Reply to “No Robust Evidence of Lumefantrine Resistance”

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Results from regular drug efficacy monitoring should always be interpreted in the context of the many limitations inherent to attributing apparent treatment failures to antimalarial resistance, as concisely summarized by Hamed and Kuhen (1). Notably, in study settings where direct supervision of the evening doses of artemether-lumefantrine (AL) is operationally infeasible or culturally unacceptable, low efficacy can also potentially be attributed to inaccurate dosing or underdosing. Details of how we strived to guarantee participant compliance with evening doses in lieu of direct supervision are found in our original report (2). Importantly, procedures were identical in both provinces, and we have no indication that participant adherence to the evening doses or food consumption guidelines was different in Zaire Province, where we found lower efficacy of AL. While lack of direct observation of doses and nonadherence to guidelines regarding food consumption with drug administration have been shown to be associated with lower blood lumefantrine levels, they have not been directly associated with decreased efficacy of AL (3, 4).

While *in vitro* susceptibility testing requires infrastructure rarely found at drug efficacy monitoring sites, there is a long history of complementing clinical outcome data with testing for known molecular markers of resistance (5). Samples from treatment failures with mutations associated with resistance provide more evidence of resistance than clinical outcome data alone. In our study, the detection of *pfmdr1* haplotypes previously associated with decreased sensitivity to lumefantrine (6) and the absence of mutations associated with artemisinin resistance in AL treatment failures support the hypothesis of lumefantrine resistance.

Notably, the NFD and NYD *pfmdr1* haplotypes predominated not only in recrudescence infections but also in reinfections in the AL arms. Contrary to Hamed and Kuhen's assertion, reinfections observed during follow-up do provide important data on efficacy. For the calculation of uncorrected efficacy, an important outcome for therapeutic efficacy studies, both reinfections and recrudescences are considered treatment failures. The reporting and interpretation of uncorrected efficacy results are standard components of drug efficacy monitoring for two primary reasons (7–9). First, uncorrected efficacy estimates are not subject to the limitations and potential biases of using genotyping data to differentiate reinfection from recrudescence. Second, uncorrected efficacy results provide data concerning the posttreatment prophylactic effect of the partner drug in artemisinin-based combination therapies and thus the proportion of clients that will require retreatment, data of increasing interest to malaria control programs. The reinfection rates in the AL arms in Zaire and Uíge Provinces provide a good example of the potential utility of reinfection rates. The reinfection rate in Zaire (13%) was measured as more than twice the rate in Uíge (5.1%). This was despite our screening data, where 67% of the children screened tested positive for malaria in Uíge, com-

pared to 53% in Zaire, indicating that transmission was almost certainly higher in Uíge at the time of our study. This unexpectedly high rate of reinfection in Zaire could therefore point to a parasite population that is less sensitive to lumefantrine and that consequently has a higher likelihood of successfully invading patients with subtherapeutic doses of lumefantrine following AL treatment (10).

Finally, we would like to reaffirm that while certain screened children had parasitemia levels above 100,000 parasites/ μ l, only children with parasitemia levels between 2,000 and 100,000 parasites/ μ l were enrolled in the study, as described in Materials and Methods. Given that no children with parasitemia levels above 100,000 parasites/ μ l were enrolled in any of the study arms at either site, differences in hyperparasitemia rates between the Uíge and Zaire AL arms cannot explain the difference in efficacy as Hamed and Kuhen suggest.

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