Author’s response to reviews

Title: Task shifting in active management of the third stage of labor: a systematic review

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Author’s response to reviews:

Utrecht, 21 February 2017

Dear Dr. Nawsheen Boodhun,

We would like to thank the reviewers and editorial team for their constructive feedback to improve on our manuscript “Task shifting in active management of the third stage of labor: a systematic review”, in which we evaluated the evidence on the effect, acceptance and safety of task shifting of components of active management in third stage of labor.

Kindly find our point-to-point response to each comment below highlighted in blue; the responses in italic type, any change in the manuscript is added as plain text. We updated the manuscript accordingly.

We hope that you find this version suitable for publication.

On behalf of the co-authors,

Tessa Raams, MD

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# Editor:

Please revise your manuscript to include all the following sections under the heading 'Declarations':

- Ethics approval and consent to participate
- Consent for publication
- Availability of data and material
- Competing interests
- Funding
- Authors' contributions
- Acknowledgements
- Authors' information (optional)

If any of the sections are not relevant to your manuscript, please include the heading and write 'Not applicable' for that section.

Response:

Thank you for your careful observation, the heading ‘Declarations’ was added and completed.

Reviewer #1: This systematic review evaluates the evidence for task shifting of AMTSL to unskilled birth attendants or self-administration of uterotonics for prevention of PPH in LMIC. The review covers an important topic in terms of policy change and uses appropriate and robust methods to gather the evidence. Reporting is clear and concise. I have a few comments/suggestions for improving the manuscript:

1. The authors are concerned about the lack of primary studies evaluating the components of AMTSL other than uterotonics. As far as I am aware, other components of AMTSL such as controlled cord traction is not recommended and may be dangerous when administered by unskilled attendants. There is now growing evidence to show that uterotonic administration is the most important component of AMTSL. I would therefore suggest that the authors focus their review on this aspect only.

Response: We would like to thank reviewer 1 for his/her review of our manuscript. We agree with reviewer 1 that administration of uterotonics is the most important component of AMTSL and according to the WHO guidelines on prevention of PPH all delivered women should be offered uterotonics. The other components of AMTSL have inferior rolls in reducing PPH.
Therefore, we amended the background section according to the recommendations in the WHO guidelines (page 3):

“Active management of the third stage of labor (AMTSL) consists of a set of components aimed at the prevention of PPH [3,4]. AMTSL includes the administration of uterotonics (for example oxytocin or misoprostol) preferably within one minute after delivery to all women, controlled cord traction (CCT) to stimulate placental delivery, uterine massage to activate uterine contraction and assessment of uterine tonus every 15 minutes during two hours postpartum to early identify uterine atony [1,4–6]. The World Health Organization (WHO) recommends AMTSL to be performed by skilled birth attendants, accredited health workers trained in the management of pregnancy and delivery [7]. WHO recommendations regarding implementation is component-dependent: uterotonics are recommended for all delivered women, CCT is considered optional in settings with skilled birth attendants, continuous uterine massage is not recommended if prophylactic oxytocin is provided and uterine tonus surveillance is recommended for all delivered women [4,7–9].”

“In 2012 the WHO published recommendations on task shifting in maternal and newborn health care in an attempt to optimize the potential of the existing health workforce [14]. These recommendations include for example the administration of misoprostol by lay health workers to prevent postpartum hemorrhage. However, these recommendations do not include all components of AMTSL. The effects of task shifting of individual components of AMTSL, such as uterine massage, have never been reviewed [14].”

2. I am not clear as to why a meta-analysis could not be done, especially since the authors have calculated the relative risk of PPH in each of the included studies. All the studies report a reduced risk of PPH although some did not reach statistical significance. Under the circumstances I would expect to see minimal statistical heterogeneity although the authors describe clinical heterogeneity. This should not matter hugely as studies conducted in different locations will use different definitions etc.

Response: Thank you for mentioning this important topic. We decided not to perform a meta-analysis due to substantial heterogeneity in study settings and interventions that did not allow for a meaningful pooling of results. For example, as we illustrate in supplementary file two, data were collected in different ways and also definition of PPH differed broadly between study groups. We added this consideration to the discussion on page 10.

