Author's response to reviews

Title: Population awareness of risks related to medicinal product use in Vientiane Capital, Lao PDR: a cross-sectional study for public health improvement in low and middle income countries

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Author's response to reviews: see over
Dear reviewers,

We would like to thank you for having carefully commented our paper, and for letting us the possibility to improve our manuscript. We apologize for the lack of rigorous explanations that have made this manuscript unclear.

Would you please find below the detailed answers to your comments and questions. All the corrections, except the discussion -that has been entirely rewritten- are highlighted in the text of the revised manuscript. We hope that this revised version will respond satisfactorily to your questions.

Referee 1

Major Compulsory Revisions

Methods
1. Please explain a little more about the sampling of districts and village’s and why 30 villagers per district required.

With the aim to get a representative study population of Vientiane Capital districts, two urban districts (Xaysetha and Sikhottabong) were randomly selected among the four urban ones, one (Naxaithong) among the three peri-urban districts and one (Sangthong) among the two rural districts of the province (simple random samplings).

In a previous study in Zimbabwe (Stein et al. Self-medication in urban and rural Zimbabwean communities. Br J Clin Pharmacol. 1989), the prevalence of citizens unaware of the potential harm induced by OTC drugs was 65%. Based on this prevalence, we aimed to include 87 to 350 villagers, allowing a precision between 5 and 10%. This interval was conditioned by the lack of availability of skilled interviewers with medical or pharmaceutical degree. We calculated that three interviewers could interview 10 villagers per village and per day. With an estimated rate of refusal of 20%, 12 villagers were thus included per village. Three villages per district (this number was chosen for convenience) were randomly selected by simple sampling among the villages with at least one health facility (health centre, hospital, private clinic or private pharmacy), representing 8.2% (n=12) of all the eligible villages (n=146) in the four surveyed districts.

As also requested by the referee 2, we added this paragraph in the revised manuscript (P7 175-189).

What alternatives were considered instead of including 16 year olds?

Given the aim of our study and the authorizations from the Ethics Committee, we only included the heads of the households or, in their absence, another adult (≥ 16 years old) of the household.

2. Were the number of households the same in each cluster in the villages were there was not a village list?
Considering the number of villagers per village, the number of clusters per village and the average number of people per household in Vientiane capital (source: Statistical yearbook 2012, available at http://www.nsc.gov.la/en/PDF/Final%20Statistical%20Year%20book%202012.pdf), we estimated that there were 6 to 18 households per cluster. We assume this range has not affected our results.

3. Please explain more about the translation and back-translated process and the characteristics of the translator(s).

The translation from English to Lao was performed by Dr Naphaphone Phalivong, a Lao pharmacist with a strong background of English practice, as she had lived in Europe for 8 years. She was also currently involved in translation (Laotian to English and English to Laotian) of documents for the University of Health Sciences. In addition, the translation of the technical words corresponding to the measures of the outcome of interest (section C) and the section D of the questionnaire was checked by two pharmacists (Dr Lamphone Syhakhang and Dr Chanthanom Manithip), both having performed a PhD in public health in Sweden.

The back-translator, Dr Valy Keoluangkhot is a medical doctor with a Tropical Medicine and International Health degree. She is a teacher at the faculty of Medicine of the University of Health of Laos and also the head of the infectious disease ward at Mahosot hospital. She was explained the aim of the study and the targeted population, and then asked to translate the Lao version of the questionnaire into English. She verified that the technical Laotian words used for measuring the outcome corresponded to the words used in the first English version of the questionnaire.

Were there discrepancies and how were they resolved?

After translation and back-translation, no discrepancies for the questions used for the measures of the outcome were highlighted.

We added precisions on the translation and back-translation process in the revised manuscript (P9 L216-221).

4. Please explain more about the pilot and how did you check how terms such as ADR and Pharmacovigilance system were understood?

During the pilot survey, the villagers were explained the aim of the pilot, as well as the aim of the survey. For Section C and D of the questionnaires, after each question they were asked to tell if all the words were understood and they were asked to comment their answers to the questions.

