Author's response to reviews

Title: Why are children not vaccinated against measles? A cross-sectional study in two Nigerian states

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Version: 2
Date: 4 August 2014

Author's response to reviews: see over
Dear Editors

We are grateful to all three reviewers for their detailed and constructive comments. We believe we have been able to address them all in the revised manuscript. Our point by point response to the comments is set out below.

Please note that we have also changed the order of authors of the paper; Dr Cockcroft is now the first author as well as the corresponding author.

We hope that the revised paper will be acceptable for publication in Archives of Public Health.

Sincerely

Anne Cockcroft

Responses to reviewers

Reviewer 1: Solen Kernéis

The authors estimated the vaccine coverage against measles and investigated the barriers to immunization on a large sample of children aged 12-23 months, in two Nigerian states. The methods are appropriate and well described, and Discussion/conclusions well balanced and adequately supported by the data.

Major comments:
1. My major concern stands on the fact that vaccination status relied only on maternal recall, with no written confirmation. Although it is understandable in the context, it should be emphasized as a notable limitation. Did the other studies (references 5 and 6) use the same methodology?

Response 1:
We have expanded the Limitations section to discuss further, with additional references, the issue of relying on maternal recall for estimating vaccination coverage. There is evidence from resource poor settings that relying on maternal recall is no worse than seeking information from vaccination cards; only a minority of children have cards available and the accuracy of the written information on the cards is poor.

The DHS (reference 5) and the MICS (reference 6) surveys used information from vaccination cards, when available, and maternal recall when no card was available to estimate vaccination coverage. The report of the MICS survey noted that vaccination cards were available for only 29% of the eligible children. In both the MICS and the DHS, vaccination rates estimated by the two methods were similar. We have added a note to this effect in the first paragraph of the Discussion.
2. I think that it would be more appropriate to summarize the two paragraphs of the Methods and Results sections on the use of the results of this study to guide discussion with health authorities in the discussion, since they do not formerly present data obtained from the study.

Response 2:
We have summarised and moved these two paragraphs to the Discussion.

Minor comments:
3. In the paragraph reporting the views from the focus groups, it is not clear to me if reasons why children are not vaccinated were given by the order of frequency ("some groups said", "many groups blamed", "many focus groups"...).

Response 3:
Since these are qualitative data, we did not consider it appropriate to present the reasons in order of the number of groups that mentioned each one, implying a frequency distribution among the groups. Rather, we have described common themes that were present among the group reports. We clarified this in the Methods.

4. Please define more precisely the variables that were included in the bivariate analysis. Does it mean that for each variable studied in the univariate analysis, the analysis was adjusted on the state (Cross River/Bauchi)?

Response 4:
The entire analysis, including the bivariate analysis and the adjustment for clustering (some might call this a univariate analysis, since it considers one potential determinant at a time) was carried out for the two states separately. We have clarified this in the Methods.

5. Did the authors collect data on the number of doses of measles vaccine received by the participants? If this information was not collected, it could be notified in the discussion.

Response 5:
The vaccination schedule in Nigeria calls for one dose of measles vaccine to be administered at nine months of age. The questionnaire asked the mother if the child had received this single dose of measles vaccine. We have added a brief description of the schedule for childhood vaccinations in Nigeria in the Background.

Reviewer 2: Pierre Verger

Major comments
This is an interesting article about a very important public health subject: children vaccination against measles. The authors made considerable efforts to collect information about vaccine coverage in two Nigeria states and document factors associated with measles vaccine shots, through a quantitative survey: factors have been documented at individual, household and community level. They have also implemented focus groups to get better insight into the reasons alleged for under-
vaccination or vaccine refusal. Despite interesting and useful results, this article would gain in a more precise redaction on several aspects.

Comment 1
Moreover, the presentation of the results of two different study designs in the same article (quantitative and qualitative) is unusual and questionable; this choice probably led the authors to present the results of the focus groups in a very concise way, and in doing so, they have probably lost part of the richness of their results. I note that they do not discuss the results of the focus group in the discussion section. These results should be presented in a separate paper (given also the efforts implied by collecting this qualitative information: FG in each of 90 communities x 2 (states) x 2 (gender stratification) = 360 focus groups of 8-12 persons.

