Reviewer's report

Title: Misoprostol for postpartum hemorrhage prevention at home birth: An integrative review of global implementation experience to date

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Reviewer: Nancy L L Sloan

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Misoprostol for postpartum hemorrhage prevention at home birth:
An integrative review of global implementation experience to date

Summary: The review presents important and original information. However the range (rather than inverse proportion weighted analyses to aggregate and interpret data) presented do not support the interpretation of the findings or some of the conclusions. In addition, the manuscript is wordy throughout (akin to a report) and would benefit from careful editing. The text is about twice as long as necessary and laborious to read. Some strong editing could make reading the manuscript enjoyable instead of a chore. The manuscript has some good information that merits better analysis. The reception of the manuscript would be greatly improved by making the reading a pleasant experience.

1. Is the question posed original, important and well defined?
The research question posed by the authors is easily identifiable and understood. The review presents important and original information, though its definition could be improved as specified in the detailed comments.

2. Are the data sound and well controlled?
No. The authors describe some of the data limitations, but do not present them with sufficient clarity (see suggestions to modify Tables). The range analysis of the data do not provide valid comparisons necessary to support the interpretation of the findings. The final objective, regarding hindrance of institutional delivery, requires a simple comparison that is not presented.

3. Is the interpretation (discussion and conclusion) well balanced and supported by the data?
No, the range (rather than inverse proportion weighted analyses to aggregate and interpret) data presented do not support the interpretation of the findings or some of the conclusions.

4. Are the methods appropriate and well described, and are sufficient details provided to allow others to evaluate and/or replicate the work?
No. The inclusion/exclusion criteria are not clearly described in a manner that permits replication or comprehension.
5. What are the strengths and weaknesses of the methods?

The strength of the effort is that this is apparently a comprehensive review. The weaknesses are in the data analysis, which must be strengthened to permit valid inference. There should be available free, user-friendly software to accomplish this. Alternatively, assistance from a statistician or demographer in these analyses may facilitate their correct completion. The less critical, but still important weakness is the manuscript composition.

6. Can the writing, organization, tables and figures be improved?

Enormously. The manuscript is wordy throughout (akin to a report) and would benefit from careful editing. The text is about twice as long as necessary and laborious to read.

7. The requested revisions are specified below.

8. Are there any ethical or competing interests issues you would like to raise?

No, however the protection of human subjects requires better (more detailed) description.

Detailed comments

1. Protection of Human Subjects: The statement is insufficient. Please state "All data collected were de-identified. The Johns Hopkins University, Bloomberg School of Public Health Institutional Review Board found the research exempt from approval based upon ..... (something like "45 CFR 46.101(b)(2), ), 45 CFR 46.101(b)(4) and 45 CFR 46.101(b)(5) exemptions from 45 CFR part 46 requirements from all 45 CFR part 46 requirements", please see http://www.hhs.gov/ohrp/policy/index.html#topics or contact your IRB administrator to obtain and provide the information)

2. Literature review: Please replace with

We conducted a PubMed search using the keywords “misoprostol AND “postpartum hemorrhage” AND “home OR community .” for peer-reviewed literature published between XXXX and XXXX [years]. This information was supplemented by a web-based of the grey literature, including non-peer-reviewed publications and project reports using the same terms above. We also conducted a directed search of the websites of anticipated implementing organizations, and professional networks to to identify published and unpublished information from research, pilot and full-scale community-based misoprostol PPH prevention programs. We also made direct inquiries to agencies known to be engaged in this work from which their representatives shared program reports and evaluations.

3. Inclusion and exclusion criteria: Please edit for clarity, as above. The statements " substantial detail" and "did not sufficiently detail the methodology or results" are insufficient. The authors need to describe the required information on methodology or results necessary for inclusion in the review. This may be a statement as simple as "Studies and programs were included in the review that
described the location and population in which the program or research was conducted, described the dose, formulation (oral, sublingual, buccal, rectal) and mechanism of misoprostol provision, specified the number of women to whom misoprostol was provided and the number who consumed the misoprostol. Studies and programs were included in the correct consumption analysis if they additionally provided information on when (ante, intra and post-partum) the misoprostol was consumed and the dose consumed. The review includes information on side effects when that information was available. (This is just an example of the type of statement needed). Or state, "Studies and programs providing information on X, Y, Z (column 1 of figure 2) were included.

