Author's response to reviews

Title: Recurrence of perinatal death in Northern Tanzania: A registry based cohort study

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

Thank you for the invitation to resubmit our manuscript entitled: Recurrence of perinatal death in Northern Tanzania: A registry based cohort study. We real appreciate for the reviewers for their useful comments and suggestions to help improving our manuscript. We have now modified the manuscript to incorporate reviewers’ comments and suggestions. Please find our responses are indicated in a red colour. Changes in the main text are all in track changes.
Reviewer 1: Birgit Reime.

Minor comments:

Abstract: fine. Statistical methods could be added.
Statistical methods are now mentioned.

Introduction:
End of first paragraph: This reference should be numbered and listed in the reference list.
This is a publicly open web-page with tabulated registry data. We are happy to move this to
the reference list if that is the editor’s preference.

Methods:
The setting and recruitment of the women becomes clear. Identification of women also well
described. I would like to have more information on the statistical procedures. SPSS version
18 is PASW?
Yes, SPSS was for a period also called PASW.

In terms of the t-tests conducted, were the preconditions fulfilled or would have been a non-
parametric test more adequate?
Student’s t test was conducted to compare means for continuous variables for which the mean
could be assumed to be normally distributed. This is unproblematic for means of hundreds of
observations of relatively symmetrically distributed variables. In our opinion this does not
deserve to be mentioned in the text.

Which (STATA?) command did you run for the “clustered analysis technique” to account for
repeated measures from the same mother?
With “perinat1” and “perinat2” as dummy variables for perinatal death in the first and
subsequent pregnancy, adjusting for maternal age (“motherage1”) and education (“medu1”),
and with the variable “hosnum” identifying the mothers:
xi:binreg perinat2 i.perinat1 motherage1 medu1 , rr nolog vce(cl hosnum)

Results:
On page 8, 2nd para, relative risk estimates should be accompanied by confidence intervals.
We agree, and have added 95% confidence intervals in the text.

Clear presentation of results. I appreciate the separation of results according to stillbirths and
neonatal deaths.

Discussion:
The discussion outlines the results in the light of the previous literature very well. However,
as in the result section, from the discussion it does become clear which ones of the results
refer to significant and which ones to non significant results.
We have addressed this problem in the text by indicating subheadings and revising the comparison with other studies.

The authors discuss the limitations of their study, e.g., potential bias due to incomplete follow-up.
I do not understand the meaning of the first sentence of page 12.
The strengths of the study are e.g., the thorough design and the access of confounders that other studies, based on vital data, do not offer.
We have revised this statement: “The strengths of the study are the standardized data collection, the prospective design and the information on a high number of confounders and clinical details.”

The last sentences and the conclusions leaves room for 1-2 sentences on the potential measures for prevention of recurrence of death.
What kind of special attention etc?
This is a key question, and we wish we could give more specific recommendations. Clinicians should make sure they are aware of any previous losses for women attending antenatal care or presenting for delivery, since that piece of information identifies women and a babies with particularly high risks. Limited resources may be directed towards these babies. What specific interventions that would be appropriate for the mother and the baby are questions for further investigation. We now specify these implications in the conclusion.

Tables:
Table 2: Induced labour could be a consequence of complications and may not be associated with perinatal deaths after adjustment for confounders.
Table 2 is just describing associations for the first births. We do not imply that induction could cause perinatal death. Rather it could be a marker of complications, as stated by the reviewer. In the next analysis (tables 3-4) we investigate whether this information on first births could predict the outcome of future births.

I do not understand what it means that reference groups of unaffected women are not shown.
What is “no perinatal death” if not unaffected?
We realize that the design of the table was confusing and have decided to include the reference group for each clinical subgroup.

Reviewer 2: Regine Unkels

Major compulsory revisions

Abstract

Background paragraph: Your results and discussion suggest that you aimed to estimate the risk of recurrent perinatal death and underlying factors

Methods
Your results and discussion suggest that a case control study design would be more appropriate.

We are sorry that we have not been able to convince the reviewer that this is a prospective cohort study, but we are unable to see what would give rise to the question of a case-control design. We attempt to provide a clear definition of the cohort and the follow-up of this cohort with its limitations in the text.

Paragraph 2: If I understand paragraph 4 correctly the data you collected prospectively were from 2008 to 2010 though in paragraph 2 you state you collected data prospectively from 2000 to 2010. If the follow-up period was at least 2 years for some and 6.6 years for others the data seem to be a mixture of retrospective and prospective data. This needs more elaboration. It might be useful to add a timeline here for better understanding.

