

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Medical injection and infusion practices among HIV-seronegative people and people living with HIV: a behavioural survey of ten HIV testing and opportunistic infections/antiretroviral therapy sites in Cambodia
AUTHORS	Seang, Kennarey; Khim, Keovathanak; Vyas, Kartavya; Khuon, Dyna; Saphonn, Vonthanak; Gorbach, Pamina

VERSION 1 – REVIEW

REVIEWER	Altaf, Arshad Aga Khan University, Research Office
REVIEW RETURNED	20-Jun-2022

GENERAL COMMENTS	<p>Title: Please add an "s" after injection and infusion, i.e., injections and infusions.</p> <p>Abstract:</p> <ul style="list-style-type: none">-Please revise the opening sentence of objectives and phrase it in an active voice.-Please rephrase the second sentence of objectives. You can break it down into two sentences for clarity.-Participants: Please revise "250 patients" to "250 PLWH" and kindly use this same term in the rest of the manuscript. <p>Methods:</p> <p>Study setting: opening sentence: Please clarify if Cambodians refers to both groups of participants ie PLWH and those who were HIV negative?</p> <p>Table 1: Please rephrase. "Feeling drunk monthly or more often." This will not be clear to a great majority of readers.</p> <p>Table 1: Please rephrase for clarity. What do you mean by "workplace"? Aren't these PLWH and HIV negative study participants?</p> <p>Table 2: Please rephrase the title of table 2. Suggestion: injection seeking behaviours of study participants...</p> <p>Table 2 injection and infusion use: suggestion: replace given with received.</p> <p>Table 2: Please rephrase to more than last year to more than a year ago.</p> <p>Page 18; line 40-41: When reporting results, please state only facts. You can use words like substantial or significant in the discussion/explanation/conclusion section.</p> <p>Page 25; lines 13-14: please provide a reference for this statement.</p> <p>Page 25; line 44: What do you mean by this? Please clarify what kind of digital platforms are available. Also, is there any crude data available about communities in rural areas in Cambodia have smart phones?</p>
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REVIEWER	Makuza, Jean Damascene Rwanda Biomedical Center, Institute of HIV, Diseases Prevention and Control
REVIEW RETURNED	21-Jul-2022

