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Title	Descriptive Study: Hepatitis B Testing and Linkage to Care in a Canadian Urban Tertiary Referral Centre
Authors	Keith CK Lau BHSc; Abdel Aziz Shaheen MD; Alexander A Aspinall MD; Tazuko Ricento; Kamran Qureshi; Stephen E. Congly MD; Meredith A Borman MD; Saumya Jayakumar MD; Bertus Eksteen MD; Samuel S Lee MD; Laura Stinton MD; Mark G Swain MD; Kelly W Burak MD; Carla S Coffin MD
Reviewer 1	Dr. Tim Lee
Institution	BC Cancer Agency, Cancer Control Research Program
General comments (author response in bold)	This is an interesting study and a well-written paper, characterizing the monitoring and treatment plan of HBsAg+ patients in Calgary, Alberta. Among the 1214 individuals with positive HBsAg test results, only 10.3% of them received all four laboratory assessments. Then 117 patients with significantly elevated ALT values, only 31 (42%) received hepatitis B treatment. On top of it, among the 31 patients with significant ALT and viral load values, only 13 of them had anti-HBV treatment. These findings strongly suggest gaps in care for CHB patients in Calgary, a major city in Canada. **Thank you for your comments.** 1. My only comment is related to the abstract, which states that "non-parametric statistical methods were used for analyses." According to page 6, lines 38-41, "we used Fisher Exact test or Chi Square test for categorical data and Kruskal Wallis or Student's t-test for continuous data, where appropriate." It seems that both parametric and non-parametric tests were used. **Thank you, we agree with this statement and have modified our abstract accordingly as observed on page 4, line 28.**
Reviewer 2	Alan Huang, MPH, MSc
Institution	Board Member and Community Programming on Viral Hepatitis, Hepatitis C Education and Prevention Society (HepCBC)
General comments (author response in bold)	Introduction 1. Page 5/20, Line 48: sentence fragmentation. **Thank you. We agree with this statement and have modified this sentence, page 5, line 40.** 2. Page 5/20, Line 55: Reference #9 was cited to indicate that PHAC report is inconsistent with BCCDC report, and that BCCDC report "indicates a much higher incidence and prevalence of CHB in the province of BC". However, the reference cited did not indicate this reasoning. In 2013, BC's rate of CHB and unknown is 26.4 per 100,000 population, which is indeed higher than PHAC's reported rate of CHB in BC (23.4 per 100,000 population). But BC's reported data is higher since it includes both CHB and unknown, whereas PHAC's reported data only included CHB. Only certain cities within BC had a significantly higher rate (e.g. in 2014, Richmond had a rate of 96.5 per 100,000 population due to immigration from HBV endemic regions, compare to the BC Provincial rate of 24.3 per 100,000). If the Authors intend to compare regions within BC and Alberta where there is a significant higher rate of CHB due to immigrants coming from HBV endemic countries, please cite appropriate references for comparison. a. BCCDC data on CHB: Figure 14.1, page 47: http://www.bccdc.ca/resource-gallery/Documents/Statistics%20and%20Research/Statistics%20and%20Reports/Epid/Annual%20Reports/AR2014FinalSmall.pdf b. PHAC data on CHB: Table 2, page 20: https://www.canada.ca/content/dam/phac-aspc/documents/services/publications/diseases-conditions/report-hepatitis-b-c-canada-2013/pub-eng.pdf **Thank you for these comments. Our intention is not to compare the CHB rates between BC and Alberta, but to demonstrate the inconsistencies between data collection and characterization of the epidemiology of CHB within Canada. We recognize the confusion of this sentence format and have adjusted it accordingly to clarify our intent, (please see page 5-6). We also agree that the differences in the rates observed between the 2013 PHAC and the 2014 BCCDC reports are likely to be accounted by the inclusion of the "unknown" cases. Nonetheless, this aspect again demonstrates the inconsistencies in classification as well as collection of CHB epidemiological data within Canada** Methods Inclusion/Exclusion criteria 3. The Authors only included those with a provincial health number, which means that new immigrants who just arrived in City of Calgary are excluded from the study (i.e. those who just arrived in Canada have to wait 6 months before receiving a PHN in Alberta). This exclusion may be important in estimating the burden of disease, especially when the Authors referenced a few times that the increase in chronic CHB is likely due to immigrants from endemic countries. **Thank you for your comment and we agree with this statement. Our exclusion of that particular subset of individuals is a limitation of our study which is was noted in our manuscript (page 12, line 35-37). We have modified our manuscript to clarify recognition of this limitation. However, this also highlights that CHB disease burden may be underestimated in a large Canadian centre.** 4. Referral to specialists may not be necessary if the primary physician is able to treat and follow-up with the patients. Unless a clear guideline exists in Alberta where referral is needed for all cases of chronic infection, it is possible that primary physician can take on the role of prescribing medication and follow-up, should the primary physician be trained or knowledgeable in the field. In some cases, the primary physicians may consult with a specialist on diagnosis and/or treatment without actually referring the patients to the specialist. Hence, it is somewhat misleading to look at referral vs no referral to specialist as a way to determine care delivery. **Thank you for your comment. In Alberta, a primary care physician cannot prescribe a second generation HBV nucleoside analog (i.e., Tenofovir or Entecavir) or Pegylated Interferon. The Alberta provincial laboratory limits HBV DNA testing to a maximum of 2 tests unless ordered by a specialist in hepatology or infectious disease. However, we agree with the comment that many primary care physicians may be able to manage CHB, perform follow-up and hence we recognize that this is another potential limitation of the study. This information is clarified in the discussion on page 12, lines 44-52** 5. Are there data for other indicators of acute infection available to differentiate between acute vs chronic HBV infection? For example, anti-HBV core IgM antibody (before IgG is produced) can be used to indicate acute infection (BCCDC's guideline; reference #9 cited by the Authors). **We agree that serological indicators of acute infection would be helpful, however this laboratory data was not**

