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Title	Hepatitis C virus infection in First Nations populations in Ontario from 2006 to 2014: a population-based retrospective cohort analysis
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Reviewer 1	Nance Cunningham
Institution	Medicine, The University of British Columbia
General comments (author response in bold)	This study provides important useful observations about Canada's HCV epidemic, and can inform policy makers designing the HCV elimination effort. It confirms the status of First Nations in Ontario as a population which should be prioritised in testing and treatment for hepatitis C to avert poor outcomes. Specifically, this study aimed to document age-standardised testing and diagnosis of HCV in registered First Nations populations in Ontario, with some limitations inherent to the data. Findings from this study emphasize the necessity of strong partnerships with Indigenous peoples to diagnose the significant level of HCV infection. The valuable data about location co-morbidities and can help to form those partnerships, and to guide prioritisation and testing strategies. **The authors thank the reviewer for carefully reading the manuscript and their comprehensive comments and suggestions. We agree with the comments and suggestions of the reviewer and have addressed them below and incorporated them into the revised manuscript as indicated.** Abstract Generally the abstract is informative, balance, and well organised. **The authors thank the reviewer for their comment.** The abstract refers in line 49 to "efforts to eradicate HCV" but the correct term is "eliminate", as HCV could be re-introduced. **The authors thank the reviewer for this suggestion. Abstract line 49 (the last sentence) has been revised to read "efforts to eliminate HCV".** Introduction 1. The introduction gives concise and relevant figures. However, the estimated prevalence and estimated proportion of undiagnosed cases come from two different studies, and refer to different years. The estimate of 44% undiagnosed comes from Trubikov et. al 2014, and the estimate is for the year 2011. The prevalence estimate for 2011 in the Trubikov paper is 0.64%. What is cited in the text is a prevalence of 0.8% which is found in Shah citing Rémis. Rémis made a model predicting 0.78% prevalence in 2007. Rémis's model estimates 21% undiagnosed in 2007, based mostly on data from 2004 and earlier. While HCV is a slowly changing epidemic, it would be better to use estimates from the same study unless there is some reason unknown to the reviewer justifying the choice of only one aspect of each study. The Trubikov estimates use data collected closer to the midpoint of the time period of this paper, and so seem like they would be most appropriate. The reviewer acknowledges that there may be reasons not relevant to this paper that the authors chose to cite the two figures from different sources, and that this paper is not the place to discuss the reasons for regarding one as more reliable than the other. However, the years the different estimates refer to should be reported.

	The authors agree with the reviewer's comment. The introduction (page 4 line 8) has been revised to read "In 2011, the estimated prevalence of chronic HCV in Canada was 0.6% to 0.7%, with 44% undiagnosed." The references have been revised to cite Trubnikov et al. 2014. 2. The rationale is well explained and the objective is clearly stated. **The authors thank the reviewer for their comment.** Methods 1. Please put in full name of ICES at first use, p3 line 46. **The authors thank the reviewer for their comment. In 2018, the institute formerly known as the Institute for Clinical Evaluative Sciences formally adopted the initialism ICES as its official name. This change acknowledges the growth and evolution of the organization's research since its inception in 1992, while retaining the familiarity of the former acronym within the scientific community and beyond. Therefore, ICES is not an acronym for a full name.** 2. The study design, setting, variables, participants (including eligibility, selection, and follow-up) and data sources were very clear and appropriate. However, one aspect of the cohorts was not immediately clear. There are three cohorts: tested, diagnosed, and no test. They are not explicitly presented as nested or mutually exclusive, and the reader may suppose either way. The annex makes it clear that the 'diagnosed' are nested in the 'tested', but it would be preferable to mention the nesting in the text as well. **Not all of those in the diagnosed cohort received their first test during the study observation period. Some were tested prior to 2006 and then received their first diagnosis after 2006 (study start). We have extensively revised Figure 1 to make the cohort selection more clear. We have also revised the first paragraph of the section "Study Design and Population" and added the following details:** **"We conducted a population-based retrospective study in three cohorts of First Nations individuals in Ontario aged <106 years, who from January 1, 2006 to December 31, 2014: 1) received their first HCV test, determined by looking back to 1999 ("tested cohort"); 2) received at least one positive test result (antibody or RNA) for HCV infection ("diagnosed cohort"); or 3) had no record of an HCV test, determined by looking back to 1999 ("no test cohort"). Patients in the tested cohort had to have their first test in 2006 to 2014, while the positive test for patients in the diagnosed cohort could have been after an initial negative test, which could have been prior to 2006. Therefore, not all the patients in the diagnosed cohort were nested within the tested cohort."** **In addition, to add clarity, the second sentence in the second paragraph under the "Study design and Population" section was revised to:** **"Records of HCV testing from January 1, 1999 to December 31, 2014 were obtained from Public Health Ontario (PHO), a central hub for Public Health Unit specimen testing."** 3. This paper uses all records for the defined population, so study size and bias were not issues within the analytical frame. Statistical methods were clear.

