Author's response to reviews

Title: Trends in all cause and liver-related hospitalizations in people with hepatitis B or C: a population-based linkage study

Authors:

Heather F Gidding (hgidding@nchecr.unsw.edu.au)
Gregory J Dore (gdore@nchecr.unsw.edu.au)
Janaki Amin (jamin@nchecr.unsw.edu.au)
Matthew G Law (mlaw@nchecr.unsw.edu.au)

Version: 2 Date: 20 October 2010

Author's response to reviews: see over
Responses to reviewers' comments

MS: 1949218944211241

Trends in all cause and liver-related hospitalizations in people with hepatitis B or C: a population-based linkage study Heather F Gidding, Gregory J Dore, Janaki Amin and Matthew G Law

Reviewer 1: Ann-Sofi Duberg (5098759344406577)

Q1. This is a large record linkage study (probabistically linked) where the size is a major strength. Some of the results concerning the HCV infected population have been recently published (reference 22). Now the aim was to compare the overall burden and trends in hospitalization rates in people notified with HBV or HCV infection in New South Wales (NSW), Australia. The hypothesis is not presented.

Author response: The authors have modified the second paragraph of the introduction to emphasise the hypothesis as follows:

‘In particular, we hypothesize that trends in hospitalization rates for advanced HBV and HCV-related liver disease may be diverging, given that HBV therapy can be utilized in liver failure [8-13] and has been shown to reverse decompensated liver disease [14-15].’

Q 2. The discussion and conclusion focus too much on the improved therapy for HBV infection. As the authors couldn’t link to treatment records they should be more careful in their conclusions about the effect of treatment. Improved HBV therapy could possibly contribute but probably together with other factors to be discussed. The aim of the study was to compare the burden and trends, could you discuss the results from some other points of view?

Author response: See detailed answers below for response

Q 3. All together I think the study is of interest to demonstrate the burden and trends in hospitalization rates in the HBV and HCV infected population – though the results for the all cause hospitalisations is probably more related to life style than to the HBV/HCV infections.
Author response: The authors agree that the differing burden between all cause hospitalizations for HBV and HCV is related to the differing epidemiology of the two populations and this is discussed in the second paragraph of the discussion section.

More detailed comments by manuscript section:

INTRODUCTION

Q 4. First sentence: “…infection with hepatitis B virus (HBV) or hepatitis C virus (HCV)…”

Author response: The authors have added ‘virus’ as follows:

‘Chronic infection with hepatitis B virus (HBV) or hepatitis C virus (HCV) is associated with increased morbidity and mortality.’

Q 5. Second paragraph, 2nd sentence: Is this a presentation of your study or hypothesis? As you don’t have treatment information the results of the study will only be able to suggest an effect of improved therapy (not provide evidence).

Author response: The authors have changed the wording as follows:

‘A population-based study examining trends in hospitalization rates, especially for liver-related admissions, may suggest an effect of improved therapy on disease burden.’

Q 6. According to the aim this is a study of the burden and trends in hospitalization rates, could you introduce something more on trends, for example the increasing burden of HCV?

Author response: The authors agree that a comparison with the burden of HCV is important. These data have already been reported separately (see Gidding et al, J Gastroenterology and Hepatology, 2009) but we have expanded on our reference to this paper and the most recent report of national notification data in the fifth paragraph of the discussion as follows:

‘The burden of non alcoholic liver disease was expected have increased during 2000-2006. This is because the disease cohorts are aging, as well as continuing to expand, albeit at a slower rate than in previous decades (Gidding, 2009 #473;National Centre in HIV Epidemiology and Clinical Research, 2009 #337).’

Q 7. Some older references on HBV therapy could be left out. The long-term effect of HBV therapy is not completely understood yet. Lamivudine and adefovir could reverse decompensated liver disease caused by HBV, but with drug resistance came relapse of
liver decompensation. Consider if references 14-15 are too old. Entecavir and tenofovir will probably improve the long-term outcome – we will see in the future…

Author response: The authors have added two more recent references regarding the treatment of advanced HBV-related liver disease and removed three older references to HBV therapies used to treat liver failure.

METHODS

Data sources

Q 8. In this section I miss information on the HBV infections included, acute and/or chronic infections? Not until the end of the discussion part you mention that only chronic HBV infections were included. How did you differentiate acute/chronic HBV infections?

Author response: The following has been added to the first paragraph of the methods section to explain the case definitions for inclusion:

‘A notifiable HBV case required detection of HBV surface antigen or HBV DNA, while a notifiable HCV case required detection of anti-HCV antibody or HCV RNA.’

The paper aimed to examine chronic HBV and HCV infection, however, due to data limitations distinguishing acute cases from chronic was not possible. The authors have expanded the discussion of this limitation in the last paragraph before the conclusion as follows:

“Second, while the aim of our study was to examine morbidity in cases of chronic HBV and HCV infection, more than 65% of HBV records and 77% of HCV records did not specify whether a case was acute or chronic and only 2% and 1% of cases, respectively, were recorded as newly acquired. For this reason all records were included, which would lead to an underestimate chronic HBV and HCV-related morbidity as some of the notified cases may have cleared their infection.”

