Author’s response to reviews

Title: Antimalarial drugs for preventing malaria during pregnancy and the risk of low birth weight: A systematic review and meta-analysis of randomized and quasi-randomized trials.

Authors:

FLORY T MUANDA (flory.muanda-tsobo@umontreal.ca)
SONIA CHAABANE (sonia.chaabane@umontreal.ca)
TAKOUA BOUKHRIS (takoua.boukhris@umontreal.ca)
FABIANO SANTOS (fabiano.santos@mcgill.ca)
ODILE SHEEHY (odile.sheehy@recherche-ste-justine.qc.ca)
SYLVIE PERREAULT (sylvie.perreault@umontreal.ca)
LUCIE BLAIS (lucie.blais@umontreal.ca)
ANICK BERARD (anick.berard@umontreal.ca)

Version: 2
Date: 16 June 2015

Author’s response to reviews: see over
June, the 16th 2015

Dear Editor,

We are delighted to submit our revised manuscript entitled "Antimalarial drugs for preventing malaria during pregnancy and the risk of low birth weight (LBW):

A systematic review and meta-analysis of randomized and quasi-randomized trials which is being considered for a publication in the BMC Medicine (manuscript MS 1747032375167477).

We thank the reviewers for their constructive comments and careful attention to detail in reviewing our manuscript. We believe we have addressed all the issues raised and the revisions have substantially improved the manuscript. As requested, you will find our response to each comment itemized one by one. The modifications are also highlighted in the final document.

We sincerely believe that our revised version of the manuscript is now ready for publication in BMC Medicine.

Sincerely,

Flory Tsobo Muanda

University of Montreal and Research Unit on Medications and Pregnancy, Research Center CHU Ste-Justine 3175, Côte-Sainte-Catherine, Montréal (Québec), Canada, H3T 1C5

Email address: flory.muanda-tsobo@umontreal.ca

Corresponding author:

Dr Anick Bérard, Research Chair on Medications, Pregnancy and Lactation, Faculty of Pharmacy, University of Montreal and Director of Research Unit on Medications and Pregnancy, Research Center CHU Ste-Justine 3175, Côte-Sainte-Catherine, Montréal (Québec), Canada ,H3T 1C5.

Email address: (anick_berard@umontreal.ca)
Authors’ response to reviews

Title: Antimalarial drugs for preventing malaria during pregnancy and the risk of low birth weight (LBW): A systematic review and meta-analysis of randomized and quasi-randomized trials.

Authors:

Flory Tsobo Muanda (flory.muanda-tsobo@umontreal.ca)

Sonia Chaabane (sonia.chaabane@umontreal.ca)

Takoua Boukhris (takoua.boukris@umontreal.ca)

Fabiano Santos (fabiano.santos@mcgill.ca)

Odile Sheehy (odile.sheehy@recherche-ste-justine.qc.ca)

Sylvie Perreault (sylvie.perreault@umontreal.ca)

Lucie Blais (lucie.blais@umontreal.ca)

Anick Bérard (anick.berard@umontreal.ca)

Version: 2 Date: 16 June 2015

Authors’ response to reviews: see over
Reviewer's report

Title: Antimalarial drugs for preventing malaria during pregnancy and the risk of low birth weight (LBW): A systematic review and meta-analysis of randomized and quasi-randomized trials.

Version: 1 Date: 30 April 2015

Reviewer: Darren C Greenwood

Reviewer's report:

This is a well conducted and presented systematic review, on an interesting topic.

- Major Compulsory Revisions (which the author must respond to before a decision on publication can be reached)

None.

- Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1. The box sizes / areas on the forest plots should represent the amount of information, i.e. be in proportion to the weights. The tick marks on the horizontal axis should be round numbers, e.g. 0.5, 0.2, 1.0.

Authors’ response: We thank the reviewer for this comment. As requested, we added box sizes/area representing the amount of information and round numbers on the each forest plot horizontal axis.

2. The risk of bias assessment should be included in a table, e.g. supplement 3.

Authors’ response: We thank the reviewer for this comment. The risk of bias assessment was included in a table. See in additional file 4 table2.

3. There is no such thing as p=0.00. This probably means p<0.01.
Authors’ response: we thank the reviewer for this comment. Modifications have been made and $p = 0.00$ has been replaced by "...$p<0.01$" (See in page 12, line 12)

4. Some exploration should be conducted into how the excluded outlying study differed from the others, e.g. design, population, etc.

Authors’ response: we thank the reviewer for this comment and clarification has been added to the text. See in page 12, line 24 and page 13, lines 1-3.

The excluded outlying study used a cluster randomized design in which the units of analysis (health centres) were not selected randomly; this may introduce a selection bias. In addition, statistical analysis did not take into account efficiently variability within and between clusters. This may explain why this study was an outlier in our analysis.

