Author's response to reviews

Title: Direct economic burden of hepatitis B virus related diseases: Evidences from Shandong, China

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Dr. Emily Crow
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Ref: No. MS 2078141726154108- Direct economic burden of hepatitis B virus related diseases: Evidence from Shandong, China

Dear Dr. Crow,

Thank you very much for your letter as well as the two referee reports. We have carefully revised our paper, following your suggestions and addressing all the concerns the two referees raised. Following your recommendation, this manuscript has been proof-read and edited by a native English speaking colleague, who has over ten years research experience (including professional writing) in health services research.

In this letter, we would like to provide a point-by-point response to all the concerns. Referees’ comments are shown in italic, followed by our responses. In the manuscript, all the additions and changes are shown in bold.

Referee 1

1. These results may not apply to “average” individuals infected with hepatitis B.

We agree with the reviewer’s comments. In 2009, we followed up the positives of HBsAg (hepatitis B virus Surface Antigen) through a community-based cross-section survey carried out in Shandong province in 2006. We found that only two cases were admitted among 46 cases of chronic hepatitis B. The Annual direct cost per case is US$ 334.29 which is similar with the study by Hu and Chen (our citation 3).

As the reviewer pointed out, this sample is based on individuals who have come into the hospital as inpatients. Addressing this referee’s comments, we have added the following in the discussion of limitations of our study in our paper (page 13):

“Finally, our study does not capture the full burden of disease because it does not survey individuals infected with hepatitis B who were not hospitalized during the sampling period.”

2. Readers cannot discern whether the detailed results in table 3-5 are statistically significant.
Following the referee’s comment, we revised Tables 3 to 5 (now tables 4 to 6) and included the results of statistical significance.

3. If the authors were to examine these differences more carefully, presumably there could be more nuance in the discussion and conclusions based on this information. Currently, the conclusion is generally “hepatitis B is expensive”. But, many other studies already show that. Are there more nuanced conclusions like, “costs of end-stage liver diseases caused by hepatitis B like decompensated cirrhosis and liver cancer can consume up to or more than a family’s annual disposable income. Coverage for these disease conditions should be a priority for future health reform.”? If there are more nuanced conclusions, it would be nice to see them.

We agree with the referee that our results could be explored to reveal more policy implications. In our Conclusion section, we expanded on our discussion by stating: “For instance, patients with severe hepatitis B or primary liver cancer suffered a high economic burden even after insurance reimbursement, spending 137.45% and 149.50%, respectively, of their household annual income.”.

Minor Essential Revisions:

Authors should define “severe hepatitis B”. When I have seen the term “severe” for hepatitis B, it usually is used in conjunction with “acute” hepatitis B or reactivation. The authors should clarify what the definition of “severe hepatitis B” is.

On page 6, we now provide a clear definition of severe hepatitis B. The diagnostic standard in this paper for severe hepatitis B is: Prothrombin activity below 40% and serum bilirubin more than 10 times normal.

Reviewer 2

1. The authors should add a flow chart summarizing the sampling of participants for interview.
   1) All patients meeting ICD-codes from Major Epidemic Network database
   2) Number excluded due to duration of hospital stay≤7 days and other medical reasons for hospitalization
   3) 45 excluded due to uninsured status and number of refusal etc.: We thank the referee for this excellent suggestion. We now include in our manuscript a new Figure (Figure 1, page 26) to illustrate the sampling process.

2. Re-do the analyses after excluding the 45 uninsured patients. This would simplify analyses and would focus on the message of economic burden on the insured patients. It
is important to stratify the analyses for patients recruited from tertiary hospitals and secondary hospitals because the level of hospital is your sampling frame and the costs may differ by level of care.

We have followed the referee’s suggestion and re-did the analyses after excluding the 45 uninsured patients. The results are presented in a new Table 7 (page24). On pages 11-12, we summarized the results.

3. Provide the ICD-10 codes for the six HBV diseases in Methods

We have followed the referee’s suggestion and now include the ICD-10 codes for the six HBV diseases in a new Table 1 (page18).

Table 1  ICD-10 codes of HBV-related diseases

<table>
<thead>
<tr>
<th>Classification</th>
<th>ICD 10 code</th>
<th>ICD 10 Title</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute hepatitis B</td>
<td>B16.902</td>
<td>Acute hepatitis B without icteric</td>
</tr>
<tr>
<td></td>
<td>B16.901</td>
<td>Acute hepatitis B with icteric</td>
</tr>
<tr>
<td>Severe hepatitis B</td>
<td>B16.906</td>
<td>Severe hepatitis B</td>
</tr>
<tr>
<td></td>
<td>B16.908</td>
<td>Acute Severe hepatitis B</td>
</tr>
<tr>
<td></td>
<td>B16.909</td>
<td>subacute severe hepatitis B</td>
</tr>
<tr>
<td></td>
<td>B18.102</td>
<td>Chronic severe hepatitis B</td>
</tr>
<tr>
<td>Compensated and decompensated cirrhosis</td>
<td>K74.601</td>
<td>cirrhosis of liver</td>
</tr>
<tr>
<td>Primary liver cancer</td>
<td>C22.001</td>
<td>Hepatocellular carcinoma</td>
</tr>
</tbody>
</table>

4. Delete the row labelled as “Total” in Table 2-5. Not sure what the numbers mean—the AVERAGE?

Following this suggestion, we have now deleted “Total” in Table 2-5. The numbers in the table are the average.

5. Number in table 2-5 was for “per admission”? Have the authors estimated the total costs in a year and divided the cost by the number of admissions if the patient had two or more hospital admissions. Was this mis-label as per case in the past 12 months (not per admission)?

- Yes, Number in table 3-6was for per average annual admission.
- Yes, the total costs in a year and divided the cost by the number of admissions if the patient had two or more hospital admissions.
- per case is replaced by per admission in the paper.

6. The authors should report the medical cost from the CURRENT hospital admission for which the costs were directly obtained from the hospital financial database. Please report the cost obtained from interview in a separate table or row in order to estimate the total medical cost in past 12 months.
We have followed the referee’s suggestion and added Table 8 and 9 to report costs from the hospital data and the interviews separately (page 24-25).

7. The distribution of medical costs usually skewed to the right (a long tail) and median is probably more appropriate than mean. Alternatively the authors can report the distribution by categories (e.g., related to the annual medical household income level--% cost lower than the income, % cost greater than 1 time and % greater than 2 times of income etc).

We have followed the referee’s suggestion and added a new Table 10 (page 25) to report. In addition, the Kruskal-Wallis test is used to provide the statistical analysis on in table 2, table 3, table4, table5, table6, table7, table8, table9, and table10.

8. Overtreatment and over-medication are among the reasons for high costs. The authors may discuss the high cost of acute HBV (unnecessary treatment? and the cost of nutrition supplements etc as means to contain cost).

The reviewer pointed out a very important policy implementation of the study. We addressed this point is “Conclusion” on page 14.

In addition, we revised the AUTHOR’S CONTRIBUTION on page 14-15.

We believe that our paper has improved through the review process, and would like to resubmit our paper for publication at the BMC Health Services Research.

Sincerely yours,

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