Author's response to reviews

Title: Integrated monitoring and evaluation and environmental risk factors for urinary schistosomiasis and active trachoma in Burkina Faso before preventative chemotherapy using sentinel sites

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Dear Editor,

Thank you very much for allowing us to resubmit our manuscript for publication in your subject-specific journal, BMC Infectious Diseases. We have addressed the comments by providing a point-by-point response to the referees’ comments as well as the editorial requests and by revising our manuscript accordingly.

We attach our revised manuscript, and we hope that the modified version is now suitable for publication in BMC Infectious Diseases.

Kind regards,

Artemis Koukounari on behalf of all the authors.

A Koukounari
Jonathan King

Reviewer’s report:

The authors present results from a cross-sectional integrated schistosomiasis (SCH) and trachoma (TRA) clinical assessment among a fixed cohort of school children 7-11 years of age in 21 sentinel sites in Burkina Faso. Prevalence estimates for these villages are reported for SCH infection and clinical signs of active trachoma in addition to results of an exploratory analysis of associations of the diseases with environmental and weather data. The authors should be commended on planning and implementing integrated disease assessments to be used to monitor and evaluate national program activities aimed to control SCH and eliminate blinding trachoma in the absence of such guidelines and recommendations from WHO. The authors have addressed some important issues surrounding the integration of disease assessment and the limitations of the methods that were utilized.

We wish to thank the referee for acknowledging our efforts in this respect and for a very thoughtful, insightful, and helpful report.

However, the reader is left unsure of the specific questions posed by the authors and the purpose of the study. The title indicates that the manuscript is a risk factor assessment for both diseases, but it seems as though there are two parallel stories being told. The first and most relevant to NTD programs is the feasibility and programmatic interpretation of integrated assessments of SCH and TRA using sentinel sites. The second is the associations found between extrapolated weather data and the diseases which programmatic relevance is not clarified.

Our aim was to indeed study both diseases and to evaluate the feasibility and programmatic interpretation of such integrated assessments of these, using sentinel sites. With regards to associations found between interpolated weather data and the diseases, such results can inform the construction of reliable disease maps and mathematical modelling efforts of these two NTDs as well as the ‘E’ component for the SAFE strategy in the case of trachoma. In light of the comments by the referee, we have revised the title, introduction, methods and discussion sections to highlight and clarify the aims of our study and analyses.

The authors selected a cohort of children 7-11 years of age from schools in the selected sites and interpreted the findings of the school sample as a proxy for community prevalence as accepted by the WHO for SCH control programs. However, the authors excluded the age groups most appropriate for assessing either disease; children 10-14 years for SCH and 1-9 years for TRA. The authors have done well in discussing the limitation of trachoma findings due to the age group selected, yet still suggest trachoma interventions using WHO thresholds established for a different age group.

We completely agree that the most appropriate ages for assessing the prevalence and associated morbidity of both of these diseases may well not be entirely equivalent to/compatible with the design of the sentinel site surveys described in our paper. However, there was a reason for our choice to recruit a longitudinal cohort of 7-11 years old at baseline, and this was that we would be able to follow-up these same children during three years and thus we wanted to increase participation and make these surveys logistically manageable.

Regarding schistosome infections, the monitoring and evaluation of the age group we have chosen has proved logistically and scientifically viable as well as cost-effective across a range of studies and programmes. Regarding trachoma infections, and recognising the potential limitations of the age-group investigated here, in this manuscript we recommend that the current protocol should be implemented only in hypoendemic trachoma areas of Burkina Faso if MDA treatment decisions and intervention with the full SAFE strategy are to be made based on results arising from similar study designs. We recommend this assuming that there is also a peak shift of the maximum infection prevalence towards younger ages (i.e. slightly greater than 5 years of age in the hypoendemic; slightly under 5 years in the mesoendemic, and very low (under 1 year) in the hyperendemic areas).

We have therefore revised the discussion section in order to address these points and achieve further clarity for future valid recommendations for MDA design and interpretation.

