**Author’s response to reviews**

**Title:** Hepatitis B/C in the countries of the EU/EEA: a systematic review of the prevalence among at-risk groups

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Hepatitis B/C in the countries of the EU/EEA: a systematic review of the prevalence among at-risk groups

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Sarah Larney (Reviewer 1):

This paper presents estimates of the prevalence of HBsAg and anti-HCV in three risk groups - men who have sex with men, prisoner, and people who inject drugs - in the countries of the EU/EEA. Estimates are presented at the country level. No regional estimates are calculated. I have several concerns with this paper, some overarching and some more specific.
1. Overarching concerns:

The rationale for the study is somewhat weak. Why this region in particular? It is said that current estimates need updating, but the reviewed studies go back to 2005, which doesn't seem up to date. As noted in the introduction, there have been multiple reviews of HBV/HCV in risk groups in various groups of countries (Europe, global). In the final paragraph of the introduction, the authors need to make a stronger case as to why this review, and why now (e.g. to provide baseline data towards elimination targets?)

- This study is part of larger ECDC project to update and extend the previous ECDC review (Hahné et al. BMC ID, 2013) that included data published up to mid-2009. The present study includes data published in the 5.5 years after that. The search timeframe overlaps slightly with this previous review for a number of reasons including the expansion of the search to include all EU languages, the addition of the prison population and the joining of Croatia to the EU in 2013.

- Further explanation on the rationale for the study has been added at the end of the introduction.

2. The pooling of study findings seems to have been done by summing denominators and numerators. This is a bit simplistic - why wasn't a meta-analysis done where multiple studies were available for a country?

- The pooling method we used is a simple fixed effects method which we feel is a valid approach to pooling where we believe the studies undertaken are functionally very similar and drawn from a somewhat similar population (which we deem they are given the application of pooling only to higher quality studies). We only pooled high quality studies within one risk group to limit transferring bias in our pooled results. A fixed effects meta-analysis would produce a very similar point estimate (albeit with a wider CI) to that produced by this method. Furthermore, standard meta-analytic techniques do not cope well with zero event data.

3. Did the authors consider using meta-analysis to provide a summary estimate for the region?

- We did not consider pooling across EU countries for three key reasons. First, there are too many countries unrepresented. Secondly, there are large differences in the general population prevalence between countries that would also be reflected in risk groups. Third, there is considerable heterogeneity in study design across risk populations. We feel these are very strong sources of bias that would invalidate an EU estimate.
4. I'm not clear why estimates for MSM and prisoners are presented as forest plots and those for PWID are in a table.

- This decision was made to allow for the inclusion of more detail in the presentation of the PWID data (in table format).

5. It also may be useful to include all estimates for HBsAg in one forest plot, with sub-sections for each risk group, and all estimates for anti-HCV in another. It was difficult to compare across risk groups with data presented in different formats and plots.

- The heterogeneity in prevalence across risk groups would make the scale unreadable in a forest plot combining estimates across risk groups, especially for anti-HCV given the very high prevalence among people in prison (>50%). A Forest plot with all estimates for HBsAg and for anti-HCV would also be unreadably long, and occupy up to two pages of the article.

6. The search was completed in March 2015 - nearly two and a half years ago. The review may be more useful if the searches and results are updated.

- This review was part of a much larger project reviewing, synthesising and analysing the prevalence in these three risk populations together with the general population, first time blood donors and pregnant women (the latter three populations are included in this study: Hofstraat, S. H. I., A. M. Falla, et al. (2017). "Current prevalence of chronic hepatitis B and C virus infection in the general population, blood donors and pregnant women in the EU/EEA: a systematic review." Epidemiol Infect 145(14): 2873-2885. It takes a long time to conduct a review of this scale across so many countries with so many languages. We feel this study expands and updates the previously published EU study and contributes 5.5 years of new data.

7. Given there are a lot of acronyms in this paper, I wonder if some of the less frequently used acronyms could be spelled out at each use?

- Yes, definitely. We have removed a number of acronyms and used the full terms to improve readability.

8. Abstract: Where the authors state that highest HBsAg was found in prisoners, followed by PWID and MSM (and similar statement for anti-HCV), it seems that this ranking is based on the highest point estimate in each risk group. I'm not sure it's valid to say one group has higher prevalence on this basis, given that there is considerable overlap between HBsAg/anti-HCV
estimates between groups. This is where a regional summary estimate may be useful (although I do accept that there may be considerable/too much heterogeneity for this to be meaningful), to enable direct comparison of one estimate per risk group.