3. I am concerned however, about the differences in the control groups in the studies. The authors describe usual care as no uterotonics - therefore one would expect administration of any uterotonic to have an effect on prevention of PPH. But this is not task shifting - this is evaluation of misoprostol administration versus no treatment. Ideally, task shifting should be evaluated against administration of misoprostol by skilled versus unskilled attendants under the same conditions.

Response: We very much agree with reviewer 1 that evaluating the effect of use of (for example) misoprostol by unskilled SBAs versus no misoprostol - as is unfortunately standard care in most
rural areas, evaluates the efficacy of misoprostol itself instead of task shifting. Unfortunately, no studies were found comparing use of uterotonics by SBAs compared to unskilled SBAs in the same circumstances. We do realize the difference in these outcomes. For this reason, we also evaluated the safety and acceptance of community distribution.

Accordingly, in the discussion we added the following (page 11):

“All studies evaluating the safety of community distribution of misoprostol, compared reduction of PPH to standard care, which is (mostly) no use of uterotonics. No trials exist comparing effect on PPH of uterotonics by unskilled birth attendants compared to administration by skilled attendants. However, to not only focus on effect of uterotonics itself but also evaluate effect and safety of task shifting in rural areas, this systematic review also included safety and acceptance of community distribution.”

4. There is ample evidence to show that ideally AMTSL should involve administration of oxytocin by skilled attendants at birth. I am therefore a little surprised to see that the RR for PPH was less than this procedure through administration of misoprostol by unskilled persons. Is this likely to be due to publication bias?

Response: We can only postulate to the reason, however, we suspect this may be linked to the incidence of PPH in the control group in both type of study settings. In a setting where births are not attended by skilled attendants, the prevalence of PPH is likely to be high and the effect of an intervention relatively larger than in a setting where skilled birth attendance is available. Reliable measurement of blood loss may also be lower in rural settings compared to facility-based deliveries. In addition, publication bias could have played a role too. These considerations confirm our decision not to conduct a meta-analysis, because of the incomparability of the various settings.

5. Minor issues: please spell out inclusion and exclusion criteria (1); what is meant by 77,337 pregnant women? (2) What is attribution bias? Did the authors mean attrition bias? (3)

Response:

1) Thank you for this feedback. We corrected the words.

2) 77,337 pregnant women is the total number of women that delivered at home in the study of Prata et al in 2012. As postpartum interviews were conducted for every 20th woman who delivered and the research team stopped collecting data after completing 3016 interviews, not all 77,337 women were followed-up.

3) Thank you for noticing this. We indeed meant attrition bias and corrected it accordingly.
Overall comments:

In light of WHO's Optimizing health worker roles guidelines to improve access to key MNH interventions (2012) and other efforts around task-sharing, this is an interesting paper and topic worth exploring further. The role that women and lower level care providers can play in home-based PPH care, including self-administered uterotonics, is very critical to examine and understand in terms of safety, acceptability, and effectiveness. However, I have some reservations about the aim of this analysis as stated in the abstract and background and elsewhere in the paper in reference to 'task-shifting AMTSL to unskilled birth attendants.' For one, some of the AMTSL components are no longer recommended as routine components (i.e. controlled cord traction, uterine massage) and there are recommendations against their practice if the provider lacks appropriate skills. Thus, the goal really is not to task-shift at all some of the AMTSL components.

I think the paper and analysis would be much clearer if the analysis was focused on the task-sharing of uterotonics administration as opposed to task-shifting of AMTSL (since this acronym tends to refer to all components). Indeed the authors did end up focusing on the uterotonic in their analysis, but I think the background and stated aims for this paper/analysis may result in some confusion up front about what the goals/recommendations are around AMTSL and who should be doing what.

I also feel that task-shifting interventions and access to care needs to be accompanied by more contextual information. Successful effect of task-shifting cannot be evaluated alone by clinical outcomes and I think the feasibility/acceptability factors are the most important piece.

Response: We would like to thank reviewer 2 for his/her review of our manuscript and the important topics he/she mentioned.