During the survey, the positive respondents to both questions of interest also made comments. To the question on what an adverse drug reaction is, they mainly quoted symptoms of adverse reactions such as allergic and gastro-intestinal symptoms. Sometimes they even spontaneously associated the culprit medicine to the symptom (e.g: ‘ampicillin can cause allergy’). Some also tried to give a definition of an ADR with their own words (e.g: ‘it is when new symptoms appear when you take a medicine’).
One paragraph has been added in the methods (P9 L223-226) and one paragraph in the results (P12 L294-298) of the revised manuscript.

We did not have any technical mean to check on the understanding of pharmacovigilance. However, the interviewers were told to read the explanatory sentence several times if the respondent expressed difficulties to understand.

5. How did you determine the questions you used to determine whether a villager was unaware of medicine risks? Please expand on this. What if the respondent answered negative for one question but not the other?

Two questions were used to determine the outcome of interest: ‘Have you ever heard what an adverse drug reaction is?’ and ‘Do you think that modern medicines can be harmful in case of normal use and normal doses?’

The term Adverse Drug Reaction is conventionally used by the WHO to define “a response to a drug which is noxious and unintended and which occurs at doses normally used in humans”. ADR is also a term used for communication on drug safety in validated sources of information (i.e summary of products characteristics and leaflets of the pharmaceutical products). These are the reasons why we asked the citizens if they have heard of what an ADR is. To avoid desirability bias, we asked the positive respondents to comment on that positive answer. Therefore, we verified their understandings (please cf. to the answer of your previous question).

However, when the term ADR has never been heard by a villager, it does not necessarily mean that he is not aware on medicines risks. In order not to underestimate the awareness of the population, we decided to combine this question with the second one that is ‘Do you think that modern medicines can be harmful in case of normal use and normal doses?’. This question was adapted from another study from Zimbabwe where the villagers were asked: ‘Can any over-the-counter drug be harmful?’ (Stein et al. Self-medication in urban and rural Zimbabwean communities. Br J Clin Pharmacol. 1989). We deliberately chose to add ‘in case of normal use and normal doses’.

We have now expanded on this in the revised manuscript (method P8 L208-213 and discussion P15 L374-380).

If the respondent answered negative to one question but positive to the other, we considered him to be aware on medicines risks. In total, among the 55 villagers considered as aware, 48 had heard of what an ADR is but answered negative or were unsure about the harmful effect in case of normal use; 2 had never heard what an ADR is but knew that medicines can be harmful in case of normal doses (they talked about gastric pain or kidney disorder in their comments); 5 had heard about ADR and knew about the harmful effect in case of normal use.

This is summarized in the new revised manuscript (P12 L294-298).
6. It is not clear if this is a validated instrument or one developed for this study. Can you expand on this?

**We developed this questionnaire for the purpose of this study.**

At the time of our study there was one existing questionnaire called the ‘beliefs about medicines questionnaire’ (BMQ), developed by Horne et al. *(Horne et al. The beliefs about medicines questionnaire: The development and evaluation of a new method for assessing the cognitive representation of medication. Psychology and Health, 1999).* However, to our knowledge the BMQ assesses the influence of beliefs about medicines on treatment adherence. As the BMQ-General scale does not aim to assess the awareness of the population on medicine risks in particular with normal doses or normal uses of medicines, we chose to develop our own questionnaire but its validity and reliability have not been tested. Nevertheless, one of the questions used to measure the awareness of the respondents (‘Do you think that modern medicines can be harmful in case of normal doses and normal use?’) was derived from the question ‘Can any over-the-counter drug be harmful?’ used in a survey performed in Zimbabwe *(Stein et al. Self-medication in urban and rural Zimbabwean communities. Br J Clin Pharmacol. 1989)*

A paragraph of explanation was added in the methods of the revised manuscript regarding the development of the questionnaire (P8 L200; 208-212), and the choice of the outcome of interest was discussed (P15 L374-380).

One more recently developed scale “Perceived sensitivity to medicines (PSM)” would have been more appropriate for the objective of our study. However, this scale has been developed after we performed our study *(Br J Health Psychol. The perceived sensitivity to medicines (PSM) scale: an evaluation of validity and reliability. Horne et al. 2013)*

As also requested by referee 2, we added a sentence in the revised manuscript (P8 L200).

7. Please explain the steps you took to ensure meaningful informed consent from the 16 year olds and why parental consent was not obtained. Please comment on gatekeeper consent and how this was obtained.

