Author’s response to reviews

Title: Effect of anthelminthic treatment on helminth infection and related anaemia among schoolage children in northwestern Ethiopia

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Author’s response to reviews:

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Dear Editors of BMC Infectious Disease

Thank you for sending us the comments of the reviewers who have carefully commented and evaluated our manuscript. As you will see we have gone a considerable way to meet their reservations and to follow their advice.

We hope that you will find our response acceptable and we look forward to your decision,

Dear Reviewers

Thank you for the constructive comments you have made towards the improvement of this manuscript. We have taken most of your comments and revised the manuscript accordingly. Point by point response to your concerns is listed below.

Yours sincerely

Abraham
Reviewer reports:

Reviewer #1: INFD-D-16-00006

This study assessed the impact of anthelminthic treatment on the prevalence and intensity of intestinal helminth infection, haemoglobin level and prevalence of anaemia among about 400 school-aged children in Ethiopia. The authors assessed whether the impact differs between helminth species and whether is dependent on intensity of infection. Changes in infection intensity, haemoglobin levels and presence of anaemia were assessed 4 weeks after treatment. As the authors discuss in the manuscript, there was no placebo-treated control group in the study, making it difficult to draw firm quantitative conclusions on the impact of anthelminthic treatment on haemoglobuline levels and anaemia.

Page numbers refer to the doc INFD-D_16-0-00006.pdf.

MAJOR COMMENTS

1. The conclusion should be rephrased, to acknowledge that only the short-term effects of treatment have been assessed (1 month after treatment). Both in abstract and in main text.

Response: We have included the phrase ‘one month after treatment’ in the conclusion both in the abstract and main text. (Abstract: page 2, line 50; main text: page 14, line 330).

2. Page 6, line 13 (Methods, section on study area and population): this study is longitudinal, not cross-sectional!

Response: We have replaced the word cross-sectional with longitudinal in the method section (Page 5 line 90).
3. Was the second measurement of infection intensity and haemoglobulin done in all children, or only in those who were found positive and hence received treatment? If the latter is true, the study does not adequately mimic the potential impact of mass treatment (where treatment is given irrespective of underlying infection status). Those uninfected at baseline and not-treated could serve as a control group.

Response: As stated in the method section (Page 5, line 144, 145; Page Page 6, line 122, 123), second measurement of infection intensity and haemoglobulin after one month was done only in children who were found infected with helminth and hence received treatment. In light of this, we have discussed lack of appropriate control group (e.g. placebo treated group or measurements of changes in the untreated group) as a limitation of the current study. (page 13; line 283-285). However, we also acknowledge your comment that the study does not adequately mimic the potential impact of mass treatment (where treatment is given irrespective of underlying infection status) as it lacks second measurement of infection intensity and haemoglobulin in children who were uninfected and hence untreated at baseline. Hence we have discussed this as a limitation of the study in the revised manuscript (page 13; line 280-283).

4. Table 3. It would be useful to briefly characterize the employed statistical methods again. Was it a univariable or multivariable analysis? Also, in what unit is egg intensity expressed. In view of the very low values for beta, it might be worthwhile to express egg counts in a different unit. Explain the abbreviation AOR? How many children were included in this analysis?

Response: We have included the following information in table 3

- The type of regression analysis used for generating results on table 3 as footnote: β* (regression coefficient): based on multiple linear regression analysis adjusted for age, gender, nutritional status and multiple helminth infection. aOR**(adjusted odds ratio): based on multiple logistic regression analysis adjusted for age, gender, nutritional status and multiple helminth infection.

- Explanation for aOR and β mean

- The number of children included in the analysis
The beta values express mean haemoglobin differences (not egg count differences). However, we agree that the beta values in g/dl unit scale are small. Hence we have changed the haemoglobin levels to g/l unit. Thus the beta values are now increased somehow.

5. Table 4. See previous comment

Response: We have included information on the type of t-test and z-test used for testing differences in mean haemoglobin level and prevalence of anaemia on table 4 as a footnote:

p-values*: based on paired t-test (mean haemoglobin differences between before and post treatment) and z-test of proportion (changes in the prevalence of anaemia before and post treatment)

p-values**: based on unpaired t-test (compared the magnitude of changes in haemoglobin level between two groups) and z-test of proportion (compared the magnitude of changes in the prevalence of anaemia between two groups)

We have also converted the mean haemoglobin levels into g/l unit.

MINOR COMMENTS:

6. Page 1, abstract: the abstract is very long with about 400 words and is also a bit wordy. I suggest to shorten it to 250-300 words.