GENERAL COMMENTS	<p>Thank you for this opportunity to review this paper exploring the prevalence and practice of unsafe injection among PLHIV. It is great to rule out the cause of transmission among HIV positive and HIV negative rather than HIV negative only. This paper is important as it brings information needed on the unsafe medical infection/infusion practices and their association with HIV infection in Cambodia. This will help in bringing insights into the prevention and elimination of HIV/AIDs in Cambodia. Apart from that, it used a sufficient sample size, and in different provinces of Cambodia which could increase the validity of this study. However, this study has some gaps which need to be addressed before its publication, the main one is to correlate objectives, results, and conclusions which are not linked, it will be also better to look at how the title changed a bit for incorporating all results. Let us pass through these gaps in the following lines:</p> <p>1) The title: I suggest changing the title and adding the correlation or association between unsafe injections and HIV infection in the Cambodian population because when you see the present title you have the impression that the study was done only among PLHIV.</p> <p>2) Abstract: - For participants, you said 250 patients and 250 HIV-negative, it is good to use HIV positive not the patients as everyone living with HIV is not necessary a patient. - In the result, I do not see any prevalence of unsafe injection as presented in the title, only rates are presented and the interpretation of 95% CI of the aOR is not correct which leads to an incorrect conclusion.</p> <p>3) Introduction: - For the rationale, it could be better to add the literature review showing in detail the practice of unsafe injection worldwide, in developing countries and in developed countries as it is known that majorities of PWID are located in developed countries and interventions put in place to prevent the unsafe injection. - Its contribution to HIV acquisition could also be demonstrated in this part. - I intended to see the prevalence of this unsafe medical injection in PLHIV in countries other than Cambodia and the correlation between HIV and unsafe medical injection but I did not see them in the literature review. I recommend authors to look for kinds of literature talking about them and insert them in the manuscript.</p> <p>4) Methods - Study settings: The author said that there were 52 HIV voluntary testing sites in Cambodia and HIV/AIDS treatment and care clinics (called Opportunistic Infections/Antiretroviral Therapy (OI/ART) sites but did not mention how many sites were used. We recommend them to indicate in this part how many were used and how many participants were picked for each site. - Inclusion and exclusion criteria: Line 34-44: try to correct the grammatical English In this part how about people with unknown or undetermined status, I think that have to be considered in excluded people. - Study design, sampling, and recruitment: page 10, line 10, the</p>
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	<p>author said that “at selected HIV clinics in five provinces and the capital city of Cambodia”. This refers to what I requested in study settings to indicate the number of sites selected. On the same page, in line 27, the author said “First, we selected 10 sites.....”, it is supposed to have Secondly, other sites may be. I recommend they correct this by adding those remaining sites or changing the structure of the sentence or saying if only 10 sites were only used.</p> <p>- Definition and classification: only the outcome was partially defined as they did not indicate what is the type of variable. The exposure was not defined and how it was tested (for example the type of tests and their specificity and sensitivity). By the way, it is better to give more details on covariates presented in Medical history and behavior characteristics.</p> <p>On page 12, lines 24-27, this part of the last sentence could be moved to inclusion and exclusion criteria.</p> <p>- Statistical analysis: “we reported the P derived from Poisson regression” how Poisson regression was used in the cross-sectional study?</p> <p>As in this study, PLHIV were matched with non-HIV people, it could be better to show how matching was done in statistical analysis and show how the similarity or difference for characteristic distribution was assessed (SMD or P-value).</p> <p>On page 13, line 4, the authors said; “we performed a logistic regression, adjusting for sex, age, education, occupation, residence location, injection preference, and other risk factors”. Why did they adjust for these variables? How those variables were selected?</p> <p>5) Results</p> <p>- In Table one, there are some terms that were not defined in the methods, and any person from outside Cambodia cannot understand them easily, this is an example of the current address where we have provinces and Phnom Penh which is not known. I suggest explaining in the methodology the key variables.</p> <p>I may see one variable with 26.4% of the missing value, do not think you need to run a sensitivity analysis for justifying your results?</p> <p>- Injection/infusion use: On page 15, lines 38-51, this part talking about the prevalence of injection/infusion is very important and could be seen in the abstract, and even talking about it in the conclusion.</p> <p>- Association between unsafe medical injection/infusion and HIV: According to results from the logistic regression, there is no statistical association between unsafe medical injection/infusion and HIV for both crude and adjusted. Therefore, the interpretation given by the authors is not true, we recommend they rectify their interpretation of this association.</p> <p>6) Discussion</p> <p>- There was no discussion about the association between unsafe medical injection/infusion and HIV which is the main research question. Please discuss this.</p> <p>- Limitation 1- You have to explain which bias should occur with self-recall.</p> <p>- Limitation 2- The association was assessed meaning that this study was not only prevalent- You should recommend further studies considering the timing.</p> <p>- How about the non-random sample collection scheme and external validity?</p> <p>- I would also suggest presenting the strengths of the study along with limitations.</p> <p>7) Implications on policy and practices</p> <p>- This study has shown the high prevalence of unsafe injections/infusions in both HIV+ and HIV- people and there was no statistically difference between the two populations, so the</p>
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	<p>recommendation of strengthening the education on best and correct practices in drug injection/infusions could be done not only in HIV health facilities but also in all other types of health facility.</p> <p>8) Conclusion</p> <p>- On page 25, the second sentence talks about the extremely high prevalence of unsafe medical injection/infusions in the central and north-eastern parts of the country. This was not shown in the results, I recommend to the authors conclude using findings from the study.</p> <p>- This affirmation “PLWH were more likely to have received unsafe last injection/infusion within the past year” is not true according to the results gotten, I recommend rectifying it.</p> <p>9) References</p> <p>This study has very few references (14) and I recommend to add more references.</p>
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VERSION 1 – AUTHOR RESPONSE

1. Responses to Reviewer 1 – Dr. Arshad Altaf (Aga Khan University)

Dr. Arshad Altaf,

We deeply thank you for your time and valuable comments and suggestions to strengthen our manuscript. We have addressed all of your concerns and comments, in details, below.