5. Where meta-analysis and forest plots are stratified, it is useful to present the test for between-subgroup heterogeneity. As far as I can see, the authors comment on the results within each subgroup, and how they differ from each other, but have not presented this formal test of whether their differences could be just chance.

Authors’ response: we thank the reviewer for this comment. Test for between-subgroup heterogeneity has been added for each subgroup analysis. See in page 13, line 16. "... (Test for heterogeneity between subgroups: $P$-value=0.075)"

See in page 14 line 3"... (Test for heterogeneity between subgroups: $P$-value<0.01)".

See in page 14, lines 11-12."... (Test for heterogeneity between subgroups: $P$-value=0.102)"
Discretionary Revisions (which are recommendations for improvement but which the author can choose to ignore)

None.

Quality of written English: Needs some language corrections before being published

Authors’ response: The manuscript has been reviewed accordingly by English speaking (mother tongue) reviewer.

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

Declaration of competing interests: I declare that I have no competing interests.

Reviewer's report

Title: Antimalarial drugs for preventing malaria during pregnancy and the risk of low birth weight (LBW): A systematic review and meta-analysis of randomized and quasi-randomized trials.

Version: 1 Date: 18 May 2015

Reviewer: Andy Stergachis

Reviewer's report:

Major Compulsory Revisions:

1. Define quasi-randomized. Do the authors use this term synonymous with quasi-experimental?

Authors’ response: We thank the reviewer for his comment.

Quasi-randomized studies are clinical trials in which subjects are assigned to different treatment groups using non-strictly random methods of allocation (alternation, date of birth, medical record number, etc.) (The Cochrane Collaboration, 2008).

Definition of Randomized and quasi-randomized controlled trials has been added to the manuscript. See in page 6, lines 17-22
"RCTs were defined as clinical trials in which individuals or other units were assigned to different treatment groups using randomization allocation such as random number, computer-generated random sequences, tossing a coin, and draw lots. Quasi-randomized studies are clinical trials in which individuals or other units are assigned to different treatment groups using non-strictly random methods of allocation. Examples of quasi random methods of assignments include alternation, date of birth and medical record number. (The Cochrane Collaboration, 2008)

2. Note that there is a lack of head-to-head, i.e., drug vs. drug comparisons.

We thank the reviewer for his comment.

We agree with the reviewer that there is a lack of head-to-head randomized controlled trials (RCTs) evaluating potential alternatives to intermittent preventive treatment (IPTp) with sulfadoxine-pyrimethamine. This sentence has been added to the introduction section "(See in page 5, line 13). However, in our study, we included all head to head RCTs comparing sulfadoxine-pyrimethamine to mefloquine or antibiotics published recently.

See in page 5, lines 15-16.

" … However, given increasing of resistance to this drug, some head-to-head RCTs comparing sulfadoxine-pyrimethamine to mefloquine or antibiotics have been published recently [16-18].

3. Very few trials contribute to the analyses. Please note. E.g., n-1 in Figure

Authors’ response: we thank the author for his comment. Our literature search retrieved 1306 articles. Following our inclusion criteria 25 RCTs were included in our review. Of the 25 RCTs, 10 compared antimalarial drugs vs placebo or no exposure; five RCTs compared three doses or more to two doses of sulfadoxine-pyrimethamine; two RCTs compared weekly chloroquine vs two doses of chloroquine; five RCTs compared sulfadoxine-pyrimethamine vs chloroquine; two RCTs compared sulfadoxine-pyrimethamine vs mefloquine, one RCTs compared azithromycine-sulfadoxine-pyrimethamine vs sulfadoxine-pyrimethamine; one RCTs compared sulfadoxine-pyrimethamine vs cotrimoxazole. Therefore, for randomized placebo controlled-trial, enough data was available to perform the meta-analysis. However, for head to head RCTs (especially for alternatives to sulfadoxine-pyrimethamine), only few trials were included in the analysis. This
highlights the need of conducting new head to head RCTs with additional medicines for the prevention of malaria during pregnancy.

4. Some results are first presented in Discussion, e.g., bottom of page 11.

Authors’ response: We thank the reviewer for his comment. all of our results discussed in our manuscript has been reported in the” result section", however we refer to a study that was not presented in the "introduction section" Modifications have been made and this sentence has been added to the introduction. See in page 5, lines 4-7.

"In contrast, a cohort study conducted in central Africa in 2012 showed that the level of drug resistance may modify the effectiveness of sulfadoxine pyrimethamine; nevertheless this result should be interpreted with caution given the study design limitations

5. There is no mention of safety of antimalarial. Note as limitation.

Authors’ response: we thank the reviewer for his suggestion. We added a mention on safety of antimalarial during pregnancy as one of our limitations in this study.

