Author's response to reviews

Title: Re-Thinking The Perception Of Hepatitis B Virus Infection Risk In Asian Immigrants To The U.S.: A Prevalence Study On Hepatitis B Virus Infection Among First Generation Korean Immigrants In The Southern California Inland Empire.

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We thank the reviewers and the Editors of BMC-ID for their review of our manuscript, their helpful comments and recommendations, and the opportunity to respond with our revision. We are providing point-by-point-responses to the critiques and a revised version of the manuscript with tracked changes as well as a “clean” version. Thank you for your consideration.

Responses to Reviewer #1:
1) “Introduction section is too long. Please cut down by at least 50%”. We feel the content and length of the introduction is appropriate and it provides fundamental background material on the topic, in particular as it relates to demographic data in the geographical area studied. Reviewer #3 has also asked for minor revisions in the introduction. Currently the length is only about 650 words. Reviewers #2 and 3# have not made any comment on the manuscript length.
2) “The paper has major formulation issues. Many sentences are not clear.” This manuscript was again reviewed by the two senior authors (MM and BR). Both are native English speakers. Other than some changes in a few sentences requested by Reviewer #3, we disagree with this critique. We note that Reviewer #2 comments that the manuscript is “very well written”.
3) “The aim of the study is vaguely formulated.” The aim of this study has been revised to provide more clarity. See Background, last paragraph, last sentence.
4) “It might be interesting to make a figure of the percentage of infected, immune, susceptible individuals.” We disagree. Such a figure would be redundant with the text.
5) “Quality of written English: Not suitable for publication unless extensively edited.” We respectfully disagree; see comments above.

Responses to Reviewer #2:
1) “The glaring weakness of this study is the small sample size which limits their ability to draw definitive conclusions.” We disagree. The population of first generation Koreans in the IE is about 19,000 [20]. Sample size calculations for prevalence studies [Naing L, Winn T and Rusli BN (2006). Sample Size Calculator for Prevalence Studies. Available at: 
http://www.kck.usm.my/ppsg/stats_resources.htm] including an estimated HBV prevalence as low as 2% and has high as 8% (with and without Finite Population Correction), and a 95% CI concluded to a minimum of 300 subjects (precision= 0.05) required for this screening. A 0.025 precision is reached with 936 subjects. We therefore consider our study to have enough power to draw conclusions of prevalence in this particular population. Furthermore, as described in our discussion our study sample was similar in key socio-demographic characteristics when compared with the most recent ACS data [21] on East Asian residents in San Bernardino and Riverside. Lastly when bearing in mind the population’s involvement in religious congregations [24], we believe our selected locations for screening allowed representative sampling.

Responses to Reviewer #3:
1) “When I read the title I thought the paper would describe how Korean immigrants perceive their risk for hepatitis B. As this is not covered I would suggest to change the title to better reflect the content of the paper.” We agree, and have changed the title to: “Lower Than Expected Hepatitis B Virus Infection Prevalence Among First Generation Koreans in the U.S.: Results of HBV Screening in the Southern California Inland Empire.”

2. “In the background section it is mentioned when the US started vaccinating, and when the WHO recommendations were made. It would be informative to include when vaccination started in Korea.” We agree and have included this information in: background, third paragraph, second sentence.

3. “On page 5 (last paragraph of background) it is stated that it is difficult to estimate HBV prevalence among Koreans. But why is this so? It looks like the authors intend to say there are no data available, which is a different issue.” We agree on the need to reformulate this sentence to better describe the issue. We wrote in background, last paragraph, first sentence: “While there is a reasonable expectation of greater HBV prevalence among immigrants compared to the general U.S. population, there is no data regarding HBV prevalence among Koreans in the Inland Empire.”
4. “In the methods on page 6 term reflex is used. I have never heard of this term. Can this be explained? It looks like it can just be replaced by ‘test’.” The term Reflex is of common use in diagnostic laboratory testing and a standard term for referring to confirmation or supplemental results. Reflex testing occurs when an initial test result meets pre-determined criteria (e.g., positive or outside normal parameters), and the primary test result is inconclusive without the reflex or follow-up test. We believe the term best reflects the actual methodology and thus should remain in the manuscript in the methods section. It has been replaced where used in the results section (see below).

5. “Page 7, last paragraph. The authors explain they calculated weighted prevalences but it is not clear where these weighted prevalences are presented in the results, and it is not clear what the authors wish to achieve with weighing. This should be explained.” Please see a detailed and revised section on statistical analyses at the end of the methods section, which clarifies this question.