collected in the current study. However, not all cases of positive IgM anti-HBc are due to acute HBV infection. In some cases, chronic HBV reactivation, with high replication can also lead to positive IgM anti-HBc.

Results

6. Page 8/20, Line 40: …median 2.5 logIU/mL… (Figure 1C shows 2.4 logIU/mL)

7. Page 9/20, Line 43: …84.6% (230/273) tested HBeAg negative… (Table 1 shows 231/273)

8. Page 10/20, Line 10: …231 [89%] negative… (Table 1 shows 317 [89%])

We thank you for your comments. We have fixed these typographical errors as reflected in our revised manuscript on page 9 line 5, page 10 line 10, and page 10 line 30, respectively.

Other comments:

9. Reporting of percentage needs to be consistent (e.g. some percentage values were reported without decimals and rounded to whole numbers, while some percentage values had one decimal value)

We thank you for your comment. We have dealt with these inconsistencies as reflected in our revised manuscript.

Interpretation

10. The Authors were not able to differentiate between acute vs chronic HBV infections, and cited reference #9 (data from BC) to indicate that acute cases are relatively small in general. This differentiation is quite important as acute cases may not require follow-up and/or referral to specialists, thus skewing the No-Specialist Consultation data in Table 1.

11. Alberta actually has a much higher acute rate, and much lower chronic infection compare to BC, suggesting that there might be higher acute HBV infection in the study population. Using BC data does not support Authors' claim that acute infection in the study population "is minimal". This, again, may change the Results and possibly lower the number of individuals requiring specialist referral and/or follow-up in Table 1.

a. In 2013, Alberta had 3.5 times higher the rates (per 100,000) of acute infections compare to BC (https://www.canada.ca/en/public-health/services/publications/diseases-conditions/report-hepatitis-b-c-canada-2013)

b. In 2013, Alberta had almost 40% less the rates (per 100,000) of chronic infections compare to BC (https://www.canada.ca/en/public-health/services/publications/diseases-conditions/report-hepatitis-b-c-canada-2013.html)

We agree with these statements (10 and 11) that Alberta and BC rate of acute and chronic infections are not comparable. This has been modified accordingly in our revised manuscript. However, the inability to differentiate the acute from chronic infections is unlikely to significantly impact our results. Based off the Report of Hepatitis B and C in Canada 2013, the estimated rate of acute HBV infection is 0.7/100,000. Using this rate within the population of Calgary in 2014 (approximately 1.1 million), the estimated number of acute HBV infection cases is approximately 8 cases, which we believe would be negligible in terms of affecting our results. Alberta has initiated universal childhood vaccination since 1997, and most Canadian born persons are at low risk for acquiring acute HBV infection. Hence, we believe that the majority of 1200 cases that tested HBsAg positive in a 1-year period in our study are likely chronic HBV carriers and not due to an outbreak of acute HBV infection.

