First clinical evidence of drug-resistant malaria mutations gaining

April 15 2021

Credit: CC0 Public Domain

New data provide the first clinical evidence that drug-resistant mutations in the malaria parasite Plasmodium falciparum may be gaining a foothold in Africa. The study, conducted in Rwanda, is published in *The*

Lancet Infectious Diseases journal and finds for the first time that the mutations are associated with delayed parasite clearance, as was first shown in South-East Asia when artemisinin-resistance started to emerge.

The study also finds that the mutations are more prevalent than previous studies have reported, indicating likely transmission of the mutations, and raising concern about further geographical spread of resistance.

There are an estimated 229 million cases of malaria worldwide, and there were 409,000 deaths from malaria in 2019—of which 274,000 (67%) were among children under 5 years. 94% of all malaria cases and deaths occur in Africa, and experts have long been concerned about the potential emergence of drug resistance across the continent. While the efficacy of current therapies remains high, the authors call for more intensive surveillance in Rwanda as well as neighbouring countries to help monitor the spread of mutations and inform public health actions.

"Mutations can emerge spontaneously, and previous studies have pointed to isolated cases of resistance. However, our new study shows that resistant isolates are starting to become more common and most importantly, are associated with clinical implications (delayed parasite clearance)," says lead author Dr. Aline Uwimana, Rwanda Biomedical Centre, Kigali, Rwanda.

Co-author Dr. Naomi Lucchi, CDC Resident Advisor for the U.S. President's Malaria Initiative adds: "our study showed that the treatment for malaria in Rwanda is still 94% effective, but new studies and ongoing monitoring are urgently needed."

Artemisinin-based combination therapies (ACTs), introduced in the early 2000s, are currently the most effective and widely used treatments for malaria caused by Plasmodium falciparum. ACTs combine an

artemisinin component that clears most of the parasites from the patient's body within three days, and a long-acting partner drug that clears the remaining parasites.

Resistance to the artemisinin component of an ACT is suspected if the presence of the parasite remains after day three of treatment (called delayed parasite clearance). This drug resistance is associated with parasites carrying mutations in the Plasmodium falciparum kelch 13 gene (pfk13). Currently, ten mutations in pfk13 have been confirmed as markers of artemisinin partial resistance (including R561H, P574L and C580Y), and several other mutations (referred to as candidate markers) have been identified as potentially associated with resistance.

Partial artemisinin resistance was first identified in Cambodia in 2008. It is now well-documented in many South East Asian countries, where the C580Y mutation is common. Evidence from the Mekong region has shown that once artemisinin resistance becomes prevalent, resistance to the partner drug often follows, resulting in ACT treatment failure.

In 2006, Rwanda introduced artemether-lumefantrine (an ACT, and the most widely used antimalarial) as the first-line treatment for malaria. The World Health Organization recommends therapeutic efficacy studies at least every two years for monitoring the efficacy of ACTs and the tracking of resistance through molecular markers. When ACT efficacy is confirmed to be below 90%, replacement with an effective antimalarial is recommended.

One such study was performed in Rwanda among children aged 1-14 years in 2013-2015 in Ruhuha and Masaka. The R561H mutation was observed in 7.4% of P. falciparum parasites collected in Masaka, and a low prevalence of the P574L mutation was reported in isolates collected in Masaka and Ruhuha in 2013-2015 and in Huye in 2015. However, the presence of these mutations was not found to be associated with delayed

parasite clearance and the therapeutic efficacy of ACT was confirmed at over 97% in both sites.

In 2018, another therapeutic efficacy study was conducted, the results of which are reported in this new article. The pfk13 R561H and P574L mutations were present in 12.8% (28/218) and 0.9% (2/218) of pre-treatment samples, respectively. For the first time, this study shows that the pfk13 R561H mutation was associated with delayed parasite clearance, although the efficacy of artemether-lumefantrine remained high. Genetic analysis of pfk13 R561H mutants indicated their common ancestry and local origin in Rwanda.

The study was conducted across three sites in Rwanda (Masaka, Rukara, and Bugarama). 224 children aged between 6 months and 5 years who had a P. falciparum infection were treated with a three-day course of artemether-lumefantrine and monitored for 28 days, with weekly blood collections. 8/51 (15.7%) participants in Masaka and 12/82 (14.6%) in Rukara had detectable parasites three days post treatment, according to WHO criteria for partial resistance. The therapeutic efficacy was estimated at 94-97%.

Writing in a linked Comment, Professor Philip Rosenthal, University of California, San Francisco, U.S. (who was not involved in the study), says: "Recent data suggest that we are on the verge of clinically meaningful artemisinin resistance in Africa, as emerged in Southeast Asia over a decade ago. With resistant genotypes emerging and continued heavy drug pressure, we may anticipate continued selection of resistance. Loss of artemisinin activity will in turn threaten ACT partner drugs. Loss of efficacy of key ACTs, in particular artemether-lumefantrine, the most widely used antimalarial, may have dire consequences, as occurred when chloroquine resistance led to enormous increases in malaria deaths in the late twentieth century. Although it is impossible to predict the pace of progression of drug resistance in

Africa, close surveillance for genotypic and phenotypic evidence of artemisinin and partner drug resistance, with prompt replacement of failing regimens, may save many lives."

More information: Association of Plasmodium falciparum kelch13 R561H genotypes with delayed parasite clearance in Rwanda: an open-label, single-arm, multicentre, therapeutic efficacy study, DOI: 10.1016/S1473-3099(21)00142-0 , www.thelancet.com/journals/lan … (21)00142-0/fulltext

Provided by Lancet