All data are collected prospectively by the birth registry. As with most cohort studies, inclusion of the cohort takes time and we collected first-births of women from 2000 to 2008. Each of these women were followed for future births up to 2010, some from 2000 and some from 2008, all with a minimum of 2 years follow-up and with a median follow-up time of 6.6 years. This is of course not the only use of this birth registry, but since we had planned to use the registry for recurrence studies, we were careful to collect a unique identification number for mothers who entered into the registry. The identification number enabled identification of a woman’s future births within the registry. We discuss the limitations of this follow-up mechanism.

Paragraph 3: It is not clear to me whether everything described here (interviews) is a routine part of the registry or belongs to the study design. I think it is important to describe the registry a bit more: Is it paper-based or computer-based, which data are entered. How are researchers alerted that a woman came back who already delivered and how did you make sure she gets the same ID. This will make later issues around limitations due to loss to follow-up clearer.

We have tried to make this clearer in the text. There was no data collection in addition to the collected registry data. The registry collects information by interview and abstracts from medical record on a four page form. Data collection is done by specialized and trained midwives and the data are entered into a computerized database system. The birth registry has been described in the text. Issues related to consistent use of the identification number has also been described; in fact all women who deliver at KCMC are assigned a unique id-number which is constant in their subsequent births at KCMC. This makes sure a woman’s medical record is identified and is part of the routine at the hospital department.

Paragraph 3: I would advice to explain in more detail issues around consent. Did the women give consent to be entered in the registry or in the cohort study? I don’t think that verbal consent is enough and it is not clear from your description whether the women who were interviewed were informed about the study.

We have described the issues around consent. All women who deliver at KCMC are interviewed after giving consent; women are given information regarding the objectives of the registry project and its advantages with regard to women reproductive health matters prior the
interview. To our experience, most of these women consent to participate. This procedure has been approved by the IRB at KCMC.

Paragraph 4: There is confusion over the definition of your cohort between this paragraph and figure 1. There are an exposed (865) and an unexposed cohort (18,936) from the text but a cohort of all 19,811 mothers who delivered in figure 1. I don’t think the latter is the correct definition. As well I think the difference in size of both cohorts is too big. As well a study cohort must be formed and completed before the beginning of a prospective study. The way you describe it some women had a shorter follow-up time than others.

The discrepancy in the figure has been corrected. There was a typographic error of 865 instead of 875. We created a cohort study within the prospectively collected registry data. Among the 19,811 women in the cohort, 3909 showed up with a subsequent birth. We may have caused confusion by referring to the 3909 women as the cohort (in Table 2). This should now have been fixed. Not all women in the cohort have a subsequent birth, and among those who have, only an estimated 58% are captured by the registry.

Paragraph 5: You need to explain how you came to your sample size. As well I would assume there is a difference in risk of perinatal death in mothers with a recurrence in the next pregnancy after the first death and in mothers who have a live baby in between. You included women with 2 – 4 subsequent pregnancies. I would assume this may make analysis more difficult and introduce a bias. For the same reason I find it difficult to define the first pregnancy of a study participant as the first pregnancy recorded in your database. A woman who has delivered 3 live-born babies outside KCMC, then one stillborn baby in KCMC has a different risk of recurrence than a primipara with one stillborn in KCMC.

We have explained in the method section how we arrived at the final sample size after all exclusions. We studied all mothers in the registry (target population) who met the inclusion criteria. We have also explained how to deal with methodological challenges when analyzing the repeated data (in our case births of the same woman). The analysis per order of subsequent pregnancy has been described in the text. However, due to small number of women who were recorded with a 3rd or 4th birth do not give enough power for proper sub-analyses as requested by the reviewer. We decided, however, to include them in our recurrence estimation without conditioning on the outcome of intermediate births to increase our sample size.

**Results**

It is very difficult to understand which group of women is referred to in the different paragraphs. I would advice to use subheadings to group your findings, e.g. according to your tables (general predictors, predictors in women with previous live birth, predictors in women with previous perinatal death.). I would advice to add the analysis of recurrence risk per order of subsequent pregnancy (2nd, third, fourth subsequent pregnancy) as this may vary. We have now included subheadings, but still think more sub-analyses should be avoided with this small sample size.