Exclusions

Q 9. First sentence: “within 14 days of diagnosis” - which diagnosis? I assume you mean the HCV or HBV diagnosis but that should be clarified (HBV/HCV/HIV/principal diagnosis?).
Author response: the authors have clarified the wording by adding ‘HCV or HBV’ to this sentence as follows:

‘For the study cohorts, all hospital admissions before or beginning within 14 days of the HCV or HBV diagnosis (or earliest of the two diagnosis dates if co-infected) were excluded to reduce the bias towards higher rates of admission around the time of diagnosis [McDonald, 2008 #427] (n= 38 922, 15.3%).’

NB only the hospital admissions have primary and secondary diagnoses, not the notifications.

Q 10. *1 Could you explain why you chose only 14 days for the exclusion of admissions? Have you made any analyses to decide this time interval? Do you know if excluding admissions for 14 days reduced most of the bias?

Author response: In order to allow comparisons across studies, we used a previously determined exclusion period for hospitalizations reported by McDonald et al. We also (visually) confirmed that a 14 day window accounted for most of the increase in admissions around the time of diagnosis in our cohort.

Q 11. Last sentence: admissions for extracorporeal dialysis were excluded. Did you ever think of excluding these individuals (not only the admissions) from the analyses? These patients often have a nosocomial HCV infection and are high consumers of health care (related to the kidney disease).

Author response: We included all patients to accurately assess admissions rates for other causes. We agree that patients with nosocomial acquired HCV infection may be higher users of health care. However, it was not possible to differentiate the cases who acquired their HCV infection nosocomially from those that did not.

Q 12. *2 Did you consider excluding or giving details about the admissions for diagnostic liver biopsies (if liver biopsy is a reason for inpatient care in Australia)? Probably more HCV than HBV patients have been admitted for liver biopsies – this could bias the comparison of liver diagnosis admissions.

Author response: The authors agree that in a more detailed analysis it would be informative to examine rates of admission for liver biopsies. Unfortunately, for this analysis we only had diagnosis codes and liver biopsy is a procedural code.

Statistical analyses

Q 13. Second line: again… “14 day after diagnosis” – which diagnosis?
Author response: the authors have clarified the wording by adding ‘HCV or HBV’ to this sentence as follows:

‘For the study cohorts, all hospital admissions before or beginning within 14 days of the HCV or HBV diagnosis (or earliest of the two diagnosis dates if co-infected) were excluded to reduce the bias towards higher rates of admission around the time of diagnosis [McDonald, 2008 #427] (n= 38 922, 15.3%).’

Q 14. *3 To calculate the SHRs you have used the hospitalization rates for the NSW population including the HCV and HBV infected individuals (I assume). This is probably negligible for the “all cause” hospitalizations. However, for the liver and liver cancer hospitalizations the admissions in the study population could have major impact on the NSW population rates, resulting in too high expected and too low SHRs, especially in the HBV cohort. Could you make a rough estimate of the annual number of liver/ liver cancer admissions in the HBV/HCV group and what percentage they constitute of the annual liver admissions in the NSW population, and discuss the impact on the results.

Author response: The authors thank the reviewer for highlighting this point. Of the 11,413 hospital admissions for non alcoholic liver disease, 19% were from either the HBV or HCV cohorts; 14.5% from the HCV and HCV/HIV cohorts combined and 3% from the HBV and HBV/HIV cohorts combined (Table 1, below). About one quarter of all liver cancer admissions were from the disease cohorts, with similar proportions from the HBV and HCV cohorts (Table 2, below).

We were unable to exclude the disease cohorts from the reference population as these two data bases were not linked. However, we feel that use of a reference population including the disease cohort is a valid comparator and this method has been used in several other published linkage studies.

To highlight this point the authors have added to the limitations section of the discussion as follows:

‘Third, we were unable to exclude members of the disease cohorts from the reference (NSW) population. Although the cohorts only accounted for 1.5% of all cause hospitalizations in the NSW population, they accounted for one quarter of the liver cancer and 19% of the non alcoholic liver disease admissions. A comparison with the non infected population would therefore have yielded higher SHRs.’
Table 1: Number and percent of all NSW hospitalizations by year: non alcoholic liver disease

<table>
<thead>
<tr>
<th>Year</th>
<th>NSW population n</th>
<th>HCV cohort incl HIV n (%)</th>
<th>HBV cohort incl HIV n (%)</th>
<th>HBV/HCV n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>964</td>
<td>121 (12.6)</td>
<td>48 (5.0)</td>
<td>9 (0.9)</td>
</tr>
<tr>
<td>2001</td>
<td>1900</td>
<td>259 (13.6)</td>
<td>65 (3.4)</td>
<td>12 (0.6)</td>
</tr>
<tr>
<td>2002</td>
<td>1957</td>
<td>261 (13.3)</td>
<td>65 (3.3)</td>
<td>19 (1.0)</td>
</tr>
<tr>
<td>2003</td>
<td>1896</td>
<td>260 (13.7)</td>
<td>74 (3.9)</td>
<td>17 (0.9)</td>
</tr>
<tr>
<td>2004</td>
<td>1881</td>
<td>276 (14.7)</td>
<td>47 (2.5)</td>
<td>23 (1.2)</td>
</tr>
<tr>
<td>2005</td>
<td>1870</td>
<td>326 (17.4)</td>
<td>44 (2.4)</td>
<td>26 (1.4)</td>
</tr>
<tr>
<td>2006</td>
<td>945</td>
<td>157 (16.6)</td>
<td>16 (1.7)</td>
<td>5 (0.5)</td>
</tr>
<tr>
<td>total</td>
<td>11413</td>
<td>1660 (14.5)</td>
<td>359 (3.1)</td>
<td>111 (1.0)</td>
</tr>
</tbody>
</table>