See in page 19, lines 25-26 and page 20, lines 1-4.

"...seventh, safety of antimalarial drugs during pregnancy is a concern. Despite the fact that many RCTs have reported antimalarial drugs side effects, very few use appropriate methods of pharmacosurveillance to detect and evaluate safety signals. Therefore, there is a need to implement standardised methods of collecting and reporting adverse event in RCTs which will help to build a centralised pharmacovigilance database and to identify efficiently safety concerns."

6. Justify why the authors did not assess small for gestational age or prematurity.

Authors’ response: we thank the reviewer for his question. Indeed, a systematic review that includes small for gestational age (SGA) or preterm birth (PTB) is an interesting question as LBW may be a consequence of SGA, PTB or a combination of both. However, SGA are not systematically reported in RCTs as an outcome of interest. In our review, only one RCT has reported SGA as one of their outcome. (Nosten et al., 1994).
A recent Cochrane systematic review and meta-analysis showed that antimalarial drugs were not associated with PTB. (Radeva-Petrova, Kayentao, ter Kuile, Sinclair, & Garner, 2014). Another meta-analysis showed no difference in PTB when three doses or more of sulfadoxine-pyrimethamine were compared to two doses of this drug (Kayentao et al., 2013). Therefore the association found with LBW may mainly reflect an association with fetal growth rather than with PTB. Nonetheless, further RCTs assessing both SGA and PTB are needed.

See in page 20, lines 4-12

"...Eighth, LBW may be a consequence of small for gestational age (SGA), (preterm birth) PTB or a combination of both. SGA are not systematically reported in RCTs as an outcome of interest. In our review, only one RCT has reported SGA as one of their outcome [47]. However, a recent Cochrane systematic review and meta-analysis showed that antimalarial drugs were not associated with PTB [6]. Another meta-analysis showed also no difference in PTB when three doses or more of sulfadoxine-pyrimethamine were compared to two doses of this drug [7]. Therefore the association found with LBW may mainly reflect an association with fetal growth rather than with PTB. Nonetheless, further RCTs assessing both SGA and PTB are needed. ."

7. Label the plots.

Authors’ response: We thank the reviewer for his comment. We labeled each plots according to BMC Medicine instructions for authors.

8. Zang formula for transformation of OR to RR - justify its use as this is controversial. We recommend its careful use, it would be better for the authors to use the numbers from the reviewed papers and compute the relative risk from there.

Author’s response: we thank the reviewers for his suggestions.

Given the controversial use of Zhang method for transformation of OR to RR, we used the Mantel-Haenszel method to compute RR.

See in table 1

Tiono et al : IPT SP vs weekly CQ : RR 0.47, 95% CI 0•27- 0•82.
**Weekly CQ vs IPT CQ : RR 1.52, 95% CI 0.94- 2.45.**

**Kayentao et al : IPT SP vs weekly CQ : RR 0.78, 95% CI 0.61- 0.99.**

**Weekly CQ vs IPT CQ : RR 0.92, 95% CI 0.75- 1.14.**

9. **Figures: not log OR. Should be RR.**

**Authors’ response:** we thank the reviewer for his comment. All the figures have been labelled as suggested.

10. **Justify why they excluded studies of women who are HIV+.**

**Authors’ response:** We thank the reviewer for his comment. Indeed a systematic review that includes HIV positive pregnant women is an interesting question given that co-infections with malaria and HIV are frequent among pregnant women in Sub-Saharan Africa. However a recent meta-analysis that included HIV positive pregnant women was available in the literature (Kayentao et al., 2013) and since then only one head to head RCTs conducted among HIV positive pregnant women has been published (Gonzalez et al., 2014). Therefore, a systematic review in this sub-population at present would not provide additional evidence given the limited number of RCTs published after the last meta-analysis.

See in page 7, line 2-4.

"...Indeed, a recent meta-analysis that included HIV positive pregnant women was available in the literature[7] and since then only one head to head RCT conducted among HIV positive pregnant women has been published[21]. ”

**Discretionary Revisions:**

1. **Present the section on risk of bias as a Table not in narrative of manuscript.**

**Authors’ response:** we thank with the reviewer. As suggested, we added a table on the risk of bias.

2. **Discuss the potential for misclassification of the outcome of LBW.** This can arise based on when the infant was weighed. There are adjustments available but unclear if
authors employed these in their original research reports. It is critical they explain how weight at birth was collected and/or imputed.