Response 1
The study did include both quantitative and qualitative results on this problem. Mixed Methods Research is increasingly recognised as providing insights beyond what can be gleaned from either quantitative or qualitative methods alone. Respecting this new and promising trend in modern research, we feel it is important to retain quantitative and qualitative methods and findings in the same article. We clarified in the revised Discussion how the qualitative findings give context to the quantitative findings.

Comment 2
Same comment about the use of the study findings sections (method and results).

Response 2
We recognise some authors might use the material to publish several papers; we believe it is more useful for readers to access the material within this same article.

Introduction
Comment 3
To which extent would vaccination help reducing mortality due to malaria and even diarrhoea?

Response 3
We have re-worded the Background to avoid the misleading implication that vaccination could reduce deaths from diarrhoea and malaria.

Comment 4
Could the authors provide some information to the reader about national official recommendations regarding measles vaccination in Nigeria (schedule, number of recommended shots, vaccine coverage objectives...) and the possible between-states variations (both in recommendations and vaccine modalities and organization)?

Response 4
The vaccination schedule in Nigeria calls for one dose of measles vaccine to be administered at nine months of age. The aim of the national immunisation policy is 90% coverage with all vaccines by 2020. We have added a brief description of the schedule for childhood vaccinations in Nigeria in the Background.
Comment 5
Why were the Cross River and Bauchi states chosen for the surveys?

Response 5
The survey was undertaken as part of the Nigeria Evidence-based health Services Initiative (NEHSI). This project aimed to support planning of more effective health services at State level. Two states were selected for this project, in discussion with the federal government: one from the north of the country (Bauchi) and one from the south (Cross River). The survey reported in this paper took place in the two states that were included in the overall NEHSI project. Indeed, as described in the paper, the findings from the survey were discussed with health planners in the two states.

Comment 6
A concise paragraph presenting results already published in Nigeria and comparable countries about determinants of measles vaccine acceptation would be welcome. This would help justifying the choice of categories of factors studied.

Response 6
We have added a brief paragraph in the Background about the determinants of measles vaccine coverage already described in Nigeria, trying to avoid duplication with the Discussion section.

Methods
Comment 7
The sampling methods should be presented first and the survey procedures after. Inclusion and exclusion criteria should be clearly presented.

Response 7
We revised the Methods description. All children under four years old in the households were included.

Comment 8
Please provide a reference for the stratified last-stage random cluster sampling and a clearer explanation about correspondence between the clusters and the geographical and/or community levels.

Response 8
We have clarified the description in the Methods. This was a standard stratified random cluster sample. Enumeration areas from the latest census were stratified into urban and rural areas and then a random sample of EAs from each State was drawn.

Comment 9
The sentence “each cluster comprised contiguous households radiating from a random starting point” in unclear. As the strategy aimed at including 100 children per cluster and the number of children per households may vary, did the authors take into account in the analysis the unequal probabilities of inclusion for each children?
Response 9
There were more children per household in Bauchi than in Cross River. However, they often had different mothers, as polygamy is common in Bauchi. We did not make any particular adjustment for the differing number of children per household but analysed the two states separately.

Analysis:
Comment 10
The sentence about the data entry procedures is not necessary. The statistical package used for the analysis should be presented at the end of the analysis section.

Response 10
We have shortened the sentence about the data entry procedures.

We mention that analysis relied on CIETmap software, which provides a user-friendly interface with the standard statistical programming language R, and provide a reference.

Comment 11
The strategy of analysis should be presented in more precise way: apparently, the authors used logistic regressions. As the authors aimed at testing individual as well as aggregated variables at community level multilevel logistic regression analysis is a priori more appropriate than logistic regression analysis (which does not allow the consideration of an individual level embedded in an aggregated level (community level)).

Response 11
We allowed for the cluster sample by applying the Lamothe cluster adjustment to the multivariate analysis we conducted using the Mantel Haenszel procedure. The cluster adjustment with a non-fixed OR produces findings (at least with large datasets from stratified random cluster samples) similar to those from generalized linear mixed model analysis. We have cited a paper in support of this. In the present study, the results of the analysis with the cluster adjustment with the fixed OR were similar to those of an analysis with the cluster adjustment with a non-fixed OR. In response to the request for a multilevel analysis, we have shown the findings with the cluster adjustment with a non-fixed OR.

Comment 12
The presentation of the factors being analyzed should be made in differentiating between socio-demographic characteristics (education level) and attitudinal factors (e.g.” considering worthwhile to immunize one’s children”). The choice of specific factors such as “possession of a birth certificate” should be justified.