Table 2: number and percent of total NSW hospitalizations by year: liver cancer

<table>
<thead>
<tr>
<th>Year</th>
<th>NSW population n</th>
<th>HCV cohort incl HIV n (%)</th>
<th>HBV cohort incl HIV n (%)</th>
<th>HBV/HCV n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>346</td>
<td>28 (8.1)</td>
<td>48 (13.9)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>2001</td>
<td>809</td>
<td>94 (11.6)</td>
<td>117 (14.5)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>2002</td>
<td>810</td>
<td>117 (14.4)</td>
<td>104 (12.8)</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>2003</td>
<td>903</td>
<td>103 (11.4)</td>
<td>121 (13.4)</td>
<td>3 (0.3)</td>
</tr>
<tr>
<td>2004</td>
<td>859</td>
<td>101 (11.8)</td>
<td>89 (10.4)</td>
<td>4 (0.5)</td>
</tr>
<tr>
<td>2005</td>
<td>1094</td>
<td>143 (13.1)</td>
<td>141 (12.9)</td>
<td>5 (0.5)</td>
</tr>
<tr>
<td>2006</td>
<td>502</td>
<td>45 (9.0)</td>
<td>66 (13.1)</td>
<td>6 (1.2)</td>
</tr>
<tr>
<td>total</td>
<td>5323</td>
<td>631 (11.9)</td>
<td>686 (12.9)</td>
<td>21 (0.4)</td>
</tr>
</tbody>
</table>

Q 15. Ethics?

Author response: The authors thank the reviewer for highlighting this omission. This section has been added at the end of the methods.

RESULTS

Description of cohorts

Q 16. Did you have information on country of origin (for table 1)?

Author response: Unfortunately COB is not routinely recorded on the notification data base.

All cause hospitalizations

Q 17. Second paragraph, 2nd sentence (and Fig.1), “all disease cohorts had a secondary peak in less than 30 years old”, were there enough individuals age <30 y in the co-infection cohorts to draw conclusions from the higher rates in the younger age groups?
Were the higher SHRs in the younger age groups statistically significant in the co-infection cohorts?

Author response: The table below lists the sample sizes, rates, SHRs and 95% CIs for the <30 year age group for all cause hospitalizations. The rates and SHRs for the HIV co-infected cohorts are statistically significantly higher than in the mono-infected cohorts.

Table: rates per 100 person years and SHRs with 95% CIs for the <30 year age group by disease cohort for all cause hospitalizations

<table>
<thead>
<tr>
<th>Cohort (&lt;30 yrs)</th>
<th>No. of hosps</th>
<th>Rate/100 pyrs</th>
<th>95% CI</th>
<th>SHR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCV</td>
<td>25461</td>
<td>36.1</td>
<td>35.7-36.6</td>
<td>2.0</td>
<td>2.0-2.0</td>
</tr>
<tr>
<td>HBV</td>
<td>5637</td>
<td>14.1</td>
<td>13.7-14.5</td>
<td>0.8</td>
<td>0.7-0.8</td>
</tr>
<tr>
<td>HBV/HCV</td>
<td>1142</td>
<td>46.9</td>
<td>44.2-49.7</td>
<td>2.6</td>
<td>2.5-2.8</td>
</tr>
<tr>
<td>HCV/HIV</td>
<td>309</td>
<td>98.1</td>
<td>87.7-109.6</td>
<td>5.7</td>
<td>5.1-6.4</td>
</tr>
<tr>
<td>HBV/HIV</td>
<td>55</td>
<td>57.3</td>
<td>44.0-74.7</td>
<td>2.6</td>
<td>2.6-4.3</td>
</tr>
</tbody>
</table>

Q 18. *4 Last paragraph: As liver related admissions constitute only about 2% of the all cause admissions the decline is probably unrelated to the HBV and/or HCV infection. For the discussion section: What is the situation in the NSW population? Is there a decline over years? Reduction in hospital beds? Other explanations? Maybe a result of bias, excluding only 14 days after notification will probably result in too high hospitalization rates the first months and then a decline. How many of the patients were notified during the study period 2000-2006 (with risk of introducing this type of bias)?

Author response: The hospitalization rates for the NSW population increased slightly over the review period, in contrast to trends for the HBV and HCV mono infected cohorts. Reasons for the decline in all cause admissions for these two cohorts are unclear but, as the reviewer suggests, are unlikely to be related to liver disease-related admissions. They are also unlikely to be due to the short exclusion window of 14 days, as rates after this window were reasonable consistent over time (ie the bias was considered to be removed by this short exclusion period based on visual inspection of the data).

The proportion of cases notified during the review period is included in Table 1.

As suggested, the authors have added a section to the second paragraph of the discussion about the downward trend in all cause hospitalizations as follows:
‘Reasons for the downward trend in all cause hospitalization rates between 2000 and 2006 for both the HCV and HBV mono infected cohorts are unclear, as rates for the NSW population increased over the same period.’

Non alcoholic liver disease

Q 19. (*3) See comment under statistical analyses! Could the SHRs (especially for HBV) be too low as the NSW population rates include the HCV and HBV infected population?

Author response: See above for response.