We agree with reviewer 2, as also mentioned in response to reviewer 1, that administration of uterotonics is the most important component of AMTSL and according to the WHO guidelines on prevention of PPH all delivered women should be offered uterotonics.

Therefore, we changed the background section according to the recommendations in the WHO guidelines. (page 3)

“Active management of the third stage of labor (AMTSL) consists of a set of components aimed at the prevention of PPH [3,4]. AMTSL includes the administration of uterotonics (for example oxytocin or misoprostol) preferably within one minute after delivery to all women, controlled cord traction (CCT) to stimulate placental delivery, uterine massage to activate uterine contraction and assessment of uterine tonus every 15 minutes during two hours postpartum to early identify uterine atony [1,4–6]. The World Health Organization (WHO) recommends AMTSL to be performed by skilled birth attendants, accredited health workers trained in the management of pregnancy and delivery [7]. WHO recommendations regarding implementation is component-dependent: uterotonics are recommended for all delivered women, CCT is considered optional in settings with skilled birth attendants, continuous uterine massage is not
recommended if prophylactic oxytocin is provided and uterine tonus surveillance is recommended for all delivered women[4,7–9].”

“In 2012 the WHO published recommendations on task shifting in maternal and newborn health care in an attempt to optimize the potential of the existing health workforce [14]. These recommendations include for example the administration of misoprostol by lay health workers to prevent postpartum hemorrhage. However, these recommendations do not include all components of AMTSL. The effects of task shifting of individual components of AMTSL, such as uterine massage, have never been reviewed [14].”

Specific comments for Background section:

Page 3, lines 10-18: According to WHO's 2012 guidelines on PPH, controlled cord traction and uterine massage are NOT recommended practices for all women (now optional). I think describing these components as cornerstone interventions of AMTSL is slightly misleading in this opening paragraph.

Response: Thank you for this feedback. Considering the above, we changed the background section, as elaborated in the previous response.

Page 3, lines 33-39: Similar to above comments, it says 'Task-shifting AMTSL (components) to CHWs and TBS who attend home deliveries…has been explored as a community-based strategy,' but I don't think this statement accurately represents the original goals of the trials included in this systematic review. Most of the community-based trials focused on the uterotonic administration and did not look at 'task shifting AMTSL components' (i.e. whole package).

I would strongly recommend re-writing the background section to avoid general reference to 'AMTSL' (consider deleting from the title as well?), since this description and its acronym has several different meanings.

Response: Considering the above, we amended the introduction/background (page 3)

“In 2012 WHO published recommendations on task shifting in maternal and newborn health care in an attempt to optimize the potential of the existing health workforce [14]. These recommendations include for example the administration of misoprostol by lay health workers to prevent postpartum hemorrhage. However, these recommendations do not include all components of AMTSL. The effects of task shifting of individual components of AMTSL, such as uterine massage, have never been reviewed [14].

Furthermore, we amended the methods section that the included studies were not about task shifting perse, but we indirectly measured the effect and safety of task shifting (see response below).

Specific comments for Methods section:
Page 4, lines 8-10: Refers to inclusion of 'trials evaluating effect of task shifting of components of AMTSL', however, I think it needs to be clarified that the original trials did not set for to measure the effect of task-sharing. The 'task shifting' phrase/discourse is being applied after the fact and used by the authors of this systematic review as new lens for analysis of the results. Thus, I would recommend modifying how you describe the trials selected and their goals.

Response: thank you for your correction. We agree with this comment and re-described the trials included and their goals and aims (page 4).

“Type of study: Randomized controlled trials (RCTs) or quasi-experimental trials evaluating the effect of implementation of components of AMTSL to unskilled birth attendants or women on the incidence of PPH compared to the current situation, which is mostly no implementation of components of AMTSL at all. No restrictions on language and publication date were applied. Case reports, reviews and proceedings were excluded. [ … ] Type of intervention: Trials evaluating the effect on outcome measures of implementation of administration of uterotonics (oxytocin or misoprostol), controlled cord traction, uterine massage, assessment of uterine tonus during two hours postpartum to unskilled birth attendants in areas without standardized postpartum care according to AMTSL. By evaluating the effect and safety of AMTSL performed by unskilled birth attendants, effect and safety of task shifting is indirectly measured. Task shifting is defined as a process in which tasks are moved from skilled to less skilled health workers [14].“

In the ‘result section’ we also clarified the studies’ results and our interpretation of task shifting of these results (page 6).

