Article details: 2019-0103	
Title	A Nationwide Descriptive Study on the Epidemiology of Chronic Hepatitis B Virus Infection (The Canadian Hepatitis B Network)
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Reviewer 1	Ming-Lung Yu
Institution	Department of Internal Medicine, Kaohsiung Medical University, Kaohsiung City, Taiwan
General comments (author response in bold)	(There are no comments).
Reviewer 2	Jane Buxton
Institution	School Population and Public Health, University of British Columbia, Vancouver, BC
General comments (author response in bold)	Thanks for the opportunity to review this article which describes chronic HBV cases from 8 provinces. It is good to see a summary with such a large sample size (>9,000) There is a very impressive list of co-authors. **Thank you. The co-authors directly supervised or organized data collection submitted and obtained local hospital or university ethics approvals, and signed data sharing agreements after legal contract review with the Canadian HBV Network c/o the University of Calgary. All authors provided available clinical information or laboratory testing data, feedback on the manuscript and assumed responsibility for data integrity and conduct of the study at their site.** 1) In acknowledgments- Mark Khan at Gilead is thanked but not clear what role he played. **The acknowledgements have been updated.** 2) Some of the sites listed do not have a city eg Bailey health Clinic and University Health Network which would be helpful to identify where and # patients from each. **This is clarified.** ABSTRACT 3) I would prefer to see people first language i.e. persons with chronic HBV rather than defining individuals by an infection. Not clear this is only chronic HBV and excludes acute. **This has been addressed in the Abstract (page 4, line 101)** 4) Interesting comment re “under-appreciated” by whom? Thank you. This comment is removed from the Abstract conclusions as was not based on a systematic survey study. Collectively the co-authors represent many of the largest academic and community

	clinics in Canada for viral hepatitis treatment. The original abstract statement was based on unanimous expert opinion of members involved in the Canadian HBV Network and experience during our interactions with patients, patient advocacy groups, trainees, health policy/decision makers, and research funding agencies. This perception is reinforced by media release from International Coalition to Eliminate HBV (ICE-HBV) and recent publication in the Lancet Gastroenterology and Hepatology, 2019. "*Inexplicably, despite the huge human and economic toll of chronic hepatitis B (HBV), research remains largely underfunded*," (Dr. Peter Revill, senior scientist at Royal Melbourne Hospital's Doherty Institute, ICE-HBV president). INTRODUCTION 5) Mentions overall prevalence of CHB declined in Canadian born individuals due to childhood vaccination – true but this is as acute infections reduced and especially some provinces with infant (rather than childhood vaccinations) make a difference as it's the babes that are more likely to go onto chronic infection- or is that what is meant by childhood versus adolescent programs. **Thank you. This is clarified on page 5, line 137. Historically both acute and chronic hepatitis B infection was higher in Canadian-born individuals from communities with higher prevalence of the disease (i.e., First Nations) and persons with risk factors for exposure to blood-borne pathogens (i.e., occupational exposure, persons who inject drugs). The risk of chronicity following viral exposure is related to the age of infection, with >90% of infants and ~50% of children up to age 8 developing chronic infection, compared to ~1-2% of healthy immunocompetent adults. Following universal childhood vaccination, chronic infection has declined in Canadian born persons, but due to the impact of immigration from HBV endemic regions, hepatitis B remains an ongoing cause of significant liver disease in Canada.** 6) Page 5 last paragraph is this meant to be long-form census? **Yes. This refers to the Government of Canada long-term census. (page 5, line 142)** METHODS 7) Sampling frame is not clear – I understand it is data shared by members of CHBN but are these random patients extracted from all patients seen, all patients seen in a particular year or patients seen ever. Was it the same for each reporting site? If comparing provinces would be good to know if sampling was different. **Thank you, the sampling frame is clarified on page 7, line 177. All patients were seen in clinic after January 2012, cross-sectional data analysis was done on the most recent patient record submitted. Some sites had larger, more comprehensive longitudinal electronic repositories, others had limited electronic data, and submitted available data in online portal after manual chart review of known cases. Thus, while sampling differences would have affected our ability to compare interprovincial differences, it is interesting for readers to appreciate a snapshot of available data of persons with hepatitis B from each jurisdiction.** 8) Why were only mono-infected shared- understandable for fibrosis and treatment perspectives but it would have been informative and helpful to know how many