Q 20. First paragraph, 2nd sentence, 2nd part “…accounted for a higher proportion of all and liver disease-related hospitalizations”. Please clarify the meaning of this sentence, do you mean proportion of all cause hospitalizations and of all liver hospitalizations in each cohort? You have not presented what you mean by liver disease-related hospitalisations, which ICD codes did you include?

Author response: The authors have clarified this sentence as follows:

‘Compared with the HBV mono-infected cohort, the HCV mono-infected cohort had significantly higher hospitalization rates and SHRs, and non alcoholic liver disease accounted for a higher proportion of all hospitalizations and all liver disease-related hospitalizations in the cohort (Table 2; \( P = 0.002 \) and \( P < 0.001 \), respectively).’

The definition (including ICD codes) of all liver disease-related admissions is included in table 2.

DISCUSSION

Q 21. *5 Second paragraph: The discussion on the divergent trends in non-alcoholic liver hospitalizations in the HCV and HBV cohort focus too much on HBV therapy. Improved HBV therapy could possibly contribute but probably together with other factors. As you can’t link to treatment records you should be more careful in your conclusions about this. You discuss this again on page 11, this discussion is interesting but dominates, try to shorten.

Author response: The authors have considerably reworked the discussion and reduced the emphasis on explaining the trends in non alcoholic liver disease.

Q 22. The aim of the study was to compare the burden and trends. What about the increase in the HCV-cohort? Is the HCV-epidemic also in NSW reaching the point when
many HCV patients have been infected for 30-40 years with a high risk of liver complications, demonstrated as an increase in the trend analysis? According to the all cause admissions a decrease seems to be the general trend, maybe as a result of a change in society, (maybe a reduction in hospital beds?) or as a result of bias (see comment “all cause hospitalisations”).

Author response: We have expanded our discussion of the increased burden of HCV-related liver disease in paragraph 5 of the discussion (see answer to Q 6 above) and included discussion on the trends in all cause hospitalizations (see answer to Q 18 above).

Q 23. You don’t mention the limitations with the registers, for example the coding not always being perfect (how could the physician responsible of the coding discriminate non-alcoholic and alcoholic liver disease in patients with HCV and drug abuse?).

Author response: The authors agree that there is likely to be some misclassification of alcoholic and non alcoholic liver disease diagnoses. In Australia, discharge diagnosis coding is carried out by trained coders in each hospital, based on clinical notes. The misclassification bias is likely to be non differential and there were no changes to the coding procedure over the period of the review. Therefore coding errors are unlikely to explain the divergent trends.

This limitation has been added to the last paragraph of the discussion as follows:

‘Sixth, there is likely to be some misclassification of alcoholic and non alcoholic liver disease diagnoses. However, this misclassification is likely to be non differential and there were no changes to the coding procedure over the period of the review. Therefore coding errors are unlikely to explain any divergent trends.’

Q 24. Page 11, 2nd paragraph, line 4 and 5, the spelling of tenofovir.

Author response: Spelling corrected from tenofivir to tenofovir in 2 places.

Conclusions

Q 25. The aim was to study the burden and trends, the conclusion should focus on your findings, with some possible explanations. Non alcoholic liver admissions constitute 1% of all admissions, then it’s very hard to believe that improved HBV treatment would have any significant impact on widening the HBV/HCV gap in hospital related morbidity overall. For non-alcoholic liver disease HBV treatment could possibly contribute but I think your conclusion is too certain.
Author response: The authors agree that it is unlikely that the changes in all cause admissions are due to an impact of HBV treatment. We have modified the conclusion to clarify this, reduce the certainty of our assumptions, and focus more on the increasing burden of HCV liver-related morbidity as follows:

‘The decline in HBV-related liver disease may, at least in part, be due to improved treatment of advanced HBV-related liver disease and the greater reduction in morbidity from non alcoholic liver disease in the HBV/HIV infected cohort supports this assertion. For the HCV infected cohort, liver-related morbidity is increasing and improved treatments, especially for advanced liver disease, and higher levels of treatment uptake are required to reverse this trend.’

Table 2

Q 26. Could you please clarify what you present in the column “% Liver disease admissions”, is this the percentage of all liver admissions in each cohort? If so, what is included in all liver diseases (ICD codes)? Obviously not only non-alcoholic liver disease and primary liver cancer, please clarify!

Author response: The authors have clarified the contents of the column by expanding the title of the column to include ‘all’ liver disease and also expanding the associated foot note as follows:

‘† Percent of all liver disease-related admissions within each disease cohort: includes non alcoholic liver disease (ICD-10-AM codes K71-77), primary liver cancer (ICD-10-AM codes C22), viral hepatitis (ICD-10-AM codes B15-B19), and alcoholic liver disease (K70).’
Reviewer 2: Scott McDonald (1949771986441100)

Major compulsory revisions

Q1. Why was alcoholic liver disease excluded from the definition of liver disease? This is not explained anywhere in the paper, but upon reading the title and abstract I assumed this would have been examined. Previous study by the same authors showed a larger burden from ALD in an HCV-infected cohort than from HCC (Gidding et al. 2010, J Hepatol). Also an increasing trend of an average of 6.8% per annum implies high public health relevance. This question applies to the def’n in the footnote of Table 2.

Author response: The authors agree that ALD is an important issue for HCV and, as highlighted by the reviewer, these results have already been presented in a previous paper. In contrast to HCV, there were only 111 hospitalizations for ALD in the HBV cohort over the entire review period. In addition, we wanted to look at the potential impact of antiviral therapy and so focused on liver disease associated with HBV and HCV infection specifically (non alcoholic liver disease). We have clarified the title, text and table 2 footer and column heading to clarify the types of liver disease examined (see also answers to reviewer 1 for details of changes to table and text).

