Author's response to reviews

Title: The role of nutrition in integrated programs to control neglected tropical diseases

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Author's response to reviews: see over
We thank the reviewers for the time they have spent in reading and commenting on our article. Our responses are shown in blue beneath each point.

Referee 1: Eric Ottesen

Indeed, the abstract is better than the body of the paper in making 2 valid points: 1) ?in controlling NTDs ?mass drug administration?? is only the start of the process of recovery?; and 2) ?there is a major role for nutrition?..and behavior change activities to build on the benefit of treating NTDs with drugs.? In fact, I would go further with the second point to make the more positive statement that the drug treatment programs in place now provide unparalleled opportunity to make enormous gains by adding a nutritional component to these large-scale programs. This is what needs to be stressed, not deficiencies due to lack of complete comprehensiveness of the NTD programs today. It is more than obvious that all the current NTD efforts are carried out in resource-constrained environments; rather than to decry the absence of a potential complementary initiative, the authors should take advantage of their insight and experience to promote the opportunities these ?incomplete? programs offer.

We have revised the last sentence of the Abstract to make this point more clearly

With respect to the text changes that need to be made:

1) Page 4: the comment about preventive chemotherapy not preventing reinfection pertains to some of the NTDs (the citation is correctly to STH), but not to all.

The point is relevant to all helminths listed in Table 1: there are infectious stages present in the environment either as eggs or larvae on the soil or as stages undergoing development in intermediate hosts before becoming infectious. The only infection for which this is not true is *Chlamydia trachomatis*. We have added some words to make it clear that this refers to the helminths listed in Table 1.

2) The maps in Figure 1 are not compelling and, as presented and described, do not make a point more than the statement that NTDs, underweight and anemia are all prominent in SSA.

We thought that the map would show readers where in Africa NTDs and these conditions occurred and it would be visually eye-catching. As the associations are not clear we have replaced the maps with a graph that shows the association between the number of NTDs per country in 47 countries and the average prevalence of anaemia and underweight. The values of r, the correlation coefficient, are all statistically significant. We hope that this makes the point more clearly. We recognise that association is not causation, but the needs for treating NTDs and chronic undernutrition tends to be in the same countries.
3) Figure 2 means nothing to me. If there is an important message here, it needs to be identified more clearly.

We have revised the text and the legend to the Figure to explain it more clearly.

4) Page 6: ??there is a goal to eliminate onchocerciasis and lymphatic filariasis in the Americas? needs to be expanded, as the goal to eliminate LF is global.

We have revised the text to say that the aim is to reduce worm loads for intestinal helminths and schistosomiasis although there is a global goal to eliminate onchocerciasis and lymphatic filariasis.

5) Page 9. The statement that ?? the public health implications for the NTDs listed in Table 1 are that being well-nourished generally mitigates disease and disability, and may also help prevent reinfection? is something that could be said about essentially every disease and is more a platitude than a compelling critique of current NTD programs.

We have deleted the sentence.

6) Table 1. This is described as a list of NTDs for which ?there are single dose treatments available?. It indicates that Loa is not in the WHO listing, but it should not be in this Table either, since ivermectin is not a ?single dose treatment? for Loa. There is none currently.

We have dropped Loa loa from the Table.

7) Table 2. It is always difficult to display the costs of the drugs in NTD programs. Ivermectin is listed as free, but the same should now be said of the mebendazole and albendazole because of the new donations. Also Zithromax is the major azithromycin used for trachoma, and it is not only free as well but is valued at a cost much higher than that listed in the Table.

The costs of all treatments except for ivermectin are provided by UNICEF (shows by superscript a in the table). UNICEF does not supply ivermectin, presumably because it is provided free. Some drugs may be valued at a higher cost presumably for tax purposes, but we felt that the UNICEF price was likely to be the lowest available purchase cost for countries wanting to buy these drugs. We have added the nominal cost of Mectizan. We have explained in more detail that purchase costs depend on many factors. We have added the recent offer by GSK to make albendazole available free through the WHO.

8) Page 14. The comment about ?anger and suspicion? among Tanzanians ?because the drugs did not alleviate the symptoms of disease for adults? cites
a very inferior review article that deserves little credence? not that it is
impossible that such feelings could exist in some individuals, but clearly this is
not at all the attitudes of essentially all treated Tanzanian (and other)
populations.

The authors of the paper that we cite are both at the London School of
Economics, which has a modest reputation. The journal that their paper was
published in is ranked by Journal Citation Reports, which means that it is peer
reviewed. This indicates to us that the authors’ conclusions should be given
some credence. Nevertheless we have edited the line now to say: the
program was not perceived to be useful by some beneficiaries, so removing
the pejoratives.

Referee 2: Xiao-Nong Zhou

The manuscript could be published after minor revised.

Main Comments

The manuscript reviewed the update progress on the role of nutrition in the
integrated control program after overlook the relationship between nutrition
and NTDs.

