Author's response to reviews

Title: Accessibility and Potency of Uterotonic Drugs purchased by Simulated Clients in Four Districts in India

Authors:

Cynthia Stanton (cstanton@jhsph.edu)
Deepak Nitya Nand (ndeepak@path.org)
Alissa Koski (adkoski@gmail.com)
Ellie Mirzabagi (ellie.mrzabagi@gmail.com)
Steve Brooke (sbrooke@path.org)
Breanne Grady (bgrady@path.org)
Luke C Mullany (lmullany@jhsph.edu)

Version: 3
Date: 2 September 2014

Author's response to reviews:

September 2, 2014

Dear Ms. Janelyn Ann Cruz and Dr. Tim Colbourn,

Thank you for your careful review of our manuscript (MS: 1246552391229085). Accessibility and Potency of Uterotonic Drugs purchased by Simulated Clients in Four Districts in India. We have revised the paper in response to reviewer comments. Our responses are in TRACK CHANGES in the manuscript document. Our responses to Reviewer comments are in bold italics below. Please do not hesitate to contact me should you have further questions.

Cynthia Stanton, on behalf of all co-authors

MS: 1246552391229085

Accessibility and Potency of Uterotonic Drugs purchased by Simulated Clients in Four Districts in India

Cynthia Stanton, Deepak Nitya Nand, Alissa Koski, Ellie Mirzabagi, Steve Brooke, Breanne Grady and Luke C Mullany

Dear Dr Stanton,

Your manuscript has now been peer reviewed and the comments are accessible in PDF format from the links below. Do let us know if you have any problems opening the files. Please also take note of the editorial comment below.
Editorial Comment:

"The authors should be commended on an important and thoroughly undertaken study. Only minor revisions are required (see reviewers comments and below). I think you’ve already met some of the concerns of the reviewers e.g. you state that valethamate bromide is not a uterotonic drug in line 75 (although it is used for ?uterotonic purposes?), and state why multiple ampoules were purchased from each pharmacy in lines 115-6; but please provide a full response to all of the reviewers? comments along with your revised paper.

I think reviewer 1?s request to test other drugs can perhaps be mentioned as an area for further research in the discussion, but shouldn’t delay the publication of this study, which already contains ample important and useful information on the drugs that have already been tested.

A couple of additional minor points I picked up on when going over the paper are:

1. Table 1: You seem to have the populations of Uttar Pradesh and Karnataka the wrong way round (though you have it correct in lines 89-90 of the text). Please check that all other indicators, and the rest of the data in Table 1 is in the correctly labelled row.

Thank you for your careful read of the paper. Yes, the population totals were flipped. I have checked all of the other indicators now and they are fine. I corrected the population totals for UP and Karnataka in Table 1.

2. Given the results in Table 6, it would be useful to plot Figures 1 and 2 by state to see how the different storage conditions in each state are associated with API over time (same also goes for Review 2? s comment on line 296 about different ages of drugs per state on average ? I assume this is known and could be added to the paper? Also, any information on exposure to light?)"

In the revised paper, we have added two Figures and now provide graphs by state and by uterotonic drug. We did not ask specific questions regarding the storage of methylergometrine and exposure to light. We assume that any drugs stored on shelves would be exposed to at least some daylight even if they were packaged in cardboard boxes.

Referee 1:
http://www.biomedcentral.com/imedia/1701350984127072_comment.pdf

Referee 2:
http://www.biomedcentral.com/imedia/1864118105136604_comment.pdf
We would be grateful if you could address the comments in a revised manuscript and provide a cover letter giving a point-by-point response to the concerns.

Please also ensure that your revised manuscript conforms to the journal style (http://www.biomedcentral.com/info/ifora/medicine_journals). It is important that your files are correctly formatted.

We look forward to receiving your revised manuscript by 24 August 2014. If you imagine that it will take longer to prepare please give us some estimate of when we can expect it.

You should upload your cover letter and revised manuscript through http://www.biomedcentral.com/manuscript/login/man.asp?txt_nav=man&txt_man_id=1246552391229085. You will find more detailed instructions at the base of this email.

