Author’s response to reviews

Title: Molecular epidemiology of hepatitis B virus infection in Norway

Authors:

John Pettersson (john.pettersson@gmail.com)
Solveig Myking (solveig.myking@fhi.no)
Hilde Elshaug (hilde.elsehaug@fhi.no)
Kirsten Ege Bygdås (KirstenIreneEge.Bygdas@fhi.no)
Kathrine Stene-Johansen (Kathrine.Stene-Johansen@fhi.no)

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Author’s response to reviews:

Response letter regarding manuscript "Molecular epidemiology of hepatitis B virus infection in Norway" (INFD-D-18-02058)

Dear editor Yi-Hua Zhou,

We wish to thank the editor and reviewers for their constructive comments and feedback and for the opportunity to submit a revised version. Therefore, we have revised the manuscript thoroughly following the review. Below you will find a point-by-point response to all comments/questions raised:

Editor Comments:

-“The quality of writing needs improvement. A professional native English scientific writer should review the final revised manuscript before resubmission”.

Authors response: To improve the English, we have let Prof. Eddie Holmes (the University of Sydney) read the manuscript and corrected any English writing that is incorrect.
“Overall, the manuscript can be shortened by deleting some general statements in the introduction and discussion”.

Authors response: Agreed, we have attempted to do so while revising the manuscript. Please see the attached version with track-changes where redundant sections that have been removed.

“Page 2, line 36: “HBV small S-gene” to “HBV S gene”. The “small” is not adequate, and please change the term in all other places”.

Authors response: This has been corrected in the manuscript.

“Page 2, lines 54-56: “more than 290 million people” (ref. 5) is overestimated. Please consult a letter on the prevalence (Xu C, Chen T. Global prevalence of hepatitis B virus infection and prevention of mother-to-child transmission. Lancet Gastroenterol Hepatol. 2018;3(9):598-599.) and two other articles (Lancet. 2015; 386 (10003): 1546-55. Lancet 2018 Nov 24.; 392: 2313–24) and revise the manuscript to update the epidemiology of hepatitis B in the Introduction”.

Authors response: The introduction has been updated to account for the uncertainty in the estimate. New references have been added. Note that the updated references does not show as updated in the track-changes version as there were errors when updating the references.

“The ref. 2-4 are out of date, and ref. 5 is somewhat misleading. Please cite recently published data (Hutin Y, et al. Access to treatment for hepatitis B virus infection—worldwide 2016. MMWR Morb Mortal Wkly Rep 2018; 67: 773–77, and others)”.

Authors response: We have updated this section also such that the references are more up-to-date and accurate. Note that the updated references does not show as updated in the track-changes version as there were errors when updating the references.
-“Page 2, line 62: “the surface antigen” to “hepatitis B surface antigen””.

Authors response: This has been corrected.

-“Please leave a space between the number and the equal sign (=). It should be “n = 8”, not “n=8””.

Authors response: This has been corrected.

-“Page 5: The details of PCR conditions, such as the thermal cycling conditions, can be omitted”.

Authors response: The section has been updated and the PCR conditions have been omitted.

-“Please carefully check each reference, and revise them if not correct. There are many incorrect inputs or other mistakes in the references, such as the journal title of the 1st reference”.

Authors response: We have gone through the references and hope that they all are correct in the current version.

Reviewer reports:

Zhi Chen (Reviewer 1): “This paper analyzed 1,157 HBV small S-gene sequences collected from patients in Norway, and investigated epidemiological data from the Norwegian surveillance system for communicable diseases. The authors found the distribution of HBV genotypes in the Norwegian population is dominated by genotype D (32%) followed by genotype A (22%), B and C (18% and 18% respectively), and E (7%). They showed that the patients in Norway were
primarily to have been infected with HBV of genotype A and D. There are some grammar mistakes in the manuscript. Please carefully modify the whole manuscript.”

Authors response: We thank Zhi Chen for taking the time to review and help improve our manuscript. We have carefully modified that whole manuscript and improved the English grammar following review by a native English speaker (Prof. Eddie Holmes).

