Reponses to 1st set of comments from reviewer 1: Olusola Ojurongbe

1. Unfortunately, this study is not well executed, and an extensive major review will be required. The focus of this study is quite confusing. It is not clear why the authors are investigating dhfr and dhps mutations in this cohort. The country is not currently using Sulfadoxine-pyrimethamine (SP) for treatment, and the cohort being investigated also did not use SP either. WHO currently recommends SP for prevention among pregnant women and children (in some cases). Neither of these groups is being studied. The author needs to justify the reason for SP mutation analysis in this study. What would have been more interesting would have been PFCRT gene mutations since amodiaquine is still being used as a partner drug for artesunate.

   Reply 1: Thank you for your suggestion. This information has been included in the introduction and discussion of the study.

2. The authors stated in the abstract section that the "study sought to verify the genetic mechanism of resistance to sulfadoxine-pyrimethamine." The genetic mechanism was not performed as stated by the authors in conclusion. All that the author did was report the mutations in dhps and dhfr genes. The identified mutations were not studied for their contributions to resistance in this cohort. While these mutations are well known for their contributions to resistance, many studies have reported these mutations without much compromise in SP cure rate, meaning that other additional factors are needed for resistance to occur. So for the authors to state that "we provide molecular data verifying the genetic mechanism underlying SP resistance" is not correct.

   Reply 2: Thank you for your feedback. The abstract and the objectives of the study have been reviewed. The information has also been included in the introduction and discussion of the study.

3. The authors stated that the patients were followed up. In Malaria studies, the standard WHO method of following up patients is to be observed on days 0, 1, 2, 3, 7, 14, 21, and 28 or up to day 42. This will allow the definition of treatment failures (early, late, clinical, and parasitological) and adequate cure. The authors stated "responded" or "Did not respond. "How did they arrive at this outcome? Was this outcome based on fever or parasite detection? What type of failures are they considering? is it re-infection or recrudescence? All these are important in the analysis of and contribution of gene mutations to resistance. In my view, since the authors did not genotype the samples collected on the days that the patient "Did not respond," this part should be expunged as it has little or no contribution to the data being presented.

   Reply 3: Thank you for your suggestion. This has been included in the methods and results of the study.
4. It would be nice if the author could explain why only eight samples were successfully sequenced out of nineteen.

Reply 4: Thank you for your comment. This has been included in the discussion of the study

Reponses to 2nd set of comments from reviewer 1: Olusola Ojurongbe

1. I will suggest you include some of the information in your response to my comment that justifies the need to carry out pf\textit{d}h\textit{f}r and pf\textit{d}h\textit{p}s mutations in the introduction. For example, “Eritrea changed drug policy from SP to ACT in 2007” and the fact “SP has only been used as a first-line treatment in combination with Chloroquine in malaria treatment for the general population” this information will help the reader to appreciate the need for pf\textit{d}h\textit{f}r and pf\textit{d}h\textit{p}s mutations surveillance in your study.

Reply 1: Thank you for your suggestion. This information has been included in the introduction of the study

2. Although the scope of your study did not include in vivo study, the reported drug outcomes needed to be explained for reproducibility purposes. On what day after treatment was the “responded” or “did not respond” determined? Eight patients underwent re-treatment with quinine, how many days after the initial treatment? This information should be presented since this is a standardized research

Reply 2: Thank you for your suggestion. This information has been included in the methods and results of the study