Author's response to reviews

Title: High burden of hepatitis B infection in Northern Uganda despite nine years of childhood hepatitis B vaccination: results of a population-based survey.

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The Editor

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Re: Response to reviewers’ comments on manuscript MS: 1152278792749821

We thank the editors and reviewers for their helpful comments on our manuscript entitled “High burden of hepatitis B infection in Northern Uganda despite nine years of childhood hepatitis B vaccination: results from a population based survey”

Please find below our responses in plain text and the reviewer’s comments in bold. The revised manuscript with revisions made highlighted for clarity is also attached.

Reviewer #1. Elisabetta Franco

The work raises an interesting point regarding the introduction and policy of vaccination against hepatitis B virus in Uganda, but the content doesn’t match the title and the stated objective. In fact, despite the nine years of childhood hepatitis B vaccination and the official data, that report 79% coverage, only ten children in the 1-14 years group result vaccinated and 3 of them had have a lifetime exposure. It’s impossible to draw conclusions on this basis.

It is true that from this data it is difficult to draw concrete conclusions. However the information on vaccination was based on self report, which may not be accurate. The data derived from our study clearly indicates that the coverage is low in this part of the country.
Major compulsory Revisions

1. There is a possible presence of bias because males were not proportionally selected. The authors should better describe the available members' selection method; specifically it is not clear why if a simple random sampling was used, the number of women is so elevated and why children are so underrepresented.

The sampling design produced a probability sample of who could be found in the household at the time of the survey. Consequently the study shows that adult men and younger boys are less likely to be at home and the data make inference to this population. Given that we do not have a census either of the study catchment area or of the households at the time of interviewing, creating weights to account for this will not be possible.

2. The presence of HBsAg in a single sample suggests the presence of infection, but it is impossible to distinguish if the respondents have a chronic or a recent infection. The authors should eliminate the term 'chronic' when speaking of HBsAg positivity.

The term 'chronic' has been removed.

3. It is not clear and how if the authors have acquired informed consent or assent for children aged 1-7 years.

We have revised the manuscript to show that informed consent was obtained from participants that were aged 18 years and above. For participants below 18 years, informed consent was got from the parents or guardians with assent from participants 8-17 years, in addition to informed consent.

4. The authors should explain who responded to the questionnaire when children or adolescents were selected.

For adolescents in particular, they answered themselves, but could easily refer to their caretakers when they needed to. For younger children parents provided the answers.

5. It is not clear how the predictors have been chosen by the authors. Some not significant predictors have been included in the tables while others that are described as significant in the paper have been excluded.

The variables were included in bivariate and multivariate analysis if they had p-values less than 0.2 or if they had theoretical importance (i.e. reported in the literature as predictors of hepatitis B infection). The latter consideration led to examining family history of liver disease, vaccination history, education on HBV infection, and for older persons scarification and number of sexual partners.

6. In Table 3, the reference population for the crude odds ratio should be always the same (Look at gender)

This has been corrected on table 3.
Minor essential revisions

1. The absence of table 1 does not allow the evaluation of the demographic data described in results
We apologize for this omission. Table 1 has now been included in the manuscript.

2. The authors should better describe the topographic division of the Gulu Municipality, because in the methods they describe the Parishes and villages while in the results they refer to the sub-counties, never described before.
The Municipality has four sub-counties, each consisting of four parishes. We considered the 16 parishes for probability sampling proportionate to size. This has been clarified in the manuscript.

3. In the Patients and Methods section, the first time the term ‘households’ is used it is written in the wrong way.
This has been corrected

4. In the Results the respondents were 804. It would be better to call the 790 enrolled in the study ‘participants’ and not ‘respondents’
The term ‘participants’ has been used as suggested.

5. The literature Nr [12] about the prevalence of receipt of the third dose the HBV vaccination was recently updated. The authors should update their data.
New data has been cited in the document

6. The literature Nr [4] should be move near the sentence ‘in South Africa’ to which it refers.
The change has been effected

7. According to the systematic random sampling described the maximum number of selected subjects should have been 800. The authors should describe how they reached 804 respondents.
During this study, we selected 8 parishes by probability sampling proportionate to size forming clusters from which 100 households from each of the parishes were selected by systematic random sampling. The households were numbered consecutively. However the number we got exceeded the expected 800 participants because there was misnumbering of the households which led to a repetition of 4 numbers. This has been explained in the revised manuscript.