- We can see the point here given that no statistical testing was conducted we cannot say ‘higher’ with statistical certainty. We have adjusted the text to describe the data in a more nuanced way. As in point 3, we consider pooling/meta-analysing across countries to be a very biased exercise.

Introduction:

End of first paragraph - a reference for the statement regarding the threshold for a favourable cost effectiveness ratio would be good.

- There is limited systematic/multi study data testing the ICER relating to prevalence. Further, an EU threshold cannot be given as this varies per country. We have adjusted the text accordingly.

HBsAg and anti-HCV should be defined at first use.

- Done, good suggestion.

As noted above, introduction should end with a stronger rationale for why this review is important.

- Done. We have further explained the scope and background to this study at the end of the methods.

Methods:

The authors should justify here their decision to use only EMCDDA data to assess prevalence in PWID.

- A key responsibility of the EMCDDA is to review, synthesize and report data from all EU/EEA Member States on the prevalence of key infections in PWID. Furthermore, they include
unpublished data in their repository that is not available in literature. We have added in more detail on the decision in the relevant section of the methods.

- As we explain further in the discussion:

“EMCDDA were recently identified by another wide-ranging systematic review as the source of the most routinely collected, European-level data on the viral hepatitis prevalence among PWID.”

The study flow chart is useful for understanding the search process - I suggest it be included in the main paper rather than appendix materials.

- We feel this is a good suggestion. If the editor agrees, we can incorporate this suggestion.

Under sub-heading 'Data extraction' - I may be confused, but I think the section that reads "one article may therefore include more than one study" is possibly supposed to be the other way around - should it be one study includes more than one article?

- With the sentence we convey situations in which one journal article might include data on multiple sample for example a sample among adult prisoners and on a sample among juvenile prisoners, or samples collected at two time points. In these cases, we extracted the prevalence data separately i.e. by study.

As noted above, the approach to pooling seems simplistic. Why wasn't meta-analysis used at the country level?

- The methodology we selected to pool (high quality) estimates was a simple fixed effects method to produce a weighted prevalence, giving higher weight to larger studies. As describe previously, in Main Point 2 above, pooling was only conducted at a country level among prisoners and PWID when the samples shared study characteristics. In our view, the results from this fixed effects pooling analysis would be similar to a fixed effects meta-analysis.
Results

The results section is quite dense and difficult to follow at times. Breaking up some of the long paragraphs may help. I would also argue that it's not necessary to present every estimate in text, but could just refer to the highest/lowest countries (and a regional summary estimate, if available) and refer to Figure.

- We have broken up each population paragraph into subsections, one for HBsAg and one for anti-HCV. We feel an important task of systematic review is to summarise the granularity of the data available for the reader and feel it is a useful level of detail for readers interested in this topic.

Uncertainty around estimates is not always presented - recommend that 95% confidence intervals be presented with all estimates in text.

- We feel this would this make the text rather more unreadable, given the concerns about the lengthy nature of the results. These ranges can be seen clearly in the figures and the tables.

The sub-headings that being 'The prevalence of chronic viral hepatitis' need to be changed as the HCV results relate to antibody prevalence, not chronic infection.

- True, good point. This has been amended as suggested.

Discussion

- This is quite a long section and could be edited down. One paragraph that strikes as somewhat extraneous is the discussion of Hungary's results. There is overlap in the confidence intervals of HBsAg estimates for prisoners and PWID, so I'm not convinced it is that much of a difference. I'm also not that convinced by the explanation given for this difference - current harm reduction service use does not necessarily relate to prevalence of infections that have been acquired sometimes many years ago.

- We agree with the reviewer than our discussion here is probably too detailed and that differences may actually be more due to random error/difference in sampling rather than due to
significant differences in prevalence, especially as we did not perform any statistical testing. We have edited this paragraph in the text to better reflect this more nuanced conclusion.

The paragraph beginning "Our study seeks to contribute" (line 52 of p. 15 on reviewed manuscript) includes information that could be useful for improving the rationale for the study in the Introduction.

- Thank you for this suggestion. We have included this at the end of the introduction as suggested.

Rachel Sacks-Davis, PhD (Reviewer 2): This timely systematic review of hepatitis C synthesises recent HCV and HBV prevalence estimates for selected risk groups in Europe. The PWID estimates are derived from the EMCDDA repository and the estimates for prisoners and MSM are derived from a systematic review. The review provides a useful updated synthesis of data for prisoners and PWID in particular but is limited by the exclusion of migrants as a risk group for HBV and HIV infected MSM as a risk group for HCV. The paper would be improved by the inclusion of tables summarising the study characteristics, risk of bias and results.