Q 2. Contrasting trends for non-ALD in HCV and HBV cohorts (with latter decreasing, and even more so for HIV/HBV cohort). The authors suggest an impact of treatment on these population-level rates. I would have liked to see more evidence for this suggestion - which occurs several places in the Discussion - but also alternative explanation raised. For instances, could the denominator from which HBV rates are computed be increasing over time (due to earlier diagnosis or improvements in case-finding)?

Author response: The authors have considerably reworked the discussion to more clearly state the evidence for our assertion. The key areas are: In theory rates of nALD should be increasing in the HBV cohort as they are for the HCV cohort, but improved HBV treatment, its effectiveness at reversing and treating advanced liver disease and greater treatment uptake could explain why population-level morbidity is decreasing in the cohort. The findings are also consistent with liver transplant and mortality data.

Both the HCV and HBV cohorts are expanding, but at a slower rate than in past decades. Notification rates have especially declined in young adults. The average age of both cohorts is therefore increasing (rather than decreasing as would be the case if there was earlier
detection) and case finding and surveillance has not changed over the period of review. We are therefore unable to come up with alternative hypotheses for to explain our findings. However, we have added the following to highlight this in the text:

‘This is unlikely to be due to differential changes in case finding, which remained relatively constant over the review period’.

Q 3. All-cause SHRs for HBV are lower than expected from the reference population. Possible reasons for this are only touched upon briefly on p.10. What are the implications for comparison of both rates and SHRs between HBV and HCV cohorts?

Author response: The authors have added a sentence to this section to indicate that if health care utilisation is lower in the HBV cohort than in the general population then our analysis will underestimate the true burden of morbidity associated with HBV. The sentence is:

‘If it is the latter explanation, the comparative burden of morbidity associated with HBV may be an underestimate.’

Q 4. The observation that the HBV-monoinfected cohort have a 2-fold higher hospitalisation rate and SHR for liver cancer compared with the HCV-monoinfected cohort is surprising. What are the reasons for this?

Author response: We have expanded on the discussion about the HCC results as follows:

‘The higher hospitalization rates for primary liver cancer in the HBV-mono-infected cohort compared with the HCV mono-infected cohort may be because a higher proportion were infected at an early age (in their country of birth) and therefore have a greater cumulative risk of disease progression [45]. This may also explain the high SHRs in the less than 40 year age groups. However, this cannot be proven as only date of diagnosis (which may occur many years after the date of infection) is reported so we are unable to confirm what age cases were infected. Another reason for the difference may be that HBV-related liver cancer can occur in the absence of cirrhosis due to the direct oncogenic affects of the HBV virus [46]. Therefore, even if the overall cirrhosis risk is similar there may be a greater risk of liver cancer in HBV cases. Our results are consistent with other populations-based linkage studies in Australia which show a significantly higher mortality from, and incidence of, liver cancer in people with HBV compared to those with HCV [47-48].’

Are mortality rates for HCV-infected HCC patients higher?
Author response: An analysis is currently being undertaken at our Centre to examine survival in HBV and HCV cases with HCC and preliminary findings suggest survival may be better in the HBV cohort. Further analysis is, however, required before these results can be referenced.

Q 5. Supply figures showing temporal trends in rates and SHRs, as this is the focus of the paper.

Author response: The mean changes over time presented in Table 3 represent changes adjusted for within patient clustering, as is appropriate for the analysis of hospitalization data where there are multiple admissions (outcomes) per person and these outcomes are correlated. The graphical presentation of crude trends doesn’t reflect the trends adjusted for within patient clustering (which can’t be presented graphically) and we feel the latter is a more appropriate method of analysis (highlighted as a strength of our study in the discussion). In addition, we already have 3 figures for the age trends and the tabulated mean changes and 95% CIs can be presented in one table.

Q 6. (p.11) Given the report of relatively low treatment uptake (need to cite uptake values), it seems doubtful that a difference in treatment uptake among HCV and HBV monoinfected patients could influence population-level temporal trends. Please further justify this explanation.

Author response: The authors had added figures for the level of treatment uptake to the text. See response to Q 2 for how we have modified the discussion to more clearly justify our claim. We don’t believe it is the level of HBV treatment uptake per se that has led to the decline in hospitalization rates, but the fact that the people receiving this treatment are those most at risk of HBV liver-related morbidity and that treatment of these people is likely to reduce morbidity.

Q 7. Limitations are not as comprehensive as they could be. Mention should be made of the fact that diagnosis of HBV/HCV occurs many years after infection; what are the implications differences in this lag time between infections for the paper's findings?

Author response: The authors have considerably expanded the limitation section of the discussion. It is likely that a higher proportion of HBV cases were infected as young children, and the impact of this (and the limitation that we do not have age at infection) is discussed in the section about liver cancer rates (see Q 4 above).

Discretionary revisions
Q 8 Discretionary revision 1. (p.10) The higher all-cause morbidity in <30 years HCV cohort (Gidding et al. 2010) do not really 'show' an association with lifestyle factors, only that lifestyle-related hospital admissions represent a large portion of the burden.

Author response: The sentence has been reworded as follows: ‘A high proportion of the all cause hospitalizations amongst the HCV cohort in the less than 30 year age group has previously been reported to be lifestyle-related admissions such as drug and alcohol use [24].’