Authors’ response: we thank with the reviewer for this comment. There is a potential for misclassification of the outcome of LBW as the timing of measurement, method of gestational age estimation and details on the scales used for birth weight were not often provided in RCTs included in our review. This may introduce a non-differential outcome misclassification which may bias estimates toward a null effect. However, this limitation regarding timing of measurement, method of gestational estimation and scales used for birth weight is common in RCTs conducted among pregnant women in malaria endemic regions. Indeed, a systematic review showed that only 33% RCTs gave information on the timing of measurement and provides details on the scales used for birth weight. Also, despite the fact that 77% reported the method of gestational age estimation, most of RCTs use the symphysis-fundal height (SFH), an inaccurate method to estimate gestational (Rijken et al., 2011). This highlights the need for standardised method for birth weight measurement and reporting in future studies.

See in page 19, line 24-26 and page 20, lines 12-19.

"Ninth, there is a potential for misclassification of the outcome of LBW as the timing of measurement, method of gestational age estimation and details on the scales used for birth weight were not often provided in RCTs included in our review. This may introduce a non-differential outcome misclassification which may bias estimates toward a null effect. However, this limitation regarding timing of measurement, method of gestational estimation and scales used for birth weight is common in RCTs conducted among pregnant women in malaria endemic regions [60]. This highlights the need for standardised method for birth weight measurement and reporting in future studies"

3. Supplemental Table 1: eliminate some of the columns.

Authors’ response: we thank the reviewer for his comment. Following reviewer’s comment, some columns in the supplemental table 1 have been deleted.

4. Note in Discussion that additional medicines for the prevention of malaria in pregnancy are the subject of trials underway through the Malaria in Pregnancy Consortium.
Authors’ response: we thank the reviewer for his suggestion. The following sentence has been added to the discussion.

See in page 17, lines 24-25 and in page 21, lines 2-4.

"Furthermore, additional medicines for the prevention of malaria in pregnancy are the subject of trials underway through the Malaria in Pregnancy Consortium (MiP)."

Quality of written English: Not suitable for publication unless extensively edited

Authors’ response: The manuscript has been reviewed accordingly by English speaking (mother tongue) reviewer.

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

Declaration of competing interests:

Reviewed by Andy Stergachis stergach@uw.edu), Stephanie Kovacs (kovacs2@uw.edu), and Orvalho Augusto [orvaquim@gmail.com].

Andy Stergachis is an investigator with the Malaria in Pregnancy Consortium and serves on the Access and Product Management Committee for Medicines for Malaria Venture.
Reviewer's report

Title: Antimalarial drugs for preventing malaria during pregnancy and the risk of low birth weight (LBW): A systematic review and meta-analysis of randomized and quasi-randomized trials.

Version: 1 Date: 26 May 2015

Reviewer: Kassoum Kayentao

Reviewer's report:

General comments:

1. Please explain beneath of each forest plot, the meaning of different elements of the graphs (e.g. vertical line indicates..., black dots indicate.....)

Authors’ response: we thank the reviewer for his general comment. We explained the meaning of different elements of each forest plot according to BMC instructions for authors. See in page 23, lines 1-24; page 24, line 1-11.

2. For each forest plot, please indicate the following points:

a. A good label for study ID; the current contents under study ID does not reflect only study ID in any graph

b. Display data counts (n/N) for each group

c. Display the labels of the comparison groups

d. Provide a label indicating the treatment effect to either side of the graph e. Can the authors display references similarly in all the graphs? There are figures with authors

f. Also I would ask to provide reference numbers in superscript each time an author is cited in graphs

Authors’ response: we thank the reviewer for his general comment. We indicated all following points mentioned above as recommended by the reviewer for each forest plot. Rather than
displaying data count in each forest plot, we used RR as some of the RCTs reported adjusted estimates. Nevertheless, the information on the data counts is available in the table 1.

3. The authors made the hypotheses that gravidity and SP resistance influence the effect of treatment, and results were stratified based on these possible effect modifiers. One potential factor that could influence more the effect of treatment, which is HIV status, has been excluded since the selection process of the articles. As the prevalence of HIV is important in area of Africa where also SP resistance is higher, one can wonder if the overall findings can be applied to East, South and Central Africa. I would suggest to take this component in to account and do stratified analysis to look at its impact on the effect of treatment.

Authors’ response: we thank the reviewer for his interesting comment to improve the present manuscript. We agree that sulfadoxine-pyrimethamine resistance profile and HIV prevalence may vary according to African regions. The limited number of RCTs available precludes stratification analysis; however when we restricted our analysis in RCTs conducted in East Africa we did not find any effect of sulfadoxine-pyrimethamine in reducing the risk of LBW in this region.

4. Through the manuscript, the term “impact of” is used; one can wonder if this term is appropriate, because this is not a causal association study. It is preferable to use association instead.