Figure 1 is also inadequate. Some specification of the exact reasons why studies/programs were excluded is needed (like, 58 peer reviewed publications, 7 included, and add a box for excluded with something like 21 "not a misoprostol study or program", 8 did not provide coverage, safety or side effects statistics, 10 did not do X, XX Other reason for exclusion – this last category should include #25% of the excluded reports/publications)

Major Compulsory Revisions

1. Data analysis: Para 3: Sums are likely inappropriate for data aggregation across sites. Traditional meta-analysis should be used (with inverse probability estimation) – there is free and user-friendly software (RevMan) to produce such statistics to compare levels of coverage by strategy for example.

2. Results: needs to reiterate basic information in figure 1, state how many were from peer reviewed publications, reports, networking informal information source (e.g., not a publication or published report); need to state how many were research, how many were programs. Table 1 should describe program strategies even if not a study, even just to say "national" or "subnational" or "regional" program. It would be wonderful to specify the distribution timing, cadre and administration method for each of the 18 included studies/programs on Table 1. You can still summarize the results of this as done on Table 2.

3. The results comparing distribution timing, cadre and administration methods would be more methodologically sound by using inverse probability analysis as suggested above. Comparing ranges of unrepresentative and unweighted data does not provide meaningful comparison or generalizable information. Much of the interpretation made in the results section is based on methodologically inadequate aggregate results (not meta-analysis), so one cannot really know whether a statement such as "However, distribution rates (or rate ranges) achieved were similar between community health workers and TBAs, and less favorable for health workers/ANC providers" and coverage rates were highest when CHWs distributed misoprostol and coverage rates were lower when health workers/ANC providers were the distributors of the medication" are actually true or not..This depends upon the number of observations (and appropriately weighted analyses).

4. Table 4 and Change in Facility Birth Rates: Requires some information or estimation of national changes in facility birth rates in similar time frame.

5. The method of maternal death assessment should be described in the
methods section (and perhaps commented upon in the discussion section), but not in the results section.

6. Uterine rupture – important to know and state whether these were among the maternal deaths reported.

7. Discussion section: Paragraph 8: The interpretation may or may not be correct; what is required (at minimum) are data from the area or country regarding the % change in institutional deliveries. One cannot argue that home base misoprostol is or is not detracting from institutional delivery without such comparative data.

8. Discussion: Actually, it might be possible to compare effectiveness of one program against many (pg 10 first 2 lines). Leave it at "not your intent to do so."

9. Discussion section: Would be greatly strengthened by transferring all results interpretative statements in to the discussion section. For methodologic reasons (range rather than correct inverse probability data aggregation and analysis), the statements in paragraph 7 in the discussion section are actually unknown; without correct aggregate analysis there is no way to know if this interpretation is or is not correct.

10. The statement that "All but one program made an attempt to identify and record the number of maternal deaths in the program’s target area, and specifically, the number of maternal deaths that occurred among women who took misoprostol" means that the denominator of that one program should be removed from the denominator used when describing the number of deaths for the number of women assessed. If that one program had a very large number of women, it could change the implications.

11. Analysis/interpretation: Without appropriate meta-analysis, cannot fairly state "The findings presented in Table 6 suggest that certain distribution timings or certain distributing or administering cadres had higher reported cases of PPH" even the statement "however, these findings must be interpreted with caution. Many factors could have influenced the number of reported PPH cases, particularly the differences in reporting blood loss measurement with or without accompanying tools." is insufficient as the largest challenge to the statements validity is inadequate methodology in the analysis.

12. Conclusions: Unsure if the data or analyses justify the statement "Findings from this review should promote understanding about the outcomes of various programmatic approaches, and address certain outstanding concerns, by describing the outcomes of program outreach" and do not justify the second and third sentences of the second paragraph.