As explained in the response to your question n°1, the respondents were all adults (≥16 years old in Laos).

Also where did the interviews take place and how was confidentiality assured or were there any issues of confidentiality and if so how were these managed?

The interviews took place either in the office of the head of the village (in 2 villages), at the temple of the village (in one village), or in the households (in 9 villages). Either the head of the village or a mandated assistant was present during some of the interviews, but the aim of the study and the confidentiality concerns were explained to the head of the village or his mandated assistant who agreed to stay apart from the interview. Sometimes other family members or neighbours came and listen to the interview. It was thus difficult to maintain strict confidentiality.

A paragraph was added in the methods (P9 L228-229) and confidentiality issues are discussed in the revised manuscript (P14 L349-352).
Discussion
8. Can you comment on the 100% response rate? High response rates are not unusual in Lao PDR but how and by who were the respondents in the villages where a list of the households was available approached in the first instance? Could this have affected the response rate?
In villages where we could randomly select the households through the list of the households, the head of the village contacted the head of the household or his/her wife/husband and an appointment was made. When the selected households could not be contacted, they were directly approached at the time of the study by the head of the village or his mandated assistant that was accompanying the research team.
We believe one reason why there was no refusal is because government staffs (represented by the head of the village or his mandated assistant) have a strong influence on the citizens in Laos.

We have discussed about the response rate in the revised manuscript (P14 L347-349).

And the quite large difference in male and female respondents? Was this a feature of the survey design – e.g. the time you went to the village? The research team went to the village mainly during working hours and this might explain why half of the respondents were women.

A sentence has been added to the manuscript (P14 L343-344).

9. Please provide a reference or evidence to support the claim that ‘The majority of the Lao population in the province of Vientiane Capital considers traditional medicines as safe or has no opinion about their risks.’
Indeed, that was not clear enough in the initial manuscript. This is a result of our study, this is why there is no reference.
We have now made it clearer in the revised manuscript (P15 L383).

10. The section ‘Implications and reflections for policy and research is too simplistic and does not flow well. More innovative solutions are needed and more concrete examples – how do patients transform for example from passive recipients to active partners? What would it take to achieve adequate labelling and package inserts? How would this be regulated?
Pharmacists are often the preferred sources for drug safety information (and sometimes diagnosis) what would it take to engage these actors in training and engage them to pass on information? As you mention labelling of medicines will be insufficient for the purpose of raising awareness of rural patients (also the most vulnerable based on your study) on drug safety.
We have now taken these comments into account to rewrite the discussion in the revised manuscript (P14 to P18).
11. Achieving universal health coverage and effectively regulating the pharmaceutical industry (formal and informal providers) are important but long term objectives – what can be done in the interim? What are the risks for pharmacists and how can these be mitigated?

Indeed, these are long-term objectives.

In the interim, trainings of pharmacists (with University degree) and ‘assistant pharmacists’ need to be improved in order to increase quality of the services and to restore the trust of the population in formal providers. In line with this, several efforts have been recently made. For example, several young teachers of the faculty of pharmacy have been trained abroad and since 2014 the curriculum ‘assistant pharmacists’ (3-years) is run by the Faculty of Pharmacy.

The training of the pharmacists and medical students is addressed in the discussion of the revised manuscript (P17 L423-424).

12. It is partly because prescription drugs are readily available that people self-medicate but also because of failures of and a lack of trust in the health system – again while a long term project this needs to be acknowledged

It is true that the availability of prescription drugs is not the only factor associated to self-medication. We believe that the trust in the health system could be gained progressively by encouraging efficient communication between the population and actors of the health system (for example through the creation of drug information centers). This was developed in the discussion of the revised manuscript (P17 L422-423; L429-434).

Discretionary Revisions

1. Was there any mention of perceived differences in efficacy between medications from China, Vietnam and Thailand

Our study did not aim to assess differences in efficacy between medicines. There was no mention of differences in safety by the interviewees.

2. There are likely to be other reasons as well that explain why urban residents have better access to information on medicinal products – can you discuss these too

As suggested by Syhakhang et al., people in urban areas may have better opportunity to receive information on drugs from the regulatory authority (Syhakhang et al. Knowledge and perceptions of drug quality among drug sellers and consumers in Lao PDR. Health Policy Plan. 2004). However, without any example for this assumption, we prefer not to mention this in this article.

