

## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Containment of Antibiotic REsistance - measures to improve antibiotic use in pregnancy, childbirth and young children (CAREChild): a protocol of a prospective, quasi-experimental interventional study in Lao PDR.
<b>AUTHORS</b>	Machowska, Anna; Sihavong, Amphoy; Eriksen, Jaran; Vongsouvath, Manivanh; Marrone, Gaetano; Sychareun, Vanphanom; Hanson, Claudia; Keohavong, Bounxou; Brauner, Annelie; Mayxay, Mayfong; Kounnavong, Sengchanh; Lundborg, Cecilia

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Amelia Hollywood University of Reading, UK.
<b>REVIEW RETURNED</b>	29-Jul-2020

<b>GENERAL COMMENTS</b>	<p>This paper is a protocol of a prospective, quasi experimental interventional study in Lao PDR, exploring measures to improve antibiotic use in pregnancy, childbirth and young children. This study has been awarded funding and received ethical approval. This is an important study regarding antibiotic use and antibiotic resistance in Laos.</p> <p>The paper contains some useful information however it needs proof reading for grammatical and typographical errors in order to ensure the methods described are sufficient to allow the study to be repeated.</p> <p>The authors need to be clear on the tense used, as some aspects have happened and some are planned in the future, therefore this should be made clear in the language used.</p> <p>Abbreviations should be written in full, with their first use e.g. LMIC and ANC.</p> <p>In the qualitative section, it needs to be made clearer whether the participants will be interviewed and/or given questionnaires to complete. For the interviews, an indication of the interview schedule would be useful.</p> <p>Page 10 line 13 - how many mothers and HCPs were involved in the FGD and interviews?</p> <p>Page 14 line 49 – an error – ‘date management’ should this read ‘data management’?</p> <p>Page 17, line 8 - Table 1: for the structured interview is the reported practices self-reported? This should be made clear. And if not it should be made clear how it is being reported in the interview.</p>
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<b>REVIEWER</b>	David Desseauve CHUV
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	<p>centre hospitalier universitaire vaudois</p> <p>Dr David DESSEAUVE - MD, PhD Département de gynécologie-obstétrique / Femme-mère-enfant Avenue Pierre-Decker 2, CH-1011 Lausanne</p> <p>+41 (0)79 55 68259 MOBILE +41 (0)21 314 45 76 secrétariat david.desseauve@chuv.ch www.chuv.ch/obstetric-research-lab <a href="http://www.chuv.ch/dgo">http://www.chuv.ch/dgo</a></p>
<b>REVIEW RETURNED</b>	06-Aug-2020

<b>GENERAL COMMENTS</b>	<p>Thank s to the editorial board to give me the opportunity to review this research protocol. The challenge raised by the authors to contain antibiotic Resistance is great and thank to the authors to do this in their country. This research protocol is tricky, and I think that some clarifications are necessary to a better understandability of this research.</p> <p>MAJOR COMMENT:</p> <p>1- There is a floating in the design of the study for the readers. The aim of the study in the abstract “This project aims to fill the knowledge gaps regarding antibiotic use in relation to pregnancy, childbirth and early childhood in Laos with the long-term aim to contain ABR” is very general, and didn’t correspond with the primary that authors want to assess “The primary outcome is the proportion of uncomplicated vaginal deliveries where antibiotics are used.” As I understand, authors wants to evaluate the effect of large educational intervention focus on the use of antibiotics during pregnancy and childbirth and to assess mid-term consequences.</p> <p>2- In this way sample size have to be reevaluated, with hypothesis on the potential impact of educational measures to change practices.</p> <p>3- The GANT-Diagramm (Fig.1) would help readers to understand the plan of the study, but it’s unreadable in this format too small... I think this study have many strengths, with too an assessment of antibiotics resistance after educational plan. Nevertheless the duplication of objectives without clear and simple research question, ask me to the feasibility and the relevance of this research in this form. I think a focus on the major research question: Impact of educational plan on the Antibiotics resuitance during pregnancy could improve quality of this research with more understandable results and a better dissemination.</p> <p>Minor Comments:</p> <p>1- I didn’t find the decalatartion of this resech in an international registry as it coulbe mandatory for publication or dissemination.</p> <p>2- The abbreviation ANC is not define in the main text</p> <p>3- Their some problem of typo, can you edit your manuscript “METHODS AND ANALYSIS: DATE MANGEMENT AND ANAYSIS”</p>
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### VERSION 1 – AUTHOR RESPONSE

Reviewer: 1, Amelia Hollywood, Institution and Country: University of Reading, UK.  
Competing interests: None declared.

This paper is a protocol of a prospective, quasi experimental interventional study in Lao PDR, exploring measures to improve antibiotic use in pregnancy, childbirth and young children. This study

has been awarded funding and received ethical approval. This is an important study regarding antibiotic use and antibiotic resistance in Laos.

The paper contains some useful information however it needs proof reading for grammatical and typographical errors in order to ensure the methods described are sufficient to allow the study to be repeated.

Response: Thank you for your comment. We have now carefully proof read the paper.

The authors need to be clear on the tense used, as some aspects have happened and some are planned in the future, therefore this should be made clear in the language used.

Response: Thank you for your comment. During the submission of the manuscript the baseline data collection was ongoing and we were planning for the following phase of the study, therefore present tense was used for the ongoing activities and future to describe next phases of the study. After receiving your comment and consulting with our study and research team which include native English speakers we decided to use the future tense to describe the subsequent steps of the project and we emphasised in the “study status”, and when necessary in the text, that the data collection process is ongoing. We hope this is clear now.

Abbreviations should be written in full, with their first use e.g. LMIC and ANC.

Response: Thank you for pointing it out and we are sorry that we missed some. We carefully reviewed that abbreviations used for the first time are now written in full.

