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Out of Africa: Increasing reports of artemether-lumefantrine treatment failures of uncomplicated *Plasmodium falciparum* infection

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The introduction of artemisinin-based combination therapies (ACTs) to treat *Plasmodium falciparum* infection in the early 2000s provided relief against the growing ineffectiveness of formerly dependable treatments such as chloroquine and sulfadoxine-pyrimethamine. Since then, six ACTs have been added to the World Health Organization's list of recommended treatments for uncomplicated *P. falciparum* infection (Box 1). Of those six, artemether-lumefantrine (AL) is the most widely used, accounting for up to 85% of all ACTs procured by large donors for sub-Saharan Africa[1] and is at the greatest threat of losing efficacy. Just as a traveller returning to the USA from Tanzania provided the first confirmation of high-grade chloroquine resistance in Africa in the 1970s,[2] once again travellers may be offering a unique glimpse of an antimalarial's worsening efficacy.

The article by Grossman *et al.*[3] in this issue adds further evidence of AL's suboptimal—and possibly waning—efficacy in treating *P. falciparum* infection acquired in Africa. This news does not come as a surprise. For at least a decade, concerning reports of suboptimal AL efficacy against *P. falciparum* have surfaced from Africa-based therapeutic efficacy studies. Nowadays, it is not unusual to see around 50% or more of children treated with AL return within 4 weeks harbouring a recurrent infection in countries such as Burkina Faso,[4] Democratic Republic of the Congo,[5] and Uganda.[6] Other, less frequently used ACTs, such as artesunate-amodiaquine and dihydroartemisinin-piperaquine, have almost always fared better in the same studies.

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Conflict of interest

None declared.

Interpreting antimalarial efficacy in malaria-endemic areas has long been complicated by the possibility of a new infection obscuring whether an antimalarial treatment truly failed or not. This requires a genotyping step that is often inaccurate and that yields data that are often misinterpreted. Because acquiring a new infection after antimalarial treatment is not possible in non-malarious countries, using returning travellers to assess antimalarial efficacy obviates the need to differentiate between a new infection and recrudescent infection. AL failures have been reported in travellers returning to the United Kingdom,[7] Belgium,[8] and the United States,[9] amongst others. Whilst important contributions to the literature, these studies did not report the total number of people treated, making it difficult to discern whether these AL failures were rare events or were occurring at concerning rates. A study of travellers returning to Sweden provided the most robust data to date on AL efficacy in travellers.[10] Of 95 returning travellers with *P. falciparum* infection between 2000 and 2015, five patients (four returning from Africa) experienced a recrudescence after treatment with AL. This yielded a 95% efficacy over the 16-year time period, an acceptable AL efficacy consistent with some studies conducted in Africa. A closer look at the data indicates, however, that the five failures occurred exclusively in the last 4 years of the surveillance, 2012–15, hinting at a worsening trend.

This new, well-conducted study[3] of travellers returning from Africa to Israel, a country with no local malaria transmission, adds another concerning chapter to the AL efficacy saga. A strength of the study was that it reviewed data from 99 travellers infected with *P. falciparum* who were treated as inpatients at one of only three hospitals, ensuring methodological consistency in AL administration and patient follow-up. Moreover, because most cases occurred in non-immune travellers, acquired host immunity was not a confounding factor. Weight, a factor that may influence AL absorption and efficacy, was compared between those with and without treatment failure and found to be similar. In an insightful analysis, the investigators stratified their data set into three time periods, showing that AL failure rates increased from 0% in 2009–12 to 9% in 2013–16 to 17% in 2017–20.

The investigators sequenced the returned travellers' parasites for mutations in the *pfk13* gene. This molecular marker has been associated with decreased responsiveness to intravenous artesunate or the artemisinin component of an ACT in countries such as Ethiopia, Eritrea, Rwanda, Tanzania, and Uganda. Similar to previous reports of AL failure in travellers returning from Africa,[7–10] no concerning *k13* mutations were found in this study of Israeli travellers. However, the investigators noted that a *Pfcoronin* gene mutation was significantly more prevalent in samples from travellers who failed treatment compared with samples from travellers who successfully cleared their infection. Although the role of *Pfcoronin* mutations in driving artemisinin resistance is still not clear, investigators should add *Pfcoronin* to the list of molecular markers of resistance explored as part of future ACT efficacy studies.

Even though mutations in the *Pfmdr1* gene have been associated with decreased sensitivity to lumefantrine, identifying a gene linked with resistance to lumefantrine, the longer-acting partner drug in AL, remains elusive. Remaining in circulation many days after its artemisinin-containing partner has been metabolized, lumefantrine effectively becomes a monotherapy,[11] one that hundreds of millions of *P. falciparum* infections have been exposed

to over the last two decades. After years of scientific debate around the existence of parasites exhibiting true, frank lumefantrine resistance, a recent case study of AL treatment failure in a returning traveller from Uganda documented high lumefantrine tolerance in inhibition assays,[7] confirming previous findings from Uganda.[12] These elegant *in vitro* studies are amongst the first showing strong likelihood of a true lumefantrine resistance phenotype, similar to how chloroquine resistance was first characterized using inhibition assays.[2] Continued overreliance on AL not only puts current patients at risk but also jeopardizes future antimalarial options. Ganaplacide, an antimalarial with a novel mechanism of action, is currently being investigated as a medicine that could be paired with lumefantrine. Introducing ganaplacide with a suboptimal partner drug could be analogous to introducing ganaplacide alone and would threaten the future of this important new drug combination, the only non-ACT antimalarial likely to be introduced in the foreseeable future. The novel triple ACT, AL+amodiaquine, is facing the same risk.

