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Article title: Global prevalence of occult hepatitis C virus, a systematic review and meta-analysis.

The Editor-in-Chief
World Journal of Methodology

Dear Editor,

We are delighted that the *World Journal of Methodology* will consider publication of our review, pending satisfactory revisions as suggested by the Reviewers.

We have given careful consideration to the Reviewer's comments and have done our best to address them all.

In green text in the response to the Reviewers comment document is a point-by-point explanation of how we have addressed the concerns and revised our manuscript. We have enclosed

1. Point-by-point response letter
2. Track-changes version of our revised manuscript
3. A clean version of our revised manuscript

We thank the Reviewers for their thoughtful comments. With these revisions, we feel the paper has been substantially improved. We hope it will receive favorable consideration for publication in the *WJM*.

Please do not hesitate to contact us should you have any additional questions or comments.

Kind regards,

Sebastien KENMOE

On behalf of the co-authors

Review Comments to the Author

Reviewer #1:

The manuscript entitled "Global prevalence of occult hepatitis C virus, a systematic review and meta-analysis" has been performed to summarize the prevalence of occult hepatitis C (OCI) among different populations and regions in the world. This is an interesting idea and a well-written report; however, I have some major and minor comments about the methodology and presentation of this review.

Authors: We appreciated the reviewer's comments, thank you.

Abstract:

1. It would be better if you express statistical methods and software used to data analysis.

Authors: Thank you for this suggestion, we expressed statistical methods and software used to data analysis.

Introduction:

2. In second paragraph, the authors gave the data mostly on HCV structure, transmission routs, and infection response to antiviral drugs. These are general facts about HCV infection but not related directly to the review topic, i.e. occult HCV infection.

Authors: Thank you for this comment, we removed this general HCV information from the manuscript.

3. You should refer to OCI prevalence range among various populations in different countries based on the findings of newly published papers and let the readers to know something about OCI status in the world.

Authors: We added in the introduction a summary of the main findings of previous reviews on OCI, thank you for this suggestion.

4. A recent systematic review discussed the prevalence of OCI in the Middle East and Eastern Mediterranean countries (Ref. 29 of this manuscript). I suggest giving a summary of its findings in the background of the manuscript.

Authors: We added in the introduction a summary of the main findings of the review by Hedayati-Moghaddam et al., as suggested, thank you.

5. Could you provide more statements of study objectives? These could be included evaluating the potential factors resulting in heterogeneity between studies, time trend of OCI rate in the studied populations and regions, and so on.

Authors: Done, thank you.

6. I suggest a brief explaining of the study implication for health professionals and researchers in the end of Introduction section.

Authors: Corrected, thank you.

Materials And Methods:

7. It would be better if you add the search strategy in PubMed in the text and remove Supplementary Table 2.

Authors: Done, thank you.

8. Could you please give the rationale for selecting studies with at least 10 participants?

Authors: As now stated in the inclusion criteria, to enhance the robustness of our estimates, we considered only studies with at least 10 participants, thank you.

9. Could you clarify this sentence “We also searched manually all relevant and critical articles on the topic to identify additional references.”? Did you mean that you reviewed manually all bibliographies of retrieved citations?

Authors: We handsearched references of included studies and previous reviews only. We have modified the text accordingly in the manuscript to remove the confusion, thank you.

10. What was your purpose of using the I2 test statistics to indicate low to moderate heterogeneity between studies? You should express the exact cut-off value of I2 used to define the heterogeneity.

Authors: We used these I2 cut-off in conjunction with the Cochran's Q-test to determine heterogeneity.

11. Some more covariates could be assessed to find the sources of heterogeneity. These include, for example, participants' gender, sample size (for example less than 100 and more), study year (for example before 2010 and afterward 2010), and risk of bias.

Authors: We totally agree with this Reviewer suggestion. We have already taken into account the variability associated with the risk of bias in the sensitivity analysis. Like all other unexplored potential sources that we have previously mentioned in our discussion, we have added to this list in the discussion these additional suggested potential sources of heterogeneity.

12. The authors evaluated the role of multiple variables in OCI rate by subgroup analysis. Maybe the readers are interested that the impact of these moderators was also estimated by running a meta-regression analysis.

Authors: done thank you, supplementary table 8 added.

13. When there is publication bias, you can apply Trim and Fill method to find more accurate estimations for OCI prevalence rates.

Authors: Done, thank you.

Results:

14. Could you check the years in this sentence “The studies were published from 1995 to 2021 and the participants were registered from 2002 to 2019.”?

Authors: It is confusing indeed, but this is due to unclear or unreported data from some included studies. We modified the sentence to remove the confusion, thank you.

15. A total of 85 studies included in the data synthesis. Thus, you should compute the numbers of interested studies out of 85 not 102 for describing characteristics of included studies (lines 241-251). You can also describe them for each OCI group separately (seronegative, seropositive, and seronegative/ seropositive).

Authors: Since a study could contribute multiple prevalence data, we described the overall prevalence data instead (102 prevalence data instead of 85 studies). We modified the terms in the manuscript to reinforce this detail. We also gave the characteristics of the prevalence data that we consider relevant, such as region, in the meta-analysis sections of the different OCI groups, thank you.

16. In line 246, you said that “most studies recruited adults (33 out of 102 assessments)”. I don’t think that term of ‘most’ is a proper adverb for describing this proportion!

Authors: Corrected, thank you.

17. In line 237, you said that 85 studies comprising 24 seropositive OCI were reviewed, and then in lines 265 you declared that seropositive OCI prevalence was estimated from 27 included studies.” Which number is correct?.

