Article details: 2015-0117	
Title	**The role of immigration in hepatitis B and C and primary liver cancer — related hospitalization risk: 2006 Census linked population-based cohort study**
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Reviewer 1	Max Trubnikov
Institution	Public Health Agency of Canada, Centre for Communicable Diseases and Infection Control
General comments (author response in bold)	1) The analysis avoids to mention and explore the fact that HCV in Canada clusters within certain sub-populations, often affected by other co-morbidities and structural conditions, and is not equally distributed within Canadian population (Trubnikov et al, CCDR 2014; 40 (19)). Some of the sub-populations considerably more affected by the above health outcomes include institutionalised groups (inmates, residents of long-term care facilities) and otherwise not covered by the Census populations (Aboriginal people living on-reserve, homeless people, the homeless, individuals severely ill with chronic conditions, often caused by HCV/HBV viruses, and recent immigrants who don't speak English or French). In addition to not including the above population groups, the analysis does not include QC data, thus limiting the inferences that can be made from it to the sub-national level and only to the studied populations. **Regarding the representativeness of the Census, please see response overall general comment #4 above. Regarding the lack of Quebec data, we qualify by saying that this study is based on data for Canada, outside of Quebec.** 2) While the analysis explores the association of the hepatitis B and C with immigration and also attempts to establish the causality, it does not explore the role of other important risk factors, such as injection drug use and sexual risks, AFTER immigration to Canada. There is a body of evidence in Canada and around the world that immigrants may turn to using injection drugs, excessive alcohol use and engage in risky sex to alleviate the challenges of re-settlement in the recipient country. **The lack of health risk factors in the dataset has already been mentioned. This study also does not attempt to establish causality. We have now reinforced the point about the lack of risk factors in the limitation section.** 3) Also, use of origin-countries prevalence to describe/predict HBV/HCV prevalence in recipient countries immigrants has been found problematic and indicative at best due to the fact that immigrants's health and wellbeing is different than it is in their origin country counterparts. Another issue is the questionable reliability/validity of HCV seroprevalence tests results in high endemic countries in Africa and Asia. As such, a direct application of origin country prevalence measures and its implications need to be carefully explored and known limitations and the effect direction need to be described. **While the origin-countries HBV/HCV prevalence may not be a perfect predictor of the same prevalence among immigrants in recipient countries as a result of the healthy immigrant effect, this is the best proxy available that can be indicative of the studied risk. The issue about questionable reliability/validity of HCV seroprevalence test has been discussed in some details in the limitation section.** 4) Age is known to be the single most important predictor of any health outcome. There is also evidence of a birth cohort effect among people affected by HCV in Canada and the US. Is it plausible that the cohort effect associated the HCV, HBV and HCC morbidity and if yes, what is direction of this association? **Yes, the babyboom and earlier generations in Canada are likely to have a higher risk for HCV. This may partly explain why this study only found a risky immigrant effect for HBV and liver cancer, but not HCV.** **Two new references added as follows:** ***Screening for hepatitis C virus infection in adults: final recommendation statement*. Rockville (MD): US Preventive Services Task Force; 2013. Report no.: 12-05174-EF-2.** **National hepatitis C survey prompts call for all Canadian boomers to get tested. Markham (ON): Canadian Liver Foundation; 2013. Available: www.liver.ca/newsroom/press-releases/29-01_2013_CLF_recommends_hepC_testing.aspx (accessed 2015 Aug. 18).**

