Author’s response to reviews

Title: Establishing the extent of malaria transmission and challenges facing pre-elimination in the Republic of Djibouti

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Author’s response to reviews: see over
Dear Editor,

Please find below our responses to the comments by the reviewers of our manuscript:

**MS: 9916124585061968 - Establishing the extent of malaria transmission and challenges facing pre-elimination in the Republic of Djibouti**

**Reviewers's report**

**Title:** Establishing the extent of malaria transmission and challenges facing pre-elimination in the Republic of Djibouti

**Reviewer:** Charles Delacollette

**Reviewer's report:**

**To be published with Minor Essential Revisions**

The paper describes the first national malaria survey in Africa incorporating -in addition to routine MIS data information - parasitological and serological markers expected to provide relevant “biological information” on the extent of malaria transmission in the Republic of Djibouti in order to ultimately explore the potential for malaria (pre-) elimination.

**General comments:**

This is a very well designed large-scale survey building on existing agreed upon methods (MIS) incorporating important up-to-date biological parameters to look at more carefully when progressing towards pre-elimination conditions and status. The sampling method has been carefully designed in a situation where events are becoming rare and increasingly patchy with a quite detailed description of laboratory, equipments and reagents used.

Authors rightly conclude that additional survey parameters used to assess transmission across the Republic provide information on the biological feasibility to (pre) eliminate malaria without too much insisting on the operational feasibility to achieve such ambitious target. I would suggest that the title reflects the study purpose (biological feasibility) which per se is a critical “decision-making” element to be considered among others by malaria national programmes. I am not a statistician so I cannot comment on statistical procedures used but authors seem to have considered all conditions / variables and parameters which might influence results and their final interpretation.

We would like to thank the reviewer for his comments. In discussing the biological feasibility of malaria elimination in Djibouti, it was inevitable not to discuss operational feasibility constraints as well to provide the readers with a more complete picture, although we acknowledge the primary focus of the paper is biological feasibility. We think therefore the current title generally captures the context of this manuscript and we would like to maintain it.

Elimination targets all malaria species. This is only on page 14 that authors mention P. vivax infections. This is a big randomly sample survey using sophisticated laboratory tools like PCR expected to give information on all malaria species. Authors should explain why they are not referring to / searching for other species infections than P. falciparum when looking at parameters to support malaria elimination.

During the parasitological survey, only *P. falciparum* specific RDTs were available for survey. We
subsequently used PCR on all the positives and a subset of the negatives to check the RDT falciparum confirmed cases. Due to logistical (particularly funding) reasons we were not able to confirm all the samples with PCR. The national malaria programme is planning to undertake an MIS next year and during this exercise it is planned that a pan-species RDT and \textit{P. vivax} serology will be implemented. We have revised the 4\textsuperscript{th} paragraph of the discussion and the first and second paragraphs of the conclusion to reflect this.

Into the conclusion section, authors should provide information on the cost (effectiveness) of the survey and recommendations on this proposed MIS+ tools for other (small?) countries facing similar challenges. Is it a survey tool to be recommended to programmes (or further adjusted?) in an increasingly patchy transmission environment with rare or no events? Is it a national survey to be repeated at regular interval when progressing toward elimination? Do malaria programmes and Governments have to rely on such (expensive?) data to inform / decide on next steps and assess progress?

We agree with the relevance of the reviewer’s suggestions here. While one can make some plausible arguments about the feasibility and cost-effectiveness of such studies for countries similar to Djibouti, it is harder to put down actual figures of cost-effectiveness because it would require a detailed analysis, not only of the money spent on each component of the survey, but also the opportunity costs due to survey work in terms of the health workers used and the researchers involved in the analysis of the data and the subsequent programmatic impact of the results of the survey. For example do results improve planning? By how much? What are the resources saved through optimal planning as a results of the study? While valuable, this is beyond the scope of this study. However we accept that this is an interesting observation/comment and does deserve more research attention

We have raised these important issues in the first paragraph of the revised conclusion section.

Specific comments:

The “MIS+ survey method” is well described sometimes with too many details on laboratory procedures making the narrative quite complex too read. Such useful details indeed could appear as foot notes or in a special annex to inform scientists.

We elected to maintain the detailed description of the survey and laboratory methods as a compromise between addressing a general readership, which is our main aim and providing sufficient information upfront for those who are technically oriented. While we sympathise with Prof Delacollete’s difficulties in reading through this section we feel that we have tried to balance the appropriate methodological detail for a diverse readership of BMC Infectious Diseases.

