

Multidrug-resistant malaria spread under the radar for years in Cambodia

February 2 2018



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The most comprehensive genetic study of malaria parasites in Southeast

Asia has shown that resistance to antimalarial drugs was under-reported for years in Cambodia. Researchers from the Wellcome Sanger Institute and their collaborators have shown that the parasites developed multidrug resistance to first-line treatments extremely rapidly. They found that one main resistant strain had spread aggressively in the five years before clinical resistance was reported. Delays in detecting the spread of resistance could threaten global efforts to eliminate malaria.

Reported in *The Lancet Infectious Diseases*, the study suggests that ongoing genomic surveillance is vital to monitor the spread of resistance, to inform public health [malaria](#) control strategies.

Malaria is caused by Plasmodium [parasites](#) and the World Health Organisation estimated that more than 200 million people were infected and nearly half a million people died worldwide from the disease in 2016*. Children under the age of five are most at risk. Malaria is a treatable disease when caught early enough, but is a huge problem in many areas due to [drug resistance](#).

The first-line [treatment](#) for malaria in many areas of the world is a combination of two powerful antimalarial drugs - dihydroartemisinin and piperazine - otherwise known as DHA-PPQ treatment. Introduced into Cambodia in 2008, this treatment was initially effective, but in 2013, clinical trials showed that the malaria parasites were resistant to both drugs. Subsequent studies have reported that resistance has since spread to Thailand, Laos and Vietnam.

To help understand future consequences and risks, an accurate picture of the initial emergence and spread of the malaria resistance was needed. Researchers analysed DNA sequence data from nearly 1500 Plasmodium falciparum parasites from Southeast Asia, including more than 450 collected in Cambodia between 2007 and 2013. This allowed them to look back in time to see how the malaria parasites treated with DHA-

PPQ evolved resistance.

The genetic study revealed that in the very same year that DHA-PPQ became the official first-line antimalarial treatment in Cambodia, a single multidrug resistant strain of Plasmodium parasite emerged. The researchers found this strain then spread aggressively, outcompeting all the other resistant malaria parasites and leading to complete failure of treatment in Cambodia. Other drugs may be effective at the moment but the situation is extremely fragile.

These findings have significant implications for management of the global health risk associated with the current malaria outbreak.

Dr Roberto Amato, first author on the paper from the Wellcome Sanger Institute, said: "Our study has provided the most comprehensive analysis by far of the parasites responsible for the outbreak of drug resistant malaria in Cambodia. It reveals that resistance to the combination therapy appeared almost as soon as that treatment was introduced as the official first line therapy and that it spread steadily and aggressively after that. Various factors allowed the extent of this outbreak to stay under the radar for years, but we show it is now possible to use modern genomic technologies to get a full picture of an outbreak."

Drug resistance is spreading across parts of Southeast Asia and experts are unclear how the malaria parasites will respond to current malaria [drug](#) treatments.

Professor Mike Turner, Head of Infections and Immunobiology at Wellcome, said: "This study confirms earlier observations that a strain of malaria, resistant to our most effective drugs, has emerged in the Greater Mekong Subregion. If this parasite strain keeps spreading and becomes dominant further afield it could devastate vulnerable populations globally.

"It is surprising to see that the parasites developed resistance so rapidly. Coordinated actions by governments and organisations to control and eliminate this parasite population are urgently needed. Real-time genetic sequencing would allow regional malaria control programmes to respond immediately to evolutionary changes in the parasite population."

Dominic Kwiatkowski, a corresponding author on the paper from the Wellcome Sanger Institute and the University of Oxford, said: "Our study shows that modern genomic surveillance can detect patterns of resistance much sooner than was possible in the past, providing vital information and allowing public health officials to respond as soon as possible. There is now an urgent need to provide national malaria control programmes with the tools for active genomic surveillance that will help to detect new emergences of [resistance](#) as soon as they arise and thereby reduce the risk of a major global outbreak."

More information: Roberto Amato et al, Origins of the current outbreak of multidrug-resistant malaria in southeast Asia: a retrospective genetic study, *The Lancet Infectious Diseases* (2018). [DOI: 10.1016/S1473-3099\(18\)30068-9](#)

*Figures from the 2017 World Health Organisation report [www.who.int/malaria/publicatio ... aria-report-2017/en/](http://www.who.int/malaria/publications/annual-report-2017/en/)

Provided by Wellcome Trust Sanger Institute

Citation: Multidrug-resistant malaria spread under the radar for years in Cambodia (2018, February 2) retrieved 22 November 2023 from <https://medicalxpress.com/news/2018-02-multidrug-resistant-malaria-radar-years-cambodia.html>

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