Multidrug-resistant malaria spreading in Asia

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Multidrug-resistant forms of Plasmodium falciparum parasites, the most lethal species causing human malaria, have evolved even higher levels of resistance to antimalarial drugs and spread rapidly since 2015, becoming firmly established in multiple regions of Cambodia, Laos, Thailand, and Vietnam, where they are causing alarmingly high treatment failure rates to a widely used frontline malaria drug combination.

The findings of two studies, published in *The Lancet Infectious Diseases* journal, reveal that by 2016-2018 malaria parasites resistant to both artemisinin and its widely used partner drug piperaquine represented more than 80% of the parasites circulating in northeast Thailand and Vietnam, despite having only emerged in western Cambodia in 2008.

These rapidly spreading parasites have also acquired new resistance mutations linked with even higher rates of treatment failure, causing failures to one of the newest and most powerful frontline drug combinations (dihydroartemisinin-piperaquine;DHA-PPQ) in half of cases in western and northeastern Cambodia, northeastern Thailand, and southwestern Vietnam in 2015-2018, further compromising efforts to eliminate the disease.

"These worrying findings indicate that the problem of multidrug resistance in P falciparum has substantially worsened in southeast Asia since 2015", says Professor Olivo Miotto from the Wellcome Sanger Institute and University of Oxford, UK who co-led the genomic epidemiology study. "This highly successful resistant parasite strain is capable of invading new territories and acquiring new genetic properties, raising the terrifying prospect that it could spread to Africa where most malaria cases occur, as resistance to chloroquine did in the 1980s, contributing to millions of deaths."

With DHA-PPQ now providing ineffective treatment and promoting the spread of resistance, the authors of a multi-country randomised trial led by Professor Arjen Dondorp from the Mahidol Oxford Tropical Medical Research Unit in Thailand, call for this commonly used frontline combination therapy to be abandoned in the eastern Greater Mekong Subregion (Cambodia, southern China, Laos, Myanmar, Thailand, and Vietnam), even in areas where resistance has only just started to emerge.

"With the spread and intensification of resistance, our findings highlight the urgent need to adopt alternative first-line treatments", says Professor Tran Tinh Hien from the Oxford University Clinical Research Unit in Vietnam co-author on the clinical study. "One option is to switch the partner drug piperaquine to a drug that is currently effective such as mefloquine or pyronaridine—as Cambodia and Thailand have already done. But there is a possibility that in the presence of artemisinin resistance, resistance to these partner drugs might develop rapidly as well. Another option is to use triple ACTs, in which an artemisinin is combined with two partner drugs instead of one."

According to Professor Mallika Imwong from Mahidol University in Thailand co-author on the genomic epidemiology study: "To stay one step ahead, continued surveillance, including genetic surveillance, is needed to map the spread of resistance in real time, so other countries can act quickly and switch drugs if needed."

More than 200 million people are infected with the malaria parasite P falciparum, which is responsible for 9 out of 10 deaths from malaria. Worldwide, antimalarial efforts are mainly dependent on artemisinin combination therapies (ACTs) that pair artemisinin with one of six partner drugs to complete parasite clearance. Introduced in Cambodia in 2008, DHA-PPQ was initially effective, but by 2013, malaria parasites had become resistant to both drugs in western Cambodia. Since

then, these resistant strains have spread to other parts of Cambodia, Thailand, Vietnam, Myanmar, and Laos.

In 2018, a genetic study published in *The Lancet Infectious Diseases* journal tracked the emergence and spread of a multidrug resistant strain named KEL1/PLA1 across Cambodia between 2007 and 2013. KEL1 indicates a specific origin of an artemisinin resistance mutation in the kelch13 gene, while PLA1 describes a specific origin of the amplification (multiple copies) of the plasmepsin-2 and plasmepsin-3 genes, which is a marker of piperaquine resistance. KEL1/PLA1 parasites carry both of these gene variants, and therefore are resistant to both components of DHA-PPQ treatment. At the time, KEL1/PLA1 had only spread within the borders of Cambodia.