The survey design has incorporated blood smears to be taken in a subsample of the investigated population in addition to RDTs and filter papers. Blood smears unfortunately were of poor quality and unable to be read. Quality assured microscopy diagnosis is so far one of the cornerstone elements of any malaria (pre-) elimination programmes. From authors’ statement, it seems that there is no national procedure towards a culture of quality microscopy diagnosis in Djibouti. Can authors comment a bit further on this?

There are important gaps in the diagnostic capacity in Djibouti in terms of microscopy and the scale-up of rapid diagnostic tests. While efforts are being made to remedy this situation there remain major challenges. We highlight the need for improved surveillance and diagnostics capacity at the end of the conclusions section.

Authors refer to biological “pre-elimination” conditions towards elimination without referring to any “decision” threshold per suggested parameter over space and time (RDTs, microscopy, sero-epidemiology or PCR). Any suggestions to be considered?
The reviewer raises important questions many of which are addressed in the recent Lancet series on malaria elimination and we cite these references where relevant. For further clarification we have included the following text and relevant references in the discussion.

The threshold of parasite prevalence seen as the benchmark for deciding whether to move on to malaria elimination or sustain low endemic control is seen as 1% parasite prevalence [3,11]. But to detect this level of prevalence requires large and expensive survey samples. The threshold for serological markers remains unclear although the absence of exposure among children under the age five years would be a good indicator that a country is approaching pre-elimination [3]. An alternative equivalent index is case incidence of 1 per 1000 persons at risk [3, 26]. To reliably estimate this index, there is need for accurate passive and active case detection data over several years [11]. This requires a properly functioning national malaria surveillance system based on a quality assured diagnostic capacity to provide the accurate information on whether Djibouti has achieved the biological threshold for elimination.

Migrant and mobile populations are critical but complex “parameters” to be factored in any pre-elimination equation as rightly mentioned by authors. Multi country approach is needed. Have authors any ideas how statistics and sampling methods targeting such special population (including from military force) could further help from an elimination perspective?

Human population movement (HPM) and its effect on malaria transmission is a complex but important aspect of malaria elimination (captured under the combined effects of receptivity and vulnerability). We have tried to highlight these issues specifically as they relate to Djibouti in paragraph 6 of the discussion. Although recent attempts have used mobile phone data to evaluate potential risks associated with HPM [ref 63], the issue of redesigning survey sampling to capture detailed HPM is one that has not been explored. Other avenues for capturing HPM malaria data include screening (and treating) of entering passengers for malaria. Ongoing work, however, aims to model the theoretical impact of HPM on malaria transmission in Djibouti. We have now expanded paragraph 6 of the discussion to reflect these issues.

Authors conclude that there is no / poor statistical correlation between fever and history of fever and biological parameters used. Any comments on this important observation pertaining to the routine use of clinical parameters towards pre elimination?

This correlation is indicative of the fact under low malaria transmission majority of fevers are unlikely to be malaria and fever as a proxy for malaria and as the basis for clinical diagnosis of malaria is poor. This is now recognised globally and by the Djibouti national malaria control programme which has already started the process of scaling up diagnostics.

In Fig3, investigated locations are classified into 3 categories: high, low and insignificant prevalence. What does “insignificant” mean? Any timeframe (how many years per location with such ranking status?)

These categories refer to high prevalence clusters (hot spots); low prevalence (cold spots) and those which clustering were not detected. The legend of the image has been revised to be clearer.

Conclusions:

This is a very interesting and original paper to be published with minor essential revisions to clarify the survey purpose and clarify / further comment on some statements, conclusions and recommendations.

We again thank the reviewer for his very useful queries and suggestions.

Reviewer: David Smith
Reviewer's report:

1. The study described in this manuscript describes the results of a large national parasitological survey recently conducted in Djibouti as part of the National MIS. The report is more than a report on the MIS because it also reports on a serological survey conducted using the filter papers collected at the same time as the rapid diagnostic test. This method (serology) has long held the promise of being able to collect important information about the history of transmission in low intensity settings such as Djibouti. The study found much higher seroprevalence than prevalence.

