Author’s response to reviews

Title: BabyGel Pilot: a pilot cluster randomised trial of the provision of alcohol handgel to postpartum mothers to prevent neonatal and young infant infection-related morbidity in the community

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Version: 3 Date: 11 Dec 2018

Author’s response to reviews:

PAFS-D-17-00197R2 - Response to reviews

BabyGel Pilot: a pilot cluster randomised trial of the provision of alcohol handgel to postpartum mothers to prevent neonatal and young infant infective morbidity in the community.

James Ditai; Julian Abeso; Nathan Mackayi Odeke; Natalie Mobbs; John Dusabe-Richards; Macreen Mudoola; Enitan D Carrol; Peter Olupot-Olupot; Julie Storr; Antonieta Medina-Lara; Melissa Gladstone; Brian E Faragher; Andrew David Weeks.
Dear Dr Melson,

Kindly find below our response to the comments by raised by our reviewers for the manuscript "BabyGel Pilot: a pilot cluster randomised trial of the provision of alcohol handgel to postpartum mothers to prevent neonatal and young infant infective morbidity in the community." (PAFS-D-17-00197R1).

Reviewer #1: comments:

Thank you for addressing some comments on the previous draft.

You are welcome and we are appreciative of your time and technical expertise invested in our manuscript.

Although the introduction and the method sections are organized nicely, you fail to response/incorporate some major comments from both reviewers. Particularly, sample size calculation, result sections and the discussion. It would be great if you go through the comments again and address them accordingly. Mention all changes in your "response to reviewer" in each page and line.

Thank-you. We have gone through comments again especially for sections of sample size calculation, results and the discussion. We have addressed these accordingly.

Additional Major comments:

Objectives:

This study seems a feasibility and acceptability study so it is better to avoid/remove the unnecessary objectives and focus on the main outcomes. For example, Objective:1 is unnecessary, 2-3,6 are assessing feasibility, and acceptability, 5-sustainability (difficult to
achieve this with this limited data/information and using the methods), 7-8 not clear and did not reflect in the method and result section clearly.

(Associate Editor: Please retain specific feasibility objectives. Although Reviewer 1 has suggested some of the be removed/collapsed across fewer objectives, in this case I believe it is important to keep these separate and ensure each objective is explicit.)

We have noted the above and thank you.

Page 7 (line 20-22): Not sure why you are planning for a separate manuscript with the same objective? Either drop this or clearly mention the primary objective/outcome of that paper rather than just saying "Other aspect of study feasibility".

Thank you, we have amended this to include the outcome of the paper.

Methods:

1. Selection of the respondents for qualitative interviews, analysis plan should clearly and separately mention.

We have structured this paper and it’s mostly quantitative in nature.

2. mama kit or Maama kit? also did not define this in the method section.

We adopted Maama Kit throughout the manuscript as this was the name adopted by Ministry of health in Uganda. Though MamaKit and MaamaKit have the same meaning with same purpose. We have now defined Maama Kit clearly under the Methods section.

We have addressed the repetition. We have dropped it from the methods and retained the one under the important changes in line with the CONSORT guideline for pilot and feasibility trials ([http://www.consort-statement.org/extensions/overview/pilotandfeasibility](http://www.consort-statement.org/extensions/overview/pilotandfeasibility)). We didn’t mention this and we have clarified the issue of the expert children across the manuscript.

4. Data analysis plan and sample size calculation: combine together and qualitative and quantitative methods should separately describe with sufficient evidence. (previous comment from both reviewers).

We have brought sample size and data analysis close to each other. We have considered this paper to be quantitative in nature based on the data collected.

4. Sample size: The author fails to put sufficient evidence to support the sample size. This is important that the author put proper justification for the prevalence estimation of the primary outcome with appropriate citation.

We have considered the previous comments from reviewers regarding sample size. We have brought sample size next to Data analysis.

Data analysis plan now clearly described.

Additionally, fails to clearly mention the definitions of feasibility, acceptable (use) in the method section (previous comments from reviewer 2).

We have mentioned the feasibility criteria for the different parameters in this pilot trial.
5. page 11 (line 57-65): not clear/repetition

We have addressed the repetition. We dropped certain statements and paraphrased the sentence.

Results:

1. Qualitative and quantitative results should put separately. Quantify the number rather than using mostly, majority (only) etc. throughout the result section.

In this paper, we have made amended the paper to concentrate on the quantitative results targeting at addressing the objectives quantitatively. We have also incorporated the %, numbers instead of using mostly, majorly only as suggested.

2. Page 12 (page 46-51): not result, this sounds like discussion.

We agree it is a discussion and we have moved it from results to the discussion section.