Authors’ response: we thank the reviewer for his comment. The term "impact" has been replaced by the term "association" throughout the manuscript.

5. Please, use italic for Plasmodium falciparum in all the text

Author’s response: we thank the reviewer for his general comment. We used italic for Plasmodium falciparum in all the text as suggested.

6. Also, indicate page number in the manuscript

Authors’ response: we thank the reviewer for his general comment. Page numbers have been added to the manuscript.
Specific comments

Title: I would suggest avoiding abbreviation “LBW” in here? As this is given in the text already

Author’s response: we thank the reviewer for his comment. We deleted the abbreviation LBW from the title

7. Introduction: last sentence of first paragraph. In the sentence “Previously, another.... LBW by 25%”. The reference cited does not show this reduction. Can the authors explain the origin of the 25% reduction from the article cited?

Authors’ response: We thank the reviewer for his comment.

In the article cited as a reference (Kayentao et al., 2013), HIV-negative G1-G2 women had a 25% reduction of the risk of LBW (See in supplemental content, etable 3). However among all HIV-negative women, authors found a 23% decrease of the risk of having a baby with LBW (See in table 2.). Modifications have been made to our manuscript and we used the results regarding all HIV-negative women (see in page 4, lines 20-21):”...by 23% among HIV negative women”

8. Method:

Data sources and search strategy: The authors excluded HIV positive pregnant women, but in two studies conducted in West Africa (Diakite et al, Valea et al) the status of HIV is unknown. How did the authors adjust for these?

Authors’ response: we thank the reviewer for his comment.

Regarding Diakite et al paper, women with known HIV infection were excluded from the study. In addition, HIV prevalence in Mali is very low (0.9%, range: 0.7-1.1 %) (UNAIDS, 2013).

For Valea et al paper, the HIV prevalence of HIV in Burkina Faso is also low (0.9%, range: 0.8-1.1%) (UNAIDS, 2013).

HIV prevalence in antenatal care (anc) was also low in both Mali and Burkina Faso (Diakite et al., 2011; Valea et al., 2010).
Similarly to Kayentao et al meta-analysis (Kayentao et al., 2013), we performed sensitivity analysis to adjust for the unknown HIV status. We found that the exclusion of these two studies (one at a time) did not change our conclusion. This was consistent with Kayentao finding:

Pooled estimates: RR 0.75, 95% CI 0.61-0.99.

Pooled estimates after exclusion of Valea et al: RR 0.66, 95% CI 0.51-0.86.

Pooled estimates after exclusion of Diakite et al: RR 0.84, 95% CI 0.67-1.05.

See in page 14, lines 21-23.

"..There was no influence of each individual study on the overall meta-analysis summary estimate after removal of each trial one at a time from the meta-analysis (Additional file 5: table 6)."

**Data extraction:**

As transmission level and drug resistance level may vary in time, were these data collected at the time of study conduct?

It is not clear what transmission means. Better to use standard definitions of transmission such as holoendemic, mesoendemic, hyperholoendemic, seasonal, etc.

**Authors’ response:** We thank the reviewer for his comment.

If available, data on transmission level and therapeutic failure to antimalarial drug were collected from each RCT. See in page 7, line 15-17.

For molecular markers of plasmodium falciparum resistance to sulfadoxine-pyrimethamine (prevalence of dhps 540 E > 50%), we used data obtained from a database that mapped dhfr and dhps genes distribution associated with sulfadoxine-pyrimethamine resistance in Africa (Naidoo & Roper, 2011). This map is currently used as a tool to track the spatial extent and temporal patterns of sulfadoxine-pyrimethamine resistance mutations across the African continent. It has been used in a recent meta-analysis that led to the modifications of current recommendations for malaria prevention during pregnancy (Kayentao et al., 2013). As recommended by the reviewer, we also used standard definitions of malaria transmission.
"...We used data obtained from a database that mapped dhfr and dhps genes distribution associated with sulfadoxine-pyrimethamine resistance in Africa [9, 12, 23]. This map is currently used as a tool to track the spatial extent and temporal patterns of sulfadoxine-pyrimethamine resistance mutations across the African continent [12]."

Statistical analysis:

Random effect model was suggested for the analysis. However fixed effect was used in some results. Can the authors explain and justify why random effects models are used for some analysis and fixed-effects models for other?

Authors’ response: We thank the reviewer for his comment. As we mentioned in our manuscript, random effect model was used for main analyses due to potential differences between study populations and interventions among RCTs. Fixed effect model was used within sensitivity analysis.

9. Result:

a. Can the authors describe the results into different sections based on the objectives stated in the introduction?

Authors’ response: We thank the reviewer for his comment.

