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## Towards real-time monitoring of artemisinin resistance



The discovery that mutations in the kelch propeller domain of the K13 gene (PF3D7\_1343700) were major determinants of *Plasmodium falciparum* artemisinin resistance has been validated by several studies in the Mekong region.<sup>1-3</sup> The particularity of this discovery is that it took place less than 10 years after the detection of the first clinical cases of artemisinin resistance in western Cambodia and probably before the spread of the mutations to neighbouring malaria-endemic regions and beyond.<sup>4</sup> This context is very unique and favours real-time monitoring of artemisinin resistance in endemic areas and anticipation of the risks associated with the emergence and spread of the artemisinin-resistant parasites, a major public health issue. Indeed, this situation is completely different to that which took place in the late 1970s, when resistant parasites emerged to the previous generation of antimalarial drugs (ie, chloroquine, sulfadoxine, and pyrimethamine) and whose associated molecular markers (eg, Pfcr, Pfdhfr, and Pfdhps) were discovered only after their spread to Africa, leading to an unprecedented increase in morbidity and mortality.<sup>5-7</sup> This favourable situation should now be used to track the spread of artemisinin resistance and mitigate its effect on malaria treatment and control programmes, especially in sub-Saharan Africa.

In *The Lancet Infectious Diseases*, Kyaw Tun and colleagues<sup>8</sup> present a detailed molecular study of K13 from *P falciparum* field isolates obtained from symptomatic patients at more than 50 different sites in Myanmar during 2013–14. The work presented here is important and very relevant, because foremost it helps identify the extent of resistance in this key country in the regional surveillance system. Indeed, the malaria burden in Myanmar is the largest in southeast Asia (1.4 million malaria cases and 2900 deaths in 2012) and, because of its localisation close to the historical epicentre of the emergence of multidrug-resistant parasites, this country is considered the main route by which drug-resistant *falciparum* malaria will spread contiguously from southeast Asia to the Indian subcontinent and then to Africa.<sup>9</sup> Second, from a methodological point of view, Tun and colleagues' study is a model of what needs to be done: a countrywide collection of samples associated with a predictive, fine-scale (5×5 km) geospatial

representation of the prevalence of K13 mutants. Such mapping provides a powerful instrument with which to predict the prevalence of K13 mutant alleles (or other data) in unsampled areas. The mapping also enables national programmes to obtain clear and useful information about the extent of resistance and thus implement appropriate actions. For the present study, the molecular data provide strong evidence that artemisinin-resistant *falciparum* malaria in Myanmar extends across much of Upper Myanmar, including areas close to the Indian border in the northwest. These data, associated with information about the presence of K13 mutant alleles in Bangladesh, advocate for a rigorous molecular survey to be implemented without delay in the Indian subcontinent.<sup>10</sup> One of the major technical issues raised in the study is the low extraction–sequencing success rate for samples obtained with rapid diagnostic tests (26%). Although this approach should be promoted because it allows the collection of blood samples of all malaria cases recorded at least in the health system, the low extraction–sequencing success rate shows that a major effort should be made to improve the performance of the DNA extraction or the PCR amplification, or to modify the format of rapid diagnostic tests for use not only as point-of-care testing for malaria, but also as blood sample sources.

In the past few decades, substantial developments have been made in plasmodium molecular biology and they have greatly increased understanding of malaria epidemiology. Previously, only incidence and prevalence were used to assess the effect of malaria control measures, but nowadays, with the introduction of high-sensitivity molecular assays, researchers can investigate the origin and the flow of malaria-resistant parasites.<sup>11</sup> In all endemic areas, a *falciparum* gene-flow map should be envisaged to help implementation of control measures and identify key sites for malaria monitoring. Importantly, in endemic countries where artemisinin resistance has been recorded, a greater parasite biomass will be exposed to partner drugs and thus molecular surveys must include partner drug monitoring, with use of molecular markers if available.<sup>2,12</sup>

Real-time detection and monitoring of the geospatial distribution of antimalarial drug-resistant parasites is now a possibility, as is prevention of their dissemination



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in neighbouring endemic areas. However, substantial work remains to be done to harmonise and validate collected data. Currently, a major concern is the interpretation of molecular data because of the high diversity of the K13 gene: except for four mutations (C580Y, R539T, R543I, and Y493H), no clinical or in-vitro data have been associated with the other K13 mutant alleles.<sup>1,3</sup> We believe that the scientific community working on artemisinin resistance should now create a consortium around a K13 reference centre that could take over the management and data validation, the harmonisation of molecular biology techniques, the provision of control samples, and the organisation of a quality assurance system, to recommend the best therapeutic options—a prerequisite to move effectively toward malaria elimination.

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We declare no competing interests.

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## Rotavirus vaccines roll-out in resource-deprived regions

Rotaviruses cause 30–50% of severe diarrhoea cases in children younger than 5 years, leading to about 450 000 deaths every year.<sup>1</sup> Infections during the first months of life are protective against symptomatic reinfections later on, setting the stage for vaccine development.<sup>2,3</sup> The existence of four major genotypes—G1[P8], G2[P4], G3[P8], and G4[P8]—created a great challenge because in-vitro studies suggested that antibodies to a specific type neutralised only that type, raising the question of whether it would be necessary for a vaccine to include all common genotypes.

During the 1990s the first licensed vaccine, Rotashield (Wyeth Laboratories, Collegeville, PA, USA), which contained an attenuated simian and three simian–human reassortant strains of the virus, showed that 70–90% of cases of severe rotavirus disease could potentially be prevented in lower-middle-income and high-income countries with vaccination.<sup>4</sup> However, intestinal intussusception was induced in about one in 11 000 children who received the vaccine, leading

to its withdrawal and posing a large challenge for new candidate vaccines because future trials needed to include 60 000 children to reasonably assure safety.<sup>5,6</sup> Post-licensure studies of the second-generation vaccines Rotarix (GlaxoSmithKline, Brentford, UK), which contains a single human attenuated strain, and RotaTeq (Merck, Kenilworth, NJ, USA) based on five human–bovine reassortant strains, suggest an acceptable class effect risk for intestinal intussusception of somewhere between one in 20 000 and one in 100 000 individuals.<sup>7</sup> Importantly, both vaccines showed high efficacy (more than 80%) against severe rotavirus disease in prelicensure studies<sup>5,6</sup> and against several predominating genotypes. As trials were progressively done in various regions worldwide, it became clear that protective efficacy for both vaccines was lower in resource-deprived countries than in high-income countries<sup>8</sup> and that efficacy might not be the same among serotypes and genotypes, especially against G2[P4].<sup>5,9</sup>

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