1 In the part of ?Distribution of NTDs and undernutrition?, three maps showing
the NTDs? distribution, undernutrition in a group vulnerable to NTDs, and
prevalence of anemia in pregnant woman, but without any explanation or
analysis on their relations.

We have replaced the maps with a figure that better shows the relationships.

2 In the part of ?Interactions of nutrition and infection?, it is better to include
the three parts. First, the impact of nutrition on the infection. Second, the
impact of infections on nutrition. Third, the interactions of nutrition and
infection. If it works, then the part of ?The specific effect of NTDs on human
nutritional status? need to be replaced by ?The mechanism of the
interaction?, in order to overcome those overlaps between above two parts.

We have revised the section and added an opening paragraph to make this
point, then reorganised the rest to follow on logically.

3 The two parts of ?Recovery after treatment? and ?Integrate control
programs? need to be merged together, since the treatment is one of
combating measures in the integrated control program. It is better to use the
title of ?Specific roles of nutrition in the integrated control program?. Then, the
specific and quantitative roles of the nutrition may be able to determined in
this review by compare several evidence-based articles.

We think that the two sections make different points that are usefully
distinguished. The first section, which we have renamed ‘Recovery of
*nutritional status* after treatment’ make a point not often appreciated, that
deworming alone is not sufficient to lead to improvements in nutritional status
or growth. Anthelmintic drugs only remove a factor that may have caused
malnutrition but they do reverse the harmful effects or deficits, that requires
food. The authors of paper 47 that we cite clearly do not understand this
point, so it is worth highlighting in a separate paragraph.

The second section is about the need for nutritional interventions within an
integrated control program, so that deworming and nutrients are not enough.
This is a different point, so requires a separate section.

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Referees’ comments that must be addressed:

1. Please provide a more thorough explanation of the maps in figure 1 (ref 1 and ref 2)

   The maps have been replaced.

2. Please expand slightly on the statement about drug treatment in the abstract to make a more positive point about drug control (ref 2)

   We have added words to say that treatment is crucial to controlling disease and transmission, but is only the start of the process of physical recovery.

3. Preventive chemotherapy does not prevent reinfection in only some NTDs; please make this point and mention that this applies to STH

   We have edited the text, but the point applies not just to intestinal nematodes, it applies to schistosomes, as there is an intermediate stage in snails, and to the larvae of filarial worms in insect vectors, neither of which are killed by drugs given to humans. The referee may argue that the life span of infected vectors is short, but so is the life of hookworm larvae. Even if mass treatment of humans was 100% effective, reinfection could occur immediately afterwards by these residual infective stages,

4. Figure 2 requires further explanation (ref 2)

   An explanation has been added.

5. The point about ??there is a goal to eliminate onchocerciasis and lymphatic filariasis in the Americas? (page 6) should be expanded to describe that elimination is a global goal (ref 2)

   This has been explained.

6. Loa loa should be removed from table 1 as there is no single-dose therapy (ref 2)

   This has been done.
7. More discussion should be included about the difficulties of costing drug treatments (ref 2)

We have added the following, which reinforces a point made by Referee 1: The purchase costs are highly dependent on the availability of generic drugs and the number of tablets purchased, while some drugs are now available free. For example, although the nominal cost shown in Table 3 of a tablet of ivermectin is USD 1.50, it has been made available free for treating onchocerciasis since 1987 by the Mectizan Donation Program.

8. Ref 2 comments that "anger and suspicion? among Tanzanians ?because the drugs did not alleviate the symptoms of disease for adults" cites a very inferior review article that deserves little credence. Please present a more balanced view here, as it cannot reflect the opinion of all Tanzanian people. If possible, please cite a primary research article here.

We refer the Referee to our response to the same point made by Referee 1 and to the edited text.

Editorial requests

1. Please clarify whether each figure was made for this manuscript, and if not, whether copyright permission has been obtained. Please note that it is the responsibility of the author(s) to obtain permission from the copyright holder to reproduce figures or tables that have previously been published elsewhere.

Yes, all figures have been created for this paper. Figure 1 has been changed from maps developed by Dr Zhang to show a plot of the associations between data derived from primary sources, which are cited, and is original. Figure 2 presents the conceptual model in a very different way from the original, which used boxes and standard deviations, so it is novel. We can provide a scan of the original to show that the figures are nothing like each other, or it can be found on page 146 of Scrimshaw et al. (1968). Figure 3 is a typical flow chart used in compartmental models of infectious diseases but was designed for this review. Figure 4 was designed by the authors.

2. Please expand the Authors' contributions section to include whether YZ, CM and SB were involved in the drafting or revising of the manuscript, and whether all authors approved the final manuscript. An 'author' is generally considered to be someone who has made substantive intellectual contributions to a published study. To qualify as an author one should 1) have been involved in drafting the manuscript or revising it critically for important intellectual content; and 2) have given final approval of the version to be published. Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content. Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
Yes, all authors have contributed, both to drafts of the report from which this paper was derived and to the drafting and revising this paper as well. All authors have approved the final version of the paper.