Major revisions:

1. It is not clear why the particular risk groups (MSM, prisoners, PWID) were chosen relative to other potential risk groups. E.g., migrants for HBV, people living with HIV, HIV infected MSM, etc. Migrants are mentioned as a group in the Supplementary material but not in the main text. Migrants is a major exclusion as an HBV risk group and this should be acknowledged in the Discussion section. In the WHO testing guidelines, people living with HIV and HIV-infected MSM are mentioned as potential risk groups and prevalence of HCV at least is generally believed to be elevated in HIV-infected MSM but not necessarily in HIV-uninfected MSM.

- We agree that it is somewhat unclear why we limit our search and analysis to these three populations. We have added some more detail into the rationale for the study paragraph at the end of the introduction. To reply directly about the exclusion of migrants, there was a simultaneous review into the burden of chronic viral hepatitis among migrants coordinated by
ECDC and conducted by some authors of this paper. We did not want to directly duplicate that work. We have added a point in about this in the rationale section.

- The key rationale for these populations is that our study is part of a much larger study to update and expand the search for estimates in low risk populations (the general population, pregnant women and first time blood donors) and as a comparison to include the three largest (in size) high risk groups to discern differences between high and low risk. We had the strategic goal to inform primary and secondary prevention planning and monitoring.

2. Although I assume that studies of exclusively HIV-infected MSM were excluded, this should be stated explicitly.

- They were not excluded during the title, abstract or full text screening phase but only data on HIV-MSM were extracted. We have clarified our approach in the methods.

3. The risk of bias data is not described in detail in the Results section - it would be useful to include a table of studies summarising the risk of bias in each study.

- These results along with more details about the included studies in MSM and prisoners have been added into the supplementary appendix. There is also a sentence in the results informing readers of this.

4. It would also be useful to include a Table summarising the study characteristics, number of participants and prevalence for each study.

- See point 3.

5. In the Discussion the authors state that the findings don't support continuing to screen MSM for because prevalence is not >2% in that group but there is variation between countries and diseases. If the results from the studies were pooled, the point estimates for Estonia and Croatia would be>2% for HCV and for HBV all countries and some other countries for HCV, the confidence intervals include 2%. I don't think this this conclusion is adequately supported by the findings.

- We can see the point here and have adjusted the text to reflect a more cautious and nuanced conclusion on the MSM data.
6. In the Discussion section page 16, the "limitations of the study" are mentioned but they are not described explicitly. These should be described.
   - The limitations are explicitly detailed on p.13.

7. The conclusion is very general and doesn’t specifically relate to the study findings.
   - We agree in hindsight and have revised the conclusion to relate to the study findings.

Minor revisions:

8. In the Results section, in the section on prevalence in MSM, the authors suggest that there was an increase in HBsAg prevalence and decrease in HCV antibody in Estonia but it is not clear that time trends in the prevalence of either disease are supported by the data. It seems unlikely that HCV antibody prevalence could change so much in such a short time frame, and it is not clear that either "change" is statistically significant. Both studies are small and it is more likely that the different results reflect random variation.
   - We agree with this point and have removed this point from the text.

9. Suggest including a completed Prisma Checklist in the Supplementary Material.
   - This has been completed and incorporated in the supplementary file (with reference to it at the appropriate section in the methods)

10. Suggest including the Prisma flowchart as a figure in the main text rather than the Supplementary Material.
    The other reviewer has also suggested this. We can include the PRISMA flowchart from the supplement if the editor agrees.

11. I suggest reducing the number of acronyms, particularly ones such as MS and NFP that are not commonly used.
    - We have done so. This was also suggested by the first reviewer, so it’s clearly an issue.
12. In the Discussion section, page 15, line 10, there is an unfinished sentence: "but that during their study…"

- This whole section about harm reduction services in Hungary, which includes this unfinished sentence, has been deleted in line with a previous reviewer comment.

13. In the Discussion section, page 16, line 24, by "intra-population infection" do you mean "transmission"?

Good point. This has been amended in the text.

14. The paragraph "The limitations of this study...link to care people infected with chronic viral hepatitis" is quite general. What improvements in study design are required? How do the limitations of the study provide ideas for future research, or do you mean that the limitations of the included prevalence studies provide ideas?

- This paragraph is about future research priorities based on the gaps in knowledge/evidence we see from the experience when conducting this study. The limitations are discussed more in full on p.13.

15. In general, the data in the Supplementary material are not referenced in the main text so most readers will not realise that they are included.

- Good point. We have incorporated more references to what is in the supplement where these arise in the text. And a general point at the end of the methods.