Reviewer’s report

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

Version: 1 Date: 26 August 2010

Reviewer: Scott A McDonald

Reviewer’s report:

This study compares the burden of HBV and HCV infection in NSW, Australia, in terms of the indirectly standardised rates of hospitalisation for liver disease and for all causes, and investigates temporal trends in these rates. The main strengths of this study is the size of the HBV and HCV-notified populations. Generally a well-written paper that provides useful data. There are several issues that require attention.

Major compulsory revisions

1. 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.

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)?

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?

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? Are mortality rates for HCV-infected HCC patients higher?

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

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?

Discretionary revisions

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

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.

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

Minor essential revisions

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.

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

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

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

p.9, last sentence of 1st para, clarify '...either HBV and coinfection or HCV and coinfection'
p.10, 2nd full para, clarification '...more often with HIV coinfection, and follow a more aggressive...' 

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

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

p.11, last para: clarification "...increasing trends in diagnosis of primary liver cancer in Australia..."

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

**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.