Author’s response to reviews

Title: Is attendant at delivery associated with the use of interventions to prevent postpartum hemorrhage at home births? The case of Bangladesh

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Version: 2 Date: 14 October 2013

Author’s response to reviews: see over
Response to Reviewers

Dear reviewers and editor,

Thank you for the opportunity to revise our manuscript entitled, “Is attendant at delivery associated with the use of interventions to prevent postpartum hemorrhage at home births? The case of Bangladesh”. We are encouraged by your interest in our manuscript and hope that we have sufficiently addressed each of the reviewers’ concerns below. We think we have improved our manuscript based on the changes we have made. We thank the editor and the reviewers for their time and their thoughtful comments and we look forward to hearing back.

Sincerely,

The Authors

Reviewer 1: Godfrey Michael Mbaruku

Reviewer’s report:
No major compulsory revision. However, the authors are strongly recommended to read and examine a recent systematic review on Misoprostol by Hofmeyr et al published by the Cochrane Database, 2013 July 15. CD 008982. doi:10.1002/146518.CD008982.pub2. In order to get a balanced view of their discussion and especially on their recommendations.

The reviewer makes a good point. The Hofmeyr review came out after we originally submitted this manuscript, but we added the following to the Discussion in order to address their findings:

“Additionally, the quest to conclusively demonstrate whether prophylactic use of misoprostol reduces mortality continues. A recent review of existing evidence found that misoprostol use for the prevention of PPH neither increased nor decreased the risk of mortality or severe morbidity. It is important to note that none of the studies included in this review were individually powered to detect significant changes in the risk of mortality, but the findings nonetheless question whether similar projects to the one presented here would actually reduce maternal mortality due to PPH [26].”

This is an extremely important article as it responds to one of the main causes of maternal mortality in developing countries. Further, it depicts another quite common bottleneck towards service delivery in these so-called countries which is the issue of severe shortage of healthworkers coupled with an erratic supply chain system.

The question is well defined and is relevant to the subject at hand. The methods are well described and appropriate to this type of study and the authors have adhered to the relevant standards for reporting and data presentation. Their discussion and conclusions are balanced and adequately supported by the data. They are also frank about the limitation of their study. The title and abstract accurately convey what has been found with a standard writing style.

The only minor omission in my view is their failure to give a balanced opinion on the limitations of lay healthworkers in the provision of this albeit very powerful drug. It can be argued that dosages may vary due to problems of storage (although the drug is said to be stable, the storage in low income households leaves some doubt), some of the so-called ‘lay healthworkers’ in some communities are old women who
may not be familiar with modern medicine and the potential misuse of the drug for some other indications.

This is a great point; lay healthworkers definitely have limitations. We added the following sentences to the Discussion after mentioning the positive findings from the TBA training evaluation: “Despite these positive training results, it is important to always consider the limitations and risks of utilizing lay healthcare workers to administer medical interventions. Trainings should emphasize that providers only use misoprostol immediately following delivery (using the recommended dosage after ensuring there is no twin) and that misoprostol is never to be used for any other purpose.”

Finally, the authors should be able to go through a recent systematic review by Hofmeyer et al, who has pointed out the pros and cons of the administration of this drug—especially on the dosages and more so if it exceeds a certain amount. They should counteract this as much as they can in order to point out whether the benefits outweigh the risks. For example, it was concluded from this systematic review that Misoprostol does not appear to either increase or reduce maternal mortality neither severe morbidity (apart from hyperpyrexia). Most importantly, there were more adverse effects in dosages of 600 micrograms (or more). Since the authors strongly recommend that the use of lay healthworkers should be used, then these adverse effects should be also considered and maybe recommend that lower dosages to be used. Indeed, they should give as a recommendation a need for more randomized controlled trials in order to prove that the drug is not only effective but more importantly safe. The subject of adverse effects should be given emphasis rather than be mentioned just as ‘minor’. This is crucial as the drug is supposed to be a life saver and should not in the end be a cause of increased adverse effects!