Additionally, the actual methods of sample selection are not clear. The reader does not know whether the list of villages from which the sentinel sites were selected is encompassing of all villages in Burkina Faso or only those which are onchocerciasis endemic. Then, once at the sentinel site, the method for selecting school children in the eligible age group was not defined. Were all 7-11 year-old children selected or only a random or convenience sample selected?
Agreed and amended. We have revised the section referring to the sample selection and size as well as list of villages included in the study design in order to improve clarity.

The authors have presented the aggregate data as prevalence. However, the prevalence measured is only relevant to the communities assessed. For this reason, it is best to present the prevalence in Table 1 only by community and add in the title “Observed prevalence in 21 sentinel schools ...” If the authors do not clarify this, the use of the word “prevalence” may be misinterpreted as an estimate of prevalence of these diseases for the country, which is misleading.

Agreed and amended. We have revised this section accordingly to improve clarity.

The level of detail in describing the basis on how the sample size was estimated is detractive to the purpose of the manuscript. If published elsewhere, the authors should simply reference the justification and remove figures 1A and 1B. If not, then the authors should consider a separate manuscript describing the justification of sample size estimates.

Agreed and amended. We have revised the Methods section accordingly and have now included figures 1A and 1B in the supplementary information.

The authors should state specifically who examined the children for clinical signs of active trachoma. As presented, the reader assumes that a different local ophthalmologist was used in each sentinel site. If more than one person was used, was a field study conducted prior to the sentinel site assessments according to WHO recommendations to ensure the reliability and agreement of the trachoma grading among the different examiners?

Agreed and amended. We have revised this section accordingly to improve clarity.

The authors should determine whether the methodology used to identify associations of disease with indicators of climate is the most appropriate. As used, SAS PROC LOGISTIC treats each child as independent from the other children. Yet, this is not correct, as all the children from one sentinel school will be assigned the same extrapolated values for the climate indicators. In essence, the sample size for the regression analysis is 21. Correlation between disease and climate may be determined by looking at community prevalence of each disease against the different environmental and climate values as was done in the supplementary tables and figures.

The sample size for the regression in the original/initial version of the manuscript was not 21 as we had included individual children-specific covariates. Nevertheless, in our revised version we have allowed for correlation between children at the same school using multilevel models for the binomial logistic regression models, and have revised our Methods and Discussion text accordingly to accommodate this.

We have simplified the manuscript by presenting only these binomial regression models because the data indicate that, conditional on the predictors, the two infections are independent. Thus Methods, Results and Discussion sections have now been revised accordingly.

If in the adjusted regression analysis there remain statistically significant associations, the authors should clarify the programmatic significance of such associations. Specifically, how would national programs use such information for monitoring and evaluating impact of interventions? Currently, the reader is not convinced of how the risk factor information is relevant to programs. While the absence of flies in a hot environment may mean less trachoma transmission by flies, trachoma is also transmitted from person to person by dirty fingers and fomites. Data and the lessons learned from these integrated assessments are important and will be useful to determine the value of this sentinel site approach to monitor and evaluate impact of interventions. The correlations found between climate and disease presented here are interesting, but the data are not completely convincing. Before recommending the manuscript be accepted for publication I would prefer to see a revised version with the points listed below addressed.

Agreed and amended. Statistically significant associations from the adjusted regression analyses can inform the construction of reliable disease maps and mathematical modelling efforts of these two NTDs as well as the ‘E’ component for the SAFE strategy in the case of trachoma. We have now included this information both in the introduction and discussion sections.
Major Compulsory Revisions

1. In the abstract, it is not justified to refer to the word “prevalence” unless it is clarified that the prevalence is an estimate only for the community or to only the 21 sites and not another larger domain. The data do not justify trachoma as a serious public health problem. The authors could use “…likely constitute a public health problem according to WHO recommended thresholds,” but the authors are limited in the interpretation of their findings on TRA because appropriate age groups were not assessed and there was no assessment of blinding trachoma in adults (trichiasis and corneal opacity).