- i. **Title:** *Please add an “s” after injection and infusion, i.e., injections and infusions*

Answer: We have slightly modified the title according to the Editor’s comments; therefore, we now use medical injection and infusion practices instead. But we have made sure that elsewhere in the manuscript, the injections and infusions are plurals as applicable.

- ii. **Abstract:**

- **Comment 1:** *Please revise the opening sentence of objectives and phrase it in an active voice.*

Answer: This is done as suggested (Abstract, objective, page 2).

- **Comment 2:** *Please rephrase the second sentence of objectives. You can break it down into two sentences for clarity.*

Answer: The second sentence had been broken down into two smaller sentences for clarity (Abstract, objective, page 2).

- **Comment 3:** *Participants: Please revise “250 patients” to “250 PLWH” and kindly use this same term in the rest of the manuscript*

Answer: This is done as suggested (Abstract, objective, page 2) and have replaced the term “patients” with “PLWH” throughout the manuscript.

- iii. **Methods:**

- **Comment 1 - Study setting:** opening sentence: Please clarify if Cambodians refers to both groups of participants, i.e., PLWH and HIV-negative study participants

Answer: We understand that the sentence might be confusing, so, we have revised the sentence to make it clearer (Method, study setting, page 5).

iv. Table 1:

- **Comment 1:** Please rephrase “Feeling drunk monthly or more often.” This will not be clear to a great majority of readers.

Answer: We have revised the sentence to from “feeling drunk monthly or more often” to “feeling drunk at least once a month” to make it clearer (Results, Table 1, page 9).

- **Comment 2:** Please rephrase for clarity. What do you mean by “workplace”? Aren’t these PLWH and HIV negative study participants?

Answer: Yes, they are PLWH and HIV negative study participants. However, one of the questions had also asked if the study participants had any contact with syringe and needles at their workplace, seeing that this might also be a risk factor. However, we have revised the sentence to “Contact with syringe and needle at their workplace” to be clear (Results, Table 1, page 9).

v. Table 2:

- **Comment 1:** Please rephrase the title of table 2. Suggestion: injection seeking behaviours of study participants...

Answer: We had revised the title of Table 2 to “injection and infusion seeking behaviours” as you suggested. (Results, Table 2, page 10).

- **Comment 2:** injection and infusion use: suggestion: replace given with received.

Answer: We had revised “injection and infusion use” to “injection and infusion received” following your recommendation. (Results, Table 2, page 10).

- **Comment 3:** Please rephrase more than last year to more than a year ago

Answer: We had revised “more than last year” to “more than a year ago” following your recommendation. (Results, Table 2, page 10).

vi. Page 18 – line 40-41: when reporting results, please state only facts, use substantial and significant in discussion/conclusion

Answer: We had revised accordingly. (Results, Table 2, page 10).

vii. Page 25 – line 13-14: please provide reference

Answer: This sentence was our opinion, we apologize for the confusion, but we have revised to sentence to avoid the misunderstanding and have also added additional reference regarding the timeframe of 12 months for estimating prevalence (Discussion, page 15).

viii. Page 25 – line 44-45: *please clarify what kind of digital platforms are available and if there is crude data available about communities in rural areas in Cambodia have smart phones*

Answer: Unfortunately, there is no data on smart phone usage in rural communities in Cambodia, but we have revised the section and added a few additional explanation regarding the digital platforms used between HIV care providers and PLWH in certain clinics or hospitals and how these platforms could be used to reach out to certain patients on other health issues, such as safe injection use (Implications on policy and practices, page 16-17).

2. Responses to Reviewer 2 – Dr. Jean Damascene Makuza (The University of British Columbia School of Population and Public Health)

Dr. Jean Damascene Makuza,

Thank you so much for your time and valuable comments and suggestions to strengthen our manuscript. We have addressed all of your concerns and comments, in details, below.

i. Title

Comment 1: *the reviewer suggested changing the title to reflect the association between unsafe injection practices and HIV-infection and both participant groups*

Answer: Because the Editor and Reviewer 1 had similar comments, we have now revised the title of the manuscript to “Behavioural Survey on Medical Injection and Infusion Practices among HIV-seronegative and People Living with HIV (PLWH) in 10 HIV Testing and Opportunistic Infections/Antiretroviral Therapy (OI/ART) Sites in Cambodia”. We feel that the revised title suggested that the injection behaviours in the study were assessed among both PLWH and HIV-negative participants (Title page, page 1).

ii. Abstract:

- **Comment 1:** *Use HIV-positive instead of patients.*

Answer: We have now used people living with HIV (PLWH) throughout in order to avoid confusion (Abstract, objective, page 2).