Please don't hesitate to contact me if you have any problems or questions regarding your manuscript.

With best wishes,

Ms Janelyn Ann Cruz
on behalf of Dr Tim Colbourn

Tel: +44 (0) 20 3192 2013
e-mail: editorial@biomedcentral.com
Web: http://www.biomedcentral.com/

To submit your revised manuscript

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When you have revised your manuscript in light of the reviewers’ comments and made any required changes to the format of your paper, please upload the revised version by following these instructions:

1. Go to http://www.biomedcentral.com/manuscript/login/man.asp?txt_nav=man&txt_man_id=1246552391229085 and log on with your email address and password.
2. With the 'Manuscript details' tab, please update the title, abstract and author details if they have changed since the previous version. It is very important that all changes are updated on this page, as well as in the manuscript file as the information on this page will be used in PubMed and on BioMed Central if your manuscript is accepted for publication.

3. With the 'Cover letter' tab, please provide a covering letter with a point-by-point description of the changes made.

4. With the 'Upload files' tab, please upload the revised version of the manuscript and press 'Submit new version'. Please wait for the confirmation page to appear - this may take a few moments.

#1 Reviewer’s report
Title:
Accessibility and Potency of Uterotonic Drugs purchased by Simulated Clients in Four Districts in India
Version:
2
Date:
15 April 2014
Reviewer:
Gunjan Singh
Reviewer's report:
This is an adequately designed study and addresses the relevant problem of medicines used for the prevention and management of post partum hemorrhage. The topic is of suitable for study as decreasing the incidence of PPH is of utmost importance for decreasing maternal mortality in India.
In the design of the study, I would like to ask about the inclusion of epidosin (valethamate bromide) which is not an oxytocic agent. Instead, in its place, newer agents like carbetocin and carboprost availability and potency could be assessed.

We opted to include valethamate bromide because we know from the
Observation of Deliveries Study in India (now published: Stanton et al. 2014. International Journal of Gynecology and Obstetrics) as well as from other studies in the published literature that it is commonly used to speed labor (thus used for uterotonic purposes). We have added a sentence to the text of the Conclusion (line 364-366) regarding the newly available uterotonics:

Should newer uter tonic drugs such as carbetocin and carbopost become commonly available in India, an expanded assessment of uter tonic drugs will also be warranted.

Regarding the sampling areas in the study, I would like to suggest that these medicines are in hospital supply and would therefore be unavailable in the pharmacies as their demand would be less. This may lead to a bias showing its unavailability in most of the pharmacies. Also, I would like to suggest to include the inbuilt- pharmacies in the private facilities in a subsequent study and estimate the difference.

We have added the following sentence to the text of the paper (line 202):

This may imply a general lack of uterotonics in stock in private pharmacies, low availability of these drugs in pharmacies given their common availability in hospitals or suspicion by the sales person leading to reluctance to sell to the simulated client in Karnataka.

Apart from these two points, the study serves its aims and objectives well.

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:
I declare that I have no competing interests

#2 Reviewer's report
Title:
Accessibility and Potency of Uterotonic Drugs purchased by Simulated Clients in Four Districts in India

Version:
2

Date:
18 July 2014

Reviewer:
Richard Lowe

Reviewer’s report:
Review of:
Accessibility and Potency of Uterotonic Drugs purchased by Simulated Clients in Four Districts in India
Cynthia Stanton, Deepak Nitya Nand, Alissa Koski, Ellie Mirzabagi, Steve Brooke, Breanne Grady and Luke C Mullany
BMC Pregnancy and Childbirth (Submitted:2014-03-02)

GENERAL COMMENTS
Overall, this is a very useful addition to the scientific literature on the issue of quality of maternal health medicines. Although there have been studies on the quality of oxytocin over time in the field, this is the first to estimate the rate of degradation of products in the field. The study provides useful supportive evidence of the contribution of this factor to general problem of oxytocin quality and some reassurance that products sampled were unlikely to be fake and likely were of sufficient potency when leaving the manufacturer.