“All studies aimed to evaluate effect and safety of implementation of AMTSL to unskilled attendants compared to standard of care ( mostly no standardized care). No trials were found reporting on task shifting of components of AMTSL from skilled to unskilled birth attendants.”

Suggest defining skilled, unskilled, and task-shifting in the Methods section.

Response: thank you for your suggestion. We added definitions of skilled and unskilled birth attendants and task shifting to the method section on page 4.

“Type of participants: Women delivering in community settings or health facility centers in LMIC without skilled birth attendants present. Skilled birth attendants are defined as accredited health professionals (midwife, nurse) who are trained to assist pregnancies and postpartum care. Unskilled birth attendants are nonprofessionals, educated in a specific task of pregnancy care and postpartum care. [24]”

Task shifting is defined as a process in which tasks are moved from skilled to less skilled health workers. [12]

Page 4, line 25: I would strongly recommend analyzing findings from trials where women self-administered separate from TBA-administered medicine. Some of the TBAs who participated in
these studies were 'trained TBAs' with a lot of skills (more than CHWs perhaps). This comment is in reference to the Mobeen et al trial from Pakistan in which I participated.

Response: thank you for mentioning this important difference. We understand that dividing the tables in table 1A (self-administered, TBA) and table 1B (auxiliary midwives, community health workers) might give the idea that a traditional birth attendant and a delivered woman are comparable in level of skills and acting. Therefore we decided to make one table for all participants, as they all followed educational programs for this specific task. See new Table 1.

Page 4, line 30: If the primary outcome is incidence of PPH, I would suggest that you specify which trials objectively measured blood loss and which ones did not (i.e. in the tables). However, in my opinion, this analysis would be sufficient if it only focused on safety, acceptability, and feasibility as opposed to PPH incidence. There have been other systematic reviews of these same community-based articles reporting on the effect of interventions on PPH incidence.

Response: thank you for your comment. Details about measurement of postpartum hemorrhage is clarified in supplementary file two. We added an extra line in the discussion section referring to supplementary file two on page 10. Also this is part of the risk of bias assessment in figure two and supplementary file two.

“Supplementary file 2 shows more details about measurement of postpartum hemorrhage in different studies.”

What about acceptability among providers? Could this be analyzed?

Response:. We agree that this could be an interesting analysis to explore. However, as this was not the aim for this article and included articles didn’t focus on acceptability among providers, we would consider this for future research.

Specific comments for Results section:

Page 6, line 34: The statement that 'controlled cord traction, uterine massage…were not reported in any of the studies' is not accurate. In the Mobeen et al trial, these components were documented and reported on. That said, I don't think this needs to be the focus of this paper.

Results:. We agree with reviewer two that in Mobeen et al., controlled cord traction and uterine massage are described in the baseline and delivery characteristics of this article. The study focuses only on effect on PPH of distribution of misoprostol and no effect of CCT and uterine massage are described. We changed this in our result section on page 7.

“Controlled cord traction, uterine massage and uterine tone assessment and their effect on reduction of PPH were not reported in any of the studies. Therefore the main focus of the remainder of this manuscript will be on task shifting of uterotonic admission.”
Overall, the results section is very long and I would put forth the suggestion to reduce the level of detail, especially if the results are contained in the tables.

Response: We fused table 1A and 1B and reduced the level of details in the results section (page 7 and 8)

“Primary outcome: PPH incidence

In thirteen studies (15,107 women) the primary outcome assessed was the incidence of PPH when uterotonics were provided by unskilled birth attendants.

The incidence of PPH in delivered women who received misoprostol tablets (n=10) was compared to the incidence in women treated by the standard care of no uterotonics (n=8), ergometrine (n=1) or methergine (n=1). Intramuscular oxytocin injections (10 international units (IU)) were provided in three studies, in one of these a Uniject device, a disposable automatic syringe, was used. The relative risks of incidence of PPH varied from 0.16 to 1 in favor of task shifting. For seven of thirteen articles relative risks were statistically significant [15,26,27,29,30,36,37].

