Rescuing artemisinin combination therapy in Africa

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Considerable effort has been made to meet the challenges posed by decreased effectiveness of the antimalarial artemisinin and its key partner drugs against *Plasmodium falciparum* in Cambodia and neighbouring countries.[1,2] Despite the threat of resistance, malaria endemicity has actually been falling over the past decade in the Greater Mekong Subregion.[3] But what if such phenomena began to unfold in Africa, in those countries where the daily incidence of symptomatic malaria cases can equal the annual burden in some Asian countries? Hypolite Mavoko and colleagues report in *The Lancet Global Health* a study[4] designed to compare current rescue treatment options for *P falciparum* malaria in Africa, should front-line therapies fail. The authors set out to formally test whether, in the event of recurrence of malaria symptoms in children receiving the recommended artemisinin-based combination therapy (ACT), retreatment with that same regimen was inferior to either an alternative ACT, or the current WHO recommendation for rescue treatment, oral quinine plus an antibiotic (in this study, quinine plus clindamycin, QnC).

The team recruited children aged 12–59 months who presented with laboratory-confirmed *P falciparum* malaria to either of two clinics, in Kinshasa, DR Congo or Mbarara, Uganda. Both sites serve populations exposed to intense malaria transmission. First-line ACT differs between these countries, with artesunate-amodiaquine (ASAQ) used in DR Congo, and artemether-lumefantrine (AL) in Uganda. In an unusual design, passive follow-up identified treated participants with recurrent symptoms within 42 days; on second presentation with confirmed falciparum malaria, these children were then randomly assigned to one of three second treatments. The first group was retreated with the same ACT as used for the original malaria episode (retreatment ACT group), the second group with the alternative ACT (AL in DR Congo and ASAQ in Uganda) and the third group with the WHO recommendation, QnC. All treatment was fully observed, and 571 randomised children were actively followed up for 28 days.

The primary outcome was the proportion of children with adequate clinical and parasitological response (ACPR) at day 28 after treatment, after PCR adjustment. The desired outcome was reached by most children in all three groups: ACPR was achieved by 91·4% of patients in the retreatment ACT group, by 91·3% in the alternative ACT group, and by 89·5% in the QnC group. This is good news, on the face of it, for national malaria control programmes in Africa. These figures suggest there is no need to pick out recurrent malaria for special treatment, as the first-line ACT appears to be no less effective against these malaria cases than against primary infections. Furthermore, some effort was made in the study to capture any evidence that retreatment might lead to an excess of adverse events among the participants. As might have been expected, adverse events were significantly more common among children receiving the same ACT twice, but none of the reported adverse events were considered serious—the researchers conclude that, when combined with results of other studies, the weight of evidence suggests re-treatment with the first-line ACT is safe.

Two caveats are worth considering here. First, as the authors correctly emphasise, retreatment with the front-line regimen might enhance development of genetic resistance in *P falciparum* populations. Current evidence from Africa suggests that small differences in susceptibility to ACT can be measured in vivo and in vitro; these are probably mediated by complex multi-locus genotypes, and are certainly not associated with variants of the *pfk13* locus as seen in the Mekong.[5–9] Failure to provide an alternative regimen as rescue treatment for recurrent cases might lead to unidirectional selection on parasite genomes. Efficacy on the front-line therapy should therefore be regularly monitored, with parasite genotyping at sentinel sites in each country.

The second caveat relates to the use of PCR-corrected data to define the primary outcome. This well established approach amplifies highly polymorphic sequences in certain parasite genes. Fractionation of these amplicons on agarose gels generates patterns that are compared between the recurrence, and the day 0 (pre-treatment) parasite population. So-called true treatment failures are expected to maintain a pattern at recurrence resembling that at day 0. Dissimilar patterns are considered to have newly arisen, emerging from the liver after circulating drug concentrations have dropped, and thus bearing a genetic signature that differs from the original infection. Unfortunately, this method is notoriously unreliable

because of misclassification errors, particularly in Africa.[7,10] Crude ACPR, without PCR correction, presents a bleaker picture of drug efficacy. In this study, crude ACPR estimates were 60·5% (retreatment ACT), 56·2% (alternate ACT), and 70·8% (QnC). This finding clearly shows a major problem: our front-line antimalarial regimens in Africa leave a substantial proportion of treated individuals with persistent parasitaemia, and thus do not prevent onward transmission to mosquitoes of drug-exposed parasites. This is of major concern, and suggests that potential strategies for improving sterile parasite clearance need consideration, such as longer courses of artemisinin combination therapy, and use of two or more partner drugs.

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I declare no competing interests.

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