Author's response to reviews

**Title:** Lymphatic filariasis control in Tanzania: Effect of six rounds of mass drug administration with ivermectin and albendazole on infection and transmission

**Authors:**

Paul E Simonsen (pesi@sund.ku.dk)
Yahya A Derua (yahyaathman@yahoo.com)
William N Kisinza (wnkisinza@gmail.com)
Stephen M Magesa (smagesa@hotmail.com)
Mwele N Malecela (mweleentuli@gmail.com)
Erling M Pedersen (empe@sund.ku.dk)

**Version:** 2 **Date:** 15 May 2013

**Author's response to reviews:** see over
Response to comments from reviewers

Thank you for the useful comments from the two reviewers. The comments have been carefully considered and detailed responses are given below.

Reviewer 1:

- **Introductory remarks:** The shift from *Anopheles* to *Culex* transmission in the study area has been described and analysed in detail in two previous publications by our group (Meyrowitsch et al., 2011; Derua et al., 2012), which are also referred to in the Discussion (p. 17). Several other papers have reported on the dramatic change in *Anopheles* populations that have taken place in coastal East Africa in recent years (especially in relation to its effect on malaria transmission), but most of these have been based on recent spot checks and ascribe the change to the recent mass distribution of insecticide treated bed nets. The uniqueness of our study is that we have longitudinal mosquito data collected over a period of many years in an area where no mass distribution of nets or other major mosquito control activities have taken place. This suggests that other factors (probably environmental) may be at least partly responsible for the observed changes, as we also discuss and analyse in the above two papers.

- **Comment 1:** The reviewer is right, - it should be 21 months. This has now been corrected in Methods (p. 5) and in the Discussion (p. 16).

- **Comment 2:** We are aware of this, although in general we do not find major differences in the results obtained with the different tests. We therefore wrote the following in the Discussion (paragraph 3, p. 16): “The change in methods for measuring both CFA and antibodies to Bm14 are not likely to have had a major impact on the obtained results, but should still be kept in mind when analyzing and interpreting the findings”. Later in Discussion of the CFA findings (paragraph 5, p. 17) we wrote: “The two tests for CFA detection (ELISA and ICT cards) have been shown to be well in agreement when measuring CFA status”, and we give a reference. Finally, in Discussion of the Bm14 findings (paragraph 6, p. 17) we wrote: “Although the different techniques used and age groups examined prevent exact comparisons, the very pronounced decrease ……indicated that a major decrease in exposure to transmission had taken place in the human population, which is also in alignment with the findings from the entomological surveillance”.

- **Comment 3:** Comparison of compliance for mf+ and mf- persons is an interesting but rather complicated issue (there have been 6 rounds of treatment and part of the study population has changed over the years, as described in the paper). In combination with more detailed interview based surveys we have chosen to address this issue in a separate paper (in preparation).
Reviewer 2:

- **Introductory remarks:** In this manuscript we aim to give an overview of the effect of MDA on infection and transmission, with particular focus on the later part of the study period. We acknowledge that the information collected over the 8 years study period is huge, and that the set-up is complex since for practical reasons some of design and methods had to change over the long study period. This is a reflection of reality, but we have done our utmost to give a clear overview presentation of activities and findings. Some of the detailed findings from the study have been published elsewhere and are referred to in appropriate places in the manuscript (such as methods, design and effect of treatment in the early period of control (Simonsen et al., 2010, 2011), and the shift from *Anopheles* to *Culex* transmission (Meyrowitsch et al., 2011; Derua et al., 2012)), and other more specific details will be addressed in subsequent papers (e.g. entomological aspects, and treatment compliance in different infection groups of individuals). We have improved on the description of treatment coverage and net coverage surveys (see below).

- **Comment 1:** As requested by the reviewer we have added a map showing the location of survey sites (Figure 1) and a table showing the timing of major activities (Table 1). Because of this, the number of subsequent figures and tables has increased by one.

- **Comment 2:** In Table 1, the sample size for males examined for hydrocele and males + females examined for elephantiasis has now been specified in a footnote. In addition some minor errors in Table 1 have been corrected. In Table 7, the sample sizes for assessment of “surveyed coverage” in the community study and the school study have been specified in the footnotes.

- **Comment 3:**
  - The net coverage surveys were included as part of the post-MDA 5 and 6 community questionnaire surveys for treatment coverage. This has now been specified and sample sizes indicated under Methods (“Assessment of Treatment coverage and bed net use”, second paragraph, p. 8-9).
  - Yes, net coverage was low and did not change much between 2010 and 2011 (but also note that the surveyed population after MDA 5 and 6 was not exactly the same). A major reason for the relatively low net coverage was that there had been no general net distribution by the Ministry of Health or other organization at the time of the surveys. This distribution only took place in September 2011 (as indicated on p. 9).

