Author's response to reviews

Title: Trends of Hepatitis A Hospitalization and Risk Factors in Canada Between 1990 and 2003

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Author's response to reviews: see over
Reviewer 1: Dr Alfonso Mele

**Q:** Case validation: not laboratory confirmed acute cases with reporting travel to hepatitis A endemic countries were classified as HAV acute cases. Did these cases have performed HBV test?
**A:** Unfortunately they were not tested for HBV.

**Q:** Which clinical events were considered for fulminant hepatitis?
**A:** The diagnostic of fulminant hepatitis was given by the treating physician. As suggested by Dr Bell we deleted this part.

**Q:** The Results section should be shortened and the reading simplified. For example:
- second paragraph: the diagnosis of hepatitis A was confirmed in 11 out of 49 (22%) died patients but the death was attributable to hepatitis A virus only in 10 of them (8 laboratory confirmed).
**A:** This section was modified

- third paragraph: 182 out of 524 (35%) patients of random sample had hepatitis A virus (157 laboratory confirmed).
**A:** The paragraph was changed.

**Q:** DISCUSSION: The generalizability of the results of the present study to all countries should be discussed.
**A:** We agree and reworked the discussion to address this issue.

**Q:** The Results section should be shortened and the reading simplified. For example:
- second paragraph: the diagnosis of hepatitis A was confirmed in 11 out of 49 (22%) died patients but the death was attributable to hepatitis A virus only in 10 of them (8 laboratory confirmed).
- third paragraph: 182 out of 524 (35%) patients of random sample had hepatitis A virus (157 laboratory confirmed).
**A:** The result section was shortened and clarified as suggested.

Reviewer 2 : Dr Steffen

1: **ABSTRACT** : In results, the number of analysed hospitalizations should be mentioned (n=1503).
**Done**

2: **TITLE** Misleading, as the analysis is limited to Quebec. It is inappropriate to generalize on Canada.
**Quebec was added to the title**

3 : **METHODS** Was the number of HA in the primary diagnosis 893 (line 2) or 883 (line 4)?
**It is 883 (and the number has been change)**
4. RESULTS In paragraph 2, the second sentence is difficult to understand; it might be better to state: 'Among the remaining 12 deceased cases, HA was the primary diagnosis in 8 patients (67%). Note that the totals do not add up correctly: If they had 49 charts to review, among those 38 had no HA, contrary to table 1 only 11 (not 12) cases remain. The manuscript may become more palatable if that part would be presented divided in - Fatal HA (pages 7, 9) - Non-fatal HA (other)

There was a misunderstanding: 12 charts had HA as the primary diagnosis and 9 of these were acute cases. However, there were 11 confirmed deceased cases in total. The paragraph was modified to clarify this. It now reads: “The chart review of the 49 deceased patients found that only 11 (22%) had a confirmed acute HA at the time of hospitalization. The proportion of confirmed acute cases was 67% (9/12) when HA was the primary diagnosis in contrast to 5% when HA was the secondary diagnosis (Table 1). Amongst these 11 confirmed acute cases, one died from an apparently unrelated pneumonia whereas death was attributable to hepatitis A virus for the other 10 (7 clearly, 3 possibly) cases.”

Q: It would be interesting to learn, who considers universal immunization in Quebec/Canada.
As this is debated, we deleted this sentence.

Q: It is astounding that cases with HA, even fatal ones, sometimes lack of laboratory confirmation - this should be commented.
A: We agree but this was mostly occurring at the beginning of the study period. We added “Of the 26 (14%) HA cases without serology testing, 16 (62%) occurred before 1994 and only 1 (3%) had no testing in 1999-2003.”

Reviewer 3 Dr Beth Bell

Q: Please provide more information about the properties of MED-ECHO, the "administrative database" of "acute care" hospitalizations in Quebec. At a minimum this information should include: What does "administrative database" mean, exactly? What is its purpose, for monitoring charges/costs? What information is included in the database and how is this information obtained? Is this a database of hospitalizations or individuals, in other words, if a person is hospitalized twice in a given year, is this two records or one? Similarly, what does "acute care hospitalizations" mean? Are the authors meaning to indicate that the database includes hospitalizations in Quebec's acute care hospitals? If so, how many hospitals is this, and what type(s) of facilities are not included in the database? What criteria are used to assign the primary diagnosis (as opposed to the secondary diagnoses)? One of the authors' main analyses and conclusions relates to the accuracy of the diagnosis of hepatitis A in the primary or secondary positions. The importance of this finding, and especially its relevance to other hospital databases, cannot be adequately evaluated without this information. I suspect that indeed these findings cannot be generalized to other such databases. If so, this should be clarified in the discussion.