In view of the growing evidence of declining AL efficacy and the rapidly emerging partial artemisinin resistance situation in East Africa, current guidelines for clinical management of imported malaria in non-endemic settings might warrant reconsideration. Options could include: extending the duration of ACT therapy by using two different ACTs sequentially, revisiting use of non-ACTs like atovaquone-proguanil, or more systematic follow-up, such as blood microscopy for confirmation of cure 21 or 28 days after treatment.

Regardless of the setting, whether in endemic countries or in returning travellers, the goal of antimalarial therapy is universal—curing a life-threatening infection in a sick patient. Because parasites do not respect borders, ensuring the best, most efficacious antimalarials are used is a joint, global effort. Surveillance of treatment response in returning travellers has historically been an integral part of identification of trends in parasite resistance, and the Grossman *et al.* article[3] is an excellent example of how surveillance of returning travellers can complement surveillance in endemic countries. Moreover, because drug treatment choice is the primary driver of selective pressure on parasite resistance to antimalarials, country or regional overreliance on a single treatment, even if it is a combination therapy, could have global consequences. Diversification of drug choice (Box 1) in endemic countries and avoiding overuse of a single therapy like AL may offer a longer window of efficacy for ACTs.

Disclosures

The findings and conclusions in this article are those of the authors and do not necessarily represent the official views of the Centers for Disease Control and Prevention or the U.S. President's Malaria Initiative.

References

1. World Health Organization. Strategy to Respond to Antimalarial Drug Resistance in Africa. Geneva, Switzerland: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO. https://www.who.int/publications-detail-redirect/9789240060265 (14 December 2023, date last accessed).
2. Campbell CC, Collins WE, Chin W et al. Chloroquine-resistant *Plasmodium falciparum* from East Africa. Lancet 1979; 314:1151–4.

3. Grossman T, Vainer J, Paran Y et al. Emergence of artemisinin-based combination treatment failure in patients returning from sub-Saharan Africa with *P. falciparum* malaria. J Travel Med 2023; taad114. 10.1093/jtm/taad114. [PubMed: 37606241]

4. Gansané A, Moriarty LF, Ménard D et al. Anti-malarial efficacy and resistance monitoring of artemether-lumefantrine and dihydroartemisinin-piperaquine shows inadequate efficacy in children in Burkina Faso, 2017–2018. Malar J 2021; 20:48. [PubMed: 33468147]

5. Moriarty LF, Nkoli PM, Likwela JL et al. Therapeutic efficacy of artemisinin-based combination therapies in Democratic Republic of the Congo and investigation of molecular markers of antimalarial resistance. Am J Trop Med Hyg 2021; 105:1067–75. [PubMed: 34491220]

6. Ebong C, Sserwanga A, Namuganga JF et al. Efficacy and safety of artemether-lumefantrine and dihydroartemisinin-piperaquine for the treatment of uncomplicated *Plasmodium falciparum* malaria and prevalence of molecular markers associated with artemisinin and partner drug resistance in Uganda. Malar J 2021; 20:484. [PubMed: 34952573]

7. Schalkwyk DA, Pratt S, Nolder D et al. Treatment failure in a UK malaria patient harbouring genetically variant *Plasmodium falciparum* from Uganda with reduced in vitro susceptibility to artemisinin and lumefantrine. Clin Infect Dis 2023, ciad724. 10.1093/cid/ciad724. Published online in press.

8. Rovira-Vallbona E, Bottieau E, Guetens P et al. Imported malaria and artemisinin-based combination therapy failure in travellers returning to Belgium: a retrospective study. Travel Med Infect Dis 2019; 32:101505. [PubMed: 31678453]

9. Bourque DL, Chen LH. *Plasmodium falciparum* malaria recrudescence after treatment with artemether–lumefantrine. J Travel Med 2020; 27:taz082. [PubMed: 31691789]

10. Sondén K, Wyss K, Jovel I et al. High rate of treatment failures in nonimmune travelers treated with Artemether-Lumefantrine for uncomplicated *Plasmodium falciparum* malaria in Sweden: retrospective comparative analysis of effectiveness and case series. Clin Infect Dis 2017; 64:199–206. [PubMed: 27986683]

11. Hastings IM, Ward SA. Coartem (artemether-lumefantrine) in Africa: the beginning of the end? J Infect Dis 2005; 192:1303–4 author reply 1304–5. [PubMed: 16136476]

12. Tumwebaze PK, Conrad MD, Okitwi M et al. Decreased susceptibility of *Plasmodium falciparum* to both dihydroartemisinin and lumefantrine in northern Uganda. Nat Commun 2022; 13:6353. [PubMed: 36289202]

Box 1:

World Health Organization recommended treatments for uncomplicated *P. falciparum* infection

- artemether-lumefantrine
- artesunate-amodiaquine
- artesunate-mefloquine
- dihydroartemisinin-piperaquine
- artesunate + sulfadoxine-pyrimethamine
- artesunate-pyronaridine

From: *World Health Organization Guidelines for Malaria*, 16 October 2023 revision.