	These considerations need to be addressed, either in the discussion or limitations sections, for the analysis to maintain its credibility. There is a number of minor things that may require onsideration/correction as well. 1) The title may need to include adjective "the {possible} role of immigration…" as other risk factors were not explored. Also, [hepatocellular] is misspelled in the title. **We did state in the limitation section the lack of key risk factors in this study. Also, we did adjust for low income and place of residence, which can be proxy for risk factors not controlled here. We do not think it is necessary to add an adjective such as 'possible' to the title. AS for spelling of HCC, it is now substituted by primary liver cancer (PLC).** 2) P4, line 33. It's not clear what prevalence the paper talks about: chronic HCV or anti-HCV seroprevalence? If it's chronic HCV, then the measure, based on the citation provided (Myers et al, 2014), should be 0.74% that can be rounded down to 0.7% (not 0.8%). If it's anti-HCV seroprevalence, than a different range around 1.0% (can be found in Trubnikov et al, CCDR 2014 40 (19) should be applied. **Prevalence here refers to chronic HCV, and we have revised the prevalence to 0.7%.** 3) P5, line 4, should read …in the burden {of} liver… **Done.** 4) P9, lines 46-51. Is the age difference significant? And if yes, can the difference in the outcomes be attributed to the fact that immigrant were older? **While the age difference is significant, the analysis already controlled for this age difference, and therefore the outcome difference cannot be attributed to the age difference between immigrant and non-immigrants.** 5) P11, line 30 should read …countries had {almost} 3-fold… as OR 2.98 is not quite 3. **Done. Now the text reads:** **immigrants from high-risk countries had almost 3-fold odds of hospitalization compared with non-immigrants** 6) P12, line1 should read This is the first {sub-national} Canadian study … given the reasons outlined in the CONCERN 1 above. **Now the text reads: This is the first national Canadian study (outside of Quebec)....** 7) P12, lines 11-14. It's a bit confusing to read about "hospitalisation" and [hospital] "admission" in the same sentence, while thinking that both terms are based on the same data element and should describe the same thing. **Done. The text now reads: immigrants have an increased risk of hospitalization for HBV and HCC, but a lower risk for HCV and all liver diseases combined.** 8) P13, line 7. The source country risk level given its ad-hoc origin in this analysis can't be "a key factor influencing the likelihood of HBV,…" but is a proxy for other currently unknown and not investigated in this analysis factors, that warrants further, more targeted and in-depth analysis. **Now the text reads: Our study also shows that the source country risk level is an important factor influencing the likelihood of HBV, HCV and liver cancer-related hospitalization among immigrants.** 9) All-other-cause mortality effect on the study analysis (pp. 14-15), the effect of co-morbid states requiring hospitalisation (addictions, incl. alcohol and drugs, overdoses), diabetes, HIV needs to be explored or discussed in the limitations. **Now the limitation section includes the following: The possibility of**