A: We added “MED-ECHO (Maintenance et exploitation des données pour l’étude de la clientèle hospitalière) is a computerized database from the Ministry of Health to monitor the evolution of hospitalization services and the population that is hospitalized. It includes data on all admissions to one of the 136 acute care hospitals in the province but excludes long term care facilities. A record is generated for each admission and data are extracted from the
hospitalization summary sheet completed by the treating physician when the patient is discharged. For each admission, the physician writes a primary, and up to 15 secondary diagnoses which are then coded using the ninth revision of the International Classification of Diseases (ICD-9). The primary diagnosis indicates the disease that lead to the admission or the complication that contributed most to the duration of the hospitalization whereas secondary diagnoses indicate underlying conditions that may or may not have contributed to the hospitalization.”

We also added in the discussion: “As diagnoses recorded in MED-ECHO are those written by the treating physician on the hospital separation sheet, the results of this study are likely to apply to similar administrative databases relying on the physicians’ diagnoses.”

Q: The authors chose to compare overall and age-specific mean hospitalization rates and risk factors for the period 1990-1997, which encompassed years with two large outbreaks, with the period 1998-2003, during which no outbreaks occurred, and conclude from this comparison that rates declined during the study period. I do not think the data necessarily support this conclusion. Given the periodicity of hepatitis A incidence, a large difference in average rates will be observed whenever outbreak and non-outbreak periods are compared; this does not imply an overall decline. Further, there is a lack of clarity about the objectives of this trend analysis. Is the purpose of examining trends to a) compare hospitalization rates during outbreak and non-outbreak periods, b) evaluate the impact of vaccination programs, or c) simply describe the rates by year? If (a), this needs be be stated explicitly, i.e., "the difference in hospitalization rates between outbreak and non-outbreak periods", rather than "decline in rates during the study period". If (b) or (c), I do not think these should be examined by comparing average rates between outbreak and non-outbreak periods. Suggestions for alternate analyses include simply giving the rates by year and describing their pattern, comparing the nadir during a "pre-vaccine" and "post-vaccine" era, or dividing the study period into equal segments. In any case, because hepatitis A incidence goes up and down "naturally", as the authors themselves indicate, conclusions about declines need to be made with caution. Same with risk factors - since the study period was divided a priori into a period when there were outbreaks among MSM and one when there were not, it is not surprising that the distribution of risk factors was different.

We agree that it appeared arbitrary and unjustified to divide the study into the outbreak and non-outbreak period and then claim that there was a decline in the incidence. We modified the introduction to provided more details about the epidemiology of HA before the study period.

We also modified the end of the introduction that now states “In this study, we reviewed a sample of medical charts of patients recorded in an administrative database as having been hospitalized with a diagnosis of HA between 1990 and 2003 in the province of Quebec, Canada, to validate the accuracy of the diagnosis. We then estimated the age-specific rates of hospitalization and trends of risk factors for hospitalized HA cases in that population.

We also modified the discussion and put more caution in the conclusions.

Q: Reference is made in the introduction to hepatitis A vaccination programs in Canada, including a suggestion that vaccination coverage is low. However, references are skimpy or non-existant, and I was left with very little information about who is getting vaccinated in Quebec. While I recognize that actual coverage data may not be available and outside the scope of this manuscript, the authors need to provide more information about hepatitis A vaccination efforts in Quebec and provide readers with at
least some sense of who might have gotten vaccinated and when. Without this it is impossible to evaluate the extent to which vaccination might have played a role in these trends.

A: We added: «Since its licensure in 1994, HA vaccine has been offered to travelers going to HA endemic countries. However, only a small fraction consult and get receive HA vaccination for which they have to pay. Apart from the intervention targeting MSM in 1996-1997 during which 15000 doses of hepatitis A vaccine were administered free of charge to approximately 8500 individuals, there has been no further mass campaign. Since 1998 in Quebec, individuals belonging to other high risk groups as defined by the National Advisory committee on Immunization (NACI) are eligible to be vaccinated free of charge. In addition to hemophiliacs, people with chronic liver disease and household contacts of an acute case of HA, these high risk groups include MSM, illicit drug users and street youths, three groups difficult to identify and reach. While a few thousand doses are distributed annually by the regional public health units, there is currently no data regarding the overall vaccine coverage.»