Following the reviewer recommendation, results were described into different sections based on our objectives

See in page 12, lines 18-19. "Antimalarial drugs for prevention during pregnancy as compared to no use of antimalarial drug and risk of LBW: meta-analysis"

See in page 13, lines 19-20. Association between level of drug resistance and gravidity and the efficacy of antimalarial drugs in reducing low birth weight: meta-analysis

See in page 14, lines 13-14. Three doses or more of the main types of antimalarial drugs as compared to two doses of these drugs and risk of LBW: meta-analysis.
See in page 15, line 4-5. Sulfadoxine-pyrimethamine as compared to antimalarial drugs alternatives for malaria prevention during pregnancy and risk of LBW: meta-analysis

b. Figure 1: Can the authors respect the structures and components of the PRISMA flow chart? This gives an easy reading to readers. Can the authors move the Hand search section box to the top of the graph? Also there is an arrow that needs to be deleted.

Authors’ response: We thank the reviewer for his comment. We made modifications in our flow chart according to PRISMA flow chart.

c. Figure 2: (Please refer to point 2 of general comments)

Author’s response: We thank the reviewer for his comment. Modification has been made on the figure 2 as suggested.

d. In Figure 3: As the number of the number of studies is limited in each subgroup, can the authors make conclusion about the impact of drug resistance on the overall effect of treatment?

To define subgroups, the authors used the prevalence of 10% to classify drug resistance as suggested by WHO for malaria treatment. However, for IPTp the threshold of 50% of DHPS 540 is suggested. It is more indicated that the authors use that threshold in place of the 10% in the subgroup analysis?

Authors’ response: We thank the reviewer for his comments.

In figure 3, we concluded that level of drug resistance may modify the efficacy of antimalarial drugs in reducing the risk of LBW. However we agree that the number of studies is limited in each subgroup. This sentence has been added to the ‘discussion section’.

See in page 16, lines 5-6.

"However, our results should be interpreted with caution given the limited number of studies included in each subgroup".
There is currently no standardised method to evaluate the efficacy of IPTp with sulfadoxine-pyrimethamine (Brabin et al., 2008).

Most of RCTs included in our review were carried out when assessment of efficacy of IPTp with sulfadoxine-pyrimethamine was using children under five years old of age.

Following WHO recommendations for malaria treatment, a therapeutic failure rate of 10% in children under five years old to classify drug resistance was used in our paper. Moreover, a previous meta-analysis also used a therapeutic failure rate in children under five years old to assess the effect of sulfadoxine-pyrimethamine resistance on the efficacy of intermittent preventive therapy for malaria control during pregnancy. (Ter kuile et al 2007)

Nonetheless, we agree that in vivo efficacy in children may not well correlate with the true resistance in asymptomatic pregnant women as they might still have partial immunity. Given that, it is currently recommended to use asymptomatic pregnant women instead of children under five to assess the efficacy of IPTp with sulfadoxine-pyrimethamine at different study sites (Brabin et al., 2008). Therefore, efforts are made to test and incorporate this new approach within National Malaria Program across Africa (Coulibaly et al, 2014)

However, translating WHO recommendations into National malaria policy remains challenging. A study showed a discrepancy between current WHO recommendation during pregnancy and national malaria policy in five African countries (Gomez et al., 2014).

Considering that no alternative for sulfadoxine-pyrimethamine will be available soon, the use of therapeutic failure to sulfadoxine-pyrimethamine in children under five years old still brings additional evidence to determine the threshold at which this drug fails to provide any benefit during pregnancy, especially in sites where data on molecular markers of plasmodium falciparum resistance to sulfadoxine-pyrimethamine are not yet available or data on efficacy of IPTp with sulfadoxine-pyrimethamine measured among asymptomatic pregnant in malaria sentinel sites are lacking.(Likwela et al, 2012).

See in page 18, lines 8-23.

"..First, measurement of antimalarial drug resistance was performed in infected children with acute malaria aged 6-59 months which may not reflect the true resistance in asymptomatic
pregnant women as they might still have partial immunity. Given that, it is currently recommended to use asymptomatic pregnant women instead of children under five to assess the efficacy of IPTp with sulfadoxine-pyrimethamine at different study sites [55]. Therefore, efforts are made to test and incorporate this new approach within National Malaria Program across Africa [56]. However, translating WHO recommendations into National malaria policy remains challenging. A study showed a discrepancy between current WHO recommendation during pregnancy and national malaria policy in five African countries. [57] Therefore, considering that no alternative for sulfadoxine-pyrimethamine will be available soon, the use of therapeutic failure to sulfadoxine-pyrimethamine in children under five years old still brings additional evidence to determine the threshold at which this drug fails to provide any benefit during pregnancy, especially in sites where data on molecular markers of plasmodium falciparum resistance to sulfadoxine-pyrimethamine are not yet available or data on efficacy of IPTp with sulfadoxine-pyrimethamine measured among asymptomatic pregnant in malaria sentinel sites are lacking.[11]."

