Reviewer's report

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

Version: 2 Date: 7 September 2006

Reviewer: Beth P. Bell

Reviewer's report:

General This is an interesting report that used an "administrative database" to characterize patients hospitalized with hepatitis A in Quebec, Canada, during a 13 year (plus 3 month) period. There are a number of problems with the way the study methods are reported and results are presented and interpreted, detailed below, that need to be addressed before the manuscript can be considered suitable for publication.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1) 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 a) 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? b) 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? c) 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.

2) 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.

3) 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.

4) 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.

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.

6) 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.

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.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

1) Please add the word "Quebec" to the title of the manuscript, i.e., "...in Quebec, Canada..."

2) 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.

3) In the paragraph in the discussionssion 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.

4) 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.

5) 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?

6) Please provide row percents for all data in table 2, not just totals.

Discretionary Revisions (which the author can choose to ignore)

1) I would be interested in more clinical details about the patients who died, such as their ages, complications and underlying medical conditions, how the patients whose charts had no mention of fulminant disease died, etc. Indeed, I think this information is of more interest than the detailed risk factor data presented in table 2, and suggest replacing this table with a table of characteristics of deaths, and putting the risk factor information in the text.
2) The authors might find the following reference of interest as regards the higher proportion of hospitalized patients > 59 years with “confirmed hepatitis A” that did not cause hospitalization. A number of these patients quite likely had false positive IgM anti-HAV results.
http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5418a1.htm

**What next?:** Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** No

**Declaration of competing interests:**
I declare that I have no competing interests.