Author's response to reviews

Title: Mortality among British Columbians testing for hepatitis C antibody

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Author's response to reviews: see over
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The Editor,
BMC Public Health

Re: Manuscript 1555644894750972; HCV mortality

The authors wish to thank the reviewers for their constructive comments on our manuscript entitled “Mortality among British Columbians testing for hepatitis C antibody”. We appreciate the time extension to which allowed us to reassess the data using a 12 month (instead of a 6 month) lagging period. The use of a 12 month lagging period did not significantly alter the conclusions but most of the figures were revised. All changes to the original document have been highlighted in yellow. An itemized response to each of the reviewer comments is included with this cover letter.

We look forward to your review of the revised manuscript.

Mel Krajden
Reviewer's report

Title: Mortality Among British Columbians Testing for Hepatitis C Antibody
Version: 1 Date: 25 September 2012
Reviewer #1: Ashley Olson

Major Compulsory Revisions

1. Page 5: It is unclear for those not familiar with the Canadian health care system what types of individuals have a personal health number. Will most individuals living in British Columbia have this? Without this information, it is impossible for the reader to understand the breadth of this study.

*We have clarified the description of the study population (page 4) to indicate that a PHN is available to all persons who have resided in BC for at least three months and indicates insurance coverage for medically necessary health care services.*

2. There is no mention of proportional hazards assumption in Cox proportional hazards models being meet. This must be added. If there is evidence of non-proportional hazards, the analysis must be amended.

*We had checked the proportional hazards assumption and no substantial departures were observed. The following statement was added to the statistical methods section: Schoenfeld residuals on functions of time were plotted and examined for each cause of death and for each group comparison (Therneau; Modeling Survival Data: Extending the Cox Model). No substantial departures from proportional hazards were observed.*

3. Page 6: What was the maximum time between two tests that was allowed for seroconverters? This should have a limit, and the distribution should be described.

*There was no time limit applied between two tests for the time dependent HCV serological groups. The text has been updated accordingly and we indicate that for seroconverters, the median duration between last negative and first positive tests is 74 weeks.*

4. Numbers in Table 4 and Supplementary tables do not agree.

*We have verified that the numbers in Table 4 (Hazard ratios between HCV serological groups) and Supplementary Table 1 (Hazard ratios for a priori mortality endpoints) are correct. Note that in Table 4, REAC and SERO groups are displayed separately, whereas in Supplementary Table 1, the REAC and SERO groups have been combined into the HCV positive group. As expected, coefficients in the model can be different however there are only small differences.*
Minor Essential Revisions

5. Page 5: Explain why individuals less than one year or older than 100 were excluded.

We have updated the text to explain. Individuals less than one year old were excluded because HCV positivity might be due to passively-acquired maternal antibody. Individuals greater than 100 years old were excluded because of possible coding errors in dates. Only six were excluded for age >100.

6. Page 5/6: It is unclear what is meant by ceasing to be registered, re-register, last registration and the censoring that is made due to this process. Is this specific to the British Columbia health system?

Ceasing to be registered occurs primarily when an individual moves out of the province and re-registration occurs when an individual returns to the province. We have updated the text accordingly.

Discretionary Revisions.

7. Page 5: Itemize data quality exclusions. If the list is too long to fit in the paper, add to a supplementary table.

The data quality exclusions have been elaborated in the text.

8. Page 13. When discussing the limitations of the study, the authors should comment on how the limitations will effect the SMRs and HRs they present in the results section.

We have noted in the discussion that the limitations would have the effect of underestimating both SMRs and HRs.
Reviewer's report

Title: Mortality Among British Columbians Testing for Hepatitis C Antibody
Version: 1 Date: 2 October 2012
Reviewer #2: Ann-Sofi Duberg

There are a few questions needed to be clarified. Considering the points in the reviewer guidelines:

1) The question posed by the authors is well defined.

2) Methods are appropriate and well described, but there are a few things to clarify.
   a. Data sources: I would like some more information about the death registry. Did you use the “underlying cause of death” (which I assume)? Is the cause of death based only on death certificates or is the death registry linked to other registers?

   We have updated the text to indicate that underlying cause of death from the registry of death certificates was used. We have also expanded the limitations section to include discussion of the possible limitations of the death registry.

   b. Time dependent HCV serological groups: Were there any time-limit for next test or were two tests the same month enough to be classified as a MNR?