Agreed and amended. In the abstract the word ‘prevalence’ has been replaced by ‘overall prevalence from the sentinel sites assessed’. We have also incorporated in the ‘Conclusion’ section of the abstract the recommended sentence with regards to the severity of trachoma as a public health problem. Finally, we have addressed the indicated limitations in the interpretation of our findings on TRA in the Discussion section of the revised manuscript as appropriate age groups were not assessed and there was no assessment of blinding trachoma in adults.

2. Referring to clinical signs as trachoma infection will be misleading to readers. Please use “trachoma signs” to replace text where “trachoma infection” is used.

Agreed and amended.

3. The authors must clarify the exact sampling methodology used and discuss any further limitations.

Agreed and clarified.

As suggested we have now removed Figures 1A and 1B from the revised version. We have also revised several sentences regarding the sample size calculations to improve overall clarity.

We have added information about the list of villages from which the sentinel sites were selected. This list encompassed villages declared to be endemic for onchocerciasis under the surveillance of APOC. Among these villages, those with the greatest prevalence of lymphatic filariasis and schistosomiasis (based on national historical data) were selected randomly. Then once at the sentinel site, the method for selecting school children in each of the ages in the 7-11 years old was random sampling.

4. The authors must determine whether the methods utilized (logistic regression of individual data) to determine associations with weather are appropriate – given that every individual in a sentinel site has the same weather values and thus are not independent. At minimum the estimates must be adjusted for this dependency in each sentinel site.

We have now allowed for the intra-correlation structure that would exist between children attending the same school using multilevel models for the binomial logistic regression models. In multilevel models, correlation is introduced through shared random effects in the linear predictor. Thus the Methods, Results and Discussion sections of the paper have been revised accordingly.

5. The authors should present prevalence data in Table 1 by sentinel site.

Agreed and amended.

6. The authors should clarify in the last paragraph of the methods section that the WHO-recommended implementation threshold for trachoma is not only to determine need for mass chemotherapy, but intervention with the full SAFE strategy and were established based on prevalence of clinical signs of disease in children 1-9 years of age. Also, the priority for surgical intervention cannot be determined by the current methodology as the prevalence of trichiasis was not assessed in adults as recommended by WHO. The authors should mention these limitations of their methodology in the discussion and acknowledge that they may not be getting a very good picture of the true trachoma problem.

Agreed and amended. We feel that this is a very important point, as it goes to the heart of selecting appropriate age groups for collective monitoring & evaluation. The distribution of infection and disease
will vary according to endemicity levels and thus we have edited our recommendations in order to reflect this in the revised manuscript. Also we have edited the last paragraph of the Methods section accordingly.

**Minor Essential Revisions**

1. *The authors should use a consistent font and font size throughout the manuscript.*

   Agreed and amended.

2. *The word “generous” in the fourth paragraph in the background section is subjective.*

   Agreed and removed.

3. *The authors should present the range of climate values found in the sentinel sites in the text of the results. Additionally, it would assist the reader to know the significance of observed differences in the range of climate values.*

   Agreed and amended.

4. *The authors should revise the last paragraph of the discussion section to clarify the point that is being presented. Currently it is not clear what the authors are trying to say.*

   Agreed and amended. We have now revised the last paragraph to clarity. Although co-morbidity from each disease is rare, lack of data in the literature for younger ages in the case of schistosomiasis drove us finally to recommend that the suggested methodology could be modified to assess the younger age groups for SCH and the younger school children for TRA. An alternative integrated methodology has been performed in another SCI-supported country (Uganda), the results of which will be described and compared to these in another article.

5. *The authors could use “national” wherever “Burkinabé” is used.*

   Agreed and amended.

**Discretionary Revisions**

1. Since co-morbidity from each disease is rare, could the authors state whether each disease should be assessed in the same child or whether the methodology could be modified to assess the younger school children for TRA and the older school children for SCH or whether SCH and TRA assessments need be integrated at all.

   As mentioned at 4th point of Minor Essential Revisions above, we now recommend that the methodology could be modified to assess the younger pre-school and school children for TRA and the younger age groups for SCH.

