Two experimental malaria vaccines show promise, with one slowing replication of active parasites in the bloodstream

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Two experimental malaria vaccines are not only safe for humans, one of those immunizations prompted a slowing of the malaria parasite's replication in the bloodstream of clinical trial participants, scientists

have found in early studies involving both shots.

Because the two vaccines were tested in Phase 1 clinical trials, more research is needed to fully understand these immunizations and the human immune response. Excitement has already begun to pervade the malaria research community, however. If the vaccines perform in future clinical research as they have in early pilot analyses, the two experimental vaccines eventually could be developed into approved inoculations. Both vaccines were aimed at preventing infection with Plasmodium vivax, one of the major species of malaria parasites.

Malaria is a parasitic infection caused by any one of four protozoan species of the genus Plasmodium. In addition to P. vivax, the other three are P. falciparum, P. ovale and P. malariae. Each is exclusively transmitted by the bite of the female Anopheles mosquito, a stealthy nighttime flyer that is most active between the hours of 10 p.m. and 4 a.m. Anopheles mosquitoes tend to attack when people are asleep.

Female mosquitoes need blood to develop their eggs, and when it bites, the malaria parasite readily flows from the mosquito's saliva into the victim's blood. Malaria is marked by a soaring fever, sweats chills, muscle aches, headache and anemia. For some people, especially children under five, it can be lethal.

"Plasmodium vivax is the second most common cause of malaria and the most geographically widespread, causing an estimated 4.5 million cases in 2020," writes Mimi Hou, lead author of the vaccine research. She is a pediatric clinical fellow at the University of Oxford in the U.K.

P. vivax is a noteworthy cause of malaria because it's more difficult to control than P. falciparum, the most common malaria parasite, and the one that pervades the African continent. P. vivax can lie dormant in the liver before becoming revived to re-infect the blood.

Writing in the journal *Science Translational Medicine*, Hou and colleagues explain that they designed their clinical research to test the experimental vaccines, VAC071 and VAC079, each of which addressed different stages of the parasite's life cycle. Both induced immunity by targeting the P. vivax Duffy binding protein, or PvDBP.

Duffy glycoproteins stipple the surface of red blood cells and are highly complex receptor sites. Normally, these glycoproteins act as receptors for cytokines released during inflammation. But P. vivax exploits these receptors, using them as ports of entry and setting the stage for an infection.

In the parallel studies, the vaccines were well-tolerated, and the vaccinated volunteers showed evidence of antibody responses. To get a solid understanding of the vaccines' effectiveness, trial participants were hospitalized and infected with P. vivax under controlled conditions. The team measured parasite growth in the blood of 19 vaccine recipients.

Although the pandemic caused an interruption in the research project in 2020, COVID didn't derail it and the research resumed in 2021. Investigators found that when given by way of a delayed dosing regimen, one of the vaccines also reduced the multiplication rate of P. vivax by 51%.

P. vivax is responsible for 42% of all cases of malaria outside of Africa, according to the U.S. National Institutes of Health, which notes that the species is found in both tropical and subtropical latitudes in Asia, Oceania and the Americas. The species was also responsible for several rare, locally acquired malaria infections this year in Florida and Texas.

In 2020, the most recent year for complete statistics, 241 million episodes of malaria caused by all four parasite species were recorded, and 627,000 deaths were reported worldwide, according to the U.S.

Centers for Disease Control and Prevention. Of these, 95% were in Africa.

Malaria is a challenging disease because the hardy, infectious parasites are capable of thriving in two staggeringly different hosts—female mosquitoes and humans. Despite the difference between these hosts, the parasites are able to complete a complex, multi-stage life cycle by finding safe harbor in each of them.

The three stages of parasite development are the ookinete, which occurs in the gut of the mosquito; the sporozoite the more mature form that is released in mosquito saliva when it bites, and the merozoite, the stage of the parasite that evolves in the human liver. But while that basically explains the life cycle for most forms of malaria parasites, including the often lethal P. falciparum, it doesn't completely explain infection with P. vivax, which has an additional life-cycle stage.

"Control of P. vivax is more challenging than Plasmodium falciparum due to several factors," writes Hou. "These include the ability of P. vivax to form dormant liver-stage hypnozoites that can reactivate and lead to relapsing blood-stage parasitemia and earlier production of gametocytes in the blood stage, resulting in more rapid transmission."

Clinical testing of the two experimental P. vivax vaccines arrives as Ghana became the first country in April to approve another University of Oxford malaria vaccine called R21, developed to prevent infection with P. falciparum. The pediatric vaccine is for children between the ages of five months and three years.

In the current P. vivax vaccine research, the shots used to immunize volunteers, were based on 10-year-old formulas, but the team contends that targeting the Duffy glycoprotein can be done using newer vaccine approaches, such as a customized mRNA platform to deliver the vaccine

payload.

Even with dreams of a possible future method of vaccine delivery, the clinical trial suggests the old-school methods got the job done. "No safety concerns were identified with the viral-vectored or protein-in-adjuvant vaccines, and no serious adverse events occurred in the VAC071 and VAC079 trials," Hou concluded.

More information: Mimi M. Hou et al, Vaccination with Plasmodium vivax Duffy-binding protein inhibits parasite growth during controlled human malaria infection, *Science Translational Medicine* (2023). DOI: 10.1126/scitranslmed.adf1782