   No time limit was applied between any two tests for the time dependent HCV serological groups as long as the two tests were within the study period and exceeded the 12 month lagging period from the first test. We have updated the text accordingly.

   c. Statistical methods, 1st paragraph, 2nd sentence, about the calculation of observed deaths: “...for each five year age group in the study cohort...”. Please clarify; I think you calculated the observed deaths for each serological group, not only the whole cohort.

   We have clarified the text with respect to calculations of observed deaths for each five year age group.

   d. Statistical methods, 1st paragraph, 3rd sentence, about the calculation of expected deaths: Also here, I assume that you calculated expected deaths for each serological group of the study population. More important, please clarify about the calculation: Did you just multiply the person-years with the BC population death rate – or did you multiply the calculated person-years for each 5-year age group in each serological group by the BC population death rate for each 5-year age group to get the correct number of expected deaths?
We have clarified the text with respect to these calculations. Expected deaths were obtained by multiplying the calculated person-years for each 5-year age group within each serological group by the BC population death rate for each 5-year age group.

3) The data seem to be sound, I have one question on the results/study population

a. Results, Table 1: The numbers in the serological groups are hard to follow because individuals change groups. Could you please check over the numbers in the table! In the text (under Study population) you write that 8,914 were excluded due to 6-month lagging, in the table there are 16,924 removed because of lagging (could the change of groups give this difference??). Also, all individuals in the study population ought to be in the SNR or REAC group from the beginning (or?), but they are not. Could you please clarify!

*The reviewer is correct— the SERO group was incorrectly added to the total number and this has been corrected. We have also revised the study population section to more clearly reflect the data quality exclusions.*

4) The manuscript adheres to relevant standards.

5) Discussion and conclusion are balanced and supported by the data. Some comments:

a. To discuss: the reliability of the cause of death register

*We have expanded the limitations discussion with respect to reliability of the death registry.*

b. Discussion, 2nd paragraph, 4th sentence: the group with individuals whose 1st anti-HCV test was reactive was older (mean 10 years) and had been infected for a longer time which is the main reason for the higher risk of liver-related mortality, and another important factor, they had survived their drug-abuse… this could be discussed. In the middle of the 3rd paragraph there is some iteration on the higher risk of liver mortality in the REAC group.

*We have updated the discussion to reflect the additional factor of surviving substance use.*

c. Discussion, 8th paragraph, 2nd sentence: I don’t think you should use the word “seroconverters” when it comes to the public health implications. Why not write something like “In the short term, young drug addicts would likely benefit more from…” eventually you could include something like “here represented by the seroconverters”

*We have updated the text with the suggested terminology.*
d. Discussion, last sentence, you forgot “with”: “…associated with HCV acquisition.”

*This has been corrected.*

e. Conclusion, 1st sentence: “… HCV positive testers.” The word “testers” could be changed to something a little more formal, maybe “individuals”? Also, next sentence could be improved, more clear and concise.

*We have replaced “testers” with “individuals”.*

6) Most limitations are clearly stated and discussed. A few comments:

a. As mentioned, the reliability of the cause of death register could be discussed.

b. The 6-month lagging: Selection bias due to a higher probability of HCV testing already sick (maybe dying) individuals could be reduced by introducing a lag time. The 6-month lagging should be discussed, this is the lag time used in several mortality studies, but for liver complications and death a longer lag time (12 months or even more) could be needed. There are some studies on this subject (#Törner A. et al. A proposed method to adjust for selection bias in cohort studies. Am J Epidemiol 2010;171(5):602-8; and #Törner A. et al. A method to visualize and adjust for selection bias in prevalent cohort studies. Am J Epidemiol 2011;174(8):969-76.)

*We have re-analyzed the data using a 12 month lag period and agree that the longer lag time may be more appropriate. We have revised the tables and text accordingly with SMRs and HRs calculated with use of a 12-month lag.*

7) Acknowledge, OK.

8) The title and abstract convey what has been found

Referring to the points above

**Major Compulsory Revisions:**
Points 2c, 2d and 3a.

**Minor Essential Revisions:**
Points 2a, 2b, 5a, 5b and 6b.

**Discretionary Revisions:**
Points 5c, 5d and 5e.

**Level of interest:** An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: I declare that I have no competing interests.