Knowing the enemy: genetics to track antimalarial resistance

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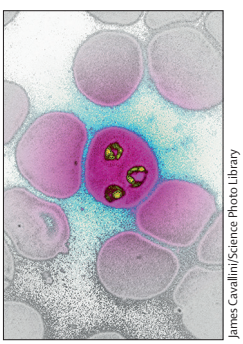

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Published Online
July 14, 2020
https://doi.org/10.1016/S1473-3099(20)30271-1

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In the absence of an effective vaccine, the efficacy of antimalarial chemotherapies underpins the success of malaria control programmes. Artemisinin-based combination therapies (ACTs), which combine fast-acting artemisinin derivatives and longer-acting partner drugs, are the mainstay of treatment of uncomplicated falciparum malaria in endemic regions.[1] However, as reported for almost all antimalarial drugs used worldwide, *Plasmodium falciparum* resistance to artemisinin is emerging.[2,3] First detected in Cambodia in 2008,[4,5] partial artemisinin resistance is now widespread in the Greater Mekong subregion.[6–9] Moreover, resistance to ACT partner drugs has become common in Cambodia, where high rates of dihydroartemisinin–piperaquine treatment failure have been observed.[10] The risk of spreading ACT-resistant parasites from the Greater Mekong subregion to Africa, as happened in the 1980s with chloroquine and pyrimethamine resistance, is a major concern.[11] The close surveillance of antimalarial resistance, predicted from the genetic variation contained in the DNA of malaria parasites, is therefore essential. Although there are some caveats (eg, the association between the molecular markers and in-vivo resistance is not always linear), this genetic information can be used to guide policy decisions.[12]

In *The Lancet Infectious Diseases*, Mallika Imwong and colleagues[15] present a comprehensive description of the geographical and temporal changes in *P falciparum* molecular markers of resistance to antimalarial drugs used in the Greater Mekong subregionin the past decade. The team investigated point mutations and amplifications in genes associated with artemisinin (*pfkelch13*), piperaquine (*pfcrt, plasmepsin-2*), and mefloquine–lumefantrine (*pfmdr1*) resistance in more than 10 000 blood samples collected from 2007 to 2018 in Myanmar, Thailand, Laos, and Cambodia. They also explored microsatellites and single nucleotide polymorphisms in the flanking regions each side of the mutations to estimate the genetic relatedness of the predominant mutants. Their results show the effect molecular data can have in informing public health interventions. Different evolutionary dynamics of antimalarial drug resistance were found in the eastern and western Greater Mekong subregion, without evidence of *P falciparum* resistance spreading. In the western Greater Mekong subregion, an almost fixed *pfkelch13* Cys580Tyr lineage (called PfPailin), resistant to both artemisinin and piperaquine (defined by *plasmepsin-2* gene amplification and specific mutations in the *pfcrt* gene) and associated with high rates of dihydroartemisinin–piperaquine treatment failure, has outcompeted other *pfkelch13* mutants. By contrast, a single artemisinin-resistant *pfkelch13* Phe446Ile haplotype predominates in the eastern Greater Mekong subregion, which spread from the northwest to the east of Myanmar without acquiring additional resistance to piperaquine. The intensive deployment of dihydroartemisinin–piperaquine for treatment and elimination purposes in Kayin state (eastern Myanmar) was not associated with further selection of artemisinin and piperaquine resistance, supporting its mass use for elimination.

This study has implications for the proactive development of interventions that can reduce the spread and impact of antimalarial drug resistance. First, the local emergence of *pfkelch13* mutants (Cys580Tyr and Phe446Ile) and their reduced regional spread contrast with the previous expansions of choloroquine-resistant and pyrimethamine-resistant parasites from the Greater Mekong subregion to Africa. However, single point mutations in the *pfkech13* gene that confer resistance to artemisinin seem to arise more frequently than the complex sets of genetic mutations associated with chloroquine (*pfcrt* gene) and sulfadoxine–pyrimethamine (*dhfr* and *dhps* genes) resistance. Therefore, the risk of local emergence of artemisinin-resistant *pfkelch13* mutants in malaria-endemic settings other than the Greater Mekong subregion might be more likely to occur than the spread of artemisinin-resistant parasites, as observed in Guyana[13] and Papua New Guinea.[14] Second, mass drug administrations used for malaria elimination do not seem to drive the selection of antimalarial drug resistance, although adequate sample sizes are essential to achieve more robust conclusions. Further studies are required to provide insights into the factors that determine drug resistance, such as the fitness cost of the mutations conferring resistance, the competition between resistant and sensitive parasite strains, and the immune status of the host population, among others. How all

these factors interact in the Greater Mekong subregion to make this area a hotspot for the emergence of antimalarial resistance is still an open question.

A better understanding of how resistance emerges and the factors that drive parasite gene flow across geographic regions are key to guiding interventions that aim to contain resistance. To obtain actionable information from genetic data, additional work is needed, including the generation of molecular and clinical databases of parasite resistance across multiple geographic regions, the validation of molecular markers linked to resistance in different geographical settings (eg, markers associated with piperaquine and lumefantrine resistance), and the definition of appropriate sampling strategies and genotyping methods, to optimise routine surveillance and to build capacity for agile evidence-driven decision making in malaria-endemic countries. We recall Sun Tzu's precept (The Art of War): "know our enemy, if we want to win the battle without loss".

We declare no competing interests.

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Polymyxins resistance among Gram-negative pathogens in India

Published **Online** November 10, 2020 https://doi.org/10.1016/S1473-3099(20)30855-0

The sharp increase in carbapenem resistance in Gram-negative pathogens during the past decade led to a resurgence in the use of polymyxin antibiotics. Despite treatment-associated acute kidney injury and varying clinical outcomes, both colistin (polymyxin E) and polymyxin B have emerged as key therapies in the management of carbapenem-resistant Gram-negative infections. Use of these therapies is particularly frequent in low-income and middle-income countries where access to novel antibiotics that are active against carbapenem-resistant Gram-negative bacteria, such as ceftazidime plus avibactam and ceftolozane plus tazobactam, is restricted. For instance, India reports one of the highest uses of polymyxins in hospitals globally, prompted by substantial levels of carbapenem resistance in *Klebsiella pneumoniae*, *Pseudomonas aeruginosa,* and *Acinetobacter baumannii*.[1] A retrospective study that examined antibiotic resistance in a large number of isolates from blood samples collected across India reported very high carbapenem resistance rates of 56·6% for *K pneumoniae*, 46·8% for *P aeruginosa,* and 67·3% for *A baumannii*.[2] These high carbapenem resistance rates have compelled clinicians in India to rely on polymyxins as salvage therapy.

India is known for poor antibiotic stewardship practices that are reflected in the high antibiotic