Paragraph 3: RR for all these conditions was higher than RR for perinatal death quoted in paragraph 2. But this finding is never assessed in the discussion although from what you write
pre-eclampsia, low birth weight and prematurity in the first pregnancy seem to be more important predictors than perinatal death. All three may share the same underlying pathology with each other and with perinatal death; as well there is an increased recurrence risk for all three conditions on their own. It would be important to address this finding somewhere in the discussion.

We now mention the sub-groups with higher risks in the discussion.

Paragraph 4 and 5: Please refer to table 4 in the text. The findings you describe here are important but they are not addressed in the discussion. I recommend that you address the finding that a perinatal death of a term baby or with normal birth weight has this recurrence risk and that the RR is higher than for preterm babies or low birth weight.

We have addressed these findings in the discussion, but avoid simple repetition of results.

Discussion

Your discussion focuses very much on risk factors for recurrence (exposure), however your study design is set around outcome (recurrence) as a variable of interest.

We are sorry, but we did not understand this comment.

Paragraph 1: As this is the beginning of your discussion you should explain what you mean with the baby’s “condition” (You are talking about perinatal outcome at first delivery as a strong predictor for the outcome in a subsequent pregnancy, or about low birth weight or prematurity??). In the next phrase the risk needs to be defined (risk of what is 9%?). Next phrase: “If a previous baby was also born preterm or....(in addition to what? Do you mean to say that if a baby was dead and also preterm etc.)

Risk in this paper is always the risk of perinatal death in a subsequent birth. The reviewer is correct. We use the term the baby’s condition as the general term, which may be measured by variables birth weight, born preterm, died in the perinatal period etc. We use different aspects of the condition of a previously born baby to predict risk of future babies.

Paragraph 5: An important limitation of this study is the fact that it is facility-based and the fact that KCMC is the biggest hospital can also introduce biases (who are the women who choose to deliver there)

Yes, this was and is a key question in the discussion.

Paragraph 5: The number of women included (24,443) and the time period (2002-2010) here do not match with the figures mentioned in the method section and in figure 1.

This should now be clear.

Paragraph 6: According to the methods section women who were referred for medical reasons were excluded from the study and their data would thus not be available for a sub-study.
We excluded women who were referred for their first birth. We could still perform a sub-analysis excluding women who were also excluded for their second birth.

Conclusions
I think you cannot infer from women in Kilimanjaro Region to women in Africa. I would advise to make it less general and say women in Tanzania. The statement in your second phrase is valid for every setting in the world and this recommendation already exists in Tanzanian National guidelines and WHO recommendations. Could you add here the findings from your study that was new or more important, e.g. the finding that especially women with normal term babies and perinatal death may have a high risk for recurrence? As well your recommendation should be more specific in terms of interventions needed. I agree that for the finding I’ve mentioned above, it is difficult to think of an intervention to avoid a recurrence here. To me your finding suggests that there are other factors contributing to these recurrences which we didn’t identify yet. So here, more research is needed. A disaggregation of data the stillbirth sub-set into fresh and macerated stillbirth might deliver a clue here. As well this finding may suggest problems in monitoring during delivery and this could be your argument. Underlying here may be a context-specific perception about perinatal death which prevents providers from seeing mothers with term and normal birth weight babies as at risk.

We agree, and have incorporated the reviewer’s advice regarding generalization of our findings to women in Tanzania instead of Africa. We also have proposed some recommendations/interventions to be considered to reduce recurrent perinatal death, however, still more community or population research is needed to confirm our findings and identify other risk of recurrence of perinatal death especially for women with a previous term or normal birth weight babies who died perinatally.

Discretionary revisions

Background
Research question not stated.
It should now be clearly stated.

Paragraph 1: As your study is about facility-based perinatal mortality I recommend not to cite the results of community-based studies without mentioning that they will differ significantly from each other in terms of quantity and underlying factors.

We have commented on the potential reasons for differences in perinatal mortality between studies.

Methods
I would advice to use sub-headings (e.g. birth registry at KCMC, sample size calculation, sampling method, data collection, data analysis).

Yes, we now propose some sub headings.
Paragraph 4: Here you state that women who were referred for various medical reasons were excluded from the study initially but in discussion paragraph 5 you write about a sub-study after exclusion. That is not quite clear to me.

Yes, we understand the reviewer’s concern. The sub-analysis was carried out to investigate whether a tendency to selectively refer subsequent high risk pregnancies for delivery at the hospital would bias our recurrence estimates. This point was also addressed above. We found little evidence of such bias.