Adverse effects are important to consider and we appreciate this comment. The side effects, while uncomfortable, are transient and have not been associated with any long term morbidity, or mortality. Despite this, it is critical that programs and policies balance effectiveness and potential for side effects to utilize the lowest possible dosage. The RCT by Elati et al demonstrated that 200 µg, 400 µg, and 600 µg had similar results in terms of uterine pressure but all doses had higher adverse effects than oxytocin and 600 µg had the highest level of side effects (including hyperpyrexia). We agree that if effectiveness is not significantly compromised, lower dosages, with lower associated side effects, should be utilized. Further studies are needed to confirm these findings. We added the following to address the issue of side effects and dosage: “Side effects, although not addressed in this study, are an important consideration that program planners and policymakers should take into account. Health interventions, especially those implemented at home, should always aim to have as few side effects as possible. The potential benefits of an intervention should be weighed against the risk of side effects. In the case of misoprostol for PPH prevention, the potential reduction in the risk of PPH is greater than the potential harm of the transient side effects associated with 600 µg of oral misoprostol use; none of the side effects have been associated with long term morbidity or mortality. Studies have demonstrated that lower doses of misoprostol are associated with similar levels of uterine pressure but less adverse effects, which seems to indicate that lower doses could be used with similar levels of effectiveness [25]. A non-inferiority trial will be required to determine whether 400 µg or 200 µg of misoprostol is as effective as 600 µg in the prevention of PPH.”

Regarding Hofmeyer and the risk of mortality, we added the following: “Additionally, the quest to conclusively demonstrate whether prophylactic use of misoprostol reduces mortality continues. A recent review of existing evidence found that misoprostol use for the prevention of PPH neither increased nor decreased the risk of mortality or severe morbidity. It is important to note that none of the studies included in this review were individually powered to detect significant changes in the risk of mortality,
but the findings nonetheless question whether similar projects to the one presented here would actually reduce maternal mortality due to PPH.”

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests: I have no competing interests

**Reviewer 2:** Mosiur Rahman

**Reviewer’s report:**

**Major compulsory revisions:**

Overall, this is an interesting paper and highly publishable. The data come from a large intervention study with the subpopulation of women who delivered at home; giving a sample size of 67,611. The topic itself highlights important issue that trained TBAs can have a significant impact on utilization of interventions to prevent postpartum hemorrhage in home births. However, this paper needs further major revisions to come a definite and concrete conclusion.

1. Methods:
   i) What's the rational of applying those 5 socio-demographic variables in the multivariate analysis, why others important variables were not considered such as economic status of the respondent

   *We selected those 5 socio-demographic variables based on the available variables in the ANC card/postnatal data. Socioeconomic status was not included in the analysis because this information was not collected in these data. If available, we would definitely have looked at socioeconomic status, in addition to other variables.*

   ii) Here is some explanation needed for measurement decisions. Why is age grouped? Was continuous measure attempted and they proved to provide non-linear results? If not, then I don’t see the point of grouping the variables since information is lost.

   *We used these age categories because we thought that there might be important distinctions or differences across age that would not be linear, which we found to be true. We use these specific age categories because these 5-year increments are commonly used in other analyses and help to define specific populations, like adolescents and young adults, who may have different prevalence of intervention utilization.*

   iii) The authors need to point out how they dealt with missing variables.

   *We think that this reviewer is referring to the missing values of variables within specific observations. In the logistic regression, any observations with missing values for any of the variables dropped out and were not included in the analysis. This resulted in a 4% reduction in the number of observations, which we were not concerned about. We included the following statement in our Methods section:*
“Observations with missing values for any of the variables included in the logistic regression were dropped. This resulted in a 4% reduction in the number of women included in the final analysis.”

iv) On page 6 lines 3-4, the authors mentioned that “using results from the bi-variate analysis, all covariates associated with the use of the study intervention (dependent variable) at the p less than or equal to 0.20, to include the variables in the multivariate model. Please provide the reference for that.

Bivariate analyses were conducted to select potential covariates. We used a conservative criterion of P < 0.20 for the bivariate analyses in order to ensure that significant covariates were not omitted from the multivariate model. It is well-known that variables that do not show a significant association with the outcome in bivariate analyses may be significant in the multivariate analysis, but all of the available covariates we hypothesized to be associated with use of the intervention were associated at the P<0.20 level, thus all were included in the multivariate analysis. We do not have a specific citation for this methodology; it is simply a systematic approach we (and other researchers) use to select covariates to include in multivariate analyses.

v) It would be nice if the authors discussed about the training procedures of TBAs in the methods section.