Response 12
We have re-ordered the factors examined into groups as suggested by the reviewer. We have added a note about why a question about birth registration was included.
Comment 13
The section “using the study findings”: this section should be deleted even if some points are indeed interesting for the discussion section.

Response 13
We have moved a summarised version of this paragraph into the Discussion section.

Results
Comment 14
The response rates (or refusal rates) should be provided for both states.

Response 14
The fractions shown in Table 1 indicate the level of missing data for individual variables. We have included a note of overall response rates for the two states at the beginning of the Results.

Comment 15
Socio-demographic characteristics of the two samples should be compared to the extent possible to those at state level.

Response 15
We have interpreted this as being a request to compare the socio-demographic characteristics of our sample in the two states with those reported from other surveys. It is beyond the scope of this paper to make such a comparison in any detail. We have added a sentence in the Results to indicate that the educational levels of the mothers in our sample were similar to those reported among women aged 15-49 years in the 2008 DHS sample in the two states.

Discussion
Comment 16
Page 11: explain why adding information from vaccination cards does not improve accuracy: this is a rather counterintuitive statement for a reader unfamiliar with context of the study.

Response 16
We have expanded the Limitations section to discuss further, with additional references, the issue of relying on maternal recall for estimating vaccination coverage. There is evidence from resource poor settings that relying on maternal recall is no worse than seeking information from vaccination cards; only a minority of children have cards available and the accuracy of the written information on the cards is poor.

Comment 17
The rest of the discussion should not include the results of the focus groups but rather compare the results with already published studies.

Response 17
As explained above, this is a Mixed Methods study, with qualitative findings giving context to the quantitative findings. We have made this clearer in the revised
Discussion. The Discussion includes comparison of the quantitative findings with those of other studies.

Comment 18
The authors should underline which results are new in the Nigerian context and give more insight to the reader on the results discrepancies between the two states.

Response 18
We have added some text to highlight new associations in the Nigerian context and to give more insight into the different associations with vaccination in the two states.

Minor comments
Comment 19
Table 1
Subtitles for each variable category should be included for the clarity of the table; individual socio-demographic variables, attitudinal and behavioral variables and community variables should be clearly distinguished.
First column; please find a way to avoid repeating children at each line
Second and fourth column: could be deleted.

Response 19
We have revised Table 1 accordingly.

Comment 20
Tables 2 and 3 a and b
I would suggest to present univariate and multivariate results in the same tables, with one table for each state.

Response 20
We tried to do this but in the end we decided that it was confusing and therefore we prefer to retain the present arrangement of the tables, showing first the bivariate associations and then the multivariate associations.

Reviewer 3: Arnaud Le Menach

The authors performed two cross sectional surveys and carried out focus group discussions in two states in Nigeria (Bauchi and Cross-River) to estimate measles vaccination coverage, and understand the reasons for non-vaccination.

The authors found that vaccination coverage was low especially in Bauchi state, and highlighted the main factors for non-vaccination. The study is interesting, especially as the authors used quantitative and qualitative approaches for a direct impact on decision-makers. However I have a couple of comments below

(Major Compulsory Revisions):
Introduction:
1. 1st paragraph: Childhood mortality related to malaria (and to some type of pneumonia or diarrhea) will not be reduced by vaccination. The authors should not make this association.

Response 1:
We have re-worded the Background to avoid the implication that vaccination could reduce deaths from diarrhoea and malaria.

2. Overall there is some context missing around the measles situation and its vaccination in Nigeria. I would suggest to reformulate the introduction:
   a. Focus the first paragraph on measles disease situation worldwide and in Nigeria (morbidity, mortality currently and over the last years, where is malaria in Nigeria, is it only a childhood disease or do we observe outbreaks in older population as well...)
   b. Add a paragraph about measles vaccination in Nigeria (what is the protocol, for whom, when is it distributed, how)
   c. Add a paragraph about what is known regarding vaccination and barriers to vaccination in Nigeria, and why this study is needed. A lot of publications have been done on measles vaccination in Nigeria, and it would very helpful to understand the rationale for this study.

Response 2:
We have revised the Background section to include the situation about measles in Nigeria, the protocol for vaccinations in Nigeria, including for measles vaccination, and published evidence about factors related to measles vaccination in Nigeria.