In a new genomic epidemiology study, an international team of scientists investigated the evolution and spread of KEL1/PLA1 from 2007 up to 2018. By analysing the genomes of 1,673 P falciparum samples from 19 provinces across Cambodia, Laos, northeast Thailand, and Vietnam, they found that KEL1/PLA1 had spread rapidly from Cambodia across all the surveyed countries, with prevalence rising to higher than 50% in all regions apart from Laos (figure 1B).

These KEL1/PLA1 parasites maintained a high level of genetic relatedness reflecting their common origin. Importantly, several genetic KEL1/PLA1 subgroups have recently emerged that carry mutations in the chloroquine resistance transporter (crt) gene, which increase the parasites' ability to resist piperaquine—causing a proliferation of biologically fitter and increasingly resistant parasites.

These findings are supported by interim evidence from a multi-country randomised trial evaluating the efficacy, safety, and tolerability of triple ACTs (artemisinin plus two partner drugs) compared with current ACTs (artemisinin plus one partner drug) in areas with multidrug-resistant falciparum malaria. The Tracking Resistance to Artemisinin Collaboration (TRACII) reports preliminary data for 140 patients (aged 2 to 65 years) with uncomplicated falciparum malaria from 7 sites in Cambodia, Vietnam, and Thailand treated with a standard 3-day course of DHA-PPQ between 2015 and 2018.

Results suggest that the failure rate for DHA-PPQ has now reached 27% in northeastern Cambodia, whilst in western Cambodia it is 62%; and reached 53% southwestern Vietnam, and 87% in northeastern Thailand (table 3; figure 1).

The researchers also noted substantial increases in the frequency of genetic markers of artemisinin and piperaquine resistance across the region over the past decade. In particular, they found a rapid increase in the newly described crt mutations that contribute to piperaquine resistance and have an additive effect on treatment failure with DHA-PPQ. In 2015-2018, 74% (272/375) of resistant parasite samples from Cambodia, Thailand, and Vietnam carried crt mutations associated with piperaquine resistance, compared with 5% (20/368) in 2011-2013 when these mutations were only present in western Cambodia.

"These results suggest that the P falciparum co-lineage resistant to DHA-PPQ has now acquired crt mutations linked with even higher rates of treatment failure. These have immediate public health importance as they may continue to evolve, producing biologically fitter parasite strains more capable of surviving treatment", says Professor Dondorp. "Accelerated efforts to eliminate all P falciparum in the Greater Mekong Subregion are urgently needed to avoid further spread of these difficult-to-treat, highly resistant parasites, which have the potential to cause health emergencies regionally, and possibly globally."

The authors of the randomised trial note that overrepresentation of potential recurrent infections might have led to an underestimation of the efficacy of DHA-PPQ in primary infections. The authors of the genomic epidemiology study point out that the trends they describe rely on opportunistic sampling, combining data from multiple varied studies, resulting in temporal and geographical diversity, which may limit the conclusions that can be drawn. They add that longitudinal surveillance would benefit from systematic, comprehensive, and maintained sampling.

Writing in a linked Comment, Dr. Didier Ménard from the Institut Pasteur in France, says: "[These] two studies illustrate the accelerated pace at which P falciparum resistance to DHA-PPQ has evolved and spread across Southeast Asia, decimating its efficacy...[and] clearly highlight the urgent need for adopting new and effective treatments (such as triple ACTs or the ACT artesunate plus pyronaridine). They also evoke advantages of implementing a regional strategy rather than country-specific programs to address population movements and integrate region-wide clinical and genetic surveillance systems into a coordinated campaign whose goal is to achieve malaria elimination in Southeast Asia."]

More information: William L Hamilton et al, Evolution and expansion of multidrug-resistant malaria in southeast Asia: a genomic epidemiology study, *The Lancet Infectious Diseases* (2019). DOI: 10.1016/S1473-3099(19)30392-5

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