2. *Second paragraph in the methods section, the authors could list by name the target districts where integrated distribution occurred in 2007.*

   Agreed and amended. We have listed the names of these 3 districts in the indicated section. These were: Tenkodogo, Koupela and Bogandé

3. *Fifth paragraph, whenever cluster random sampling designs are used for trachoma prevalence assessments, the expected prevalence is estimated. Historical data was available in the literature to help make estimates. The authors may be better off to not mention why they did not incorporate the preferred method and simply state that the purpose was to utilize a novel integrated method.*
Agreed and amended.

4. I was saddened to hear of the recent death of one of the authors, Dr. Bernadette Yoda. If allowed by journal policy, the authors could consider writing an obituary in honor of her life and work in the acknowledgments.

Agreed and amended. We have updated the acknowledgments section accordingly.

Tony Fulford

Major Compulsory Revisions

1. It is not clear why schistosomiasis and trachoma and their co-infections in particular were made the focus of this paper.

We feel that the referee is correct in pointing out that perhaps the motivation of the paper was not sufficiently clear in the original version; we hope that we made it clearer in the revised version of the manuscript, as we describe in the following:

There are a number of key reasons why the relationship between schistosomiasis and trachoma, and their co-endemicity, were made the focus of this paper –both from a perspective specific to Burkina Faso, and from that relating to the recent increase in integrated Mass Drug Administration (MDA) for these Neglected Tropical Diseases (NTDs) in general, across much of sub-Saharan Africa.

As regards Burkina–the country of focus here–in 2007 drugs were distributed for schistosomiasis, soil-transmitted helminthiases and trachoma, as an integrated package in three target districts. In 2008 these efforts were scaled up to include the lymphatic filariasis and onchocerciasis programmes as a platform from which to implement a fully integrated MDA campaign on a national level. Thus at the time these surveys were planned, integrated assessments of schistosomiasis and trachoma, as well as their co-infections, using sentinel sites, were made the main focus of these surveys. An evaluation of the feasibility of using this ‘standardized’ sentinel site design is thus of relevance to both diseases, to Burkina Faso in particular and to several of these integrated programmes across sub-Saharan Africa in general.

Indeed, as regards to the latter point (that of integrated NTD control across sub-Saharan Africa), there is also a need to approach the exploration of the distribution and co-endemicity of those infections prevalent in each country. Finally, there is increasing interest in trying to deliver some of the relevant treatments in the modality of school-based programmes, and schistosomiasis and trachoma lend themselves to this approach.

2. The statistical analysis is possibly okay but not always adequately explained. It was not clear, for instance, how or whether allowance was made for clustering in the analysis: individuals living in the same village are likely to be more similar to one another than to other study members.

We apologise if the statistical analyses and methodological details were not presented in sufficient detail. In response to comments from both referees, we have now allowed for correlation between children at the same school using multilevel models for the binomial logistic regression models. We have simplified the manuscript by presenting only these binomial regression models because the data indicate that, conditional on the predictors, the two infections are independent. Thus Methods, Results and Discussion sections have been revised accordingly.

3. Nor was it clear how the multinomial logistic regression was used to test whether the predictors of schisto and trachoma found by separate analysis of these infections were sufficient to explain their joint distribution. The motivation for, and interpretation of, this analysis also requires more explanation. Are the authors proposing some special environmental conditions that particularly allow (or disallow) the occurrence of co-infections? (It seems so, although it is hard to imagine a mechanism for this.) Or does the presence of one infection reveal some unmodelled environmental factor...
Influencing the other infection? The question that makes the most sense to me is to ask whether environmental factors are sufficient to explain the correlation (positive or negative) between the two infections. It is not clear to me how, or whether, this analysis addresses this question. Furthermore, since the data set only has 28 individuals with co-infections and the predicted prevalence of co-infection assuming the two infections are distributed independently is quite close to what is actually observed, there doesn’t seem to be much of a case to answer.

In response to the referees concerns, we have simplified the manuscript by presenting only these binomial regression models noting that the data indicate that, conditional on the predictors, the two infections are independent.

