A doctor shows antimalarial drugs to a mother and son in Mali.

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RESISTANCE TO KEY MALARIA DRUGS CONFIRMED IN AFRICA

Artemisinin-based treatments are taking longer to clear infections. But they are still working — for now.

By Max Kozlov

Scientists have confirmed that malaria parasites in Africa have developed resistance to a key family of drugs used to protect against them.

"We've all been expecting and dreading this for quite some time," says Leann Tilley, a biochemist at the University of Melbourne in Australia, who researches the molecular basis of antimalarial resistance.

Signs of drug resistance have long been present in Africa: for instance, in Rwanda between 2012 and 2015, scientists detected[1] the existence of gene mutations associated with resistance in malaria parasites. A study published in *The New England Journal of Medicine* on 23 September[2] bolsters these findings by showing that such mutations are causing an observable drop in antimalarials' ability to quickly treat people with the disease.

The 'gold standard' treatments for malaria — the drug family including artemisinin and its derivatives — are often administered alongside 'partner' drugs in what are called artemisinin-combination therapies (ACTs), because it is more difficult for parasites to develop resistance against multiple drugs.

The first signs of resistance to artemisinin and its relatives appeared in Cambodia in the early 2000s. Within a few years, malaria parasites in southeast Asia began to evade some of the partner drugs in the ACTs, too, rendering some of the most effective drug cocktails against malaria useless in the region and sending public-health officials scrambling to find combinations that still worked.

For resistance to now hit Africa is particularly dire, says Tilley. More than 90% of malaria cases and deaths worldwide occur on the continent. It is also a concern that the study found evidence that resistance in Africa arose independently of the resistant parasite strains in southeast Asia, meaning the strains now in Africa might continue evolving, to culminate in a 'super resistant' parasite that becomes dominant, she says.

In the study, conducted in Uganda from 2017 to 2019, researchers treated 240 people who had malaria by giving them intravenous artesunate, a potent derivative of artemisinin, three times over one day, followed by a standard three-day course of ACT pills. Doctors typically administer artemisinins without partner drugs only to people with severe malaria.

The team found that, for 14 participants, it took longer than 5 hours to clear half of their malaria-causing parasites (*Plasmodium falciparum*), which meets the World Health Organization (WHO) definition for resistance. (People with malaria usually clear half the parasites within a couple hours of treatment with artesunate.) Parasites in 13 of these participants had one of two concerning mutations in their *kelch13* gene, which has been linked with antimalarial resistance in southeast Asia[3].

Although the mutations had already been detected in malaria parasites in Africa, "we didn't know if these parasites were actually resistant to drugs in humans", says Toshihiro Mita, a parasitologist at Juntendo University in Tokyo, and a co-author of the study. This investigation, and one published in April[4] in *The Lancet Infectious Diseases*, confirmed scientists' suspicions.

The April study reported the results of a three-day course of ACT pills in children with malaria in Rwanda. Some of the children still had parasites after completing the treatment, and more than 10% of the parasites had one of two *kelch13* mutations that are indicative of resistance, but are different from those observed in Uganda.

'A major wake-up call'

For now, there appear to be few clinical consequences of the artemisinin resistance, explains Philip Rosenthal, an infectious-disease clinician at the University of California, San Francisco, who works with the WHO to study malaria in Uganda. The parasites take longer to clear in some severe cases, and they might return within a week or so, but the ACT of choice in much of sub-Saharan Africa — a combination of artemether, another derivative of artemisinin, and a partner drug called lumefantrine — seems to still be effective.

Nonetheless, Rosenthal says the findings are a "major wake-up call": if resistance continues to spread, as it is expected to, and the parasites become resistant to lumefantrine, the result could be disastrous. "In Africa, where huge numbers of young children are treated in rural clinics with very little infrastructure, losing your main drug could be really devastating," he says.

This study puts even more pressure on researchers and drug makers to find another viable treatment or a vaccine for malaria, in case there is more evidence that ACTs are failing in the future, says Pascal Ringwald, who leads the WHO Global Malaria Program's Drug Resistance and Containment Unit. "I expect to see many more reports of artemisinin-resistant strains in the next few years," says Ringwald, "because they're already popping up like mushrooms."

1. Uwimana, A. *et al. Nature Med.* **26**, 1602–1608 (2020).
2. Balikagala, B. *et al. N. Engl. J. Med.* **385**, 1163–1171 (2021).
3. Ariey, F. *et al. Nature* **505**, 50–55 (2014).
4. Uwimana, A. *et al. Lancet Infect. Dis.* **21**, 1120–1128 (2021).