Urgent action is needed to confront artemisinin partial resistance in African malaria parasites

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Resistance to antimalarial drugs is a recurring challenge for effective treatment of *Plasmodium falciparum* infection and for achieving the goal of eliminating malaria[1]. Beginning with chloroquine, resistance has compromised the efficacies of most major classes of antimalarial drugs. Partial resistance to artemisinin (ART-R) is becoming a major threat to the efficacy of artemisinin-based combination therapies (ACTs) and intravenous artesunate, which are critical for the treatment of uncomplicated malaria and severe malaria, respectively. Already ubiquitous throughout the Greater Mekong subregion of Southeast Asia, ART-R has emerged in several countries in eastern Africa[2]. For the prevention of a potential public health disaster in sub-Saharan Africa, the time for decisive action to confront emerging ART-R is now.

ACTs, which include a fast-acting artemisinin derivative and a longer-lasting partner drug, were globally adopted as first-line therapy for uncomplicated *P. falciparum* malaria in the early 2000s. In Africa, ACT partner drugs are mainly lumefantrine or amodiaquine. The current evolution of ART-R in eastern Africa recalls the earlier situation in Southeast Asia, which within less than a decade saw ART-R dominate parasite populations[3]. ART-R is mediated mainly by mutations that alter the *P. falciparum* Kelch13 (K13) protein propeller domain, and it manifests clinically as delayed parasite clearance in patients treated with an artemisinin derivative or an ACT[4]. In Africa, ART-R has been confirmed in Rwanda, Eritrea, Uganda and Tanzania, where multiple validated or candidate K13 ART-R mutant variants have been observed (including R561H, R622I, C469Y/C469F, A675V and P441L)[5,6]. ART-R associated with mutant K13 is also suspected in Ethiopia and Sudan[7,8]. These data from Africa provide clear evidence of multiple independent origins of artemisinin-resistant parasites, which indicates that containment and control measures will need to be implemented on multiple fronts.

In Southeast Asia, valuable lessons were learned from the largely successful containment of ART-R and resistance to ACT partner drugs, achieved mainly by effective control of malaria transmission, including improvements in drug treatment monitoring, vector control, surveillance and community engagement[4]. Bodies such as the Regional Artemisinin Resistance Initiative and the Asia Pacific Malaria Elimination Network were established and have ensured continued regional collaboration and the sharing of information, resources and strategies. The strategy for mitigating ART-R in Africa, recently issued by the World Health Organization (WHO), is designed to catalyze a rapid, concerted response[1]. The strategy recommends four concomitant pillars: improving surveillance for resistance and monitoring of drug efficacy; optimizing and better regulating the use of diagnostics and therapeutics to limit drug pressure; reacting to resistance by limiting the spread of antimalarial-drug-resistant parasites; and catalyzing research and innovation to better leverage existing tools and to develop new tools against resistance. Each pillar needs to be tailored to the local in-country context. However, without an urgent global consensus on declaring ART-R an emergency, and without the necessary concomitant financing and regional coordination, little progress has been made toward operationalizing the WHO strategy.

Actions are needed now. First, given the experience in Southeast Asia, political will and commitment are needed to urgently take on the challenge of ART-R in Africa. At a global level, substantial commitment to empowering knowledgeable public health management, including financial support, is needed to tackle the problem holistically. The WHO Global Malaria Programme is critical for ensuring standardized data collection, efficient information flow and a coordinated response. Governments in the resistance hotspots and beyond need to acknowledge the urgency of the issue and to agree to coordinated actions both individually and regionally. Advocacy and buy-in from governments and global malaria partners will allow increased resources and technical expertise to enable updated treatment guidelines based on emerging resistance patterns. Regional coordinating mechanisms, with rapid sharing of standardized and validated data, knowledge and experience, will be critical.

Second, surveillance of disease, *Anopheles* mosquito vectors and interventions must be strengthened; this should include genomic platforms, therapeutic efficacy studies and parasite phenotypic analyses to monitor the spread of resistant parasites and assess the impacts of antimalarial mitigation efforts. The COVID-19 pandemic led to a major expansion in available laboratory capacity in Africa. Investment is needed to negotiate costs of reagents and equipment, establish norms and processes for data generation and sharing, and develop the capacity to translate molecular, clinical and parasitology data into policy decisions.

Third, a more tailored approach to malaria control in sub-Saharan Africa must be implemented, akin to elimination efforts in other regions, whereby suitable packages of interventions are selected to target malaria at the subnational level within specific ART-R risk populations. Targeting should focus on infection (symptomatic and asymptomatic, across all ages), should be guided by data and should combine multiple interventions, including vector control, case management, chemoprevention, vaccination, and social and behavioral change communication. Priority interventions can include the tailored deployment of triple or sequential ACTs or multiple first-line therapies[1]. The addition of transmission-blocking drugs, such as single low-dose primaquine, may help reduce the spread of ART-R[9]. Access to vaccines against malaria (RTS/S or R21), including their use in combination with chemoprevention, is expanding for at-risk young children, and ideally will later expand to older age groups. As learned from the response to COVID-19, the development of non–artemisinin-based antimalarial drugs and other prevention tools such as monoclonal antibodies must be accelerated.

Fourth, local stakeholders and affected communities must be empowered to identify operational challenges and, with technical support, design solutions to overcome these challenges. Leadership at the local level is needed to understand the reasons for the failure of malaria control in a particular geography and what response will be suitable to prevent the spread of ART-R. Effective engagement with local communities is an essential element of the comprehensive strategy for ART-R mitigation.

Fifth, as described in the WHO mitigation strategy for ART-R in Africa[1], basic, operational and implementation research must be enhanced to address key questions of high relevance to control and elimination programs. These include efforts to identify mediators of the resistance of *P. falciparum* to partner drugs. Recent reports suggest that parasites with lower susceptibility to lumefantrine are already circulating in Uganda, where K13 variants are now present[10]. Increased national and regional collaboration by research, health and other relevant sectors needs programmatic support to accelerate the identification of the drivers of resistance and to mitigate their impact.

ART-R has emerged in Africa. The public health community must not stand by and watch resistance spread unchecked, morbidity and mortality increase, and years of investment in improved malaria control be lost. The warning lights are on amber; the world cannot afford to wait for the lights to turn red. The right tools to be proactive rather than reactive are available. Now is the time for action with a well-resourced and coordinated global response.

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Competing interests

The authors declare no competing interests.

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