3. The first part of the last paragraph is more related to the selection of the study sites and should be moved to the method as explained below.

Response 3:
We have moved the sentence describing the context of the two provinces into the Methods

Method:
4. From a formatting perspective I would suggest to follow a standard way to present the methods:
   a. Study population and site (some of it is in the introduction, but what is the measles situation in those two states, why were they selected, what is the study population?)
   b. Survey design
   c. Data collection
   d. Data Analysis

Response 4:
We have re-ordered the Methods accordingly.

5. More information should be provided about the sampling design (how was the sampling size estimated, to detect what difference?)
Response 5:
We did not conduct a formal a priori calculation of sample size. Our sample size at State level was much larger than that of national surveys such as the DHS or MICS. The STROBE guidelines do not state that a formal sample size calculation is always required for cross-sectional studies and recommend “Do not bother readers with post hoc justifications for study size or retrospective power calculations” (Vandenbroucke et al, 2007, PLoS Med, 4(10):e297. doi:10.1371/journal.pmed.0040297). The same guidelines point out the uncertainties of a priori sample size calculations. In the present paper, the large sample size is reflected in the relatively narrow 95% confidence intervals around the OR estimates. We have added in the text the 95% CI around the weighted percentages of the main outcome (measles vaccination status) in the two states. The narrow confidence intervals reflect the relatively large sample size.

6. What is a last stage sampling (a two-stage cluster sampling?)

Response 6:
We have clarified this in the Methods. This was a random cluster sample, stratified by urban/rural location.

7. Some details could be summarized throughout the method: for example about the operational implementation of the quantitative and qualitative surveys, the software description, the list of variables is actually in the tables, it could be summarized by main categories with a questionnaire in SI)

Response 7:
We have tightened the wording and reduced some material. We added some material in response to comments from other reviewers.

8. The section about using the study findings is very interesting but is more related to the discussion, and use of the study findings

Response 8:
We have summarised this paragraph and moved it to the Discussion section

9. Why did the authors decide not to analyze the data for both states together: it would be interesting to have results within each state and for the two states together

Response 9:
We set out from the beginning to analyse the two states separately. Analysing them together could be misleading and suggest that they somehow together represent a larger entity, even the whole country, but this is not the case. Also, the intention was to provide state-level results to be used for local planning in the two states separately. We have further clarified this in the Methods section of the paper.

10. A couple of relevant covariates potentially explaining measles vaccination coverage seem to be missing: such as religion, ethnicity (linked to different cultural background), knowledge of measles, access to care (such as where children go in case of fever). The author should specify whether this information was collected/analyzed, and if not why it was not done, and explain it as a limitation.
Response 10:
We collected and used information about awareness of vaccinations, perceptions of importance of childhood vaccinations, and access to care in terms of the presence of a health facility providing vaccinations in the community. We did not ask about knowledge of the disease measles. We did not specifically collect information about religion or ethnicity at individual level. The predominant religion in Cross River is Christianity, while in Bauchi it is Islam, and ethnicity patterns are also very different between the two states. We have noted in the expanded Limitations section that we did not collect information about religion or ethnicity at individual level, and that these factors may have been related to vaccination status.

11. Regarding the outcome “injection into the upper arm at 9 months”. It seems that this question could be confused with other vaccination which are not measles?

Response 11:
We used wording in the local language that is clearly recognised by parents as being the measles vaccination, and checked this during pre-testing of the instrument. We have clarified this in the Methods.

12. Why did the authors not check the vaccination card? It could have helped quantify the uncertainty around the estimation.

Response 12:
We have expanded the Limitations section to discuss further, with additional references, the issue of relying on maternal recall for estimating vaccination coverage. There is evidence from resource poor settings that relying on maternal recall is no worse than seeking information from vaccination cards; only a minority of children have cards available and the accuracy of the written information on the cards is poor.

Result
13. Why are there more mothers (and households) than children? The study population being children aged 12-23 months, the number of mothers for which data were used should be the same or smaller

Response 13:
The findings reported in this paper regarding vaccination in children aged 12-23 months are part of a larger study about illnesses and their management among children aged 0-47 months. The number of mothers mentioned (23,547) includes mothers of all children aged 0-47 months. To avoid confusion, we have removed this number from the text.