	were excluded for each of HCV, HDV and HIV co-infection and also if the ages, sex and genotype differed with those who were coinfected. **Thank you, assessment of co-infection was beyond the scope of current study. The Canadian HBV Network has ongoing studies and manuscripts in progress on HBV/HDV coinfection (Osiowy et al., abstract presentation Global Hepatitis Summit 2018) and HBV/HIV coinfection (Cooper CL et al., abstract presentation AASLD 2018). (This is noted on page 7, line 193)** RESULTS 9) It was disappointing to not see breakdown of results by age and sex. For example, women may be identified at an earlier age as routine testing occurs in pregnancy and if younger more likely to be HBeAg reactive. Treatment may also be associated with pregnancy to reduce transmission to the neonate. **Thank you, we agree this is an interesting question. We analyzed available clinical and demographic data based on sex (Table 3, page 9, line 247). We also analyzed HBeAg status based on age cut-off of > or < 40 years (Table 3, page 9, line 247). As noted, given the limited clinical data available from some study data sets submitted by participating sites, we cannot conclude whether this data is representative of all people living with hepatitis B in Canada.** 10) Genotyping stated as being limited- but not clear who more likely to get tested. **Thank you. Genotyping is not a routine clinical test and not offered by most provincial or hospital testing labs. The majority of data is available from clinics that have analyzed genotype through other clinical efforts or research studies. In general genotyping is done in patients who are being considered for interferon therapy, which is not approved in BC or ON for hepatitis B. This is noted on page 8, line 202.** CONCLUSION 11) States epi data important to inform programs to improve prevention, diagnosis and treatment access but does not give examples how or in what way – i.e. the so what of the paper. **Thank you. We acknowledge the study limitations, yet it contributes new knowledge on hepatitis B epidemiology and liver disease in Canada. The available information on HBV ethnicity and genotype may inform possible response to novel antiviral agents in development. The data on current nucleos(t)ide analog treatment, many who require long-term therapy, provides insight into the current burden of health-care costs and shows differences due to provincial reimbursement. The study reinforces need to improve screening in high-risk groups (i.e., persons from HBV endemic countries) and highlights the need for a universal, coordinated infant HBV immunization program. To date no nationwide studies on HBV have been published, hence this is novel and Canada-specific data (see page 13, line 349)**
Reviewer 3	Morris Sherman
Institution	Division of Gastroenterology, University Health Network, University of Toronto, Toronto, Ont.
General comments	Dr Coffin and her colleagues from across Canada have collected a series of more

(author response in bold)	than 9000 cases of hepatitis B and described the population in detail with regard to important variables, such as age, gender, ethnicity and various virological markers such as viral load and e antigen status. 1) This is a cross sectional study and reflects the geographic distribution of contributing physicians as much as the geographic distribution of patients. **Thank you. The study includes investigators from larger urban centres in Canada. In general, most patients with hepatitis B are seen in tertiary referral, specialist clinics in urban centres. The main prescribers for hepatitis B drugs are by designated specialists (including patients referred from rural communities). We acknowledge that we have missed data especially from other large viral hepatitis clinics in BC and ON that were not involved in the current study. This is discussed on page 13, line 337.** 2) The authors claim that hepatitis B is under appreciated in Canada, but this manuscript does not provide evidence for that conclusion. There are no prevalence data (not that prevalence data is available since few provinces collect this data). There are no longitudinal data to indicate what happens to these individuals. How many develop cirrhosis, liver cancer, liver failure and need transplant? This is what is important. A case series such as this one really does not provide a lot of information that is useful. **Thank you. This limitation is discussed on page 13, line 337. We acknowledge that a cross-sectional case series such as this one cannot provide prevalence data or report on long term liver disease outcomes. However, the data does provide useful and interesting information, especially given the minimal published recent data in Canada on patients living with hepatitis B (i.e., epidemiology, demographics, treatment, and genotype). Collectively, the co-authors represent the largest clinics in Canada for viral hepatitis treatment.** **The statement regarding HBV underappreciation is based on unanimous expert opinion, collective experience during our interactions with patients, the general public, patient advocacy groups, trainees, health policy/decision makers, and research funding agencies. This perception is reinforced by media release from International Coalition to Eliminate HBV (ICE-HBV) and recent publication in the Lancet Gastroenterology and Hepatology.** **"*Inexplicably, despite the huge human and economic toll of chronic hepatitis B (HBV), research remains largely underfunded*," Peter Revill, senior scientist at Royal Melbourne Hospital's Doherty Institute.** 3) The authors point out that hepatitis B is a notifiable disease, but only acute hepatitis B is notifiable. Health Canada does not collect data on chronic hepatitis B. **Thank you, this is noted in our paper (page 5, line 128)** 4) There is no discussion of biases that might be inherent in this sample collection except for a discussion about geographic differences and the concentration of immigrants from endemic areas in larger metropolitan areas. For example, could the fact that these data are from most academic centres reflect a more severe spectrum of the disease, since inactive disease might not be referred for specialist care? Other similar biases might also exist. **Thank you. We have revised our manuscript to acknowledge and discuss these biases (see page 13, lines 337)**

	5) Table 1 describes the provincial differences in several demographic data. p Values are quoted but the comparator is not given. What is the reference value for each of the columns? Same problem with table 2. **Thank you. The comparator is the national average and is corrected in new Table version.** 6) Figure 1 has the same problem. Which is the reference value? **Thank you, this is corrected in new Table version.** 7) In figure 2, the authors have looked at differences between the variable in each province and the national average of that variable. I am not sure that this is a valid comparison because the inclusion of the individual provincial data in the national average automatically skews the national average towards the particular provincial average, especially for provinces contributing large populations to the database. The comparison should be between the national average minus the particular provincial population, and the provincial population. **Thank you, we have corrected this analysis in new Table version.** 8) Figure 2D is meaningless. Displaying differences in fibrosis level by province suggests that there is a link between where a subject lives and the severity of fibrosis. If this link is present it is at best indirect, and is a reflection of the population in that province rather than the geographic difference. Furthermore, there are no significant differences between provinces in fibrosis levels, so why display this graphically? **Thank you. We have removed Figure 2 from the paper. Large data sets were submitted from BC, AB, MB, ON, including data on fibrosis severity. We do not propose that the specific geographic/province of residence is linked to fibrosis risk. However, the information on stage of liver disease per province may be of interest to CMAJ readership (i.e., health policy makers and public payers) given the existing disparities between access to HBV treatment in Canada. In BC and ON (until recently) reimbursement for second generation NA is only for persons with cirrhosis, yet other provinces do not have such restrictive criteria (Congly and Brahmania, CMAJ-Open 2019).**