- **Comment 2:** *Include prevalence of unsafe injection in results and correct the aOR interpretation*

Answer: We have now included unsafe injection prevalence rate in the result section of the abstract as well. However, we maintained the interpretation of the aOR. The point estimate and the CI are suggestive that our data is compatible with a positive association, despite having 1 included in the CI. We understand the conventional regard concerning the CI and its interpretation. However, similar to the recommendation to not base an interpretation on whether or not a p-value is less than or above 0.05^[1], a CI should be seen as a range of values which are compatible with the data, other than whether or not 1 is included. Both the point estimate (1.84) and the CI (0.71-4.80) are suggestive of a possible positive association, i.e., the interval contains a wider range of

values which are above 1 and relatively fewer values which suggested the opposite direction.

iii. Introduction:

- **Comment 1:** *Add more literature review on unsafe injection practices worldwide as the majority of PWID are in the developed countries.*

Answer: While we agree that more literature review could be added, we'd also like to point out, however, that our study population pertains only to those having been diagnosed with HIV already and those who got tested negative for HIV. In Cambodia, PWID is under a separate national program. The present study aimed to assess unsafe injection seeking behaviours outside of the population who uses drugs; hence, recruitment at the HIV clinics. In addition, although not separately shown in Table 2, the number of participants who reported self-injections (other than in the context of diabetes) is extremely low, as we specifically expected this population to be when choosing HIV clinics for recruitment. The majority of our participants did not get HIV through unsafe injections. This is also part of the reason the literature review had been limited, as pointed out by the reviewer, since most literature centred on PWID (in the context of unsafe medical injections) and HIV acquisition, our paper hypothesized that even outside of drug use, PLWH might tend to overuse their medical injection, which in itself is unsafe, but also, they might be using unlicensed medical care services for these injections.

- **Comment 2:** *Demonstrate the contribution of unsafe medical injection in PWID to HIV acquisition from literature*

Answer: Please see answers to comment 1 above as well. What the reviewer suggested is important but might be more fitting for slightly different research question, the population we had in our study would not help to answer the question posed. However, we feel the reviewer raised an important point, we added several references on medical injection practices in PWID to HIV acquisition, and others on medical injection practices worldwide (Introduction, page 4-5). However, we have explicitly highlighted the fact that our study is slightly from a different perspective and in which the population of interest is not PWID, as in most previous work (Introduction, page 5). Additionally, our study' aim was to assess if PLWH (who do not inject drugs) sought more injections (both unnecessary and unsafe ones) compared to those without HIV.

- **Comment 3:** *Include more literature on unsafe medical injection prevalence in countries other than Cambodia and correlation between unsafe medical injections and HIV*

Answer: Please see answers to comment 1 and 2 above as well. We have added some more work on the correlation between unsafe medical injections and HIV (Introduction, page 4-5). Regardless, we maintained similar stand on the aim of the study, which is not to prove the correlation between PWID and their unsafe injection practices and HIV but rather, we wanted to test the hypothesis that PLWH (who do not inject drugs) sought more medical injections (which might be both unnecessary and unsafe) compared to those who were HIV-negative.

iv. Methods:

- **Comment 1 – study setting:** *Indicate how many sites were selected to be study sites and how many participants were picked at each site.*

Answer: We had revised the study setting to now include all this information suggested by the reviewer. We have changed “study setting” to “study design and setting” so that the information will not be repeated (Methods, study design and setting, page 6).

- **Comment 2 - inclusion and exclusion criteria:** *revise English and indicate how people with undetermined status were handled*

Answer: We had revised the sentences and added that people with undetermined status were not included (Methods, inclusion and exclusion criteria, page 7).