3. The discussion can be more concise and focus on the key points and interpretation

The discussion was rewritten as suggested. Initially of 1532 words, that of the revised manuscript is now of 1273 words (P14 to P18).

Level of interest: An article whose findings are important to those with closely related research interests

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

1 Overall, the definition of urban and rural should be more carefully studied. For example, in the reference paper 19, urban, rural or remote was defined by ‘distance in travel time (hour) from provincial capital.’ In this paper, however, the definition is not clear. In the discussion, rural in Vientiane Capital and rural in Savannakhet in ref 19 are considered similar or the same.

Four urban and three peri-urban districts of Vientiane Capital were previously differentiated according to the delimitation of Vientiane Municipality (Mobillion et al., available online at: http://eps.revues.org/3243). The two other districts of this province were not qualified as urban or peri-urban. However, the distance in travel time from the center of Vientiane City (Mahosot Central Hospital) to the district hospital of these two districts (above 2h) corresponded to the definition of rural districts of another province by Syhakhang et al. (Syhakhang et al. Knowledge and perceptions of drug quality among drug sellers and consumers in Lao PDR. Health Policy Plan. 2004).

We added these two references in the Methods of the revised version of manuscript (P7 L178-179).

2 Data collection (P7~ L171~)

How was the number of villages (three per district) decided?
Please explain about your sample size calculation?

In a previous study in Zimbabwe, the prevalence of citizens unaware of the harmfulness of OTC drugs was 65%. Based on this prevalence, we aimed to include a sample size of 87 to 350 villagers, that would allow a precision between 5 and 10%. This interval was conditioned by the lack of availability of skilled local interviewers with medical or pharmaceutical degree. We calculated that 3 interviewers could interview 10 villagers per village and per day. With a number of refusal estimated to 20%, 12 villagers were thus included per village. For convenience, we included 3 villages, randomly selected per district.

We finally included 144 villagers, with no refusal, and we obtained a prevalence of unawareness of 61.8% with a 95% confidence interval of (53.8-69.8).

According to your request of an explanation on our sample size calculation (also requested by referee 2), we have now added a paragraph in the Methods of the revised version (P7 L180-189). In addition, we have added the confidence interval of the proportion in the results section of the revised manuscript (P10 L258).

Why were household heads assigned as interviewees? Family caregivers should have been more appropriate interviewees for your study purpose.

According to the Laotian authors of this manuscript, in most Laotian family the heads of household or their wives are the caregivers. This is why we chose to interview them preferentially, as mentioned in the discussion (P14 L345-347).
Recall bias should have been avoided. For example, in Table 3 (last medicines used within the previous 12 months), about 40% of the medicines were not identified. On what basis, was the time period "12 months" decided?

We made the hypothesis that our sample size was too small to be sure to include patients having recently used medicines. This is the reason why we decided to enlarge the targeted period to 12 months, instead of 2 weeks that are usually investigated in household survey of medicine utilization (Bertoldi et al. A descriptive review of the methodologies used in household surveys on medicine utilization. BMC Health Services Research, 2008).

We have now replaced the verb “recall” by “give” (P11 L269) in the results. We have discussed on the existence of the potential recall bias in the revised manuscript (P16 L403-405).

How the questionnaire was developed? Any references/ How about its reliability  and validity?

At the time of our study there was one existing questionnaire called the ‘beliefs about medicines questionnaire’ (BMQ), developed by Horne et al. (Horne et al. The beliefs about medicines questionnaire: The development and evaluation of a new method for assessing the cognitive representation of medication. Psychology and Health, 1999). However, to our knowledge the BMQ assesses the influence of beliefs about medicines on treatment adherence. As the BMQ-General scale does not aim to assess the awareness of the population on medicine risks in particular with normal doses or normal uses of medicines, we chose to develop our own questionnaire but its validity and reliability have not been tested. Nevertheless, one of the questions used to measure the awareness of the respondents (‘Do you think that modern medicines can be harmful in case of normal doses and normal use?’) was derived from the question ‘Can any over-the-counter drug be harmful?’ used in a survey performed in Zimbabwe (Stein et al. Self-medication in urban and rural Zimbabwean communities. Br J Clin Pharmacol. 1989).

