

Treatment Failure for Malaria in Vietnam

[Announcer] This program is presented by the Centers for Disease Control and Prevention.

[Sarah Gregory] I'm talking today with Dr. Charlotte Rasmussen, a malaria expert at the World Health Organization, about drug resistant malaria treatment in Vietnam. Welcome Dr. Rasmussen.

[Charlotte Rasmussen] Thank you for having me.

[Sarah Gregory] What was happening in Southeast Asia that led to this investigation?

[Charlotte Rasmussen] The resistance to antimalarial drugs has long been a challenge in Southeast Asia. For the treatment of falciparum malaria, WHO is recommending the use of a type of drug called artemisinin-based combination therapy, or ACTs. The currently recommended ACTs are a combination of the drug artemisinin and one of five different partner drugs. Unfortunately, in parts of Southeast Asia, we've seen resistance to both artemisinin and to most of the ACT partner drugs.

Artemisinin resistance was first reported in 2008 from the Cambodia-Thailand border. It is now found in five different countries in Southeast Asia, including Vietnam. Artemisinin resistance is defined as delayed parasite clearance, and has been found to be associated with mutations in part of the parasite genome called the *Pfkelch* propeller domain, or K13.

Resistance to partner drugs used together with an artemisinin is a particularly big problem in Cambodia. As a consequence, there has been treatment failures following treatments with ACTs. This is a concern, both in terms of our ability to treat malaria in the currently affected areas, and because there is a risk that this resistance could spread to areas with a very high malaria burden, for instance, in Africa.

In Vietnam, the recommended treatment for falciparum malaria has long been the ACT dihydroartemisinin-piperaquine. This treatment has been highly efficacious in the past years. However, in Cambodia, high numbers of treatment failures have been reported for dihydroartemisinin-piperaquine.

[Sarah Gregory] Almost all the malaria patients you investigated were male. Why is this?

[Charlotte Rasmussen] In Vietnam, the species of mosquitos that can spread malaria are primarily found in or near forested areas. This means that the people most at risk of malaria are those who work and sleep in or close to the forest. This is often adult males who go to the forest to work, for instance to cut wood or bamboo. Sometimes they travel to the forest from villages close by but some workers travel long distances from areas without any malaria. They may not have any knowledge of malaria or how to protect themselves.

[Sarah Gregory] What did you find?

[Charlotte Rasmussen] So, 46 patients with uncomplicated falciparum malaria were enrolled in the study in Binh Phuoc in Vietnam. Of these, 44 patients were followed up until day 42.

Unfortunately, 14 patients did not clear their infections, meaning that they did not get cured for malaria using this three day dihydroartemisinin-piperaquine treatment.

Half of the patients were found to have parasites in the blood on day three after the start of treatment. This is a sign of delayed clearance of the parasites. The genetic analysis confirmed the presence of artemisinin resistance. Thirty eight of the patients were found to have parasites with a specific K13 mutation, the C580Y mutation, which is also the dominant K13 mutation in Cambodia. The prevalence of C580Y mutations was higher than in the last study done in this area in 2014.

The genetic analysis also showed that more than half of the patients had parasites with multiple copies of the gene *plasmepsin2*; this is considered a molecular marker of piperaquine resistance. Overall, the results showed that piperaquine resistance is now present in Vietnam, and there was a sharp increase in the proportion of treatment failures.

[Sarah Gregory] Are there any next steps?

[Charlotte Rasmussen] The treatment for falciparum malaria in this area of Vietnam has now been changed to another ACT—artesunate-mefloquine. An important step is to monitor the efficacy of this drug.

[Sarah Gregory] How are these drugs different than the other ones being used now?

[Charlotte Rasmussen] Artesunate-mefloquine is also an ACT but with a different partner drug than the one previously used—namely mefloquine instead of piperaquine. This drug was chosen partly because genetic analysis of the parasites in the study showed that the parasites from all 46 patients had a single copy of the gene *Pfmdr1*, confirming that all parasites were sensitive to mefloquine.

[Sarah Gregory] What role did you have in the study?

[Charlotte Rasmussen] I work for WHO which supports countries in monitoring that the antimalarial drug that is recommended by a country continues to work in that country. The support we provide can include financial support, training in how to do efficacy monitoring, providing quality assured drug, and reviewing the data. As resistance is such challenge in Southeast Asia, it's particularly important that the treatments here are monitored regularly.

[Sarah Gregory] Thank you for speaking with me today, Dr. Rasmussen. Listeners can read the entire April 2017 article, Treatment Failure of Dihydroartemisinin/Piperaquine for *Plasmodium falciparum* Malaria, Vietnam, online at cdc.gov/eid.

I'm Sarah Gregory for *Emerging Infectious Diseases*.

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