Reply to Cavaco et al

To the Editor—The work by Cavaco et al [1] nicely addresses the issue of the possible interplay between host genetic variation and the risk of acquiring drug-resistant Plasmodium falciparum strains. The involvement of the human genetic variation related to an impaired drug metabolism as a possible cofactor in the selection and spread of P. falciparum drug resistance was first addressed by Paganotti et al [2] for chloroquine (CQ) in Burkina Faso. The very important retrospective study performed by Cavaco et al [1] opens a new window of research related to artemisinin combination therapies (ACTs) and parasite resistance selection that is the ultimate tool in the research for drug resistance containment in malaria. However, some important points need to be clarified. First of all, the 2 studies were related to 2 very different epidemiological settings where different drugs were in use at different time points in the context of the spread of drug resistance. Both CQ and amodiaquine (AQ) are metabolized via the CYP2C8 enzyme, with the difference that CYP2C8 is one of at least 3 CYP450 enzymes contributing to the metabolism of CQ, whereas CYP2C8 is the main (or unique) actor of the metabolism of AQ. Moreover, the study of Paganotti et al [2] was focused on the defective allele CYP2C8*2, which is associated with drug metabolism that is impaired but not to a high level as high as that of CYP2C8*3. Unfortunately, the *3 allele is
extremely rare or absent in West Africa [3, 4] but is present in Zanzibar with very high prevalence, as stated by Cavaco et al [1]. Therefore, the association between CYP2C8*2 and the risk of carrying drug-resistant parasites was demonstrated by Paganotti et al [2] by analyzing a much larger number of samples than analyzed by Cavaco et al. Finally, the parasite genotyping in the 2 studies was slightly different but, most importantly, was consistent with the hypothesis that the human genetic background can drive the selection of drug resistance in malaria.

There is now strong evidence that the study of the pharmacogenetics of antimalarial drug metabolism can improve the knowledge of mechanisms of drug resistance selection and spread. Because the antimalarial regimens currently used in most malaria-endemic countries are based on ACTs, knowledge of the fraction of the population at risk for accumulating resistant parasites will help the scientific community search for parasite genetic markers related to the failure of ACTs. Identification of and testing for these markers will inform decisions about switching to other alternative drugs for this at-risk population and, ultimately, impact the success of therapies.

**Note**

*Potential conflicts of interest.* Author certifies no potential conflicts of interest.

The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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