Q 9 Discretionary revision 2. There are clearly very different risk activities/lifestyles associated with people infected with HBV compared with people infected with HCV. This is first mentioned in the Discussion. The authors should consider introducing these differences in the Methods, in the Description of cohorts subsection.

Author response: The authors’ agree that there are different risk activities/lifestyles associated with people infected with HBV compared with people infected with HCV as described in the discussion section about all cause morbidity. However, there are no data about these variables on the notification data base (see first limitation in the limitations section of the discussion) and therefore we are unable to include them in our description of the cohort and can only make suppositions about the cohort differences when explaining the results in the discussion.

Q 10. Discretionary revision 3. Table 2: I would prefer a different organisation, with the Type of admission nested under Disease, rather than as currently done.

Author response: We would be happy to re-arrange tables 2 and 3 as suggested if the Editor would also prefer this layout. However, we feel that the current layout suits the format of the discussion and results better as the comparisons being made are between the cohorts within each type of admission rather than comparing all cause with non alcoholic liver disease and liver cancer rates within each cohort.

Minor essential revisions

Q 11 p.5, 1st sen under Exclusions: admissions before or beginning w/i 14d of diagnosis were excluded. Please specify which diagnosis (HBV, HCV, HIV) in the case of coinfections.

Author response: the authors have clarified the wording as follows:
‘For the study cohorts, all hospital admissions before or beginning within 14 days of the HCV or HBV diagnosis (or earliest of the two diagnosis dates if co-infected) were excluded to reduce the bias towards higher rates of admission around the time of diagnosis [McDonald, 2008 #427].’

Q 12 p.6 Were rates calculated such that the denominator (time at risk) excluded time in hospital?

Authors’ response: Time in hospital was included in the person years of observation and we have added the following sentence to the statistical analysis section of the methods to clarify this:

‘The time at risk included the time spent in hospital as the patient was still at risk of a new episode of care with a different principal diagnosis.’

Also, given multiple hospitalisation data comprise non-independent observations, the assumption that hospitalisations are Poisson-distributed may not be warranted. See Glynn & Burrell, BMJ 2006. Did you check for over-dispersion? Or has correction for recurrent events already been done – I don’t understand what is meant by (p. 12) ”...trends presented may therefore differ from those seen for crude rates.” If crude rates are not presented in tables and figures, then this should be clarified.

Authors’ response: The authors accounted for the fact that hospital admissions are not independent observations by using a Poisson model with random effects and also calculated the CIs for the SHRs using the method by Stukel. This is included in the statistical analysis section of the methods:

‘To account for the correlation between hospitalizations for the same person, 95% confidence intervals (CIs) for SHRs were calculated using the method by Stukel et al [Stukel, 1994 #531], and a random effects Poisson regression model [Kirkwood, 2003 #534] was used to estimate the mean change in hospitalization rates over time.’

Crude rates are presented in the tables and figures, however estimation of the mean change accounted for within person clustering. The authors have clarified this by adding footnotes to Table 3 regarding the ‘% mean change’ column. We have also clarified the wording of the discussion section as follows:
‘By linkage of the cohorts to their hospital records we were also able to account for the correlation between hospitalizations for the same patient in our analyses of changes over time.’

Q 13 p.6 "interaction...time period was modelled..." Better: "interaction...time period was fitted...

Authors’ response: we have changed ‘modelled’ to ‘fitted’ as suggested:

‘An interaction term between disease cohort and time period was fitted to assess whether hospitalization rate changes differed by cohort, with the significance determined using the likelihood ratio test.’

Q 14 p.9 penultimate sentence of 1st para, specify which coinfection in "...highest in coinfection sub-populations"

Authors’ response: The discussion has been reworked and this sentence (now the first of the discussion) reworded to clarify that rates are higher in all co-infected cohorts as follows:

‘Our study revealed contrasting hospital-related morbidity among individuals diagnosed with HBV and HCV infection, and that hospitalization rates were consistently higher in all co-infected cohorts.’

p.9, last sentence of 1st para, clarify '...either HBV and coinfection or HCV and coinfection'

Authors’ response: This sentence has been removed in the revised discussion.

p.10, 2nd full para, clarification '...more often with HIV coinfection, and follow a more aggressive...'

Authors’ response: The wording has been clarified as follows: ‘In addition, HIV co-infection has been associated with higher rates of HCC than HCV and HBV mono-infection {Puoti, 2004 #512}’

p.10, 3rd para: insert "with HIV coinfection," after "...occur more often"

Authors’ response: The discussion has been reworked considerably and therefore this sentence is no longer included.

p.11 spelling: tenofovir spelt 'tenofivir' in a few instances.

Authors’ response: spelling has been corrected.
p.11, last para: clarification "...increasing trends in diagnosis of primary liver cancer in Australia..."

Authors’ response: The sentence has been clarified as follows:

‘Rates of hospitalization for both HBV- and HCV-related primary liver cancer increased during 2000–2006, consistent with the increasing number of liver cancer diagnoses in Australia {Amin, 2007 #626; Alam, 2009 #675}.’

Does the term 'separation' mean the same as 'admission'? If so, it will be clearer to the reader to use only one.