Response: We have reduced the abstract words to 351 which is allowed by the journal. However, we were not able to reduce the word count further to 300. It will lose information.
7. Page 6, line 28-33 (Methods, section on study area and population): can you briefly characterize the area of residence, prevailing housing conditions, lifestyle ethnicity and socio-economic status?

Response: We have included information about the ethnic composition of the district, socioeconomic status, housing condition (page 4, 5; line 93-96)

More than 95% of the population in the area composed of the Amhara ethnic group and agriculture and trade are the main income source for majority of the community. Most of the people in the district live in houses with iron sheets/grass roof, mud/wooden wall and mud floor.

8. Page 7, line 15-20 (Methods, section on haemoglobine measurement): can you briefly summarize the WHO guidelines: what constitutes a normal Hb range and when do you speak of anaemia?

Response: We have included information on the WHO guideline for haemoglobin cut-off values below which considered anaemia (page 6; line 117 to 119).

The WHO cut-off of haemoglobin level used for determining anaemia was 115.0 g/l for children 5-11 years; 120.0g/l for children 12-14 years; 120.0 g/l for female children of 15 years of age and 130.0 g/l for female children with 15 years of age

9. Page 7, line 26-27: 5 gm □ 5 mg

Response: 5 gm (Page 6; line 121)

10. Page 7, section ethical consideration: the information regarding treatment must be placed in a separate paragraph on treatment.

Response: We have removed information regarding treatment from the ethical section and placed it under sub heading ‘Antihelminthic treatment’ (Page 6; line 129-135)

Anthelminthic treatment

Only children who were found positive for helminth infection were treated with anthelminthic drugs. Children who were infected with STHs were treated with 400mg albendazole while those who were infected with H. nana, T. saginata and S. mansoni infection were treated with praziquantel in appropriate doses (40 mg/kg body weight). Children who were infected with
STHs and H. nana, T. saginata or S. mansoni were treated with both 400mg albendazole and praziquantel (40 mg/kg body weight).

11. Page 8, line 4-7: "…were treated with praziquantel in appropriate doses". Vague. Please state explicitly what dosages where used

Response: We have indicated the dose ‘40 mg/kg body weight’ ((Page 6; line 133, 135)

12. Page 12, line 55-56: make explicit that reference 18 only considered hookworm infection


13. Page 13, first para (lines 4-14): does variation between studies in employed diagnostic tests also contribute to between-study differences in the outcome of treatment?

Response: Yes, variation between studies in employed diagnostic tests may also contribute to between-study differences in the outcome of treatment. Hence we have included this information in the revised manuscript. (page 12; line 247,248)

Previous studies were heterogeneous in the type of drugs used for treating helminth infection, in techniques used for examining infection and measuring haemoglobin level, nature of the study population, prevalence and intensity of helminth infection and length of follow up period. These may have contributed to the differences in the magnitude of haemoglobin change after anthelminthic treatment.

14. Page 13, line 20-21: "Increase in the age and intensity of hookworm infection…" I assume this refers to the age of treated children rather than worm age or so. Please rephrase to clarify this. The same phrase occurred somewhere else.

Response: We have revised it as “Increase in the age of children” (Page 12; line 252)
15. Table 2: Consider the use of a wide table, where results for prevalence and intensity are given in different columns but on the same row. This better reflects the association between the two indicators.

Response: We have converted table into a wider format with prevalence, intensity and percent reduction data on the same rows but on different columns.

Reviewer 2

Reviewer #2: This is a well written and informative piece of research that shows the benefits of de-worming. I am pleased to accept this for publication. The English can be improved in places but this in minor. I would suggest improving the manuscript by adding to the introduction some information about these diseases as NTD's their transmission and the long term goals for NTD transmission.

Response: We have added information about helminth as NTD's and the long term goals for NTD transmission. In addition, we have edited the manuscript for language (Page 3; line 56-66).

Neglected tropical diseases (NTDs) are heterogeneous group of disease due to viral, bacteria or parasite infections such as soil transmitted helminth (STH) and Schistosoma mansoni [1]. NTDs pose public health problem for over one billion people worldwide particularly in the developing countries [1]. NTDs are responsible for over 48 million disability-adjusted life years lost each year [2].

Today a scale-up of mass drug administration program is underway in various parts of Africa, Asia and South-America to control NTDs such as schistosomiasis and STH by 2020 [1,3]. The program involves administration of anthelminthic drugs to at-risk populations, usually without prior diagnosis [4]. ... .........