	The authors thank the reviewer for their comment. Results 1. Results are very clear. Data on HCV testing, diagnosis, and prevalence in Canada is sparse, and these are very interesting results. **The authors thank the reviewer for their comment and input.** Discussion 1. Page 10 line 37: mentions 'clinically apparent infection' but the study is about diagnosed infection, with no mention of clinical signs. **The authors thank the reviewer for noting this. The line in the Limitations subsection of the Interpretation has been revised to read "diagnosed infection".** 2. Limitations clearly mention the extent of generalisability of the data, especially regarding population. However, the authors do not mention another limitation, that most of this study covers the time when interferon treatment was the only treatment available. With the availability of the more effective, better tolerated direct-acting antivirals (DAAs), the incentive for testing would rise after the study period. This is another limit on the generalisability regarding time. Given the magnitude of the difference in treatment outcomes with DAA versus interferon, I think that this is worth mentioning. **We have added to the Limitations subsection of the Interpretation (fourth paragraph, page 11) the following:** **"The widespread availability of effective, safe, short course direct acting antiviral (DAA) HCV treatments in Canada in 2014 has been associated with increased numbers of treated individuals23 and thus may have increased the incentive for testing. Our HCV testing data ended on December 31, 2014 and did not fully capture these potential consequences."** **We have also added the following reference:** **23. Schanzer D, Pogany L, Aho J, Tomas K, Gale-Rowe M, Kwong JC, et al. Impact of availability of direct-acting antivirals for hepatitis C on Canadian hospitalization rates, 2012-2016. Can Commun Dis Rep. 2018 Jul 5;44(7–8):150–6.** Tables: Table 1 1. There is a typo in the upper IQR for the tested cohort (24, should be 42?) **The authors thank the reviewer for noticing this and have corrected the typo in Table 1. We have reviewed the data and the upper IQR for median age is 44.** General Comments 1. As the years of this analysis are just before a major change which may influence the behaviour studied (namely, access in Canada to a more effective, better tolerated class of drugs, second generation DAAs), I would like to see the years covered in the title. **The authors have revised the title of the manuscript in consideration of this comment and the one below, to read "Hepatitis C virus infection in First Nations populations in Ontario from 2006 to 2014: A population-based retrospective cohort analysis"**

	2. The title identifies this as a descriptive analysis, but the abstract points out that the analysis is of a cohort, and uses administrative data, both important aspects of this study which the authors might consider putting in the title. **The title of the manuscript has been revised as described above in our response to Comment 12.**
Reviewer 2	Kate Salters
Institution	Faculty of Health Sciences, Simon Fraser University at Harbour Centre
General comments (author response in bold)	I commend the authors on this important paper which provides a high-level overview of HCV epidemiology among First Nations communities in Ontario. It is critical that the authors did this work in partnership with the First Nations HIV/AIDS Education Circle. I anticipate there was authorship and inclusion of First Nations researchers and/or health care providers on this important paper. I have one larger comment around the analysis and a few other minor comments specific to clarifying and expanding where possible in the manuscript. **The authors thank the reviewer for the thoughtful input and suggestions. The reviewer is correct that a representative from OFNHAEC (our partner First Nations community organization) and a First Nations researcher are among the authors of the paper. We agree with the other comments of the reviewer and have addressed them below.** 1. Could you clarify why the specific time period of 2006-2014 was selected? **Public Health Ontario data are external to ICES and its records have to be deterministically and probabilistically linked at the individual level to the administrative datasets held at ICES to be useful in cohort studies. At this time, the HCV testing data that are linked at ICES span 1999 to 2014. The starting year of 2006 was chosen to ensure the availability and quality of the administrative data at ICES. For example, the Ontario Mental Health Reporting System (OMHRS) did not start until 2005. We are hoping to update this study in early 2021, when the PHO HCV testing data from 2015 to 2018 are expected to be linked and available for use at ICES.