While re-checking the numbers of children aged 12-23 months in each state, we noted that a few children (some 600 in all) aged between 11 and 12 months had been included in the analysis. We have removed these children from the analysis. Thus the numbers in the revised paper are slightly lower than previously. This has not made any difference to the findings of the bivariate and multivariate analyses.
14. The quantitative results appear a bit like a repetition of the table. I would suggest to extract the main relevant information from the tables, and provide for the main significant factors OR and 95% CI insisting on what are the common factors between the two states and the main differences (rather than going first with univariate, then bivariate, then multivariate for one state, then multivariate for the other one)

Response 14:
We have revised the description of the Results, highlighting the differences between the states where relevant, and focusing on the important associations with the outcome, among the different groups of potential determinants.

15. Regarding the results of the focus group discussion the number of quotations could be reduced to a maximum of 2-3 per topic

Response 15:
We have reduced the number of quotations to not more than two for each theme described.

16. The entire paragraph on “use of findings in planning” should be in the discussion is very relevant and interesting but makes more sense in the discussion when mentioning the implications for policy makers

Response 16:
We have summarised this paragraph and moved it to the Discussion

Discussion
17. I would suggest the authors should to reformulate the discussion according to following guidelines - “The case for structuring the discussion of scientific”, BMJ, 1999 with the following categories:
a. Statement of principal findings
b. Strengths and weaknesses of the study
c. Strengths and weaknesses in relation to other studies, discussing particularly any differences in results
d. Meaning of the study: possible mechanisms and implications for clinicians or policymakers
e. Unanswered questions and future research

Response 17:
Bearing this in mind, we have re-ordered some of the Discussion section. We included the expanded section on Limitations at the end of the Discussion.

18. In the first paragraph what is the official national average?

Response 18:
We have removed the sentence referring to the “official national average”.

19. In the first paragraph - How do the observed results compare with WHO guidelines for measles vaccination coverage?
Response 19:
WHO recommends that all children should be vaccinated against measles at the age of around nine months.

20. What was the perception of measles in those communities? Did they consider the disease as an important one? The decision of vaccination also rely on the perception of vaccination safety/efficacy versus perceived risk of disease

Response 20:
We did not ask specifically about the perception of measles in the communities. However, we found that children whose parents thought vaccination worthwhile were twice as likely to be vaccinated. The focus groups discussed reasons for children not being vaccinated, and in this discussion it was apparent that some parents perceived the risks of vaccination to be greater than the risks of disease in unvaccinated children. We have highlighted this more explicitly in the Results section describing the findings from the focus groups and referred to it again in the Discussion.

21. The 5th paragraph around CASCADA is a bit confusing. It seems to be disconnected from the rest of the discussion, and the formulation itself is a bit confusing. I believe the point here is explained later in the discussion - educational campaign helps improve vaccination rate. I would remove this paragraph.

Response 21:
We have shortened and clarified the relevance of this paragraph. The intended point is about the role of discussion rather than about the role of educational campaigns.

22. Regarding the discussion round birth certificate. Mothers with birth certificates are more likely to vaccinate their child maybe because it is actually believed that vaccination is free only with a birth certificate (mothers with birth certificates may also pay more attention to healthcare?). So I am a bit confused about why the author states that “possession of a birth certificate ……, so this is unlikely to explain the association”. It seems to me that it is actually likely as a proxy.

Response 22:
We have re-worded the paragraph for clarity.

23. The 7th and 8th paragraphs are results, and should be in the results section.

Response 23:
We have revised the wording of these paragraphs to make it clearer that they are indeed discussing findings already presented in the Results section. Some re-iteration of the findings from the Results is necessary, in order to explore reasons for differences between the two states and to compare with the findings from other authors.

24. Among the limitation besides recall bias and the fact we can’t establish any causality, there are potential limitations around the missing collected variables as explained above
Response 24:
We have noted in the Limitations section that there are other factors potentially related to vaccination status that we did not collect information about, such as individual religion and ethnicity.

Conclusion
25. Is 80% considered low? Even though below WHO threshold it is quite high (or at least medium coverage)?

Response 25:
We have re-worded the Conclusion.

26. I thought vaccination was already provided free of charge? The recommendation should be more around informing that vaccination is free regardless of whether you have a birth certificate.

Response 26:
Vaccination is supposed to be provided free of charge, but there are frequent reports of health workers in Nigeria making unofficial charges for vaccination. Making parents aware that the vaccination is provided free can make them less vulnerable to demands for payment. We have re-worded the Conclusion to clarify this.