	hospitalization due to co-morbid condition, such as diabetes and HIV could be explored in the future.
Reviewer 2	Prithwish De
Institution	Canadian Cancer Society, Cancer Control Policy
General comments (author response in bold)	Major comments: 1. One important limitation of the study sample selection in examining HBV, HCV and liver cancer risk is the use of census-identified population. I'm not familiar enough with the long-form census representation of Canadians, but i suspect it doesn't appropriately cover people with no fixed address (including homeless and IDUs) and First Nations living on reserve. These populations have higher prevalence of all of the exposures being examined in the study. This Canadian-born population being examined in the study may not be entirely representative of HBV, HCV, and HCC, and will thereby bring into question the results and comparisons of risk with the immigrant populations. **See response to overall general comment #4 above.** 2. pg 7, line 18: what is the rationale for choosing a 10 year cutoff for distinguishing long-term vs recent immigrants (is there some literature that suggests that the risks are different). I think the dichotomous nature of this variable limits the regression analysis; ideally, that analysis might be better if the year of immigration was included in the model to control for period effects, which are likely relevant to the analysis given the change in profile of immigrant populations to Canada over the period of interest (i.e. the source countries of immigrants have changed over this time). **See response to overall general comment #6 above. Essentially, the choice of using 10 years as a cut-off is to examine if elevated hospitalization risk is already detected or not among the most recent immigrant group, compared to that of non-immigrants. This is why we did not keep the variable as continuous to result in greater power and precision. The change in immigrant profile and source country representation over time could be partially captured by the risk level analysis.** 3. pg8, line 51: I wonder why HBV and HCV prevalence were used as proxies for HCC risk, given that surveillance of HBV and HCV in most countries, especially developing ones, are not good? Liver cancer rates are the better measures of risk and can be found through the IARC's Cancer Incidence in Five Continents or GLOBOCAN database. **We could use the primary liver cancer rate data, but as our focus is on viral hepatitis and the majority of HCCs are due to viral hepatitis, we chose this approach. This other data is not necessarily accurate either, particularly in developing countries where the diagnosis of HCC is probably suspect (no biopsies, poor imaging studies, no performance of autopsies).** Minor comments: 1. pg 5, line 14: please check whether the hospitalizations you examined are for primary liver cancer (C22) or for HCC. Even though HCC is a subset of primary liver cancers (representing about 80% of them), the terminology should be consistent with what was analyzed. Currently, the paper refers throughout to HCC only. **Done. Yes, primary liver cancer, and not HCC, should be used instead.** 2. pg 6, line 9: it's not clear why fiscal years rather than calendar years are mentioned here with regard to the DAD and census, unless the Tax File was the determining dataset for choosing the time periods for analysis. Please clarify in the text. **The use of fiscal years instead of calendar year is due to the linking of Census data to the hospital database, which follows the fiscal year. We also clarify that in the text, as follows:** **The primary outcome was an inpatient liver-related hospitalization occurring within the 3 fiscal years from April 1, 2006 to March 31, 2009, following the accounting practices of the DAD.** 3. pg 8, line 19: it would be informative for the reader to list the range of low-income based on family size and area of residence size. **This information could be found in the document cited. We now add an example of the range as follows:** **For example, for an economic family of 4 persons, the before tax threshold was at $38,610. For the same family in rural area, the corresponding threshold was**

	at $26,579. 4. pg12, line 51: is the hypothesis that recent immigrants are younger reflected in your data? Table 1 shows the mean age of recent immigrants to be 42 years and of longterm immigrants to be 54 years. Is this stat. significant? It would be good to use this comparison to support the statement. The median ages and ranges would be informative too. **Yes, the mean age differences between recent and longterm immigrants is significant. Now the text adds:** **This likely reflects the fact that recent immigrants are significant younger than their more established counterparts (mean age of 39 vs 54, respectively), and most liver diseases including HBV and HCV typically require decades to progress to advanced stages.** **Note that data checking shows that the mean age of the recent immigrants should be 39, not 42.** 5. pg13, line 37: please specify "HBV" vaccination **Done. The text now reads: To mitigate this future disease burden, initiatives that include serologic testing, prevention measures (e.g. vaccination for HBV), public health education, disease counselling, and linkage to care among at-risk immigrants have been proposed.** 6. pg 14, line 52: can you comment on how good birthplace is as a proxy for country of origin? **As is, this comment is not clear. Is it raising the issue that immigrants' birthplace may differ from country of origin, in terms of where the immigrants reside just before immigration? Due to the lack of clarity, this comment will not be responded to.**
Reviewer 3	
General comments (author response in bold)	This work investigates hepatitis B, hepatitis C and hepatocellular carcinoma hospitalization rates for immigrants compared to those born in Canada. It is a well written paper, and the analysis is clearly presented. Hepatitis B and C as well as HCC are becoming increasingly significant health issues, and this paper utilizes a national cohort to examine some of the risk factors associated with these diseases. This work confirms what has already been largely assumed and demonstrated to a lesser extent in other work, and can be used as further evidence that a more cohesive policy on prevention, screening and treatment of hepatitis in immigrant population should be established. There are several points in the paper that require further elaboration, as well as a few points that require clarification: - Although HBV and HCV are often lumped together in both studies and policy decisions, the epidemiology of the two diseases is distinct. It would be helpful for the reader to gain an understanding of this in the Introduction: - As the authors have done for HCV (page 4 Lines 33-38), please add a sentence describing HBV risk factors (sexual contact, IV drug use and vertical transmission), as the most common risk factors differ slightly between the two diseases. **Now the text adds:** **Risk factors for HBV include sexual contact, IV drug use as well as vertical transmission (e.g. from mother to her baby); whereas most newly identified infections occur among injection drug users and infected immigrants from HCV-endemic countries.** - The proportion of cases that are a) asymptomatic and b) chronic differ between HBV and HCV (for example, these differ according to whether the case was infected as a child or an adult), and this needs to be clarified a bit more in the Introduction. This is an important point because asymptomatic cases go undiagnosed more often than symptomatic cases, and acute cases (that resolve) do not contribute to HCC. For HBV for example, most cases infected in childhood will become chronic (and are often asymptomatic), while most cases infected in adulthood will clear. It is possible that the higher rate of HBV-related hospitalizations are reflective of an immigrant population that was largely infected as children (i.e. – through vertical transmission), were mostly asymptomatic and now have chronic HBV or HCC. This is a very different scenario than a population infected through high-risk behaviours in adulthood. We cannot draw any firm conclusions based on these data about who these immigrants are and when they were infected, but I think that it is important to consider this when applying the results from this study to thinking about