In our review, we used RCTs conducted in East Africa as a proxy of regions where the prevalence of dhps 540E exceeded 50% (Naidoo & Roper, 2011).

However, as the number of RCTs was limited, it was not possible to assess the effect of sulfadoxine-pyrimethamine in region where the prevalence of dhps 540E was less than 50%.

Nevertheless, a recent meta-analysis showed that three doses or more were effective at reducing the risk of LBW in region where the prevalence of dhps540E was less than 50 %. (Kayentao et al., 2013).

Our review did not show an effect of sulfadoxine-pyrimethamine in reducing the risk of LBW in East Africa. This may be explained by the high prevalence of quintuple (dhps 540E mutation) and sextuple (additional dhps 581G or dhfr 164L mutation to quintuple mutation) mutant in plasmodium falciparum parasites. Indeed, it is known that these mutations may interfere with sulfadoxine-pyrimethamine effectiveness (Gutman et al., 2015; Harrington, Mutabingwa, Kabyemela, Fried, & Duffy, 2011; Minja et al., 2013). Moreover, dhps 540E mutation is prevalent in East Africa and the sextuple mutant haplotype has also been recently reported in this region (Naidoo & Roper, 2013). Three RCTs were included in our analysis. The first one was
conducted in Kabale in Uganda, a region where sextuple mutant haplotypes (dihydropteroate-synthase 540E mutation with additional dihydropteroate-synthase 581G) were prevalent (Naidoo & Roper, 2013). But, the second and third ones were performed in Mozambique where this mutation has not been reported yet. Nonetheless, as it might take five years in average between the collect of information on mutation molecular markers and the date of publication of the results (Naidoo & Roper, 2013), the mutation might be present in Mozambique but not yet detected (Naidoo & Roper, 2013).

See in page 16, lines 13-23.

"In addition, we demonstrated that sulfadoxine-pyrimethamine was not associated with a reduction in the risk of LBW in East Africa where the prevalence of the dihydropteroate-synthase 540E mutation exceeds 50%. Moreover, the sextuple mutant parasite has also been recently reported in this region [12]. Indeed, it is known that these mutations may interfere with sulfadoxine-pyrimethamine effectiveness [12-15]. Three RCTs were included in our meta-analysis in East Africa [42, 50, 54]. The first one was conducted in Kabale in Uganda [50], a region where sextuple mutant haplotypes (dhps 540E mutation with additional dhps 581G) were prevalent [12]. But, the second and third ones were performed in Mozambique where this mutation has not been reported yet [42, 54]. Nonetheless, as it might take five years in average between the collect of information mutation molecular markers and the date of publication of the results [12], the mutation might be present in Mozambique but not yet detected.

e. Figure S6: Is this figure about a sensitivity analysis or a subgroup analysis? Please clarify

Authors’ response: We thank the reviewer for his comment. As we mentioned in our manuscript, the figure s6 depicts a subgroup analysis of the effect of all combined antimalarial drugs in reducing the risk of LBW according to the risk of bias.
f. Table 1: Please check very carefully the names of authors. There is a typo error for names (eg, reference 28 is not well written). This applies also for figures containing this reference.

Authors’ response: We thank the reviewer for his suggestion. We checked very carefully the names of the authors in the table 1 and in figure containing this reference as suggested. Corrections have been made where needed.

g. Can the authors add a figure on the Risk of bias assessment representing the authors' judgements about each risk of bias item for included study across the domains?

Authors’ response: We thank the reviewer for this comment. We included the risk of bias assessment in a table. See in additional file 4 table 2.

10. For meta-regression it is recommended to have at least 10 observations (studies) for each characteristic modelled. The analysis conducted here does not much with this, as in any subgroup, the number of studies is less than 10. Could the authors please clarify this?

Authors’ response: we thank the reviewer for this comment.

A generally accepted rule of thumb suggests that ten events per predictor variable (EPV) maintain bias and variability at acceptable level (Gagnier, Moher, Boon, Bombardier, & Beyene, 2012). This rule is based on two simulation studies carried out for logistic and Cox modelling strategies (Peduzzi, Concato, Feinstein, & Holford, 1995; Peduzzi, Concato, Kemper, Holford, & Feinstein, 1996). It is also used for meta-regression to avoid spurious finding (The Cochrane Collaboration, 2008).

However, a recent simulation study showed that linear regression models require only two subjects per variables for adequate estimation of regression coefficients, standard errors, and confidence intervals. (Austin & Steyerberg, 2015).