Authors’ response: ‘separation’ has been replaced with ‘admission’ throughout the manuscript except where its use is required to define the study period and how the hospital data are collected.
Reviewer 3: Stephen Roberts (1185441803441860)

Minor essential revisions

1). Methods, page 4, para 2 The authors state that admissions were categorized according to the principal (first) diagnostic code. Presumably this is the principal diagnosis at discharge rather than at admission?

Author response: The reviewer is correct, the diagnosis is made at separation. We have clarified this as follows:

‘Each admission includes demographic and administrative information and diagnosis and procedure fields coded at separation according to the 10th revision of the International Classification of Diseases-Australian Modification (ICD-10-AM). For our analysis, admissions were categorized by their principal (first) diagnostic code (used to record the main condition responsible for the stay in hospital).’

2). Methods, page 5, paras 1 to 3 The technical details provided about the record linkage methods would not be familiar to many readers. They could be simplified or placed in an Appendix.

Author response: The authors have reduced the content in the data sources section. However we are also mindful of the need to include enough detail to clarify points raised by other reviewers. We would be happy to place more of the details in an appendix if the Editors felt this was appropriate.

3). Discussion, page 12, para 2 An additional study limitation that should be stated is that the trend analyses are based on relatively few years (seven).

Author response: we have included this limitation in the paragraph about the study’s limitations as follows (NB data were by financial year and included 6 years):

‘Fifth, hospital data with identifiers for linkage were only available for a six year period from June 2000, so the trends identified here need to be monitored for a longer period of time.’

4). Could the divergence of trends in hospital admissions for non-alcoholic liver disease among people with hep B and hep C be related to differences in case ascertainment for the two disorders? This should be discussed in more detail in the Discussion.

Author response: The authors have considerably reworked the discussion to more clearly state the evidence for our assertion. Both the HCV and HBV cohorts are expanding, but at a
slower rate than in past decades (this has been added to the discussion). Notification rates have especially declined in young adults. The average age of both cohorts is therefore increasing (rather than decreasing as would be the case if there was earlier detection) and case finding and surveillance has not changed over the period of review. We have added the following to highlight this in the text:

‘This is unlikely to be due to differential changes in case finding, which remained relatively constant over the review period’.

Discretionary revisions

1). Methods, page 4, paras 1 and 2 The authors cite several study information sources (NSW NDD, NHR, NAR, APDC) which should ideally be referenced.

Author response: There are no official publications describing each of the data bases. However, references which contain detailed descriptions of each data base have now been included.

2). Methods page 5, para 4 It would be informative if the authors could provide the numbers of cases that failed each of the exclusion criteria.

Author response: The authors have modified the exclusion criteria section in the methods section to include all proportions and sample sizes relating to cases and admissions that failed each exclusion criteria. Consequently the description of the cohort section in the results has been reduced so that these data are not duplicated.

3). The study provides morbidity outcomes for non alcoholic liver disease. Similar information for alcoholic liver disease would also be of interest.

Author response: The authors agree that ALD is an important issue for HCV and these results have already been presented in a previous paper. In contrast to HCV, there were only 111 hospitalisations for ALD in the HBV cohort over the entire review period. In addition, we wanted to look at the potential impact of antiviral therapy and so focused on liver disease associated with HBV and HCV infection specifically (non alcoholic liver disease).

4). The paper would also be strengthened if some information on relative mortality could be included.

Author response: The authors agree that information about the burden of mortality is important. However, these data have recently been accepted for publication as a separate analysis (see Walter et al, J Hepatology, in press). We make comparisons with this paper in
respect to the trends in liver cancer and non alcoholic liver disease in the revised version of the discussion.

5). Presentation and formatting of the Figures could be improved.

Author response: The authors have increased the font size of the legends and thickness of the lines to improve the presentation and would be happy to make further specific changes.
Reviewer 4: Robert Myers (2001391257441928)

Major Compulsory Revisions

1) Growth rates: Some of the growth rates for admissions are alarming (e.g. for liver-related admissions in HCV/HIV, the mean annual growth is 255%). Please compare and contrast these figures to others reported (e.g. Grant Hepatology 2005; Myers Can J Gastro 2008). Although these differences may relate to different definitions between studies (see below), it should be discussed. For example, in my study of Canadian data, the average annual growth rate of liver-related admissions in HIV/HCV coinfection patients was only 40% (1/6th of yours) between 1994 and 2004.

Author response: The author’s agree that some of the mean rate increases are large. However, for the HIV/HCV cohort the confidence intervals for non alcoholic liver disease are wide and almost overlap 40%, the rate increase seen in Canada. Never the less, apart from differing definitions for liver disease, the main reason for any differences is that we were looking at hospitalization rates in the HBV and HCV infected cohort so were able to account for changes in the denominator at risk and also the correlation between hospitalizations from the same person. To further accentuate this important difference and make reference to the key papers examining trends in unlinked hospital data noted by the reviewer, we have added the following to the second last paragraph of the discussion:

‘The major strength of our study is that it is a large population-based linkage study including HIV co-infection status. By linkage of the cohorts to their hospital records we were also able to account for the correlation between hospitalizations for the same patient in our analyses of changes over time. The temporal trends presented here may therefore differ from the crude rate changes reported in other studies that were unable to account for within patient clustering or increases in the HCV and HBV infected population {Grant, 2005 #432; Myers, 2008 #477; Thomson, 2008 #430}.’

2) Figure 3: The curve for HBV-SHR is unexpected to say the least, specifically the very high SHRs for patients under 39 years of age. Please discuss.