Q: In the results section, the authors conclude that "during epidemic periods, the hospitalization rates did not increase as much as the incidence rates". However, they do not provide the data to support this contention. How is "as much" defined? It certainly is not possible to evaluate this from the figure; the appearances of the two curves are entirely dependent on the scale. I am not sure what the point of this analysis is, but if the authors want to keep it, please replace the conclusion in the results with some actual relevant data, e.g., the percent difference between peak incidence rates and peak hospitalization rates during outbreak periods and non-outbreak periods. Also, because of the y-axis scale needed for the incidence data, the shape of the hospitalization rates by year by age group cannot be seen in figure 1. If the authors want to keep the incidence data, I suggest using 2 y-axes of different scales, one for incidence and the other for hospitalization. This will allow better viewing of the shapes of the curves.

We decided to delete this part of the results.

5) The authors attempt to examine a number of clinical features, including fulminant hepatitis A, underlying medical conditions, and "major complications". These terms need to be more clearly defined for these analyses to be informative. It appears that fulminant hepatitis A is defined as use of the term in the medical chart. If this is indeed the case, this analysis should probably be removed, since we have no way to evaluate what was meant exactly when this non-specific term was used nor whether patients who did not happen to have this term used in the chart might have the condition. What appears to be examples of underlying medical conditions and major complications ("e.g." is used) are provided in the relevant paragraph. Please provide the actual definitions. If the conditions listed constitute the definition, please specify this - use "i.e. not "e.g. Further, these would be quite narrow definitions. This should be taken up in the discussion.

The diagnosis of fulminant hepatitis was that written by the treating physician as well as those on complications. Because we could not verify them, we agree with the comment and decided to delete this analysis.

Q: Care should be taken in comparing data (e.g., risk factors) derived from chart review of hospitalized cases with those from surveillance data, i.e., interviews with all patients with the condition. This is done in several long paragraphs in the discussion comparing this study’s data with US surveillance data. These paragraphs should be shortened
considerably, and can be replaced with a single sentence indicating a general impression; I do not see why such a detailed and extensive comparison with US data is necessary anyway. Further, a source of US data that might provide a more valid comparison can be found in Willner IR, et al. Serious hepatitis A: An analysis of patients hospitalized during an urban epidemic in the United States. Ann Intern Med 128;1998:111-4. The case fatality rate, for example, is comparable to that reported in this manuscript. Also, there is little reason to limit comparisons to the United States; consideration of hepatitis A epidemiology in Europe, for example, would also be informative.

We agree and modified the discussion, compare our data with those from Europe and added the suggested reference.

Q: 7) How were the 2003 rates calculated, since it appears that only 3 months of data from 2003 were included? Were they annualized? If so, this needs to be specified.
A: Rates for the first three months of 2003 were annualized. We added this explanation in the methods.

Q: Please add the word "Quebec" to the title of the manuscript, i.e., "..in Quebec, Canada..."
A: Done

Q: The reference 12 after the first sentence in the paragraph in the discussion beginning "At least..." appears to be wrong - seems it should be 20.
The reviewer is right and the reference was changed

Q: In the paragraph in the discussion beginning "At least one risk factor...", please tone down or remove the several sentences related to importation of hepatitis A virus, endemicity, and "epidemic threshold". The data presented in the manuscript are insufficient to support the conclusions of the paragraph, and the relevant reference (of which the corresponding author of this manuscript is the first author) is only marginally relevant. As noted above, comparisons between hospitalized patients and surveillance data are highly suspect anyway.
A: The section described above was remove.

Q: The last phrase in the paragraph in the results about mean hospitalization rates - "...because outbreaks in MSM stopped after 1997" - is a conclusion and should be deleted from the results.
A: Done

Q: In the results where the information on the deaths is reported, the authors indicate that 1 of 11 patients with confirmed hepatitis A did not die of this? What did this person die of? Add details about patients who died.
A: We added “Amongst these 11 confirmed acute cases, one died from an apparently unrelated pneumonia whereas death was attributable to hepatitis A virus for the other 10 (7 clearly, 3 possibly) cases. The age distribution of these 10 cases was 2 patients < 40 years old, 4 aged 40-59 years and 4 who were ≥ 60 years. Three had no underlying medical conditions, three had a chronic hepatitis B, one an alcoholic cirrhosis and 3 had a cardio-vascular disease”

Q: Please provide row percents for all data in table 2, not just totals.
A: Done