Minor Essential Revisions

Background

13. Last sentence, first para: may want to note those are likely underestimates as they include both measured and estimated blood loss, the latter of which commonly underestimates loss

14. 4th Paragraph: much of this has been stated in other publications. The
paragraph can convey the information much more succinctly. Doing so will allow for including substantial points raised in this review.

15. Last Paragraph: Please replace with a more typical presentation of the objectives, something like:

We present a comprehensive review the available body of information to synthesize the global experience about completed programs of misoprostol for PPH prevention of in home births. The objectives of the review are to describe:

1 The implementation and measurement strategies of misoprostol for home birth PPH prevention
2 The success of these approaches in terms of coverage and correct use, particularly regarding self-administration after delivery,
3 Does community-based distribution and use of misoprostol influence the use of facility-based birth?

15. Data extraction: State what data were obtained/extracted (e.g., either state and delete figure 2 or just refer to figure 2).

16. Data analysis: Para 1: Please replace "(either taken directly from the report or estimated using population and crude birth rate, adjusted for the length of the intervention)" with "as reported or estimated as the product of the population, crude birth rate and intervention duration. Para 2: Please replace" (estimated by taking the denominator from the distribution rate and multiplying it by the study site's home birth rate or, if not available, the national home birth rate)" with "estimated as the product of the distribution and area home birth rates or national birth rates when area rates where unavailable.".

17. Results Para 5: Rather than saying "Several of the reports provided detail about the methods that were used to maintain accountability of the stock of misoprostol available (on hand), and/or distributed for use." State X (number) described information on stock-outs and methods used to avoid them, and X specified the number of doses distributed."

18. Results: Usually only present, but don't interpret, results. Interpretation should be reserved for the discussion section. For example, replace "Tables 2 and 3 depict the various - and sometimes multiple - approaches used by programs to distribute misoprostol to women. No particular timing was predominant among programs that distributed misoprostol prior to birth (n = 11), with programs using early, late or unrestricted distribution timing. However, the range of distribution rates was lower for late-ANC visit distribution compared to distribution at any ANC visit." X% provided misoprostol via ANC, X% by late pregnancy home visit, X% by ....; X% used some combination of these approaches." Use the same reporting format for distribution and administration. Do not explain that "no particular timing was predominant" or "the range of distribution rates was lower for late-ANC visit distribution compared to distribution at any ANC visit" – those are interpretations and belong in the discussion section. This comment applies to the remainder of the results section, much of which is presented as interpretation rather than presentation of the statistics.

19. Editing suggestions: For example,
"Recent estimates indicate that the risk for women dying as a result of pregnancy or childbirth during her lifetime range from about one in 39 among women from sub-Saharan Africa, in contrast with 1 in 3800 among women from developed countries" (41 words) could be stated "The lifetime risk of dying from pregnancy or childbirth ranges from one in 39 in sub-Saharan Africa to one in 3800 in developed countries." (24 words, e.g., 40% fewer words).

And instead of " A number of high-impact medical and surgical interventions have been tested for their efficacy in the prevention of PPH." One could say "Various medical and surgical interventions effectively prevent PPH."

Also, "A correlated body of research has emerged in the last decade that focuses on identification of safe and effective strategies for prevention and treatment of PPH in settings where oxytocin is not available or where its administration is not feasible" could be "Research supports safe and effective alternative strategies for PPH prevention and treatment in settings where oxytocin is unavailable or its use infeasible." (22 words instead of 40).

Discretionary Revisions

Title:
20. Not sure what integrative means; is there a better word (perhaps "comprehensive" or "systematic")?

Abstract:
21. You may wish to include MMR equivalent – may wish to state that even if all deaths were attributable to PPH, the equivalent (59/100,000 deliveries) is substantially lower than the average MMR in any of the countries represented by this review.

22. Conclusions: replace "early" with "ante- or intra-partum"

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

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

**Declaration of competing interests:**

The answer is no to all. I declare that I have no competing interests'