria transmission in healthy adults pave the way for further studies to determine if such an intervention can prevent malaria infection in infants, children, and

pregnant women," Dr. Seder said. "We hope monoclonal antibodies will transform malaria prevention in endemic regions."

Dr. Seder and colleagues have developed a second antimalarial monoclonal antibody, L9LS, that is much more potent than CIS43LS and therefore can be administered in a smaller dose as an injection under the skin (subcutaneously), rather than by intravenous infusion. An early-phase NIAID trial of L9LS in the United States found that the antibody was safe and prevented malaria infection for 21 days in 15 out of 17 healthy adults exposed to P. falciparum in a carefully controlled setting. Two larger, NIAID-sponsored Phase 2 trials assessing the safety and efficacy of L9LS in infants, children and adults are underway in Mali and Kenya.

More information: Kassoum Kayentao. Testing the safety and efficacy of anti-malaria monoclonal antibodies in African adults and children. Session 41—Progress in the discovery and clinical development of anti-malaria monoclonal antibodies. ASTMH 2022 Annual Meeting, Seattle. Monday, Oct. 31, 2022. 5:40 pm Pacific Time.

Kassoum Kayentao et al, Safety and efficacy of a monoclonal antibody against malaria in Mali. *The New England Journal of Medicine* DOI: 10.1056/NEJMoa2206966 (2022).

R.L. Wu et al, Low-dose subcutaneous or intravenous monoclonal antibody to prevent malaria. *The New England Journal of Medicine* DOI: 10.1056/NEJMoa2203067 (2022).

Provided by NIH/National Institute of Allergy and Infectious Diseases