Paragraph 7: Could you explain why two statistical programmes were needed?

The registry data are entered in an Access-database. Data were transferred by a routine operation to an SPSS-data file and data cleaning, generation of analysis variables and simple statistical analyses were performed in SPSS. The main analysis including analyses accounting for dependencies in the data was done using Stata version 11.0. We prefer to use the best available tool for any task.

Results

Paragraph 3: Table 3 shows the recurrence risk, but what you write here is the perinatal mortality rate.

Both are correct. We have rephrased.

Paragraph 4: Please refer to table 4 for these findings in relation to perinatal death.

Yes.

Discussion

Here as well I would advice to use sub-headings to group your discussion per “women with recurrence” and “women without recurrence”. This will inform your recommendations on what kind of additional interventions women with recurrent perinatal death should receive.

Yes, we now use some subheadings but disagree with these.

Paragraph 1: According to the research question in the abstract you aimed to estimate the risk of recurrent perinatal death. The “how” would be more appropriately clarified with a case-control design using recurrence as the outcome and the different risk factors would be the exposure.

With all respect, this proposal is confused.

Paragraph 2: At the end of this paragraph I would expect a discussion about possible reasons why the studies you quote report lower recurrence risks than yours.

The high absolute recurrence risk (but similar relative risk) compared with other studies is our main finding. We now discuss why the recurrence might be is high.

Paragraph 3: Some readers might not be familiar with the concept of precurrence risk. Please add brief explanation.

This is a good point. We have removed the term and now justify the calculation in plain words.
Paragraph 4: It would be helpful to mention the background of the studies you quote.  
We have tried to improve this.

Paragraph 4: The section about the probability of under ascertainment of perinatal death should be mentioned as well under limitations.  
We have described this aspect as a limitation.

Paragraph 7: The assumption that assignment of a new hospital id is independent to outcome of the previous pregnancy might be wrong because some women in this setting tent to throw away their old medical records because they associate them with the loss. So if your system failed to find that she had already delivered at KCMC she may not volunteer this information either due to her experiences.  
Addressed above.

Paragraph 7: Not every reader (including myself) may be familiar with the concept of selective fertility. Could you briefly explain what it includes?  
We now explain the concept in plain words.

Conclusions
Paragraph 1: Women with no perinatal death in their first pregnancy cannot have a recurrent perinatal death in their second. I propose to re-phrase like this: “the risk of recurrence of perinatal death for women in Northern Tanzania...compared to a much lower risk for perinatal death for women with no history of perinatal death in their first pregnancy.”  
We have modified the sentence according to the suggested comment.

Minor essential revisions
These have been taken into account as reviewer’s suggestions (see in the main text).

Reviewer 3: Bettina Utz

Method section should be clearer (see my comments in the text) and include inclusion and exclusion criteria. Some aspects of the method section are repeated / inappropriately placed in the discussion section (major compulsory revision).

We have modified the method section to adhere with the reviewer’s recommendations. We have indicated the inclusion and exclusion criteria. The calculation of the completeness of follow-up belongs in our opinion in the discussion, since it adds to the limitation discussion and since none of our analyses depend on it. We will follow any advice from the editor.

Unfortunately, we have been unable to access the tracked changes document referred above. We decide to send emails to editor to request more information about the tracked document but the editor confirmed receiving PDF file without tracked from the reviewer and advised to work on the comments highlighted in the report. We might have missed some important information the reviewers wanted us to address in our manuscript.
The discussion section is partly used to repeat or state findings that should be result section. Although the findings are compared with other studies, differences/similarities are often not properly discussed and often only the reference of the study is stated. This needs to be improved.

We have improved the main text with the discussion of differences between studies.

Also the limitations of this study needs to be more highlighted as especially women who lost their child previously might decide to deliver in a hospital again, whereas women who delivered a health child might not deliver again in the hospital as they feel there is no problem. This can cause calculation of a higher risk as more women who experienced problems in the first pregnancy will come to the hospital, which is not representative of the entire population.

In the current manuscript we have highlighted the limitations including the possibility of an overrepresentation of high risk women. A higher number of women seeking back to the hospital after a previous loss would not necessarily bias our estimate, only if these were a selected group of women with a higher risk in their next pregnancy. We performed a sub-analysis where we excluded women who were referred for their next birth, and this did not alter the results. We discuss this in the text.

**Note:**
The references number 8, 20 and 22 in the original manuscript has been replaced by number 19 in the current submission. We have also added new references (19 and 22).