Authors: Corrected, thank you. The correct number is 24.

18. Could you please give the p-values of estimated heterogeneity for seropositive OCI (line 268) and for seronegative and/or seropositive OCI (line 279)?

Authors: Added, thank you.

19. Please delete the legends for figures 1, 3, and 4 from the main text (lines 234, 260, 271).

Authors: Done, thank you.

20. To describe subgroup analyses results for both seronegative and seropositive OCI (lines 281-319), you don’t need to give all data provided in Supplementary Table 8. You can only refer to the subgroups with the statistically significant higher frequency rates. For example, you can say: ‘Higher proportions of seronegative OCI were estimated for studies selected participants by non-probabilistic sampling ($p=0.001$), conducted in Spain and Egypt ($p<0.001$), in Southern Europe and Northern Africa ($p<0.001$), or in countries with lower-middle income economies ($p=0.045$), investigated children ($p=0.01$) or patients with abnormal liver function, hematological disorders, and kidney diseases ($p<0.001$), and detected OCI cases by Real-time RT-PCR ($p<0.001$) or by examining liver tissue ($p<0.001$) (Supplementary Table 8).’

Authors: Corrected, thank you.

21. Please write the p-values of estimated OCI proportion for all studied categories (lines 287-307 and 312-319)?

Authors: Corrected, thank you.

22. It is expected that the authors discuss in details regarding OCI diversity observed among different countries, populations, and settings in the world.

Authors: Done thank you, we added a paragraph in the discussion section.

23. In line 345, you said that OCI prevalence was 12% for seropositive subjects. Which infection did you mean?

Authors: Corrected, thank you. This was HIV-infected patients.

Tables:

25. The number of studies for seropositive OCI is different in Table 1 from that in the text. (24 or 27?)

Authors: Corrected, thank you. The correct number is 24.

26. Please add reference in the footnote of Supplementary Table 3 (Hoy et al. Assessing risk of bias in prevalence studies: modification of an existing tool and evidence of interrater agreement. J Clin Epidemiol. 2012: 934).

Authors: Done thank you.

27. I couldn't find any citation to Table 1 and Supplementary Tables 6 & 7 in the text.

Authors: Corrected, thank you.

Figures:

28. I confused with figures numbers! Could you assign the correct numbers to main and supplementary figures and refer to them by accurate order in the text?

Authors: Corrected, thank you.

29. In the third box of figure 1, It would be better if you provide the number of duplicate records (n = 1571) instead of records after duplicates removed (n = 2379).

Authors: We have done Figure 1 in accordance with PRISMA guidelines. We added an additional box to indicate the number of duplicates excluded, thank you.

31. It is better that you provide all forest plots in the text as main figures not supplementary ones.

Authors: Figure 3 is provided in duplicate since the full version is larger than A4 which would be difficult to print. We have therefore provided the reduced version in the main manuscript (Figure 3) and the full version as a supplementary file (Supplementary Figure 1).

32. I couldn't find supplementary figure 3 in the list of figure legends (lines 601-620)?

Authors: Corrected, thank you.

References:

33. Please provide journal volume and the last page numbers for all references.

Authors: Corrected, thank you.

Reviewer #2:

Mbaga DS et al have presented the global data on OCI burden in a very systematic way. The detailed literature survey conducted for the review is appreciable. The review will surely provide an

insight towards the need for change in OCI diagnostic approaches. There are certain points to be taken into consideration:

Authors: We appreciated the reviewer's comments, thank you.

1. Line 345 and 346: Two separate values, 12% and 9% are given for significant variability in the OCI prevalence according to the category of the population in case of chronic liver disease. Authors need to clarify the correct significant variability percentage for chronic liver disease.

Authors: Corrected, thank you. The correct number is 12%.

2. Line 370-374: Authors have discussed about the limitations of the study by excluding the OCI burden from highest Hepatitis C prevalence zones such as Africa and South east Asia. In a hope to eradicate HCV by 2030, as recommended by the WHO, it is crucial to determine the burden of OCI in the highest prevalence regions, if the study 'title' includes the word 'global prevalence'. Otherwise, the data presented would not provide the actual picture of the global OCI burden. The current study must include a section in 'Abstract section' and all summary sections, stating this limitation.

Authors: Thank you for this comment, we have 4 out of 6 WHO regions represented and we have highlighted this limitation in the discussion section.

3. The manuscript suffers many grammatical flaws in certain line, e.g. line 123, 129, 130, 131, 185, 186, 187 etc...The Abstract also suffers from grammatical errors like...."The prevalence of seronegative OCI was elevated Southern Europe" ...should read, "The prevalence of seronegative OCI was in elevated Southern Europe."

Authors: We have had the complete manuscript carefully proofread by a native English speaker to correct all grammatical errors, thank you.

EDITORIAL OFFICE'S COMMENTS

Science editor:

This manuscript has been performed to summarize the prevalence of occult hepatitis C (OCI) among different populations and regions in the world. It is recommended to add OCI prevalence range among various populations in different countries based on the findings of newly published papers in the Introduction.

Authors: Corrected, thank you.

Company Editor-in-Chief

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Methodology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

Authors: We appreciated the Science editor comments, thank you. We have revised the manuscript according to the reviewers' comments in order to improve the quality of the article for publication, thank you.

Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, “Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...”. Please provide the original figure documents.

Authors: Done, thank you.

Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

Authors: Done, thank you.

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Authors: Done, thank you.

Authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

Authors: Done, thank you.

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Authors: All figures are originals, thank you.