Author response: The high SHRs in the HBV cohort for ages under 39 years is related to the fact that the NSW population rates in the youngest age groups are considerably lower than they are in the HBV cohort. In older ages the rates for the HBV cohort and NSW population are more similar, even though they are both higher. Therefore, even though the rate of liver cancer increases with age, the relative rate compared to the age and sex matched NSW
population (measure by the SHR) is highest in the youngest ages. The high excess rates (SHRs) in the young age group probably reflect a younger age at infection (therefore and earlier risk of liver cancer) compared with other causes. We have added the following to the 3rd last paragraph of the discussion (relating to liver cancer) as an explanation:

‘The higher hospitalization rates for primary liver cancer in the HBV-mono-infected cohort compared with the HCV mono-infected cohort may be because a higher proportion were infected at an early age (in their country of birth) and therefore have a greater cumulative risk of disease progression {Fattovich, 2004 #858}. This may also explain the high SHRs in the less than 40 year age groups.’

Minor Essential Revisions

1) Study Cohort: In the Methods, please provide the number of exclusions for the various reasons (e.g. dialysis admissions).

Author response: The authors have modified the exclusion criteria section in the methods to include all proportions and sample sizes relating to cases and admissions that failed each exclusion criteria. Consequently the description of the cohort section in the results has been reduced so that these data are not duplicated.

Also, if possible, please confirm the success of your probabilistic linkage methods under 'Linkage Process'.

Author response: The authors have added information about the success of the probabilistic linkage methods to the methods section as follows: ‘A random sample of 1000 NDD records and their matched hospitalization and death data were reviewed by the CHeReL with a false positive rate of 0.2% and a false negative rate of less than 0.1%.

2) Table 2: Under all cause admissions for HCV/HBV/HIV, the 95% CI of the SHR seems to be missing some digits (3.5 to .7) Also in Table 2, I am unclear regarding the column '% Liver disease admissions'. The footnote states that these include nonalcoholic liver disease and liver cancer admissions yet the numbers don't add to 100% (e.g. for HCV, they are 27.3% and 10.4%, respectively). Please clarify this since I may be misunderstanding the data.

Author response: The 95% CI has been fixed. It should be 5.7. The footnote and heading for % Liver disease admissions has been clarified to show that it relates to all liver disease admissions (including those analysed as well as viral hepatitis and alcoholic liver disease).
Discretionary Revisions

1) Outcome Measures: You have described 3 types of hospitalizations – all cause, nonalcoholic liver disease-related, and liver cancer-related (i.e. HCC and cholangiocarcinoma) - based on the principal diagnosis field. I would recommend that the data on all cause admissions be de-emphasized because the majority of these admissions are completely unrelated to viral hepatitis (e.g. previous studies have excluded obstetric admissions).

Author response: The authors have made major revisions to the discussion to expand on the viral liver related trends and burden and thus de-emphasize the all-cause findings. We included the all cause hospitalizations as a measure of the total excess burden and to allow comparisons with other studies. We feel that the lower excess all cause morbidity for HBV would be of interest to readers as this has not previously been reported.

More importantly, I would recommend that you reconsider your definitions of liver-related and liver cancer-related admissions to include all of the diagnosis fields. For example, if a patient with HCV was admitted for management of an HCC (e.g. for a TACE), they could very well have HCV coded as the primary diagnosis and HCC coded in a secondary field because HCV is the underlying cause of the HCC. As it stands, this admission would be coded as an 'all cause' admission even though it is in fact HCC-related (correct me if I'm wrong). How would the HCC data look if you considered codes for HCC within any of the diagnosis fields? On a side note, please provide a reference that confirms the validity of the diagnosis codes for primary liver cancer.

Author response: In Australia, the principal diagnosis relates to the main reason for that episode of care. Therefore, if a patient was admitted for treatment of HCV-related HCC, then the main reason for hospitalization would be coded as HCC. We used principal diagnosis to be consistent with methods used in our previously published studies. However, we did re-examine our data and the majority 60.2% of all primary liver cancer admissions were coded as the principal diagnosis.

The authors were unable to find a reference that confirms the validity of the diagnosis codes for primary liver cancer in the literature and would welcome any information from the reviewer in this regard.

In a similar manner, I would recommend that you reconsider your definitions of liver-related admissions to include complications of cirrhosis (e.g. encephalopathy, variceal
hemorrhage, SBP, etc.) rather than the frequently unrelated diagnoses with ICD-10 codes 71.0-77.8 (e.g. autoimmune hepatitis, PBC, etc.). Previous studies (e.g. Kim, Hepatology 2001; Grant, Hepatology 2005; and Myers, Can J Gastro 2008) have considered an alternative definition in which a hospitalization was considered liver-related if the principal diagnosis was HCV (or HBV); there was any diagnosis of cirrhosis, portal hypertension, or other sequelae of liver disease including primary liver cancer; or the patient had undergone a liver transplant.

Author response: The authors agree that there are several ways in which we could have analysed the data. We used the same method employed in previously published data linkage studies from our centre for consistency and comparability. The design of our study is somewhat different to those mentioned by the reviewer in that we linked known cases of HCV and HBV notified in NSW with their hospitalization data (we have now highlighted this in the second last paragraph of the discussion). Therefore we did not use the diagnostic codes for viral hepatitis hospitalizations to determine which admissions to include in our analysis but included all admissions for the HBV and HCV infected cohort and specifically examined their non alcoholic and primary liver cancer-related admissions.