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Antimalarial drug resistance—is it time to re-evaluate *Plasmodium falciparum* orthologous genes?

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The COVID-19 pandemic has wreaked havoc on malaria prevention, diagnosis, and treatment, resulting in 241 million malaria cases and 627 000 malaria deaths globally in 2020, up from 14 million malaria cases in 2019, and the disruption was estimated to have contributed to 47 000 malaria deaths, two-thirds of the 2019–20 increase.[1] Malaria caused by *Plasmodium vivax* has the potential to affect 2·5 billion people globally, accounting for 88% of people at risk of malaria overall; however, due to its more severe course, *Plasmodium falciparum* receives the most attention.[2] Despite the fact that *P vivax* has a benign malaria course, occasional occurrences of this species' malignant pattern have been observed worldwide.[3,4] Antimalarial drug resistance is on the rise, and its spread is one of the most serious risks to malaria control and eradication. In *P vivax* and *P falciparum*, resistance to antimalarial drugs such as chloroquine, sulfadoxine-pyrimethamine, and atovaquone has already been established.[5] Antimalarial drug resistance mechanisms and key molecular markers in *P falciparum* have been well described in vitro and in vivo; nevertheless, these mechanisms are difficult to assess in *P vivax* due to the absence of a cultivation system for this species.[6]

The search for antimalarial resistance in *P vivax* has centred on *P falciparum* orthologous genes (multidrug resistance, chloroquine resistance transporter, dihydropteroate synthase, and dihydrofolate reductase) being strongly (though not completely) associated to ex-vivo resistance assay outputs and in-vivo treatment failure.[7] *P vivax* does not have a reliable genetic marker for drug resistance, probably because the drug resistance phenotype is reliant on multiple convergent molecular processes for the same outcome. It is necessary to narrow down the number of polymorphisms to be able to validate resistance markers to a drug sensitivity phenotype. Unfortunately, attempts to prove genotypic resistance have failed so far due to a unavailability of continuous culturing in *P vivax*, which is essential to achieve a measurable, accurate phenotypic consequence. *P vivax* has only tentatively been associated with treatment failure despite a quantitative increase in gene expression. Consequently, there are not any clear guidelines for determining whether in-vitro responses are sensitive or resistant to antimalarials.[8]

Although molecular approaches are not the most efficient means to monitor *P vivax* treatment susceptibility, they might be a good starting point. Herein, retrospective research on mutations of well-characterised molecular markers subject to prolonged antimalarial drug pressure is possible. The most difficult challenges to understanding molecular drug resistance in *P vivax* are the parasite's complex biology, latency (dormant form; hypnozoites stage), culturing issues, and drug resistance indicators with a low degree of correlation with resistance associated molecular markers.

The understanding of the molecular basis of treatment failure in *P vivax* remains elusive[7] because putative resistance mutations are usually referred to as drug resistance indicators in the literature. Only considering these markers is insufficient for the identification of drug resistance in *P vivax*. Standardised in-vivo and ex-vivo assays with genomic research are essential to lay the foundation for tracking the dissemination of genotype–phenotype putative resistance mutations. Furthermore, in the era of drug resistance, monotherapies and malarial interventions are no longer sufficient to tackle genetically varied parasites with mutations. There is a need for novel treatments. There is not enough evidence to support putative resistant indicators; so, caution should be exercised when using these molecular markers to inform resistance levels or reformulate drug policy in a given geographical location.

We declare no competing interests. AAK and UAA contributed equally.

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