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Title	Healthcare costs associated with hepatitis C virus infection in the First Nations populations in Ontario: a retrospective matched cohort study
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Reviewer 1	Brandon Zagorski
Institution	Faculty of Medicine, University of Toronto, Toronto, Ont.
General comments (author response in bold)	I have a few comments for the authors to incorporate into the manuscript. Overall, I feel that the study and manuscript make it a necessary contribution to the literature. **The author's thank the reviewer for their thoughtful and insightful comments.** Comment 34: Cohort 1. Residence within a First Nations community ("on-reserve") or outside a First Nations Community was captured using postal and residence codes. Since the wide majority of cases where identified "outside FN community" and that the rural flag only identifies <1% of the cases overall, providing a different geographic descriptor, such as urban/non-urban, might be more informative. **Response 34: The authours thank the reviewer for their comment. We looked at many different measures for rurality. Unfortunately, most indicators use measures derived from the Census which excluded a majority of First Nations communities. Measures from indices such as the RIO (rurality index for Ontario) which are used to derive urban/non-urban indicators are based on Census subdivision. When we explored these other indicators, we were left with many missing/unknown values. In a study by Walker et al. (CMAJ 2019) 27.5% of First Nations people in their cohort of First Nations people in Ontario in 2014/2015 had missing RIO measures. Based on this, we decided to determine rurality using postal codes for urban/rural mail delivery areas. This allowed us to look for indicators of rurality in the cohort without being limited by the census measures. It has been used in the past and referenced by Statistics Canada as one definition of rurality. The reference from Statistics Canada is: du Plessis, Valerie, Roland Beshiri, Ray D. Bollman and Heather Clemenson. (2001) "Definitions of Rural." Rural and Small Town Canada Analysis Bulletin Vol. 3, No. 3 (Ottawa: Statistics Canada, Catalogue. no. 21-006-XIE).** Comment 35: Methods 1. Provide a description of univariate distribution of total costs in the cases as it compares to controls. **Response 35: The authour thank the reviewer for their suggestion. Typical of healthcare costing data, for both cases and controls, the univariate distributions of costs across subjects were skewed to the right, due to the number of individuals with very low/zero costs for the time period. We also examined the univariate distributions associated with the log of the costs and observed that after transformation of the costs for both cases and controls, the costs fit a normal distribution. Much of the data in the model (especially in the pre-diagnosis and initial phases) were low costs but still greater than 0. For example, looking at total cost values by phase, in the pre-diagnosis phase, zero costs were reported for ~14% of controls and ~1.5% of**

cases. In the initial phase, zero costs were reported for ~1.5% of controls and ~0.2% of cases. In the late phase, zero costs were reported for ~3.1% of controls and ~1% of cases. In the terminal phase, zero costs were reported for ~2.7% of controls and ~-0.7% of cases. Although the log-transformed costs did exhibit a normal distribution shape, bootstrap resampling was used to generate confidence intervals to provide more robust measures of uncertainty.

Comment 36: 2. Provide justification for using a gamma distribution with log-link and any model fit diagnostics.
Response 36: The authors thank the reviewer for their inquiry. A Modified Park's Test indicated that a gamma distribution was suitable and it was also the distribution most commonly used for this type of data. As sensitivity analyses (not reported) we also ran the following GEE models and bootstrapped the results to obtain 95% CIs:
i. GEE with a poisson log link
ii. GEE with a poisson identity link
iii. GEE with a gamma identity link
iv. As health econometrics literature has suggested that a large mass at zero can potentially be better described using a two part model consisting of a probit or logit model to measure the probability of a person having any healthcare expenditures followed by a generalized linear model to estimate costs on the resulting subset, we also ran a two-part model on each cost category as a sensitivity analysis to see its effect on cost estimates.
In all cases, we found that the results were not sensitive to the choice of model. All of the models gave very similar results. Between model results, differences ranged from 1 to 7 dollars (maximum) for parameter estimates and 1 to 16 dollars (maximum) for 95% confidence intervals. As our data were already closely matched, this was likely due to mean net costs being estimated with only disease status as a single predictor value.