3. Page 13 (26-31): did not describe clearly in the method section, how you collected this data?

I agree but we have now added a sub-section of community advisory board under the Methods to guide the reporting of these results.

4. Page 13 (33-55): This is obvious for all studies around the globe and this should not be included.

(Associate Editor: please disregard point 4/no action necessary).

Thank you.

5. Page 14 (page 36): correct tense

Thank you. We have corrected the tense
6. Page 14 (53-56) : repetition

Thank you. We have addressed this repetition.

7. Page 15 (line 11-21): Not result (Repetition of method section)

Thank you. We have addressed this repetition, by keeping it to the methods section

8. Page 15 (line 38-48): Not clear/clearly mention this in the analysis plan

Thank you. We have amended to include the inter-cluster coefficient under analysis section

9. Page 15 (line 50-63): Not result (Repetition of method section)

Thank you. We have removed the repetition

Discussion:

1. Insufficient literature review and comparison with other recent HW paper. Similar types of activities have performed in different LMIC using different products.

The role of the discussion is to explain what the results mean. Sometimes it is tempting to list all the possible interpretations and 'let the reader choose' what is the most reasonable. This is an abrogation of the responsibility of the author. As the person who analyzed the data and knows the study, you are in the best situation to explain what the most likely interpretation is and defend it. This is not to say that other important potential interpretations shouldn't be mentioned, but rather that you as the author should clearly state what you believe the data means and why. For example, if you just say our study is novel, first study, and no one did this previously, this is not sufficient. You should provide sufficient evidence to support your statement.
Thank you. We limited our discussion to the pilot findings and not necessarily compared to the existing literature on the Hand washing or hygiene practices as we are seeking more on feasibility rather than effectiveness in this pilot study. However, if you find it helpful, we can add in more literature.

2. Avoid repeating the same results in the discussion section.

Thank you. We have removed results from the discussion.

3. Page 16 (line 53): Did not see these organisms in the method section.

Thank you. We have removed this section on organisms

4. Limitations: Need a separate section to highlight the limitations of the study.

Thank you. We have added a section on limitations of the study.

Reviewer #3: I think this is a very interesting and relevant study, and community use of hand gel could be very significant in reduction of infections, so will be interested to see this trial progress.

Thank you very much for echoing on this. Actually EDCTP has awarded us a grant to fund the Main cluster randomised trial informed solely by results from this pilot cluster RCT.

A major comment, as expanded on below is that you do not detail how you measured ABHR use. As this is a key outcome, I think this needs to be made explicit.
We agree that measurement of ABHR use is key in this trial. We have included a section under methods describing how we measured the ABHR consumption.

I also do not think you present enough evidence in support of the effectiveness of expert children. I would suggest reframing this as an avenue you wish to explore further in trial design, unless there is evidence of effectiveness either from literature or from findings not presented here?

We agree there is no effectiveness data on the expert child and we have refrained from mentioning this, and only recommended exploring it further in the main trial.

Minor comments:

I think the word 'infective' is used incorrectly throughout the paper - e.g. you say infective deaths - but that implies the death causes infection in others, rather than the death is caused by infection. http://www.merriam-webster.com/dictionary/infective

Should be rephrased to infection-related death/ infection-related morbidity etc

Thank you. We have replaced ‘infective’ with ‘infection-related’

Introduction

Pg 5 line 12 - which children? Children under 5? Over what time period?

We have included children under 5 years and the time period annually.

Pg 5 line 24 - 37 - this paragraph jumps from late onset sepsis, to early onset, and back to late - I think it should be reordered, and the transition should be more explicit. As I understand it the
intervention is specifically targeting late onset sepsis, and this should be made explicit. Especially as when deaths occur in the late neonatal period (7 - 28 days) almost half of these deaths are due to infection http://www.who.int/bulletin/volumes/93/1/14-139790/en/

Thank you very much for this article. We have rephrased this section to demonstrate our area of interest of late onset sepsis.

Pg 5 line 45 - the Blencowe review is reported as finding a 'lack of quality evidence' which I think is misleading. More accurate to say the reported concluded there was limited evidence, or that evidence in support of effect was low quality - line 50 - state the 40% reduction estimate relates to newborn care practices at home.

Thank you. We have paraphrased this

Pg 6 line 15 - reference for ABHR suggested to increase compliance?

Thank you. We have referenced appropriately

Methods:

Pg 8 - Confused about timeline - study period is 8 weeks? But recruited in Aug-Nov 2015 and followed up until May 2016? How does the 8 weeks fit it?