A paragraph of explanation was added in the methods of the revised manuscript regarding the development of the questionnaire (P8 L200; 208-212), and the choice of the outcome of interest was discussed (P15 L374-380).

One more recently developed scale “Perceived sensitivity to medicines (PSM)” would have been more appropriate for the objective of our study. However, this scale has been developed after we performed our study (Br J Health Psychol. The perceived sensitivity to medicines (PSM) scale: an evaluation of validity and reliability. Horne et al. 2013).

3 Data presentation: Résultats
In Table 2, the way percentages were calculated is incorrect. For example, in District Xaysetha, the presentation should be as follows:
Out of 36 respondents, 22 (61.1%) were aware and 14 (39.9%) were unaware of medicine risks.

We did make an incorrect shortcut in the presentation of the results of Table 2 (P24). In fact, we wanted to describe the characteristics of the respondents according to their status: ‘being aware’ versus ‘being unaware’ in Table 2. We have now changed the text
related to the comments of Table 2 (P10 L258-263). In addition, for sake of clarity we have suppressed the last column of the Table 2 (P24).

In Table 3, data should be described based on 102 respondents, not based on the number of medicines they raised. For example, what % people raised that vitamins/minerals should be described.

In accordance with this comment, we have corrected Table 3 (P25) and the description of the results in the text of the revised manuscript (P11 L268-270).

4 Interpretation of the results
There are several misinterpretations on the results. For example, under "Respondent characteristics", there is a sentence "The degree of urbanization was significantly associated to the awareness of medicine risks. Respondents living in rural (Sangthong) and peri-urban (Naxaithong) areas had a higher risk of being unaware compared to those in the urban district of Xaysetha (33.7% and 27.0% versus 15.7%, respectively, p=0.001)". However, the results of another urban area "Sikhotabong" are not included in this sentence. Although Sikhotabong is classified as "urban" in the Methods section, more than half of the villagers were unaware of the medicine risks, which is contradictory to the above sentence. Results of data analysis should be carefully interpreted.

In the previous version of the manuscript, we did make a misinterpretation of the results of Table 2 (P24). Indeed, the respondents unaware were not statistically more/less frequently living in Sikhotabong (urban) or in Naxaithong (peri-urban) than those aware.

In addition, it did not appear in Table 4 (results of logistic regression) that there were no differences between Sikhotabong and Naxaithong because we chose the urban district of Xaysetha as a reference.

We have now added a sentence in the comments of Table 2 (P10 L263-264) and of Table 4 (P11 L287-291) and we have discussed these differences (P15 L368-372) in the revised manuscript.

Discussion
5 The discussion is too long. Rather than discussing the unique findings of this study, the authors are discussing those of the past studies, which should be rather quoted in the introduction. Ideally, in each paragraph of the discussion, the authors’ findings should be presented first, and then discuss how important they are.

The discussion has been rewritten as suggested in the revised manuscript.
Initially of 1532 words, that of the revised manuscript is now of 1273 words (P14 to P18).

6 Conclusion
L 432 ‘….the degree of urbanization are apparent.’ In this, the term ‘urbanization’ should be more carefully used.

We agree this term is not adapted. Wherever needed, we have corrected in the revised manuscript, using either ‘district’ (P11 L281:283) or ‘place of residence’ (P4 L117; P18 L439).

Minor essential revisions
1 L172, 178: Vientiane Capital and Vientiane province is different. The authors seem to mix up both.

Indeed, it was confusing in the previous manuscript. This was corrected in the methods of the revised manuscript (P7 L171-L179).
2 L228: Ethical approval was obtained only in Laos? When foreigners conduct a research in a developing country, it is recommended that the approval be obtained from both countries, though it might not be the must.

The study had Lao ethical approval and neither the Lao National Ethics Committee for Health Research nor any of the institutions involved required additional approval.

3 L236 ‘45.1 (SD 12.5) years old’

We have now changed it in the revised manuscript (P10 L255).

Discretionary revisions
1 L166 ‘Based on face to face interviews’ can be reviewed as this is a method statement.

We agree that this should not be in the introduction. We have now revised the manuscript as suggested (P7 L166).