12. To clinically diagnose a chronic HBV infection, the patient needs to get tested again in 6 months (i.e. chronic if still not cleared after 6 months). Since the study period is only 12 months, assuming that the infection is chronic may not be supported especially for those who received the first testing near the end of the study period.

Thank you for your feedback and we agree with your comment. This is noted as a limitation of our study on page 12 of the discussion. However, as noted, the expected rate of acute HBV is minimal. We expect that the majority of HBsAg positive cases are chronic hepatitis B carriers.

13. The authors could be correct to state that the study "may underestimate the burden of HBsAg-positive cases". However, the reasoning and the references cited in the Interpretation section, as well as the lack of ethnicity data, do not fully support that statement.

Thank you for your comment. We provide further detail in the manuscript regarding the groups and individuals excluded (i.e., physician not within health zone, those without PHN, see page 12), to justify our statement that the current study likely underestimates the burden of HBsAg positive cases. We acknowledge that the lack of ethnicity data is also a potential limitation, and have noted this in our manuscript to clarify the reasoning of our statement.

14. The Authors referenced immigrants as one of the main reasons for an increased in CHB rates in Canada in many occasions, but no ethnicity data is provided for the 1214 HBsAg-positive cases. A large proportion of immigrants coming from HBV endemic countries often do not know of their infection status, hence the burden of HBsAg-positive cases is likely higher; a reason not discussed in the Interpretations section.

We agree with this statement, but unfortunately the ethnicity data of the cases within our cohort is unavailable. We have discussed this limitation in the interpretation section on page 12.

15. Without actually determining the burden of disease, it is common to assume that "the prevalence of HBV in migrants reflect their country of origin". The Authors further cite Reference #18 (page 11/20; Line 18) to support this statement. This reference cited by The Authors only addresses prevalence of CHB in Ontario or Canada as a whole, but does not indicate rates of infection in Alberta or City of Calgary. Burden of disease in Canada may actually be lower compare to immigrants' country of origin as immigrants tend to be healthier compare to their counterparts (i.e. those do not immigrant to Canada). A recent study done in BC by Ip S et al in 2015 (https://www.ncbi.nlm.nih.gov/pubmed/26361487) examined the number of HBs-Ag-positive cases in Chinese community, which showed that the prevalence is likely lower than the country of origin (2.7% as reported in the study compare to >10% in China/Taiwan/Hong Kong). Nevertheless, the rate is still significantly higher than the national data.

Thank you, we agree with this comment. However, immigrants from HBV-endemic regions tend to have higher rates of CHB infection overall compared to Canadian born individuals. We have modified our statement to clarify our intent, page 11, line 25.

16. Canadian-born individuals are more likely to have acute HBV than CHB due to screening at birth. In many cases, no follow-up testing and/or treatment is needed as acute infection can be self-cleared if infected at later age (e.g. median age of 44 as reported in the study). If a large proportion of these 1214 HBsAg-positive individuals turn out to be Canadian-born (i.e. more acute cases than chronic cases), this would further reinforce the above mentioned point that the actual number of individuals included in the No Specialist Consultation category in Table 1 is likely lower than reported (i.e. no follow-up and/or referral to specialist is required).

Thank you for your feedback. We recognize that the lack of ethnicity data is a limitation in our study. However as noted, most Canadian born individuals are at low risk of acute HBV infection especially given universal childhood vaccination since 1997. Thus most of those 1214 cases are likely chronic HBV carriers rather than due to an

	outbreak of acute hepatitis B. 17. The Authors compared the study results to a US study (Reference #19) to show that the care delivery and outcomes are comparable/similar. However, this comparison cannot be made since: 1) demographics of the study populations (ethnicity, age, sex) are likely to be quite different (ethnicity data not provided); 2) Canada and US have very different healthcare system and access-to-care/medical coverage; and 3) health disparity exists for immigrants (i.e. higher barriers to accessing care). **Thank you for your comment. We agree that the demographics of the population is somewhat different. Again we lack ethnicity data of the individuals in our cohort and are unable to compare with that of this referenced US Veterans study. However, we predict that the access to care and medical coverage may me more comparable than the general US population as this US study focuses on the patients of Veterans Health Administration, which has health care coverage.** References/Citations 18. For references #8, #9, #11, and #17, no links and data of accessed were given. 19. Journal titles were not italicized as per CMAJ referencing guideline. **We thank you for your comments. We have adjusted these errors accordingly in our revised manuscript, page 14-18.**