	screening and/or prevention policies. **This is a very interesting topic, but this would be suitable for a future study.** 4 - The authors cite an HBV prevalence estimate of <0.5% is (drawn from Canadian Health Measures Survey results) and an HCV estimate of 0.8% (likely from the 2007 PHAC estimate by Remis et al. but the referencing was not clear). Both sources of data have been criticized by some for underestimating prevalence (Shah et al., 2013 CMAJ for HCV and media interviews in 2013 for CHMS findings). Related to this, it is well-known that a large proportion of HBV and HCV cases are unaware of infection, and findings from the CHMS study were consistent with this. It is important to clarify this in the Introduction by adding a sentence or two about the possibility that the prevalence percentages cited are likely underestimates. **Now the text reads:** **The seroprevalance of HBV in Canada has been estimated to be low, as low as <0.5% in a population-based household survey sample[9], whereas approximately 3% of new immigrants are chronically infected with this virus.[10] …… For Chronic HCV, Canada also has a low prevalence (~0.7%).14 For both HBV and HCV, there may be under-ascertainment of prevalence.** The authors chose a duration of residence of 10 years to separate recent from long-term immigrants, although it is generally thought that progression from HBV/HCV to HCC takes longer. Was the choice of 10 years arbitrary or related to this? An explanation of the rationale would be useful. **See response to overall general comment #6 above.** - The fact that only hospitalization data (i.e – the DAD) was utilized in this analysis is a limitation. What is being missed by not including HBV/HCV cases that were never hospitalized? Are immigrants hospitalized for HBV/HCV more or less often than those born in Canada (due to disease severity related to the particular genotype of disease, differences in access to primary care/specialist care, etc.?). If so, this may under or overestimate the results. **Now the limitation adds the following:** **Regarding the lack of physician claim data, if immigrants were hospitalized for HBV/HCV more or less often than those born in Canada (due to disease severity related to the particular genotype of disease, differences in access to primary care/specialist care, etc., this may under or overestimate the results.** -Related to this, in the "Limitations" section there is a sentence stating that "limited data regarding diabetes was available in the hospitalized cohort but not among those who were not hospitalized". This is a bit confusing and makes it seem as if non-hospitalized cases were included. **Non-hospitalized cases were obviously included as all who did not link to a hospital record are considered to be non-hospitalized. Our concern here is that we only have limited information on diabetes status from the hospital records among those who had been hospitalized. Among those non-hospitalized, we have no information on their diabetes status. This prevents us from the use of diabetes status as a control in the multivariate analysis.** **Now the text reads:** **Limited data regarding diabetes was available from the DAD data in the hospitalized cohort as some patients may have diabetes as a co-morbid condition. However, among those who were not hospitalized, there is no information as to whether they have diabetes or not.** - The authors do not sufficiently discuss the very interesting finding that HCV rates were lower in immigrants compared to Canadian-born individuals. There are likely several possible reasons, but this finding may be related to the age-bands that were used for analysis, and the fact that baby boomers are at higher risk for HCV. The age bands as analyzed make sense, but they split up the baby boomers amongst the two lower age-bands. If baby boomers born outside of Canada are at a similar (increased) risk for HCV as those born in Canada, this would not show up with the age-bands as they currently are (rates by age-band were not shown but I am certain that the authors examined these data as part of the analysis). If baby boomers born in Canada have an increased risk of HCV that is not shared with baby-boomer immigrants this may be one of the reasons that the ASHR was lower in immigrants than Canadian-born