We have included the following additional details about the TBA training in the Methods sections: “The training included information on myriad aspects of misoprostol use (function, dosage, timing of administration, side effects and their management, etc.) and the absorbent delivery mat. The training also covered information regarding the identification of high-risk pregnancies, danger signs of pregnancy, referral procedures, stages of labor, newborn resuscitation, maternal infection, and general use of the CDKs. Trainers particularly focused on PPH and other pregnancy complications that require referral.”

vi) Please reassure us that coercive methods were not used in data collection (this could go in the ethics section).

This is an important point to mention, thus we added the following to the sentence on ethical approval: “The RDRS staff did not employ any coercive methods to collect information from participating women and women were free to not answer any questions without penalty or impact on service delivery.”

2. Results
i) If possible, there should be more interpretation of data under the results section.

In the Results section, we mainly focused on presenting the findings, and left interpretation for the Discussion section. The Results section is small given our limited analyses, but we did expand on the presentation of the logistic regression findings. That paragraph now reads as follows: “Based on the bivariate results, all covariates were included in the multivariate model. Women who delivered at home and had an RDRS trained TBA present had 2.72 times the odds of using the interventions compared to those who had a lay person present (95% confidence interval 2.15, 3.43) (Table 2). Compared to women ages 15-19, women ages 20-24 and 25-29 were not more likely to use the interventions, nor were the eldest women surveyed (ages 45-49). However, women ages 30-34, 35-39, and 40-44 were increasingly more likely to use the interventions, and these findings were statistically significant (odds ratio 1.15, 1.16, and 1.64, respectively). Reaching secondary school or college was similarly significantly associated with increased odds of using the interventions (odds ratio 1.43 and 1.41, respectively), as was having had
a previous pregnancy (odds ratio 1.16) (Table 2). Each additional ANC visit a woman attended was associated with 2.76 times the odds of using the interventions (95% confidence interval 2.71, 2.81).”

3. Discussion:

i) The discussion section is poor starting. I could not understand what the authors tried to say in the first sentences of first paragraph and how they linked it with last sentences within the same paragraph. The discussion section should start with the solid findings of data analysis.

We agree that our main finding/contribution should be the first thing presented in the Discussion. Our first couple sentences are now: “Our primary hypothesis, that having an RDRS trained TBA present at the delivery would be associated with increased use of the interventions, was correct. To our knowledge, this is the first study to examine if type of delivery attendant is associated with the use of community-based interventions to prevent PPH at home births.” The previous first sentence has been moved to the last paragraph of the Discussion and reworded as such: “Making evidence-based interventions available is the first step to improving the safety of home deliveries in low-resource settings, but the availability of these interventions alone will not ensure usage.”

ii) The most critical issue with this study, if I understand it correctly, is that it is based on a survey of women who were self-selected to contact RDRS TBAs at the time of delivery, thus these women could be inherently different from women that did not deliver with an RDRS TBA. It is possible that the increased utilization of misoprostol and the mat among women who delivered with RDRS TBAs may be partially due to differences in these women and their knowledge of or inclination to use these technologies. Therefore, I would recommend the authors to discuss these issues in their manuscript.

This is a great point, which we try to address in the Discussion section: “Given that this data is cross-sectional, we cannot make claims of causality and alternative explanations for the findings could be made. Women who have an RDRS trained TBA present at delivery or who attend more ANC could be systematically different from mothers who had a regular TBA or lay person present, or who attended fewer ANC visits. Some unmeasured characteristic (like motivation or knowledge) could have caused the women to be more likely to have an RDRS trained TBA present, attend more ANC appointments, and to use the interventions. Alternatively, both explanations could be true and they could reinforce each other.”

iii) The authors have failed to discuss many counterintuitive findings such as age, education, gravity

We have added a paragraph to the Discussion section to provide an interpretation of these findings: “Findings related to other covariates demonstrate interesting associations. Increased age was not linearly associated with increased use of the interventions, but it did trend in that direction. This finding could be interpreted in conjunction with the fact that having had a previous pregnancy was associated with increased use of the interventions. Younger women who have never been pregnant and who may not know as much about the dangers and potential complications of pregnancy may have been less inclined to utilize these interventions in comparison to older women, who may have experienced complications first hand in previous pregnancies, or know other women who have. An alternative explanation is that these older women (ages 30-44) might have more autonomy and feel more empowered to make choices about their healthcare utilization and delivery practices than younger, nulliparous women, who may be taking direction from their mother-in-laws. This potential demonstration of autonomy is likely why women with secondary and college education are also more likely to use these interventions in comparison to women with no formal schooling. The eldest women’s
(ages 45-49) non-statistically significant and less high utilization of the interventions could be a result of having survived several pregnancies by that age and not being interested in incorporating new, unfamiliar technologies into their home delivery practices.”