The study concludes that 1) malaria prevalence is very low in Djibouti today and there is no strong evidence of high rates of malaria importation, so that it would be a place where elimination would likely be technically feasible; 2) that malaria seroprevalence is indeed, highly sensitive. It's very well written and designed and most of what I'm saying here falls into the category of picking at nits.

I confess I had to look up Getis-Ord, but I now understand a new statistical test and it was appropriate for the kind of data that they have. I did wonder whether the hot spots had significant Z-scores for prevalence separately or for seroprevalence separately, (as opposed to and/or) and whether the hot spots were in the same place. It wasn't clear and could be interesting.

We would like to thank Dr Smith for the encouraging comments. The hotspots didn’t have significant Z-scores for prevalence but had significant Z-scores for sero-prevalence and the pattern for this was similar to the one observed for the combined parasite and sero-prevalence (although data not shown). The relevant results section has now been revised to reflect this.

2. One question about the decision "not to use traditional three standard deviations above established control sera but have used a mixture model..." It would be good to know how well this has been validated for malaria markers where serology is trickier than it is for rubella and measles. This seems like it could be quite important, because of the possibility for false positives. It could, on the other hand, lead to much more reliable use of serology. It merits asking whether it has been used and validated for malaria before? It might be worth a more extensive comment one way or the other.

Defining sero-positivity is sensitive to the cut-off used and the traditional 3 STD model applies a fixed cut-off which doesn't account for overall distribution of the samples and can be inappropriate under settings of low transmission. The use of mixture models in malaria serology are detailed in (Corran et al. 2008; Stewart et al. 2009; Williams et al. 2009; Bousema et al. 2010; Cook et al. 2010), all which have been cited in the relevant sections of the manuscript. As presented in detail in the methods section of the manuscript the mixture model splits the population into two distributions, a narrower one which is made up of the non-exposed and a wider one consisting of those with variable exposure and responsiveness. Mixture models have previously been used to define anti-malaria antibody cut-offs in low endemic settings equivalent to Djibouti using similar antigens (Bousema et al. 2010- ref 28). However, we recognize the need for further sensitivity analysis of this method and have already made this suggestion in paragraph 2 of the discussion.

3. I have a couple of quibbles about language, one or two are minor but essential and worth trusting the authors to make:

Abstract line 3: "these are of less value" less than what? I suspect they mean to say that they are unlikely to find any positives and so they convey little information about malaria transmission, even with very large and expensive surveys. I think the right term is "not very efficient" Results last line: "increasing combined P. falciparum exposure" I'm not sure the word combined belongs there.

Agreed. Both changes have now been made in the abstract.
Bottom of page 3: “has low sensitivity” Again, a quibble, but they don’t mean sensitivity, which in this context, could be confused with the idea that there may be lots of low density infections that tend to be not detected when present by a single test (see their ref 27), but the fact that at very low endemicity, they are bound to find lots of true negatives and very few positives. Again, I would opt for “efficient” over some other term.

Agreed. Change now made.

Top of page 4: “define the extent of transmission” seroprevalence is telling you something about the history of transmission, not necessarily about current transmission. Add the word “previous”?

Here we disagree slightly with the Dr Smith. This study presents the combination of parasite infection prevalence and exposure in Djibouti and therefore not just about historical transmission. Furthermore while the presence of antibodies is primarily a marker of previous exposure, they could also be the result of current active infections which are at the stage where an individual’s immune system has started producing antibodies in response to the presence of the parasite.

Page 5, 2/3 down: “anticipated over-distribution” I think they mean "over-dispersion"

Agreed. Change has now been made.

Page 6, near the top: “The estimated required sample was...” required for what? Later, the text mentions net usage, but it would be worth mentioning that fact here. Also, what effect size was it powered to detect?

We have made the necessary clarifications here in the revised manuscript.

Page 12: “A unit increase...” Do age groups have units? I’m not sure what they mean. “A one age-group increase”?

‘An increase in age group’ has now been used to replace ‘A unit increase in age group”

Page 14 near the top, there's an errant “[” or it was not closed.

We thank Dr Smith for picking this out. Correction has now been made right after Ref 45

Page 15 “the significance of human population movement for the risks of imported infectious diseases, including malaria, cannot be under-estimated” Do they really mean that? Or do they mean that they should not be under-estimated. Of course it’s possible to under-estimate the risks.

We agree with the reviewer that ‘should not’ is the appropriate word here instead of ‘cannot’ and this change has now been made.

Yours sincerely

Dr Abdisalan M Noor