- **Comment 4:**
  - Considering the amount and complexity of information presented in the manuscript, which is also acknowledged by the reviewer in the initial comments, we do not find the discussion to be very long. We have done our utmost to clearly explain and interpret the findings in light of the complexity and the long duration of the study.
As regards the repetition of some selected quantitative results in the Discussion, this was done in order to present messages clearer to the reader, but we have decided to follow the reviewers recommendation and have deleted the repetitions (paragraphs 2, 5, 6, 8 and 9).

As regards the change in vector composition, this has been presented and analysed in detail in previous papers which we indicate and refer to in the Discussion (paragraph 7, p. 17): “This remarkable shift has been documented and analysed in more detail elsewhere (Meyrowitsch et al., 2011; Derua et al., 2012)”. We then go on to discuss if MDA could have a role in this shift (i.e. has the ongoing LF control played a role in the shift; - other possibilities e.g. environmental or climate change were discussed and analysed in the earlier papers, and will be so in forthcoming papers), and we conclude that whatever the reason it certainly has important consequences for the epidemiology of LF in the area (an example of the consequences this may have on transmission is furthermore given in the following paragraph 8). There is nothing buried or hidden, but considering that this shift has already been presented and discussed in detail earlier and the huge amount of other findings presented here we have to limit the discussion of each item.

As regards the “decline in all indicators examined” this is exactly what we are stating in the first sentence of the Conclusion (p. 20) and in the Conclusion in the Abstract (p. 2).

**Comment 5:**

In the Conclusion we summarize the main findings from this study and suggest ways forward. We do say that the purpose of community engagement should be to ensure higher treatment coverage (i.e. that the target population takes the MDA). It is our experience that most of the MDA target population has no idea about what is going on, they are not properly informed about timing, reason and benefits of the MDAs, they are getting fed up with the programme, and in general it is our impression that treatment coverage (outside the study sites) is lower than what we observe and report in the present study. This is what we are trying to express and warn against (in a gentle but clear manner) in the last paragraph of the Discussion (also with reference to the recent study of Parker & Allen, 2012, carried out in the same area). In the Conclusion we suggest - as the most important way forward - strengthened information dissemination and engagement of target population in activities in order to increase understanding, acceptance and ownership of the programme, and thereby to increase MDA coverage and prevent the leveling off of the effect of the control programme (expressed in a diplomatic manner in the manuscript; - we would like to be able to continue to work in Tanzania). Similarly, it is important to inform and engage the target population in relation to the bed nets, which have been distributed on a large scale without any thorough information dissemination and engagement of the target population. The bed nets are now on a large scale being used for all other purposes than human mosquito proofing.
- We have added a sentence in Conclusions saying that “Environmental management to limit breeding of the Cx. quinquefasciatus vectors should also be encouraged”, as this is also a measure that can be promoted via community engagement.

- **Minor essential revision 1:** Yes, during the first part of the study we used the Og4C3 ELISA to analyse for CFA in the community specimens (reported in detail in the earlier paper by Simonsen et al., 2010). This has now been specified under Methods (p. 7) and in Table 1.

- **Minor essential revision 2:** As suggested, “strived to” has been changed to “intended to” (p. 5).

- **Discretionary revisions:**
  - On the usefulness of the entomological indicators, this has been discussed in earlier papers by our group, which are referred to in appropriate places in the manuscript (e.g. Rwegoshora et al., 2005; Pedersen et al., 2009; Simonsen et al., 2010).
  
  - Yes, MTP is a composite indicator for which differences cannot easily be examined statistically. Instead we carry out statistics on the mosquito infectivity rates (one of the parameters in the calculation of MTP). We still think the MTP is a useful index, as it gives a good overview of the level of transmission and its change over time.
  
  - On prospects for improvement of the entomological surveillance, this is discussed on page 18 (paragraph 8 in Discussion).
  
  - On the correction factor from light traps to bites per person: Yes, we do think it is valid, as argued for by Lines et al. (1991) when it was introduced for this kind of mosquito catches in this study area (referred to in Rwegoshora et al., 2005). However, as we in this paper use it throughout the study period and we mainly look at relative changes in number of mosquito bites over time, then the issue is not really of much importance for the overall findings presented in the paper.