6. “Page 8, 2nd paragraph. A p-value of a test for difference in age distribution between men and women is presented but it is not stated in the methods which test was used. I assume it was a T-test but this should be included in the methods section.” Please see a detailed and revised section on statistical analyses at the end of the methods section, which clarifies this question.

7. “Page 8, last paragraph. What is the rationale for presenting data on alcohol consumption among participants as alcohol is not a factor you would assume to be related to having a chronic hepatitis B infection.” We agree, alcohol consumption is not a lifestyle factor that would affect vertical HBV infection. However alcohol use is certainly a risk factor for liver disease and that was the reasoning behind gathering this data, without knowing before hand what the carrier prevalence would be. We also wanted to see if alcohol consumption had any relation to extent of liver disease or vaccination rates. As such there were no clinical correlates but we feel this is important socio-demographic data which readers such as Hepatologists would be interested in knowing.

8. “Page 9, 1st paragraph. Please also report the 95% CI for the prevalence of chronic infection.” We agree. Frequencies for all serological diagnoses are now complemented with 95% CI for each serological profile in results, 4th paragraph.
9. “Page 9, 2nd paragraph. The first sentence should be moved to the second paragraph were viral load is described.” We agree, the sentence has been moved accordingly.

10. “Page 9, second paragraph. The last part about family history is unclear. First of all, make it more explicit to which group ‘This group …’ refers. I assume it is referring to those infected. If that is the case, 41.4% of those infected would have family history of liver disease (as 58.6 did not), but in the past sentence a percentage of 6.3 is mentioned.” We agree and acknowledge that this was a redaction error on our part; the results were not presented appropriately. Changes have been made to correct the reporting of HBsAg positivity stratified by family history of liver disease. See Results, 5th paragraph (Serological and Demographic correlations), last sentence: “The HBsAg positive group also denied knowledge of personal (72.4%) or family (58.6%) history of liver disease. Despite these reports, there was a higher proportion of HBsAg positive participants among subjects with a family history of liver disease compared to those without (6.3% vs. 2.3%, p=0.023).”

11. “Page 9, last paragraph. Half of those infected had been tested before. Do you also know how many of those were aware of their serological status?” Although participants were asked if they had been previously tested before the screening, unfortunately no data was collected on patient’s knowledge of previous serological status, other than vaccination.

12. “When reporting on viral load it would be informative to report the distribution across the 3 categories <2,000 / 2,000-20,000 / >20,000 as these are relevant in clinical management (AASLD treatment guidelines).” We agree and results have been categorized and are now presented as suggested in Results, 4th paragraph (Serological diagnoses), last sentence: “Among the 29 infected subjects the median DNA quantitative PCR was 285 IU/ml (29 to ≥110,000,000 IU/ml) : <2,000 IU/ml in 17, 2000-20,000 IU/ml in 3, and >20,000 IU/ml in 8.”

13. “Page 9, last sentence. I suggest to change Reflex to Further, or Additional.” We agree, the change has been made in Results, 6th paragraph (Serological and Demographic correlations), last sentence: “Further testing was not performed for one of the HBsAg positive subjects due to low sample volume”.

14. “Page 10, first sentence. The lack of health insurance appears to be a huge barrier for follow up. To avoid unnecessary costs for positive participants, has the option of using clinical indicators like HBV DNA, HBeAg and ALT to select patients for referral been considered? The majority of chronically infected patients would have inactive disease
requiring yearly follow up of ALT only.” We agree that this is a pertinent point. Patients that were HBsAg positive were offered a clinic appointment and liver US, AFP and transaminase testing all at a cut-rate institutional fee. Nevertheless many patients did not take up this offer. A more streamlined approach was not considered.

15. “Page 10. See remark 6. It is not described in the methods which statistical tests were used.” Specific tests for significance are now indicated in the description of statistical analyses for clarity: Methods, last paragraph.

16. “Discussion. This study indeed shows the prevalence among adult Korean immigrants is lower than expected, but it is still above 2%, warranting screening. This last aspect could be emphasised a bit more.” We agree. The concept has been reiterated in the conclusion section: “Despite the lower than expected HBV prevalence, an infection rate >2% indicates that this population is still at risk and should be screened. Complete serological screening testing can lead to optimal management of those individuals at risk for hepatitis B.

17. “The term rate is used throughout the paper when prevalence is meant.” We agree. The term “rate” has been changed to “prevalence” in 16 instances throughout the manuscript.