I would suggest that the authors check the statistics in Tables 2 and 3. Also, it would be helpful to clarify the drug potency results section as some of the descriptions of the results and the content of Tables 4 and 5 is a little confusing.
All of the numbers in all tables have now been verified. The population numbers for Karnataka and Uttar Pradesh were corrected in Table 1. The denominators (ie, the number of visits to open pharmacies) in Table 2 were corrected. The Reviewer also drew our attention to the fact that it was difficult to track denominators in Tables 2-4. In response, we have revised the content of Table 4.

Other discretionary revisions relate to additional information that might be included if available. Minor essential revisions are mostly related to language.

MAJOR COMPULSORY REVISIONS

1. In the methods section, could the authors please state the statistical program and method used to calculate the percentages and exact binominal confidence intervals for the study.

The following sentence was added (see line 174):
Stata (Version 11) software was used for data analysis.

While not an expert in statistics, I am concerned that there might be some inconsistencies in the data. Using an epitools calculator, calculating the estimate and exact binominal confidence interval using the Clopper Pearson method gives the same values for UP as appear in Table 2, but different values for Karnataka than those in Table 2.

The same epitools program and method gives the same values for UP and Karnataka as appear in Table 3.

The tables have been checked. Denominators for Table 2 for Karnataka have been corrected. This explains the discrepancy noted above by the reviewer.

A row was added to the table to show the number of visits to open pharmacies in each district.

Could the authors please re-check the analysis and confirm that the data in the tables is correct. Tables have been verified twice.
MINOR ESSENTIAL REVISIONS

1. Line 13. Lifesaving should be written as “Life-Saving” Now corrected.

2. Line 22. Include the word “drugs” after “anti-tuberculosis” Now corrected.

3. Line 69. Please include a reference to Concept Foundation study if possible. BMC Pregnancy and Childbirth guidelines state that unpublished documents should not be included in the Reference Lost. Thus, no change was made.

4. Line 113. Can the authors please clarify what the 90% and 50% refer to – is it the true proportion of oxytocin and ergometrine samples that are within API bounds? If the true potency rate falls between 90% and 50%, the precision would fall between 4% and 7%.

5. Line 115. Please replace “multiple” with “two”. The study methods clearly describe that two ampoules are purchased, and using “multiple” could confuse as it could imply that more than two were purchased. Now corrected.

6. Line 206 and 207. For Tables 2 and 3, please add a legend to explain the P and N in each column.

DISCRETIONARY REVISIONS

1. Line 23 -25

• Suggest rewriting this sentence to capture the requirement that drugs must be manufactured to specific standards AND undergo monitoring for quality at different points in the supply chain. They are two separate and important issues. Monitoring alone is not sufficient if the drugs have not been made to a sufficient standard. The statement now reads as follows: Globally and in India, attention has focused primarily on anti-infective drugs such as antiretroviral drugs, antibiotics, anti-tuberculosis drugs and anti-malarials [12,15] Manufacturing to specific standards and monitoring of product quality of such drugs is mandated as a prerequisite for funding from international programs such as the Global Fund to Fight AIDS, Tuberculosis and Malaria [16].

• Global fund does not just operate in low-income countries. Suggest removing “low-income”. “low-income” has been removed.

• Product quality monitoring is always mandated for Global Fund procurement. Manuscript states “often” The word “often” has been removed.
2. Line 53. Did the authors consider including the USP study conducted in Ghana in 2012 as part of the background review. The findings are available online. http://www.usp.org/sites/default/files/usp_pdf/EN/PQM/ghana-mch_mqm_report_final-mar_27_2013_rdct.pdf
Given that this reference is included in the Introduction, we do consider citation of these results as part of the literature/background review for this paper.


4. Drug Potency section – Lines 209-255
We opt to leave the citation as is. Some of this section is confusing and difficult to understand.