Comment 37: 3. Commenting on the difference between model-based confidence intervals the bootstrap counterparts would be help in understanding the reasoning for re-sampling.
Response 37: We recognize that it may have been more computationally efficient to use model-based estimates but the bootstrap allowed us to use the percentile method to estimate CIs and did not rely on statistical assumptions about the underlying distributions of the data or desired estimates. We did check the model-based CIs versus the boostrap results and they were very similar. Use of either would not have significantly impacted the results of the study.

Comment 38: Interpretation 1. Discussing the results in the context of the population burden is encouraged. a. There are approx 225/year infections that met criteria, is there any idea of the size of the population at risk to calculate annual incidence rate?
Response 38: The authors thank the reviewer for this suggestion. We have submitted another manuscript to CMAJOpen examining the epidemiology of HCV among First Nations individuals in Ontario. In that manuscript we included incidence rate and point prevalence of diagnosed infection and

testing. We also stratified the measures by those who live within and outside of First Nations communities. We hope that these manuscripts together will inform the health and economic impact of HCV infection on First Nations populations in Ontario.

Comment 39: b. This and also providing the mean time spent (denominators) in each phase will give context to help inform policy.
Response 39: The authours thank the reviewer for this comment. We have added the length of time spent in each phase to the main text in our response to comment 13. Also, the mean length of time in each phase is reported in Table 3.

Comment 40: Limitations 1. There was a brief mention of the underestimation of costs due to the utilization of NIHB. Further commenting on this limitation is encouraged.
Response 40: We have elaborated on limitations around lacking NIHB data in our response to comment 6.

Comment 41: a. For example, can the proportion of individuals that access (or do not access) OHIP services of those diagnosed from PHO lab results be estimated? b. Providing the distribution of costs (mentioned above) including zero-cost individuals may help address this.
Response 41: The authors thank the reviewer for this suggestion. We included all First Nations individuals with valid OHIP numbers and excluded those who were ineligible for OHIP (Figure 1). We can certainly identify individuals with zero OHIP costs, for any period of time, but we cannot assume that they had zero OHIP costs because they accessed NIHB-covered services. Much of the data in the model (especially in the pre-diagnosis and initial phases) were low costs but still greater than 0. We addressed the issue of NIHB-covered services in the Limitations subsection of the Interpretation, in the manuscript, and in response to comment 6.

Reviewer 2	James Ted McDonald
Institution	Department of Economics, University of New Brunswick, Fredericton, NB
General comments (author response in bold)	Comment 42: 1. The paper could benefit from more clearly specified objectives. As stated, it is an exploration of costs of HCV among First Nations (FN) population in Ontario. However, the analysis considers a range of dimensions including a standard case/control analysis that focuses on HCV costs, a comparison across phases of the disease, a comparison of on and outside of reserve residents, and a comparison by gender. **Response 42: Thank you for this suggestion. We have revised the second last sentence of the Introduction (page 3) to include these objectives. The sentence has been revised to read:** **"The objective of this study was to estimate the healthcare costs and resource utilization associated with HCV infection by phase of care, among First Nations populations in Ontario, and stratified by sex and by residence within or outside of First Nations communities."** **Because of the limit on word count in the Abstract, we did not revise the Abstract Background. The Abstract Methods described the analyses that were done.**

Comment 43: 2. Specific hypotheses (with expected directions of effect) could be outlined in the introduction and this then provides a roadmap for the reader as the results are reviewed. It would also serve to highlight what the value added for the paper is. It is not noteworthy that HCV in general is going to be associated with higher medical costs than otherwise, and that healthcare costs increase at later stages of life. [Editor note: Studies are not required to have novel findings to be considered for publication in CMAJ Open.]

Response 43: We had no hypotheses other than the expected trends that the reviewer mentions. Our First Nations community partners were interested in health care among people living in First Nations communities, so we stratified by residence within and outside of communities. We had no hypotheses about differences in health care costs between males and females.

Comment 44: a. But the key questions are how do these patterns vary between FN and non-FN residents (alluded to in the discussion section), and how do they vary among FN peoples by gender or on/off reserve (reported in the results)? [Editor note: This is something to consider in your revision, but not mandatory.]