iv) Limitation of the study should be justified

We are not sure what the reviewer means by justified, but we have added to our limitations section. It now contains the following information, which we feel are our main limitations: “A limitation of this study is that all data were self-reported by the women. Women provided information on all the covariates during their first antenatal care appointment with an RDRS CHW, and information on attendant at delivery and use of the interventions was later self-reported at a postnatal appointment. Self-reported data can be less accurate and be subject to social desirability bias. Direct observation was not possible given the number of women enrolled in the project, but efforts were made to collect pill packets after delivery from all women to assess whether the misoprostol had been used or not. Despite these efforts, if women falsely reported use of the interventions (and we do not believe women who did use the interventions would have any incentive to falsely report non-use), this would result in a non-differential misclassification that would bias our results toward the null. Thus our results would be a conservative estimate of the association of attendant at delivery and use of PPH prevention interventions.

An additional limitation is that the data are cross-sectional, thus we cannot make claims of causality and alternative explanations for the findings could be made. Women who have an RDRS trained TBA present at delivery or who attend more ANC could be systematically different from mothers who had a regular TBA or lay person present, or who attended fewer ANC visits. Some unmeasured characteristic (like motivation or knowledge) could have caused the women to be more likely to have an RDRS trained TBA present, attend more ANC appointments, and to use the interventions. Alternatively, both explanations could be true and they could reinforce each other.”

v) Need a bit more of a discussion of the self-reported bias – because interviews were based on self-reported, did the study team were able to verify by direct observation what occurred at the time of delivery.

This is a valid comment and we have provided additional information on this matter. We added the following to our Discussion section: “A limitation of this study is that all data were self-reported by the women. Women provided information on all the covariates during their first antenatal care appointment with an RDRS CHW, and information on attendant at delivery and use of the interventions was later self-reported at a postnatal appointment. Self-reported data can be less accurate and be subject to social desirability bias. Direct observation was not possible given the number of women enrolled in the project, but efforts were made to collect pill packets after delivery from all women to confirm whether the misoprostol had been used or not. Despite these efforts, if women falsely reported use of the interventions (and we don’t believe women who did use the interventions would have any incentive to falsely report non-use), this would result in a non-differential misclassification that would bias our results toward the null. Thus our results would be a conservative estimate of the association between attendant at delivery and use of PPH prevention interventions.”

4. What do you think are the implications of these findings for future programs? You mention the research implications, but what about the more practical side of it? Conclusion feels week because the implications are not discussed.
We have extended out Conclusion section to speak more broadly about the implications of these findings for future programs: “Given misoprostol’s potential to reduce PPH, it is increasingly being made available in low-resource settings, where the majority of PPH occurs. Findings indicate that a trained TBA’s presence at delivery can potentially have a significant impact on utilization of interventions to prevent PPH. PPH prevention efforts targeting home births that use advanced distribution of misoprostol should thus consider targeting delivery attendants for intervention specific training. Programs that aim to increase the safety of home deliveries should also perhaps increase efforts to enroll women in ANC and encourage attendance at multiple appointments, as ANC attendance was found to be associated with increased utilization of misoprostol and the absorbent delivery mat. These efforts, in the context of a reliable continuum of care, may help to reduce the morbidity and mortality associated with PPH in Bangladesh and other low-resource countries.”

5. Please elaborate PPH in the background of abstract section.

We have changed the first sentence of the Background section of the abstract to read as follows: “Hemorrhage is the leading cause of maternal mortality in Bangladesh, the majority of which is due to postpartum hemorrhage (PPH), blood loss of 500 mL or more.”

Generally, I believe that if you correct the errors listed above and address some of the content comments in your literature review or discussion/conclusion, your article will be significantly stronger and of more use to international health.

Level of interest: An article whose findings are important to those with closely related research interest

Quality of written English: No corrections are needed

Statistical review: No, the manuscript does not need to be seen by a statistician.

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Editor's Comment:
Also, thank you for explaining the data access/availability in your previous email. However, we must ask that a statement explaining this be also include in the manuscript itself.

As per the email exchange, we added the following to the existing section on ethical approval: “The data collected were de-identified and this secondary data analysis did not require additional ethical approval or authorization.”