Malaria: Multi-drug resistance more alarming than ever

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Credit: CDC

The efforts of the international community for the past ten years in the fight against malaria have reduced the number of disease-related deaths. The emerging resistance to standard therapies threatening South-East Asia, and new research carried out by the team led by Françoise Benoit-Vical, Inserm Research Director in the CNRS (French National Centre for Scientific Research) Coordination Chemistry Laboratory in collaboration with the Pasteur Institute and Inserm, are not reassuring factors. The in vitro examination of a strain of parasites solely exposed to artemisinin (the base compound for standard therapy) demonstrates the development of a widespread resistance to most other anti-malarial drugs. This new resistance cannot be detected by tests currently used and represents an additional threat to antimalarial treatments in the field.

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Malaria is caused by a parasite propagated through bites from infected mosquitoes from the Anopheles genus. This disease is most prevalent in tropical areas and still responsible for over 600,000 deaths each year. Policies to combat this disease have led to a 60% decrease in mortality over 15 years. However, artemisinin, the pharmaceutical base compound for antimalarial therapies, is encountering increasing clinical failure due to emerging resistance throughout South-East Asia. As of yet, this resistance has not been observed on the African continent.

Artemisinin is an active ingredient from a Chinese plant whose benefits have been known for over 2,000 years. It is used in combination with other antimalarial agents. The value of these combination therapies lies in the assurance that even if the parasite develops a resistance to one molecule, it is less likely to develop a resistance to both molecules.

Scientists must nevertheless stay one step ahead of the parasite, given the recent and rapid development of resistance to artemisinin. It is against this background that the team led by Françoise Benoit-Vical, Inserm Research Director in the CNRS Coordination Chemistry Laboratory in Toulouse, in collaboration with Inserm in Toulouse and the Pasteur Institute in Paris, is studying the resistance mechanisms developed by Plasmodium falciparum, the parasite responsible for malaria, and researching new antimalarial drugs.

Researchers have shown that parasites who survive in vitro in the presence of only artemisinin for five years develop a widespread resistance to most other artemisinin-based or non-artemisinin-based antimalarial therapies, including partner molecules present in combination therapies used in endemic areas.

Scientists have demonstrated that these parasites do not exhibit any known mutation in resistance genes. However, they circumvent the toxic effect of the drugs by a phenomenon known as quiescence. Parasites are capable of suspending their

development during exposure to antimalarial agents. As soon as they are no longer subjected to antimalarial therapy, the parasites "wake-up" and proliferate once again.

The new multi-drug resistance based on this quiescence phenomenon cannot be detected by tests currently carried out to analyse parasitic resistance. "In vitro tests carried out using the patient's blood predict high sensitivity and, therefore, the treatment's effectiveness, while parasites are resistant because they are quiescent. As such, it is essential to conduct research with relevant and appropriate tests in the field if the multi-resistant phenomenon that we identified in vitro is also present, in order to design therapeutic strategies accordingly." explains Françoise Benoit-Vical.

The ability of artemisinin-resistant parasites to develop a tolerance to partner drugs is a serious threat to combination therapy.

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