Thank you. We planned to recruit participants for 8 weeks strictly and follow up the participants for 12 weeks, which was dependent on the date of birth. We have however rephrased it and it is now clear

Pg 9 - Description of 3 moments is confusing and differs from that shown in the figure - e.g. [1] before touching the baby (with whole body wipe within 4 hours of birth).
[2] before clean or aseptic procedures (at the time of birth and application of the alcohol hand rub to the end of the cord three times a day until the cord falls off),

[3] and after body fluid exposure risk (after the mother or carer uses the toilet and after touching any surfaces)

1 - this is 2 different actions, and it reads as if the section in brackets is explaining the previous section - therefore it appears that the only action required is to wipe the baby, rather than positioning 'before touching' as an ongoing action

3 - include after exposure to child faeces in the explaining section in brackets. I suggest the description needs a bit of a reword

Thank you. We have amended the text in line with the figure 3

Pg 9 line 53 - women were instructed by who? it is not clear who actually delivered the intervention

Thank you. We have included that the recruiting research midwives delivered the intervention, and amended the text.

Outcome measurements - No information given on how ABHR use was measured

Thank you. We have included a sub-section on measurement of ABHR use.

Results - pg 14 - line 21 - Perhaps make explicit the IMCI questions which the VHWs were able to answer - I assume the 30% positive result is based only on first 4 Qu in the tool?

Thank you. We have included questions that the VHWs answered well in the tool.
Pg 15 - line 11 - See methods, no information given on how ABHR use was measured.

Thank you. We have included a sub-section on how ABHR use was measured.

Also I don't think the 'expert child' system should go here - no data presented measures the effectiveness or acceptability of the expert child? Again from line 50 - is there any data in support of this change? (even if reported elsewhere?)

We agree there is no effectiveness data on the expert child and we have refrained from mentioning this, and only recommended exploring it further in the main trial.

Discussion

Pg 16 - line 33 - as above, no data presented supports the effectiveness of the expert child, may need to present this as an idea supported by examples from literature (if there are some? I think this mechanism has been used to support ARV adherence, but I don't have exact references?)

Thank you. We have included a sub-section on how ABHR use was measured.

Pg 18 - line 4 - Needs greater clarity:

defined as any one or more of (i) diarrhoea, (ii) lower respiratory tract infections, (iii) omphalitis, (iv) IMCI danger sign(s) verified by health staff, (v) hospitalisation, and (vi) death

Are (i, ii, iii) mother reported? Or also verified by health staff?

Thank you. All are to be verified by the health worker. We have clarified this in the manuscript.

Limitations - you rely heavily on self-report for baseline hand washing figures, it would be worth mentioning limitations of this, similarly if hand rub use is measured by self report, this should be
mentioned as limitation. Is there a limitation in only targeting mothers when other household members may be engaged in care of the new born also?

Thank you. We have included a sub-section on limitations however our target population was not only mothers. It included other baby carers and we have made this clear in the text now.

Conclusion - I don't think you have presented enough evidence to refer to the expert child in the conclusion

Thank you. We agree entirely and have rephrased as above

Associate Editor comments

Reviewer 2 comments (Revision 1), which require additional action:

Site Selection: State eligibility criteria for communities up front, rather than forcing the reader to go to figure 1.” Associate editor: please note that this comment refers to the main body of the article rather than the Abstract.

Thank you. We have included a sub-section on site selection criteria.

Participant selection: “Were only those women attending the ANC days eligible for participation? What is the risk of excluding women who don't attend ANC, and who might be at concomitant risk for adverse birth outcomes (such as preterm birth or low birth weight or unskilled birth attendance) that place newborns at risk for infection?” Associate editor: the information provided on pages 8-9 does imply that antenatal clinics were used for recruitment, with potentially eligible women then followed-up by VHWs. If there were other recruitment strategies, then please report them or rephrase this sentence.

We have rephrased this sentence to show that women were screened or identified from their homes and health facilities but recruited from their homes.
Associate Editor comments

Abstract

1. Methods: criteria included in parenthesis are not informative on their own. For example it’s not clear what ‘(mean >4 times/day)’ means here.

We have elaborated on the criteria further to make it informative.

2. Results: The finding for ABHR use (Is 55-57 VHW. vs. pharmacy dispensed) isn’t introduced so far and its relevance isn’t clear without further information.

We have introduced this in the methods to make its relevance under results.

3. As per my comments (item 1, Revision 1) please summarise the aspects of feasibility which are of interest in this study.

The aspects of feasibility of interest included home recruitment with capture of GPS coordinates which ensures excellent follow up by same or different research team. The VHWs refilled the ABHR promptly and accounted for it all. The primary outcome was challenging especially completion of the IMCI screening tool in the community.