8. In table 2 there is an error in the percentage of male positive for HBsAg (70% instead of the 20%) and in the crude odds ratio.
These errors have been checked and corrected in the table
Discretionary revisions

1. In introduction, the literature Nr [3] should be cited only at the end of the sentence ‘25% in the North east’
   This has been changed and reference is now at the end of sentence

2. In the introduction the sentence ‘but its contribution to the transmission in Uganda is not studied’ should be changed in ‘but its contribution to the transmission of infectious is not studied’
   This change has been effected

3. In Patients and Methods, more recent data about the population of the Municipality should be used if available.
   There is no recent data on Gulu Municipality. The country undertakes population census every ten years and the last one was 2000. The next census has been delayed and is planned for next year. Until then the official data is from the previous census

4. In ‘Data management and analysis’ the sentence ‘prevalence of HBV... respectively’ should be better explained or eliminated.
   The explanation has been provided

Reviewer #2: Fuqiang Cui

Major Compulsory Revisions

1. What are the inclusive criteria and exclusive criteria of sampling?
   Persons were eligible for inclusion into the study if they were aged one year and above, were residents of Gulu Municipality that had been living there for six months or more, were available at home on the day of the survey, and provided informed consent to participate in the study. Informed consent for participants that were aged less than 18 years was provided by the parents or guardians. In addition, children aged 8-17 years provided assent before enrollment into the study.

2. Although the author mentions in the limitation that more females were selected can author give readers what quality control measure had been taken?
   We have noted this in the limitations arising mainly from our sampling design. When males were available at home they had a chance of being selected but since these are usually the breadwinners of the homes, often they would not be sampled.

3. The number of population under 15 is small, and author could not provide age specific prevalence for children under 14; therefore I did not find any trend by age, among children under 14 years? I would assume if the HBsAg
prevalence is high among children under 5, mother to children transmission may be a problem. So the data is less confident to say so.
It is true that there could be vertical or horizontal transmission in the lower age groups. In our analysis numbers by smaller age categories were not feasible and we did not see a trend for HBsAg by age.

4. Have author weighted the data or not, by age and by sex?
There was no weighting by age and by sex. As mentioned above, the sample represents a snapshot of who was at the household at the time of sampling. We do not have a complete census of the age/sex make up of the catchment area nor a count of those present in the household; therefore, weights were not possible. We do note that the analysis examines sex and age through stratification by these variables.

5. Does author give us more explanation about why the children under 14 had high HBsAg positive rate than population above 15 but the anti-HBe is increased by age? I believe, which does not make sense.
This has been a common phenomenon where transmission takes place in early childhood as in highly endemic regions of the world. In such cases chronic hepatitis B occurs in over 90% as opposed to <10% in those who acquire infection later in life. Co-author PO with his colleagues demonstrated increasing incidence of HBeAb with age in a cohort of patients in Uganda without increasing HBsAg. In that study the increasing HBeAb with age was associated with number of life time sexual partners an indication of continued sexual transmission but with clearance (Stabinski L, J Med Virol 2011). The Uganda national serosurvey that has been quoted in the paper had similar findings. (Bwogi J, Afr Health J, 2009) It is therefore possible to have increasing HBeAb with age without similar increase of the HBsAg.

Minor essential revisions

1. Where is table 1?
We apologize for this omission. Table I has now been included in the manuscript.

2. Can authors provide any information of mother to child transmission in Uganda?
There is no current data on mother to child transmission of hepatitis B in Uganda. However in a recent review (Otto et al, BMC Infec Dis, 2012) most transmissions in sub-Saharan Africa would probably occur horizontally other than vertically, compared to what happens in Asia. That is because of the low prevalence of hepatitis B e antigen in sub-Saharan Africa.

3. Can authors provide any evidence why the first dose is given at 6 weeks after birth? Why the policy was made like this?
The hepatitis B vaccine is being administered in a pentavalent vaccine which includes vaccine against Diphtheria, Pertussis,Tetanus, Hemophylus Influenza type B, and
Hepatitis B. Uganda and many other African countries still use this vaccine schedule. Initiating the hepatitis B vaccine separately requires a different program which brings in hepatitis B vaccine separately.

4. **Please provide the lot number of kits.**
We thought that the most important thing about the test would be the details of the testkits. The lot number may not give all the information about the testkits that have been used. The details of the tests (kit name, manufacturer, City and Country) have now been provided in the manuscript.

Thank you very much.

Yours sincerely;

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