Response 44: The reviewer mentions variations between First Nations and non-First Nations residents, gender, and on/off reserve. We assume that First Nations and non-First Nations residents refer to residents of Ontario who are and are not registered First Nations. Our purpose was not to compare these two groups of people, had the data even been available to do so. Such as comparison would not be useful to First Nations leaders. In the Interpretation we mention the results of other Canadian studies of costs in patients with HCV, liver disease, liver cancer, and at the end of life, to put our results in perspective.
The variations in patterns of costs between males and females and people residing within and outside of First Nations communities are described in the results, and shown in tables and figures. They are also discussed in the fourth and fifth paragraphs of the Interpretation section, on pages 11 to 12. We suggested some explanations for these variations but to expand on these would require making assumptions for which we have no evidence.

Comment 45: 3. Not explored in much detail are questions around direct acting antivirals.
Response 45: Our testing data spanned until 2014 and we followed patients to the end of 2017. DAAs became available in Canada in 2012 and widespread use began in 2014. Therefore, only a small proportion of our HCV cohort would be able to access DAA treatment. Information about DAA treatment was obtained from the Ontario Drug Benefit Program database. As indicated in Table 1 in Appendix 1 in the supplemental material, the ODB includes all prescriptions filled by individuals aged 65 years and older, on social assistance, or in long-term care facilities. Therefore, many individuals in our cohort were not covered by the ODB. Another limitation with respect to information on DAA treatment is that First Nations individuals are eligible for drug prescription coverage under the federally-funded Non-Insured Health Benefit program, and these data are not available at ICES (mentioned in the Limitations). We have added a sentence to the Limitations (page 13) to explain limitations in our information about drug coverage. The sentence

reads:
"Drug prescriptions, including DAAs, may be underestimated because the NIHB includes drug coverage, and the Ontario Drug Benefit program, our source of prescription information, covers only people aged 65 years and older, on social assistance, or in long-term care homes."

Comment 46: a. Incidence of receipt of this therapy is reported but not how incidence varies by reserve residence or gender, which would speak to barriers to access referenced in the discussion? [Editor note: This is something to consider in your revision, but not mandatory.]
Response 46: Thank you for this suggestion. We understand the interest in DAAs but they are not a focus in our study. Given the limitations in the information that we had concerning drug prescriptions in general and the availability of DAA treatment regimens in our study timeframe, we think that to investigate differences in DAA uptake between individuals residing within and outside of First Nations communities and between males and females would not be informative and could lead to unsubstantiated assumptions about access to care. Also, the small numbers of patients with records of DAA treatment in the initial and later phases (155 and 21 patients, respectively) could preclude stratification because cell sizes of less than 6 cannot be reported according to ICES privacy policy.

Comment 47: b. Also not analyzed is the effect of DAA receipt on healthcare trajectories. Perhaps sample sizes are too small to allow a more detailed evaluation of issues around DAA for this population?)? [Editor note: This is something to consider in your revision, but not mandatory.]
Response 47: Thank you for this suggestion. As the reviewer points out, the sample sizes are too small to explore the effect of DAA on healthcare trajectories. Our data showed that only 155 patients received DAA in the initial phase, which represent only 7.5% of the 2077 patients with time in the initial phase.

Comment 48: c. More generally, can the estimated differences in costs between cases and controls arising from HCV justify the provision of DAA – including both the costs of the therapy and costs of outreach to promote takeup? [Editor note: Could be addressed in the interpretation, within the context of the study findings of course, if you wish.]
Response 48: Thank you for this suggestion, which addresses an interesting question. However, answering this question would require a modelling approach and our study is a descriptive analysis. Furthermore, potential underestimation in our information about DAA uptake in these patients limits our ability to predict future scenarios.

Comment 49: Specific points for clarification
4. What is the Indian Register and who does it include/exclude?
Response 49: The Indian Register includes all First Nations individuals who have successfully applied for Indian status under the Indian Act in Canada. Under the Indian Act, status Indians, also known as registered Indians, may be eligible for a range of benefits, rights, programs and services offered by the federal and provincial or territorial governments. These rights and

benefits include on-reserve housing, education and exemptions from federal, provincial and territorial taxes in specific situations.