** 2. In the introduction, I would change "ongoing relationship" to something more specific that highlights the systemic racism and intergenerational trauma present. **The authors thank the reviewer for their comment. We have moved the sentence from the beginning of the second paragraph in the Interpretation section to add clarity to the introduction. The second paragraph in the Introduction has been revised to:** **"First Nations people in Canada have a history rooted in colonisation and systemic racism that has contributed to health inequities. HCV has been described as a colonial illness, with risk factors such as injection drug use, linked to this history and the trauma caused by colonial stress.[3] Higher rates of newly-diagnosed HCV infection and younger ages at diagnosis have been observed among First Nations people in Canada, compared to non-First Nations.[4]"** 3. Were data on youth/people <18 years old not available? **The authors thank the reviewer for their inquiry. As stated in the first sentence of the section "Study Design and Population", we included all individuals <106 years of age at reference date. In Table 1, the youngest age**

	group is less than 25 years of age which includes those <18 years of age. We examined this age group further, and 1974 (9.6%) of the tested, 51 (2.1%) of the diagnosed, and 48,336 (35.8%) of the no test record cohorts were younger than 18 years of age at reference date. For our measures of incidence and prevalence, we incorporated all individuals <=105 years of age. We were unable to stratify the analyses for individuals <18 years of age because that would have raised issues with small cell sizes and compliance with ICES privacy guidelines. 4. Could you look at new diagnoses as a proportion of testing? This could be a more helpful way to present the data in figures. Or perhaps, express in the figure incidence rates stratified by key characteristics and map over the testing rate as well for one clear figure. **The authors thank the reviewer for their comment. New diagnoses as a proportion of testing are difficult to look at in the administrative data due to the records of repeat testers and repeat and multiple test records in the PHO test data encompassing antibody, RNA, genotype, and viral load test results. To add clarity regarding the incidence of testing among First Nations individuals, we have calculated and presented the annual incidence of first test from 2006 to 2014. We have also included the raw data and rates for this measure stratified by community status in Appendix 3 Table 4 and Table 5. In addition, we have revised the figures reporting incidence and prevalence into one figure for testing (Figure 2). and one for diagnosis (Figure 3). In the Appendix, we have also stratified these measures by sex and created similar figures (Appendix 3 Figures 1 and 2).** **We have added this measure to the abstract, in the second last sentence of the Methods:** **"We examined cohort characteristics, and annual prevalence and incidence of testing and diagnoses."** **We also revised the second-last sentence in the Abstract Results:** **""The incidence of first test and incidence of diagnosis increased from 12.1(11.5-12.6) to 21.3(20.5-22.1) and 1.3(1.1-1.5) to 2.3(2.1-2.6) per 1000 person-years, respectively."** **We have reflected this in the revised manuscript in the last sentence of the Outcomes subsection of Methods as:** **"The annual incidences of first test and diagnosed infection per 1,000 person-years were estimated by following each individual from January 1, 2006 or date of birth until censoring (date of first test/HCV diagnosis, death, last contact date, or December 31 of each year)."** **The incidence of first test is described in Figure 2A and in the results under the subheading "Incidence and prevalence of testing" as:** **"From 2006 to 2014, the annual age-sex standardized incidence (95% CI) of first test increased from 12.1 (11.5-12.6) to 21.3 (20.5-22.1) per 1,000 person-years (Figure 2A). Within First Nations communities, it more than doubled, from 11.5 (10.6-12.5) to 25.4 (23.9-26.9)."** **We have also mapped the cumulative incidence of first test by region in Figure 6 and mentioned in the Results, at the end of subsection "Localization of rates", that the pattern of localization was similar to the pattern of the point prevalence of ever being tested:** **"The cumulative incidence rates of first test and diagnosis exhibited**

