Author's response to reviews

Title: Malaria and related outcomes in patients with intestinal helminths: A cross-sectional study

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Author's response to reviews: see over
Cover Letter

Thank you for considering the revised version of our manuscript ‘Malaria and related outcomes in patients with intestinal helminths: A cross-sectional study,’ by Degarege et al. for publication in BMC infectious disease. We are thankful to the reviewers and the Editor for the constructive comments you have made towards the improvement of our paper. We really appreciate all your remarks. We have taken all of your comments into consideration in revising the manuscript. Point by point explanations of what we have made in response to the reviewers concerns/suggestions is given in the following pages.

Reviewer 1

1. We accept the concerns of the reviewer as they were also ours. We minimized the impact of the concerned variables through making analysis after stratification by helminth and Plasmodium species and adjusting the regression model for effect of the other variables. (e.g. helminth egg intensity, Plasmodium parasitaemia level, age, sex, nutrition). Additionally, the study population is more homogenous (socio-economic status, source of income, ethnicity) and sourced from similar area. This will help to reduce variation in population demographics, local and focal distribution of worm infection and entomological inoculation.

2. We acknowledge for suggestion of splitting data rather than lumping the different intestinal helminth species as single, double and triple. Therefore, we made subdivision based on helminth species types for making separate analysis in the revised manuscript (Ms). In addition, we tried to focus more on P. falciparum, and presented summarized information in text form regarding the nature of association between intestinal helminth infections and odds of non-severe malaria or P. vivax mono-infections in the revised MS. However, we keep the data regarding association of any intestinal helminth with malaria in the revised manuscript due some reasons. Although variations in pathogenicity, immune response to different helminths species assumed to have a “stereotypical” profile. Thus, considering pooled gastro intestinal helminth in evaluating the nature of their association with malaria seem plausible. This will help to make a more general hypothesis (helminth vs Plasmodium) about the nature of interaction by the two groups of parasites.

3. There were no S. haematobium cases reports in the current study area based on the health facility report or previous studies in the surrounding. Thus, we did not consider examination of the current study subjects for diagnosis of S. haematobium infection.

4. We accepted that the research question requires modification for better clarity. Accordingly, the research question (objective) in the revised Ms is [association of intestinal helminths with prevalence and outcome of Plasmodium infection]. The variables (different helminth species, intensity and multiplicity of infection) assed are those which are directly linked with the research question. In addition to these, variables such as age, gender, and
nutrition status were also assessed for the study population on the ground that these variables reported to be associated with both helminth and malaria.

5. Accepted. As per your suggestion we have now provided information on the range of ages for the study population, how the subjects gave their consent to participate in the study, information in the consent disclosed to the study population, references made to the treatment of patients for malaria and intestinal worms, and incentives for participation in the revised version.

6. Accepted. It is now clarified in the revised version. We have now provided data for the mean egg per gram for *A. lumbricoides* and hook worm for different age groups. Thus, we deleted the phrase ‘data not given’ at the end of the paragraph in the revised MS.

7. Accepted. Pregnant women did not form part of the study population. Hence, we deleted all reference discussions to pregnant in the revised MS.

8. Accepted. Accordingly, we have now provided the information that ‘cross-sectional nature of the study design prevents from making firm conclusion about the risk or incidence of malaria due to previous status of helminth infection’ in the revised MS.

NB: In addition to the above specific changes, we edit the manuscript for the language as per your recommendation.

Reviewer 2

1. Accepted. The phrase ‘were showed’ in the data analysis section is now replaced with the phrase ‘were reported’.

2. Accepted. Sorry for the overlooking we made on the on the term ‘on top’. It was to mean ‘in addition’. Thus, in the revised Ms the term ‘on top’ is deleted and the statement is re written as ‘Helminth infection could also make the skin to be less retort to mosquito bites [35] promoting the success of sporozoite to pass through it and increasing the chance of blood stage infection.’

The degree of cutaneous retort among the study participants of the study by Hagel et al, [35] was determined based on immediate hypersensitivity reactivity whereby skins of individuals with different status of helminth infections were challenged by prick testing with purified extracts of mosquitoes. Then cutaneous sensitivity (retort) was determined by measuring the sizes (the wheel diameters) of the inflammation due to exposure for mosquito, and positive reactions were taken as diameters of >=3 milimeter. Please see the detail for the method from the article (Hagel et al 1993 vol 15 issue 6 pg 311-315. (method: skin testing, pg 2).

3. Accepted. The statement which included the phrase ‘non-severe’ in the last paragraph is now revised for clarification as ‘In the current study, infections with *A. lumbricoides*, *T. trichiura* and *S. mansoni* were positively associated with *P. falciparum* infection’
4. Yes, the sum of numbers of single infection for *A. lumbricoides*, hookworm, *S. mansoni* and *T. trichiura* (244) do not add up to 251 (total single infection). Among 251 individuals with single helminth infection, 7 were having single infection with *T. saginata*, *H. nana* or *E. vermucularis*. However, data about single intestinal helminths infection is now deleted in the revise Ms as per your recommendations below and in order to avoid repetition.

5. Accepted. We acknowledge for suggestion of splitting data rather than lumping the different intestinal helminth species as single, double and triple. Therefore, we made subdivision based on helminth species types for making separate analysis in the revised Ms.

6. Accepted. We have removed the odds ratio values which shows association of the different helminth species with malaria in the discussion section (paragraph=1, pg=13) and placed it in the result section (prg=3, pg=10).