Asgeir Johannessen, M.D., Ph.D. (Reviewer 2): “This study presents the genotype distribution and related epidemiological data from more than 1100 patients with HBV infection in Norway. The methods seems adequate and the results are presented with informative figures including a phylogenetic tree, which is the main result of the paper. The paper is worth publishing; however, I have some minor essential points for clarification, and importantly the conclusion chapter needs to be re-written.”

We wish to thank Asgeir Johannessen for reviewing our manuscript and for the feedback. Below we have made a point-by-point response to all of the comments/issues raised by the reviewer:

1. Abstract:
   -“a. Results: it is very general, I would prefer some more details. B, C and E were from Asia and Africa, can you specify? For example that xx% of B and C were from East Asia (or South-East Asia). Or that E was from West Africa.”

Authors response: We have attempted to add some more detailed information in the abstract that hopefully will help the reader to understand the results of the study better.

   -“b. Conclusion seems completely unlinked to the Results? You have not mentioned anything in Results about where patients said they were infected. Don't introduce new information in the Conclusion. Please re-phrase based on your results. The sentence currently in Conclusion must either be moved to results or deleted.”
Authors response: We agree to some extent. The results could have been formulated more clearly, and we have attempted to do so in the current version, as to highlight the main conclusions in relation to the results.

2. Introduction:

-“a. 2nd paragraph, line 63-64: According to reference 5 there are not that many countries with more than 8% prevalence. Please be more precise. “

Authors response: The references and text have been updated following the editors suggestions. In reference #3 there are several countries with high endemicity. E.g. For Africa as a whole, the mean endemicity is above 8%. Please see the updated text.

-“b. 3rd paragraph, line 94-96: You might want to give a few examples of clinical implications of genotype, for example that geno C is associated with an increased risk of HCC, or that geno A has a favourable response to treatment with pegylated interferon.”

Authors response: We have added examples to give some clinical relevance and background regarding different genotypes.

-“c. Last paragraph, line 99-101: "In Norway" twice in one sentence, remove one.”

Authors response: Corrected.

-“d. Last paragraph, last sentence, line 104-106: I don't really see how your epidemiological study will help in patient management?“

Authors response: Agreed, in most cases genotyping is encouraged regardless of this study. We have therefore deleted the sentence.
3. Methods:

“a. Study group:

i. Better "Study subjects" or "Study population""

Authors response: Agreed, we have changed it to “Study population”.

“ii. Line 112-115: Do you need to specify this? They were very few samples (14 + 8) and from the same time period. And the Norwegian name of the clinic is not relevant. I suggest to delete the whole sentence.”

Authors response: Agreed, we have deleted this sentence.

“b. Sequence alignment, line 151-153: The number of patients who were infected in Norway vs. abroad belongs in the Results section.”

Authors response: The sentence has been moved to the results section.

“c. You should include a subsection called "Statistical analysis"”

Authors response: We are not entirely sure what this is referring to. We have not done any sub-sampling of the data or performed in depth statistical analysis as we have used all data available. A new ‘statistical analysis’-section would not add any information in this case.

4. Results:

“a. 1st paragraph, line 178: it is ambiguous, are B and C together 18% or are they 18% each. Please correct.”

Authors response: It is 18% for B and C respectively. This has been corrected.
"b. 1st paragraph, line 185-186: The sentence "Among these cases 50%..." is not very informative, I suggest to delete it. Figure 1 gives this information."

Authors response: Agreed, the sentence has been deleted.

"c. 2nd paragraph, line 198: "...different countries in Africa". All over Africa? Or only sub-Saharan or West or Central or Southern? Please specify (if possible). I thought E was rare in East Africa for example."

Authors response: Thanks for the observation. It is correct that the majority of cases with genotype E were from eastern and central Africa (south of the Sahara). The manuscript has been updated to be more specific.

"d. 3rd paragraph, line 200: "Information on transmission route..." should be changed to "...likely transmission route..."".

Authors response: Changed.

"e. 3rs paragraph, line 204-207: The sentence "In addition, the 14 strains..." could be omitted, since I assume these are included in the patients who claimed to be infected in Norway? If not, then I suggest to lump these together. It is only confusing to add another separate group. The next sentence (gender distribution) should appear at the very beginning of the Results section (among the initial 2-3 sentences), not here. Finally, the genotype distribution in men and female is not very interesting, so I suggest to delete this sentence together with figure 3."