	localization patterns similar to their point prevalence estimates (Figures 6 and 7).” **Figure 4 is prevalence of ever tested and Figure 6 is incidence of first test. Both show high rates in LHINs 7, 13, and 14. Figure 5 is prevalence of diagnosis and Figure 7 is incidence of diagnosis and both show high rates in LHINs 1, 2, 7, and 14.** 5. For clarification, did the analysis exclude pts with HCV+ baseline dates <1999? **HCV+ data before 1999 were unavailable because the Public Health Ontario HCV testing data spanned from 1999 to 2014. For 2006 (start date) prevalence estimates, we used the data on all existing cases of diagnosed and ever tested for infection starting from the beginning of the available data (1999). This has been added to the description of the three cohorts, in the Study Design and Population subsection of Methods in the revised manuscript, “1) received their first HCV test, determined by looking back to 1999 (“tested cohort”); 2) received at least one positive test result (antibody or RNA) for HCV infection (“diagnosed cohort”); or 3) had no record of an HCV test, determined by looking back to 1999 (“no test cohort”).”** 6. In many places, the authors write "more likely to", when in fact, there is no model looking at this (i.e., when comparing where pts reside). **The authors thank the reviewer for their comment. We have removed “more likely to” (only found in the second sentence of the Interpretation section) and the sentence now reads:** **“Individuals who were tested and/or diagnosed with HCV infection were older, had more comorbidities and mental health issues, and resided outside of First Nations communities, compared to those never tested.”** 7. Perhaps understanding/contextualizing a bit more of what might be going right in First Nations communities that have scaled up testing so much could be very helpful (i.e., hearing what is working, if possible, to explain how % tested tripled). **As First Nations communities are vastly diverse across the province, we were unable to comment beyond what has been noted in published literature and from what we have learned from our First Nations partners on the study regarding initiatives that may have been implemented within First Nations communities. We have provided this information in the third paragraph of the Interpretation section. Additionally, after 2014, following the launch and increased availability of DAAs, new initiatives to promote testing and treatment may have been implemented (see response to Comment 10). This study provides a high-level overview, and our next steps include knowledge translation strategies to disseminate the results to First Nations community leaders.** 8. Direct or indirect age standardization? What is the population comparison (year)? **The indirect standardization method was used with the total counts of cases/tested individuals and the total population/person-years to ensure that the reference was large enough to have well determined rates in each age/sex group and to be consistent across all measures. We are aware that by indirectly standardizing the rates we limit comparisons to future research**

	done on HCV in the First Nations population in Ontario. For this reason we included all crude rates and counts for the numerator and the denominators for each rate calculation in the supplement. **To further clarify, we revised the Statistical Analyses subsection of the Methods section (page 6) to read:** **"For each measure, the internal standard consisted of the 2006 to 2014 combined age-sex distribution of First Nations individuals tested or diagnosed in comparison to the total First Nations population."** 9. Is it possible to also include uptake of treatment rates? This could an excellent addition to this paper, if not a future paper. **The authors thank the reviewer for this suggestion. Our information about drug treatment was limited to the Ontario Drug Benefit data. The Ontario Drug Benefit program covers individuals aged 65 years and older, on social assistance, in long-term care, or with high drug costs relative to income. We were unable to obtain prescription drug claims accessed through the Federal Non-Insured Health Benefits Program (NIHB), which can also be used by First Nations people to cover drug prescriptions. For this study, we used Ontario Drug Benefit data covering prescription drug claims up until Dec 31, 2017 to capture high-level estimates of HCV treatment uptake in the cohorts.** **We have submitted a second manuscript to CMAJOpen examining the use and cost of healthcare among First Nations individuals with HCV. In this second manuscript we included the costs specific to drug prescriptions under the current limitations of the data available.**