In all studies, educational programs were organized before the start of the interventional trial. Most educational programs for community health workers, auxiliary midwives or traditional birth attendants included a multiple-days course on aspects of AMTSL, mainly focusing on administration of uterotonics. Pregnant women were educated on self-administration by nurses or health workers at antenatal care visits, both at home or in a clinic.

Secondary outcome: acceptance and safety of task shifting

In twelve studies [5,8,10,11,20,24,25,27,31-34] the primary outcome assessed was women's acceptance and safety of community distribution of uterotonics [Table 2]. In all studies administration of uterotonics was evaluated.”

Specific comments for the Discussion section:

Page 9, lines 28-36: Please revisit WHO's PPH guidelines and update this paragraph. WHO recommends administration of uterotonic by skilled and unskilled birth attendant (anyone trained in its administration including TBAs). Their current guidelines do not recommend self-administration by women, however.

Response: thank you for this feedback. We changed the sentence on page 9.

“Administration of misoprostol or oxytocin self-administered by delivered women is not yet recommended in WHO guidelines, and could be considered a strategy to further increase access to AMTSL.”

Page 9, line 42: I think it would be helpful to clarify/edit the term 'misuse' to describe it as 'mistimed administration' as opposed to misuse.
Response: thank you for this suggestion. We changed the term to ‘mistimed administration’.

Page 9, lines 51-55: I question whether the sentence on recovered/unused miso is important for this paper and for PPH programs promoting task-shifting.

Response: thank you for mentioning this point. One of the main concerns of community distribution of misoprostol may be mistimed administration or ‘community sharing’ of tablets in case of unwished pregnancy. To make sure that misoprostol is used correctly, data should be known/colllected about recovery rate.

Page 10, lines 38-40: I sort of disagree with the first cited strength of this review (inclusion of all AMTSL components). The following sentence refers to 'earlier review's' which requires citations.

Response:

1) The other components of AMTSL have inferior rolls in reducing PPH. However, as no large studies exist considering all components of AMTSL and to provide a complete analysis of what is known about all components of AMTSL and task shifting in these components, we decided to include all components.

We included a sentence about the recent studies and recommendations about controlled cord traction (page 10)

"Recent evidence indicates that omission of CCT has little effect on the risk of severe hemorrhage, and the WHO recommends not to include CCT in hemorrhage prevention programs for non-hospital settings [8,9]."

2) thank you, we added citations.

Page 10, lines 42-44: I don't understand the point about heterogeneity of interventions, especially since the focus of the review/analysis ended up being on uterotonics.

Response: Thank you for mentioning this. Data were collected in different ways and also definition of PPH differed broadly between study groups, as we illustrate in supplementary file two. This is what we mean with heterogeneity of interventions.

Specific comments for the Tables:

As per above comments, I would strongly recommend analyzing findings from trials where women self-administered separate from TBA-administered medicine. Some of the TBAs who participated in these studies were 'trained TBAs' with a lot of skills (more than CHWs perhaps).
I am not sure I understand the point of Tables 1A and 1B. What do these tables show that's not already known in the literature or from other systematic reviews of community-based PPH studies? Table 2 seems to be the most critical one for this paper/analysis.

Re Table 3 on side effects, I would suggest to the authors that they consider this table. Side effects rates by comparison arms have been presented previously in other analyses and are well-known. I'm not sure what this table adds in the context of task-shifting, especially since there is no additional information on how the side effects were managed and by whom. I also would strongly suggest deleting the column "severe side effects (abortion, pre-term)," especially since almost every row says n/a and one includes data on livebirths. The data seems incomplete and calling abortions 'severe side effects' sounds strange. If the authors want to discuss mistimed use, why not include any available info in the column on correct dose/time in Table 2?

Response: thank you for the specific comments for the tables. We decided to fuse table 1A and 1B as table 1, as we responded to one of the previous questions.

We also decided to change table 3, in which we deleted the column ‘severe side effects’. Also we changed table 3 to a supplementary file.