First Nations people who are not registered in the Federal Indian Register may be excluded because they are not eligible for registration or because they have not registered despite their eligibility. There are 236,685 self-identified First Nations people in Ontario (based on the 2016 Census). This may be an underestimate because not all First Nations communities participate in the census and because marginalized Indigenous people living in cities may be under enumerated in the Census. However, based on this, we could estimate that the registered population that we can link to ICES data (194,014) is ~80% of self-identified First Nations people in Ontario.

We have included this information in the Study Design and Population subsection of Methods (page 4) as:

"First Nations individuals in Ontario registered under the *Indian Act*[14] were identified using the Indian Register (IR). The IR includes demographic and administrative information for all First Nations individuals who have successfully applied for Indian status under the *Indian Act*."

We also added information about the individuals who are included in the Indian Register in the Limitations) (page 13) and in response to comment 19.

Comment 50: a. Table 1 provides a technical definition but the authours could include a lay definition in the main text.

Response 50: Outlined in our response to comment 49, we have added a sentence describing the Indian Register to the Study Design and Population subsection of Methods.

Comment 51: 5. Are HCV testing records comprehensive in the sense that they capture the incidence and result of all HCV tests administered in the province?

Response 51: The Public Health Ontario Laboratory database does not include all test results from private laboratories in Ontario. We have added this to the Limitations subsection of the Interpretation (page 13):

"The PHO laboratory dataset does not include all private diagnostic laboratory results."

Comment 52: 6. If individuals change on/outside reserve status over the period of observation, how is this controlled for?

Response 52: As described in Appendix 2, a flag indicating whether an individual resided within or outside of a First Nations community was generated at entry to each phase, from an algorithm that uses postal and residence codes from the Registered Persons Database (RPDB), Discharge Abstract Database (DAD), and National Ambulatory Care Reporting System (NACRS) data. Therefore, if an individual moved residence from the start of one phase to the start of another, that individual could be classified as "within First Nations community" in one phase and "outside of First Nations community" in another phase. We have added additional details to the Region of Residence section in Appendix 2. Also, to clarify that the residence flag was generated at entry to each phase, the sentence about community residence has been revised, in the Cohort characteristics subsection (page 5):

"Residence within a First Nations community ("on-reserve") or outside a

First Nations community was generated at the date of phase entry using postal and residence codes from the Registered Persons Database, Discharge Abstract Database, and National Ambulatory Care Reporting System data.[12]"

Comment 53: a. Might some of the same individuals be found in the on-reserve subsample in one phase and the outside-reserve sample in another phase?
Response 53: In addition to the response to comment 52, if an individual moved between entry to one phase and entry to the next phase, and their postal/residence codes changed, that individual could then be classified in the within First Nations community group in one phase and the outside First Nations community group in the next phase.

Comment 54: b. How common is movement from on reserve to outside reserve and vice versa?
Response 54: We were unable to examine movement between First Nations communities, in a recent paper by Slater et al. (CMAJOpen, 2019) they reference that First Nations people are more geographically mobile than other Canadians and how that can translate to incorrectly classifying community status when using administrative data. We noted this in our limitations section (page 13) in our response to comment 7.

Comment 55: 7. While the results show higher net costs for First Nations living outside of reserves for all groups except those in pre-diagnosis, the large confidence intervals mean conclusions need to be made with caution.
Response 55: Thank you for noting this. The reviewer is correct that there are large confidence intervals around many of the estimates for net costs. This is true not only for the stratification by residence within and outside of First Nations communities (Table 3 in the supplementary material), but also for the stratification by sex (Table 5 in the supplementary material). We have added a statement to the first paragraph of the interpretation section (page 10) suggesting that the large confidence intervals indicate wide variations in cost estimates and therefore definitive conclusions should be made with caution. The sentence reads:
"However, the large confidence intervals around the net cost estimates indicate wide variations and therefore definitive conclusions should be made with caution."