Authors response: Correct, these are from patients infected in Norway, so the information has removed as not to cause confusion. The gender balance information has been moved to the beginning of the results and the information on genotype difference between males and females has been deleted.
“f. Instead of the gender analysis perhaps you could say something about the time trend over these 30 years? Was the genotype distribution different in the first decade compared to the last?”

Authors response: We agree that this would have been an interesting analysis, but as mentioned previously, the sampling over time is too uneven to permit a robust statistical analysis over time (particularly before 2005 when sampling was less than 50 patients a year). However, looking from 2005 and onwards it seems that the general composition of genotypes as remained fairly constant although the number of patients differ between years.

5. Discussion:

-“a. 1st paragraph, line 232-233: No need to repeat the percentage again and again. You can simply write that geno D was the most prevalent, followed by geno A, B and C.”

Authors response: Agreed, changed.

-“b. 2nd paragraph, line 235: Write "…in Europe (including Norway), Afghanistan…” instead of "…in Europe, Norway, Afghanistan...””

Authors response: Corrected.

-“c. 2nd paragraph, line 242-245: This is one of your main findings and I think it deserves more explanation. How do you see that there have been single origin outbreaks for example? Try to explain so that the paper can be read by people with less molecular biology background. This also applies to the same topic in the final paragraph in the Results chapter.”

Authors response: We have attempted to clarify and elaborate on the results here. Please see the updated section.
“d. 2nd paragraph, line 246: Delete "extensive" as it is more political than scientific.”

Authors response: Agreed, deleted.

“e. 3rd paragraph, line 256-259: This sentence can be incorporated it in the next paragraph.”

Authors response: We have moved and incorporated this section in the following paragraph.

“f. 4th paragraph, line 266-268: Is it not possible that the clustering with non-Norwegian strains means that they have been infected in Norway by someone from Asia? Vietnamese people in Norway are probably more likely to have close contact with other Vietnamese people?”

Authors response: Yes, we agree that this is a possibility that should be pointed out. We have modified the manuscript to account for this type of contact also.

“g. 4th paragraph, line 275-280: These data are so incomplete (76% missing data) that you better delete it.”

Authors response: Agreed. The sentence has been deleted.

“6. Conclusion: This is weak. I think you should work on this to make it a summary of your study, rather than general remarks. For example, the need to genotype patients with chronic HBV infection is controversial, I personally don't think it is needed in inactive carriers (which is in line with the Norwegian HBV guidelines). The last sentence belongs in background, not conclusion.”

Authors response: We have attempted to make the conclusion more stringent and relevant to our study. Please see the new conclusions section.
“If improvements to the English language within your manuscript have been requested, you should have your manuscript reviewed by someone who is fluent in English. If you would like professional help in revising this manuscript, you can use any reputable English language editing service. We can recommend our affiliates Nature Research Editing Service (http://bit.ly/NRES_BS) and American Journal Experts (http://bit.ly/AJE_BS) for help with English usage. Please note that use of an editing service is neither a requirement nor a guarantee of publication. Free assistance is available from our English language tutorial (https://www.springer.com/gb/authors-editors/authorandreviewertutorials/writinginenglish) and our Writing resources (http://www.biomedcentral.com/getpublished/writing-resources). These cover common mistakes that occur when writing in English”.

Authors response: We have allowed Prof. Eddie Holmes to review and comment on the English. We have mentioned this in the acknowledgments.

We hope that our revised version will meet the standard set by BMC Infectious Diseases and that the manuscript could be considered for publication.

Yours sincerely,

John Pettersson, on behalf of all authors.

John.Pettersson@gmail.com | @fhi.no | @sydney.edu.au | @folkhalsomyndigheten.se | @imbim.uu.se

Infectious Disease Control and Environmental Health, Norwegian Institute of Public Health, Oslo, Norway.

Department of Medical Biochemistry and Microbiology (IMBIM), Zoonosis Science Center, Uppsala University, Uppsala, Sweden
Marie Bashir Institute for Infectious Diseases and Biosecurity, Charles Perkins Centre, School of Life and Environmental Sciences and Sydney Medical School, the University of Sydney, Sydney, New South Wales 2006, Australia.

Public Health Agency of Sweden, Solna, Sweden.