4. The argument concerning the negative binomial distribution and the plots of prevalence versus mean lost me. What was the relevance of the post-treatment data in this baseline study? Was it to prove that the distribution is overdispersed relative to the Poisson (surely we can take that as read) and therefore the negative binomial was needed? If so, demonstrating that \( k \) is a function of the mean rather undermines the argument: it implies that the variance is a quadratic function of the mean which it definitely is not in the case for the negative binomial.

We have now removed Figures 1A and 1B from the revised version. We have also revised several sentences regarding the sample size calculations to improve overall clarity.

In the current study we analyze data from baseline surveys which were performed during November 2007 and February 2008 in 21 sentinel sites across 11 regions of the country; such surveys aimed to provide prevalence estimates of schistosomiasis and active trachoma at the sentinel sites surveying the same children for both diseases at the same time. As mentioned before, these surveys were also designed to contribute to the assessment of the impacts on schistosomiasis and trachoma disease burden of the integrated NTD control program in Burkina after MDA (i.e. once the follow-up data would be collected a year later).

In order to calculate sample sizes for this study, we have used in these calculations longitudinal monitoring data from the National Vertical Schistosomiasis Control Programme (NVSCP) in Burkina Faso which were already collected during 2004-2006. For instance, an overall drop-out rate of 55% comparing survey 3 to survey 1 was observed in these NVSCP longitudinal monitoring data during 3 annual surveys over the course of the monitoring period and this was also incorporated in our sample size calculations. The computer model EpiSchisto was used to obtain infection intensity and prevalence predictions post-integration, taking into account the effect that the NVSCP would already have had on infection levels as a vertical programme before the integration. As a starting point of the integrated programme, we used the NVSCP data corresponding to the 3\(^{rd}\) annual survey during 2006 (i.e. follow-up year 2).

The relationship between prevalence and intensity of \( S. haematobium \) infection was assumed to arise from a negative binomial distribution of parasites among hosts in order to estimate, using maximum likelihood, the inverse overdispersion (\( k \)) parameter required to parameterise the EpiSchisto model.

Figures 1A and 1B in the first submitted version of the manuscript meant to illustrate these calculations, respectively, for pre-treatment baseline (2004) and 2\(^{nd}\) year post-treatment follow-up (2006) from the NVSCP longitudinal monitoring data. Also another aim for displaying these figures was to show that the \( k \) values changed over time with the intervention, a finding we took into account in the sample size calculations.

5. Generally, I found the paper too long for what it says. Some sections (e.g. the Background, the description of the inverse distance weighting – the weightings are actually proportional to the inverse distance squared) are very long-winded while some of the more crucial statistical methods and interpretations are barely mentioned at all.

We have revised the text substantially in accordance with this recommendation. We believe these changes have improved the clarity of the paper whilst, where appropriate, streamlining it.
Minor Essential Revisions

1. A particular irritation (a point that instantly rouses my suspicions about the authors’ understanding of the statistics used) is the misuse of the term “multivariate”. Both the binomial and multinomial logistic regressions are uni-variate no matter how many covariates were fitted: there is a single dependent variable for each individual (although you could analysis the multinomial data as a bivariate binary outcome – I think that would be clearer).

The referee is correct that we have used ‘multivariate’ in error where we meant ‘multivariable’. We apologize for any concern caused and have amended the text.

2. I wondered how the authors concluded that these infections were serious public health issues given that they do not seem to have looked at any morbidity measures. (The prevalence of urinary schistosomiasis at 11.8% is actually not especially high.)

We have concluded that these infections have the potential to constitute serious public health issues in Burkina Faso based on the WHO thresholds for schistosomiasis and trachoma infections. For urinary schistosomiasis, the WHO recommends that MDA be delivered to children aged 6–16 years where survey prevalence indicates that the infection ranges between 10% and 50%, which is the case here. For trachoma, the implementation of three annual rounds of community-based MDA with Zithromax is the recommended strategy if the prevalence of active trachoma in children aged 1–9 years at the district level is above 10%. We have now revised the relevant sections for the trachoma results as they most likely indicate trachoma to be a public health problem according to the WHO recommended thresholds. We have now clarified that this inference is limited in the interpretation of our findings on trachoma because the indicator age groups were not assessed here and there was no assessment of blinding trachoma in adults.