Given that a meta-regression concept is similar to simple linear regression (Baker, White, Cappelleri, Kluger, & Coleman, 2009), it is possible that the rule of thumb of 10 events per trials do not reliably apply to meta-regression procedures. (Gagnier et al., 2012)
Furthermore, other simulation studies (on logistic and Cox modelling strategies) concluded that this rule of thumb was too conservative and only five to nine EPV should be required when confounder adjustment is made. (Courvoisier, Combescure, Agoritsas, Gayet-Ageron, & Perneger, 2011; Vittinghoff & McCulloch, 2007).

Therefore, conducting a meta-regression analysis with less than 10 trials for each characteristic modelled may give an unbiased regression coefficient estimate even though it does not rule out a lack of statistical power.

See in page 19, lines 3-8.

"Although, there was a limited number of RCTs in each stratum of risk of bias, a recent simulation study showed that linear regression models require only two subjects per variables for adequate estimation of regression coefficients, standard errors, and confidence intervals [58]. Given that a meta-regression concept is similar to simple linear regression [59], we are confident that our analysis gave an unbiased regression coefficient estimate even though it does not rule out a lack of statistical power."

11. Discussion

a. 9th line from the bottom: the sentence of “Nevertheless....groups”. Can the authors provide explanation on the low power stated?

Author’s response: we thank the reviewer for this comment. 

Data from Kayentao et al review did not support an association between level of drug resistance (Prevalence of dhps 540E mutation > 50% vs Prevalence of dhps 540E mutation <50%) and the efficacy of three doses or more vs two doses of sulfadoxine-pyrimethamine in reducing the risk of LBW. However, this result should be interpreted with caution. Indeed, it was based on a sub-group analysis with only two studies conducted in regions where the prevalence of dhps 540E mutation were over 50% and five studies conducted in regions where the prevalence of dhps 540E mutation were less than 50%. Therefore, a lack of statistical power could not be completely ruled out.
However, the lack of association found in that study may also be explained by the fact that the two RCTs were conducted in regions where sextuple mutant parasites are absent.

This highlights the need of conducting more studies in these regions of Africa with different profile of SP resistance to help policy makers shape recommendations regarding malaria prevention during pregnancy.

See in page 17, lines 3-9.

"...Nevertheless this finding should be interpreted with caution. Indeed, it was based on a subgroup analysis with only two studies conducted in regions where the prevalence of dhps 540E mutation were over 50% and five studies conducted in regions where the prevalence of dhps 540E mutation were less than 50%. Therefore, a lack of statistical power could not be completely ruled out. However, the lack of association found in that study may also be explained by the fact that the two RCTs were conducted in regions where sextuple mutant parasites were absent."

12. Summary:

a. Can the authors suggest the public health implications of this study?

Authors’ response: we thank the reviewer for his question.

See in page 21, lines 5-10

"Our study supports the current WHO recommendation for IPTp with three doses or more of sulfadoxine-pyrimethamine during pregnancy for malaria prevention.

However, there is an urgent need to re-evaluate the efficacy of IPTp with sulfadoxine-pyrimethamine especially in East Africa given the increase of resistance. Also, additional medicines to replace this medication are needed, as no suitable alternative drug is available. The Continuing monitoring of effectiveness of IPT with sulfadoxine-pyrimethamine in Africa is essential."

Quality of written English: Acceptable

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

- Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this paper, either now or in the future? NO

- Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper, either now or in the future? NO

- Do you hold or are you currently applying for any patents relating to the content of the manuscript? NO. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript? NO

- Do you have any other financial competing interests? NO

- Do you have any non-financial competing interests in relation to this paper? NO

If you can answer no to all of the above, write I declare that I have no competing interests below. If your reply is yes to any, please give details below.

I have no competing interest
Again, we thank reviewers for their valuable comments. We have answered all comments and integrated them in the revised manuscript. We now feel that our revised manuscript is ready for publication in BMC Medicine.

Very kind regards.

Flory Tsobo Muanda

University of Montreal and Research Unit on Medications and Pregnancy, Research Center CHU Ste-Justine 3175, Côte-Sainte-Catherine, Montréal (Québec), Canada, H3T 1C5

Email address: flory.muanda-tsobo@umontreal.ca

Corresponding author:

Dr Anick Bérard, Research Chair on Medications, Pregnancy and Lactation, Faculty of Pharmacy, University of Montreal and Director of Research Unit on Medications and Pregnancy, Research Center CHU Ste-Justine 3175, Côte-Sainte-Catherine, Montréal (Québec), Canada, H3T 1C5.

Email address: (anick.berard@umontreal.ca)