In the qualitative section, it needs to be made clearer whether the participants will be interviewed and/or given questionnaires to complete. For the interviews, an indication of the interview schedule would be useful.

Response: We agree with the reviewer that we could have provided more details. We clarified it in the text that pregnant women and mothers will (were) participate in the FGDs using thematised guidelines for FGDs and the individual interview guide will (was) be used with HCPs. The FGDs thematised guidelines and the individual interview guide are presented in the Appendix 1.

Page 10 line 13 - how many mothers and HCPs were involved in the FGD and interviews?

Response: Thank you for your comment. We have now added the requested information in the manuscript: “Before the intervention 6 FGDs (3 groups with 29 pregnant women and 3 groups with 26 mothers with children under two years of age) will be organised in Thulakhom district, and approximately 30 HCPs will participate in the individual qualitative interviews (approximately 9 at central and provincial level, and 12 at district level).”

Page 14 line 49 – an error – ‘date management’ should this read ‘data management’?

Response: Thank you. It is now corrected.

Page 17, line 8 - Table 1: for the structured interview is the reported practices self-reported? This should be made clear. And if not it should be made clear how it is being reported in the interview.

Response: Thank you for this comment. In the structured interview we ask HCPs about their practice of antibiotic prescribing and we do not cross-check this information with other sources. We have now emphasised it in the Table 1 that it is a self-reported practice.

Reviewer: 2, David Desseauve

Institution and Country: CHUV, centre hospitalier universitaire vaudois

#### MAJOR COMMENT:

1- There is a floating in the design of the study for the readers. The aim of the study in the abstract “This project aims to fill the knowledge gaps regarding antibiotic use in relation to pregnancy, childbirth and early childhood in Laos with the long-term aim to contain ABR” is very general, and didn’t correspond with the primary that authors want to assess “The primary outcome is the proportion of uncomplicated vaginal deliveries where antibiotics are used.”

Response: Thank you for this comment. We have now modified the abstract and clarified the primary outcome of the study “The overarching aim of this project is to fill in the knowledge gap regarding antibiotic use and ABR in Laos. The primary objective is to estimate the proportion of uncomplicated vaginal deliveries where antibiotics are used and to compare its trend before and after the intervention. The secondary objectives include improving knowledge, attitude and practice regarding antibiotic use and ABR among pregnant women, mothers and healthcare providers (HCPs)”. The sample size calculation has been calculated for baseline proportion of uncomplicated vaginal deliveries and its 95% confidence interval, while the change over time will be evaluated using interrupted time series analysis. The interrupted time series analysis compares the trend of the outcome before and after the intervention in order to see if there is a significant difference between the trend before and the trend after intervention. Since it uses aggregated data, its power increases with the number of time points and it does not depend on the number of observations at each time point. Please see the references that we also included in the manuscript (Liu W, Ye S, Barton BA, Fischer MA, Lawrence C, Rahn EJ, et al. Simulation-based power and sample size calculation for designing interrupted time series analyses of count outcomes in evaluation of health policy interventions. Contemporary clinical trials communications. 2020;17:100474).

As I understand, authors wants to evaluate the effect of large educational intervention focus on the use of antibiotics during pregnancy and childbirth and to assess mid-term consequences.

2- In this way sample size have to be reevaluated, with hypothesis on the potential impact of educational measures to change practices.

Response: Thank you for your comment. Please see the response above which we believe clarifies also this point.

3- The GANT-Diagramm (Fig.1) would help readers to understand the plan of the study, but it’s unreadable in this format too small...

Response: Thank you for your comment. We would like to emphasise that the Gantt chart was submitted as a high-resolution figure according to the journal requirements and was prepared using Times New Roman font size 16 and 18. We are happy to have the Gantt chart attached as an appendix if more suitable.

I think this study have many strengths, with too an assessment of antibiotics resistance after educational plan. Nevertheless the duplication of objectives without clear and simple research

question, ask me to the feasibility and the relevance of this research in this form. I think a focus on the major research question: Impact of educational plan on the Antibiotics resistance during pregnancy could improve quality of this research with more understandable results and a better dissemination.

Response: Thank you for your comment. We are not sure if we understood your point correctly but we would like to clarify all issues.

The authors hypothesise that "...use of antibiotics for uncomplicated vaginal deliveries is high and that the educational intervention will reduce the proportion of antibiotics administered and lead to an improvement in knowledge regarding antibiotic use and ABR of both community and HCPs." please see at the end of the introduction section.

The primary objective is stressed in the abstract and also clarified above.

Please note that we do not aim to evaluate the impact of the intervention on antibiotic resistance carriage patterns. As presented in Figure 1 we will only take the microbiology samples during the pre-intervention phase to estimate the ABR situation with focus on ESBLs producing and multi drug resistant E. coli and Klebsiella spp. carriage in faecal samples among women and children.

Minor Comments:

1- I didn't find the decalartation of this resech in an international registry as it coulbe be mandatory for publication or dissemination.

Response: Thank you for this comment. This issue has been discussed broadly with the editor of the journal when we submitted the manuscript. The study is not a clinical trial, however authors decided to register it retrospectively and the study received the following identification number: ISRCTN16217522. We have now included it in the abstract.

2- The abbreviation ANC is not define in the main text

Response: Thank you for pointing it out. It is corrected now.

3- Their somes problem of typo, can you edit your manuscript "METHODS AND ANALYSIS: DATE MANGEMENT AND ANAYSIS"

Response: Thank you for pointing it out. It is corrected now. Moreover, the authors have proof read the manuscript.

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	David Desseauve CHUV Lausanne
<b>REVIEW RETURNED</b>	25-Oct-2020
<b>GENERAL COMMENTS</b>	authors had answered to all the comment with Clarity i think this protovcol could be published