- **Comment - study design, sampling and recruitment:** *revise the structure of the sentence in line 27*

Answer: Please see answers to comment 1 in methods above as well. We had now moved the requested information and other parts of this subsection to “study design and setting” in methods; we also revised the sentence structures as recommended (Methods, study design and setting, page 6).

- **Comment 4 - definition and classification:** *Indicate type of outcome variable, define exposure and how it was tested and give more details on covariates presented in medical history and behaviour characteristics*

Answer: We had added the type of variable for outcome and provided more details on the other covariates as recommended (Methods, definition and classification, page 7-8). However, for exposure status, the study team had only known HIV-positive and known HIV-negative participants being referred to them for more information on the study or consent process. The care providers at each selected site facilitated this process, we had no access to their tests or result sheets. We have added this bit of information as well for clarification (Methods, definition and classification, page 7-8).

- **Comment 5 – statistical analysis:** *Clarify the use of Poisson regression in the study, elaborate on the matching of HIV-positive and HIV-negative participants and variable selection in the adjusted regression analysis*

Answer: This is a cross-sectional study, however, a lot of prevalence reported in this study, are in fact, prevalence rates. Many of the questions asked to each participant were framed over a specified period of time. For example, how many injections have you received from care providers working in public hospitals over the past 6 months? Or how many infusions have you received from village peddlers over the past 12 month? Technically, these numbers are over a period of time as specified by the question, which means they are practically rates.

The study participants were not actually matched, except if you think about them going to the same clinics or hospitals during the data collection period. Then yes, in a way, they are matched geographically, but other than that, both HIV-positive and HIV-negative participants were sampled as they came into the clinics or hospitals for HIV care or other HIV/STD testing.

Confounding variables were selected based on prior knowledge and previous work on similar topics. Due to many of its flaws, we did not use statistical covariate selection (such as the stepwise regression), rather this is done through a “practical and theoretically-informed approach (causal diagrams using prior knowledge and other similar works), as recommended by Dr. Tyler J. VanderWeele^[2] in his 2019 article. We have added a sentence on how we chose our covariate as recommended by the reviewer as well. (Methods, statistical analysis, page 8).

v. **Results:**

- **Comment 1 – Table 1:** *Clarify Phnom Penh as some readers might not easily understand. Sensitivity analysis due to large number of missing values in one variable?*

Answer: We have revised the methods section in which at the mention of capital city of Cambodia, “(Phnom Penh)” is added (Methods, study design and setting, page 6). Additionally in table 1 now, we also specified that Phnom Penh is the capital city for clarification. We hope that this helped clarify that Phnom Penh is the capital city of Cambodia, and the rest are provinces.

Thank you for pointing out the sensitivity analysis, we rechecked the analysis and the numbers reported and realized that those were actually the combined numbers of missing values across all other behavioural risk factors, without excluding those who were not eligible to answer these questions. Take the question on hospitalization, for example, the first question would ask if the participant had ever had any hospitalization? Those who answered yes would then be asked to answer the same question but over the period of the last 12 months, and those who answered no or “not remember” would need to be excluded. By including only those who should be included, there was, in fact, no missing value in any of the other behavioural risk factors. We apologized for the misunderstanding and have corrected the footnotes of table 1 accordingly.

- **Comment 2 – injection/infusion use:** *the prevalence of injection/infusion use is important and should be seen in abstract.*

Answer: We had revised the abstract and added the prevalence of injection/infusion use as recommended (Abstract, results, page 2).

- **Comment 3 – injection/infusion use:** *rectify the interpretation of the association between unsafe medical injection and HIV.*

Answer: Please also see answers to comment 2 from the abstract section on page 3 of this response letter.

On page 159 in Modern Epidemiology (Rothman, Greenland and Lash, 3rd edition), the Chapter on “Precision and Statistics in Epidemiologic Studies”, subsection “Evidence of Absence of effect”, the authors provided great details on how conventional regard to the interpretation of p-value and confidence intervals might actually relay a message that is the opposite of the appropriate interpretation. Following this concept, we focused on the interval estimation and confidence limits to ensure the proper interpretations of the association under study. The fact that the p-value is not “statistically significant” or the interval actually included 1 is acknowledged, the aOR estimate and confidence limits clearly conveyed a possible positive association, and that was what we base our interpretation on. We, therefore, respectfully declined to rectify our aOR interpretations.

vi. **Discussion:**

- **Comment 1:** *Discuss the association between unsafe medical injections and HIV*

Answer: We have added additional discussions regarding medical injections and HIV as recommended (Discussion, page 17).