for HCV. Could the authors please comment on the lower HCV rates, and if they agree with the baby-boomer issue as being a potential reason, examine the data using different age-bands (if this is possible through census data) or by commenting in the manuscript? This is an important point relating to potential screening strategies since other jurisdictions (ie- US) recommend baby-boomer screening, so how does immigration affect this (i.e. – what is the risk of a baby boomer born outside of Canada but in a low risk country?).

Thanks for the insightful comments. The discussion now adds the following:

The result that immigrants had lower odds for HCV compared to Canadian-born individuals should be taken within the context of higher prevalence of HCV in "baby boom" Canadian-born compared to people born earlier or later than this cohort. This unique age profile of Canadian HCV prevalence was not seen in immigrants with a similar age.[33,34] This has implications on potential HCV screening strategies.[35]

- It seems from the Methods section that both SES and urban/rural residence were added to the multivariate model a priori. If this was not the case, and these variables were found to be confounding and added as the model was built, this needs to be clarified. If not, the rationale for this should be explained. Is SES or urban residence considered a proxy for high-risk behaviours? Or do the authors suspect that low SES correlates with delay in seeking care and may result in untreated HCV progressing to HCC? This point needs to be clarified, particularly because both of these variables are markers for high-risk, but not high-risk themselves.

Low income is part of the control as it is expected to be a marker for high risk behaviour, including the delayed help seeking behavior mentioned. Rural indicator is to control for the access the health care, as those living in rural area are less likely to be getting medical help, when needed.

Now the text adds: Low income was a proxy for high risk behavior, while place of residence reflects proximity to hospitals.

Minor comments:
- There is a typo in the title ("hepatocellular" not heaptocellular").

Since we have changed the title to refer to primary liver cancer, this comment is no longer applicable.

- Please add a reference for the sentence about HBV/HCV being the underlying etiology in approximately 80% of cases (Page 4, lines 17-22). This percentage is often cited but some sources estimate the percentage to be lower.

We now use the following reference:

Perz JF, Armstrong GL, Farrington LA, et al. The contributions of hepatitis B virus and heptatitis C virus infections to cirrhosis and primary liver cancer worldwife. Journal of Hepatology 45 (2006) 529-538.

- Please add a reference for the sentence about the lifetime risk of dying from cirrhosis/HCC in chronic HBV patients (Page 4, line 29-31).

Two references for the lifetime risk have now been provided.

Goldstein ST, Zhou F, Hadler SC, Bell BP, Mast EE, Margolis HS. A mathematical model to estimate global hepatitis B disease burden and vaccination impact. International Journal of Epidemiology. 2005;34(6):1329-39.

Huang Y-T, Jen C-L, Yang H-I, Lee M-H, Su J, Lu S-N, et al. Lifetime risk and sex difference of hepatocellular carcinoma among patients with chronic hepatitis B and C. Journal of Clinical Oncology. 2011;29(27):3643-50

- A few other sentences in the Introduction are missing references.

We have provided other references deemed missing, such as:

World Health Organization. Global policy report on the prevention and control of viral hepatitis in WHO Member States. Geneva, Switzerland: WHO; 2013

Sherman, M. Liver Disease in Canada- A Crisis in the Marking. Markham, Ontario: Canadian Liver Foundation; 2013.