Objectives

4. The stated objectives have been revised and there is now greater focus on the feasibility aspects of this study. Although Reviewer 1 has suggested some of these be removed/collapsed across fewer objectives, in this case I believe it is important to keep these separate and ensure each objective is explicit.

Thank you. We have kept these separate and elaborative.
5. Some of the objectives require further description and elaboration to be understood as standalone statements. For example the nature of the information provided in parenthesis following each objective varies - some refer to specific criteria while other suggests a type of evaluative method. This is a little confusing for the reader. Please ensure any pre-determined criteria relating to these objectives are clearly described. However, details around the measures should be covered in the Methods (see comment 7 below)

Thank you. We have ensured the predetermined criteria for objectives as elaborative as possible.

Methods

6. Thank you for reorganising the Methods. The sequencing of information now reads more clearly.

You are welcome.

7. Following my comments on Revision 1 (item 10), and similar comments provided by the external reviewers, there is still a lack of clarity around the methods used to obtain data and assess key aspects of feasibility relevant to your objectives. Therefore, in this section please include a clear description and (where relevant) justification of the specific methods used to evaluate these aspects of feasibility. Transparency around data collection and methods is essential.

As an example, information relevant to objective 2 (test of study protocols) and 3 (WHO infection screening tool) appears to have come from Village Health Workers/VHWs. It's important to be transparent about how this information was acquired, such as whether this took place through ad hoc communication between research team and VHWs or if there was a more formal method of capturing this information (e.g. interviews, weekly meetings, review of submitted case documents etc)? Other examples include how possible contamination to clusters in the control arm was determined? maternal infection rates also feature within the results, but we know little about how this information was acquired and whether it is reliable? This information is important if the reader is to assess the quality of the methods and the findings which follow.
Thank you. We have now included a detailed account of the outcome measurements about these aspects of the feasibility.

8. The Data Analysis section is narrowly focused on treatment of quantitative data. However, the feasibility objectives cover much more than this. Greater transparency (following point 7 above) in the methods may require further detail around analysis. Therefore, please ensure that the Data Analysis is comprehensive in its description of the treatment of all relevant study data.

Thank you. We have made the data analysis comprehensive to the results.

Results

9. In Revision 2 it is now clearer which findings are relevant to the study objectives. This is a step in the right direction, but there are still a few issues to address.

Thank you. I now feel we have addressed the issues in the revised manuscript.

10. An objective (4) is to determine the number of deliveries per village. I can’t see this reported, but may have missed it.

Thank you. Though we had included this objective prior start of the start, we later dropped it as we found no significance to the main trial. I have hence dropped it from the list of objectives.

11. Please move the statement about ignoring clustering effects (p 12, ls 61-62) to the Data Analysis section.

Thank you. We have moved this statement to the data analysis section.
12. P13: “spontaneous vaginal births were common in both (TYPES OF) cluster”. Please correct this.

Thank you. We amended this in the text.

13. P15. Please correct “inter-cluster…” here and elsewhere in the manuscript. The rationale for calculating an ICC for a composite infection measure has also not yet been introduced yet and presentation of this result is unexpected. Please give careful consideration to when and how this finding is introduced in the manuscript.

Thank you. We have corrected inter-cluster…. And introduced ICC in the analysis section before reporting it in the results section.

Discussion

14. The statement around statistically significant differences in the outcome is no longer relevant and should be removed (p 17, ls 18-19). Please ensure the Discussion is thoroughly reviewed and updated to reflect any changes to the reporting of the results.

Thank you. We have reviewed the discussion to reflect the changes in the results.

15. Following the comments of Reviewer 2 (Revision 1), please comment on the absence of an explicit behaviour change strategy to guide the intervention. What are the potential implications of this for ongoing development of the intervention, accumulation of evidence and understanding of process?

Thank you. We have included a statement on the behavior change strategy.


Thank you. We have deleted the repetition.
Tables/Figures

17. Thank you for re-ordering the sequence of Tables. Please label Table 4 to indicate the reporting of 95% CIs.

Thank you. We have indicated the 95% CIs.

18. The numbering of the Figures is still not sequential (as presented in the text) and is confusing.

Thank you. We have sequentially numbered the figures and therefore changed the figure numbering to reflect the order in the text.

19. Figure 3 ‘note’: please remove the quotation mark.

Thank you. We have removed the quotation mark.

20. Figure 5: not all text is visible within the boxes (e.g. ‘did not receive allocates…’ is cut off).

Thank you. We amended this and all text is now visible.

21. Figure 5: Please reconfigure arrows and boxes so that they fit together properly.

Thank you. We have reconfigured arrows and boxes.

22. Figure 5: Please define abbreviations (**NND)

Thank you. We have defined NND in the revised figure.