• Lines 212-216. It’s not clear why the number of successful purchases in Karnataka led to the decision to test all ampoules from these districts. Was it because the number of purchases was considered low or high? Please clarify.
If we had held to our plan of requiring a purchase of two ampoules per site, we would not have had any ampoules to test in Karnataka.

Table 4 is confusing. The first column heading says “Analysis units” under which are two columns for 1 ampoule and 2 ampoules. However, the study design requires that two ampoules per pharmacy constitutes an analysis unit. Please check and correct if necessary.

The text is correct. We have included detail regarding the number of ampoules in each sample in Table 4 to show that we did deviate from plans outlined in the Methods section (for the reason stated above). However, as described in the Methods section, a second ampoule was purchased to allow for possible breakage. The laboratory requested a back-up ampoule from each sample point. The second ampoule was not tested for active pharmaceutical ingredient.

The following sentence has been added (line 224):
However, only one ampoule per sample was tested for API. The second ampoule, where there was one, was held as a back-up in case of breakage.
Table 2 shows that 24 purchases of oxytocin were made in Bagalkot. Table 4 shows that there were 48 ampoule purchases recorded in Table 4, Table 5 also shows this (for the number of samples tested)? Were two ampoules purchased in each pharmacy? If so, then please correct Table 4 as this creates confusion about the procurement and analysis numbers.

If Table 4 is correct, then in Bagalkot and Hassan, it was possible to purchase 1 full analysis unit (2 ampoules) in each pharmacy, whereas in Agra and Gorakhpur, some of the purchases were only of 1 ampoule, as the text outlines? Please check the text in this section and Table 4 for accuracy and clarity.

We agree that in the original version of this paper it was difficult to track denominators between Tables 2-4. We have now revised the content of Table 4 to show the number of open pharmacies, the number of ampoules purchased, the number of ampoules analyzed and in a few cases, the number of ampoules reported as purchased but missing for analysis.

• Line 222. The statement “Thus, ampoules that were out of specification did not tend to be far from manufacturer limits” needs some consideration. Some of the ampoules tested were a long way from manufacturer specifications. The important finding is that these products are out of specification, regardless of how close to manufacturer specification they are.

• Line 223-224. While the median is correct to use for what appears to be a skewed distribution, I'm not sure that it really tells you much about the range of product potency. Of more concern is the fact that even though the median is around 100%, 35% of samples are out of range. I might also be concerned that the sentence could be interpreted as “on average, there is sufficient drug in the samples products”.

The sentence: Thus, ampoules that were out of specification did not tend to be far from manufacturer limits” has been removed.
• Line 238. 46 pharmacy pairs are described here, but Table 4 seems to show that only 1 ampoule from each pharmacy was collected. If this is the case, how can there be pairs of ampoules from each pharmacy? Please clarify this point and Table 4.

As stated above, the content of Table 4 has been revised and a sentence has been added to reiterate that the second ampoule was purchased in case of breakage and was not intended for analysis.

• Line 249. Did the study record storage conditions on the label for each of the samples and if so, whether the authors considered describing these conditions in the manuscript. This might help to explain the conditions of storage in pharmacies and whether it was according to manufacturer instructions or not.

Given that this study used a mystery client methodology, data collectors could not request to see the package insert. Consequently, we do not have these data to report.

• Line 272-273. It’s not clear why the description of the proportion of drugs with API less than 50% is included here. The previous sentence states that 96%-100% of samples are out of specification and it should not matter whether they are just out of, or a long way out of specification.

We opt to leave this sentence as is. We agree that all drugs should fall within manufacturer specification. However, the scale and complexity of an intervention required to address uterotonic drug potency would differ in settings where most drugs were being sold at 88% API versus 50% API.

• Line 293. Suggest using the term “potency” instead of quality. Using "potency" more accurately describes what has been measured in the study. “Quality” can also refer to other facets that include manufacturing. The word “quality” has been replaced with the word “potency”.

• Line 296. Regarding the differences in potency between states, could this have been due to different ages of drugs in each state – those in Karnataka were older than in UP? Did the authors consider exploring this in the analysis?
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:
I declare that I have no competing interests