- **Comment 2:** *discuss which bias should occur with self-recall in limitation 1*

Answer: We have revised parts of the discussion concerning recall bias to reflect the suggestions of the reviewer (Discussion, page 15).

- **Comment 3:** *Should recommend further studies considering timing in response to limitation 2*

Answer: We have added a sentence in discussion section on recommending further studies as suggested (Discussion, page 16).

- **Comment 4:** *Discuss non-random sample collection scheme and external validity*

Answer: We have revised the discussion section and added additional discussion points surrounding the non-random sampling scheme and external validity as recommend by the reviewer (Discussion, page 16).

- **Comment 5:** *Discuss strengths of the study as well*

Answer: The strengths of the study had been provided as a counter-argument to each limitation. We have also added additional sentences on the other strengths of the study as recommended by the reviewer (Discussion, page 16).

vii. Implications on policy and practices:

- **Comment 1:** *Revise recommendation as both groups of study participants have high prevalence of medical injection use*

Answer: We completely agreed with the reviewer on this. We mentioned HIV setting, specifically, since they are meeting their care providers regularly and we can, therefore, take this opportunity to counsel them on issues related to safe injection practices. This is quite the same as for those who are not in regular care. However, we have also revised this section to reflect what the reviewer felt was lacking in the messages for both participant groups (Discussion, page 17).

viii. Conclusion:

- **Comment 1:** *Conclude using only findings from the study*

Answer: We have revised some part of the conclusion and take out the sentences that were not discussed in the manuscript.

- **Comment 2:** *Revise the interpretation of aOR*

Answer: Please see answers to comment 3 in Results section (v.).

ix. References:

- **Comment 1:** *Add more references*

Answer: We have added several other references as recommended.

VERSION 2 – REVIEW

REVIEWER	Altaf, Arshad Aga Khan University, Research Office
REVIEW RETURNED	25-Aug-2022

GENERAL COMMENTS	Thank you for your understanding and flexibility in accepting the comments raised in this review—best of luck in all your future endeavours.
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REVIEWER	Makuza, Jean Damascene Rwanda Biomedical Center, Institute of HIV, Diseases Prevention and
REVIEW RETURNED	28-Aug-2022

GENERAL COMMENTS	We thank author for addressing the comments given to them however I have two comments to address: 1) Interpretation of OR and its 95% CI in abstract, results and discussion. I accept that OR of 1.84 and the 95% CI (0.71-4.80) are suggestive of a possible positive association, but this association is not statistically significant. When you make this statement make sure that it is not statistically significant. 2) Thank you for adding "Confounding variables were based on prior knowledge and literature review on similar work previously conducted" in statistical analysis but I recommend you to cite references talking about similar works and literature.
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VERSION 2 – AUTHOR RESPONSE

Responses to Reviewer 2 – Dr. Jean Damascene Makuza (The University of British Columbia School of Population and Public Health)

- i. **Comment 1:** *revise the interpretations of OR and 95% CI in abstract, results and discussion to reflect the non-significant associations*

Answer: Practices among HIV-seronegative and People Living with HIV (PLWH) in 10 HIV Testing and Opportunistic Infections/Antiretroviral Therapy (OI/ART) Sites in Cambodia". We feel that the revised title suggested that the injection behaviours in the study were assessed among both PLWH and HIV-negative participants (Title page, page 1).

- ii. **Comment 2:** *Cite the references of previous similar work to justify the choice of confounding variables selected.*

Answer: We have cited relevant literature as recommended (Methods, statistical analysis subheading, page 8).

VERSION 3 – REVIEW

REVIEWER	Makuza, Jean Damascene Rwanda Biomedical Center, Institute of HIV, Diseases Prevention and Control
REVIEW RETURNED	13-Sep-2022
GENERAL COMMENTS	Thank you to the author for accepting and considering our comments and suggestions. I am satisfied with the updated manuscript. It can be published on my side