Article details: 2019-0191	
Title	**Time trends and predictors of laboratory confirmed recurrent and severe *C.difficile* infections in Manitoba: a population-based study**
Authors	Seth R Shaffer MD, Zoann Nugent PhD, Andrew Walkty, B Nancy Yu PhD, Lisa M. Lix PhD, Laura E Targownik MD MSHS, Charles N Bernstein MD, Harminder Singh MD MPH
Reviewer 1	Dr. Mon Huin Tun
Institution	University of Alberta, Pediatrics Department
Reviewer comments and author response	1. The manuscript described a C. difficile infection (CDI) trend in one Canadian province utilizing population-based laboratory confirmed cases. The study was well analyzed, the results were concise and clear, and the manuscript was well-written. The findings of increased prevalence of community-associated CDI cases could be used to dictate new public health policies on the requirement of test for CDI among outpatients with diarrhea as well as the prevention therapy which can lead to rapid cure and prevent recurrence in the community setting. The introduction is relevant, and the authors made a systematic contribution to the literature search in this area of investigation. **Authors' response: We thank the reviewer for these comments.** 2. A sentence or two on the requirements of the research ethic approval would be beneficial. **Authors' response: We have added ethics approval statement to the manuscript** 3. Overall, the definitions for CDIs were well defined and the author employed different analysis approach to find out the incidence, hospital admission, readmission, and severity of CDIs. 4. Are all the CDI cases Toxigenic? **Author's response: Yes. We mention in the data sources section of the methods section:** **"Between 2005 and May 2013, Manitoba laboratories performed immunoassays for the glutamate dehydrogenase (GD) antigen and C. difficile toxins A and B, followed by the cytopathic effect (CPE) assay (using viable human fibroblasts) and/or culture for discordant results (i.e., GD antigen positive C. difficile toxin A & B immunoassay negative) [12 13]. Since May 2013, three laboratories (responsible for approximately 70% of the testing) implemented a Nucleic Acid Amplification Test (the Illumigene assay, Meridian Biosciences, Cincinnati, OH) for confirmation of GD antigen positive samples [13]."** 5. The study period described was inconsistent. In some part, it was stated from 2005 – 2015 and in some part it was shown 2005 – 2014 (in fig.1). **Author's response: We have corrected the reporting to the years of the data used 2005 to 2015** 6. The authors did not mention the software used for data analysis. For the joinpoint regression analysis, did the author use the special software? In addition, is the joinpoint already pre-specified and the author fit a model or there is no a

priori joinpoint but the author estimated from the data?

Author's response: We mention in the revised manuscript that we used SAS and joinpoint software packages. There was no a-priori specified join point but estimated from the data using the jointpoint software program.

7. In the method section, it was stated that multivariable logistic regression was used to test the factors associated with outcome severity. However, in the results section and in the table, it was reported as HR. Please clarify.

Author's response: We have corrected and now report odd ratios determined from the logistic regression analyses. We used logistic regression because no individual left the province in the 30 days after a CDI episode and the last 30 days of the dataset were not used in this analysis; death was an event in this analysis.

8. Figure 3: What is the title for X-axis? (days in the hospital?)

Author's response: We have added the x-axis for figure 3: days after CDI.

9. The authors should standardize the decimal places (rounded to 2 or 3 decimal places).

Authors' response: Many journals use the following rule, which we are using in the revised manuscript, but would be happy to modify as required by CMAJ open

"In general, P values larger than 0.01 should be reported to two decimal places, those between 0.01 and 0.001 to three decimal places; P values smaller than 0.001 should be reported as P<0.001."

10. Do you have a plan to conduct sensitivity analysis to report the discrepancy between ICD coded cases vs. lab confirmed CDI cases?

Author's response: Thank you for this suggestion. While we have not yet performed the suggested analysis with the entire CDI population-based dataset, we did perform similar analysis in the setting of IBD and matched controls. We reported the observed patterns were different when ICD coded cases vs. lab confirmed CDI cases were used to define CDI occurrence

Singh Harminder, Nugent Zoann, Yu B Nancy, Lix Lisa, Targownik Laura, Bernstein, Charles. ASSESSMENT OF CLOSTRIDIUM DIFFICILE EPIDEMIOLOGY AMONG INDIVIDUALS WITH IBD FROM HOSPITAL ADMISSIONS DATABASES PROVIDES A DIFFERENT PICTURE THAN THAT FROM THE LABORATORY CONFIRMED DIAGNOSIS. for poster presentation during Digestive Disease Week® at the San Diego Convention Center, San Diego, May 18-21, 2019.

We have also published the following:

Singh H, Nugent Z, Yu BN, Lix LM, Targownik L, Bernstein CN. Hospital discharge abstracts have limited accuracy in identifying occurrence of Clostridium difficile infections among hospitalized individuals with

	inflammatory bowel disease: a population-based study. PLOS ONE 2017 Feb 15;12(2):e0171266. 11. The authors reported that limitation of unavailability of antibiotic prescription data. **Authors' response: We did not have access to inpatient prescription data.** 12. It was concluded that recurrent CDI was associated with increased hospitalizations and re-hospitalizations. Nonetheless, prolonged hospital stay, ICU admission and presence of underlying malignancy also increase the risk of CDI and hospital readmission. It will be beneficial to find out the effect of those factors on the CDI severity and hospital readmission. **Author's response: ICU admissions are part of the severity definition, as such, as all with ICU admission were characterized as severe CDI. Hence, we cannot determine effect of ICU admission on CDI severity.** **We did not have access to the Cancer Registry for the current study and hence we cannot accurately define underlying malignancy (especially the date of underlying malignancy). In addition, as mentioned by the editor, there are many analyses already in the manuscript.** **We have now evaluated the effect of length of hospitalization (categorised by median length of stay for those included in the respective analyses) on CDI recurrence (table 2), CDI severity (table 3) and hospital readmission (supplementary table C) and have added the results to the footnotes of the respective tables. Those with longer hospital stay prior to the CDI onset had higher risk for CDI recurrence as well as severe outcomes, but no effect on readmissions.**
Reviewer 2	Dr. Sanal Madhusudana Girija
Institution	Institute of Liver and Biliary Sciences, Molecular and Cellular Medicine, New Delhi, India
Reviewer comments and author response	1. Pg-8 Line 23 Rate of HCF associated cases per 100,000 person years? **Author's response: Correct, We are reporting rates per 100,000 person-years** 2. Line 25 Please mention in person years. **Author's response: We are not certain which results the reviewer is referring. We are reporting rates in person-years.** 3. Use the same unit/style for easy understanding and comparison of data. It is good to show as graphs. **Author's response: We agree in general. However, occasionally different units are used for lower frequency of events.** 4. line 28: May also include percentages in brackets **Author's response: We are not certain which results the reviewer is referring. We have tried to include percentages in brackets**

	5. Line 33 CDC, Atlanta, US? **Author's response: Yes, CDC refers to the Centers for Disease Control and Prevention in Atlanta, USA.**
Reviewer 3	Mrs. Claire Nour Abou Chakra
Institution	Université de Shebrooke, Microbiology and Infectious disease
Reviewer comments and author response	This study has an added value on knowledge about C.diff infection in Canadian provinces mainly in the absence of an accurate national surveillance system. Few comments mainly about the presentation of findings: 1. Introduction: the authors are relying on studies from the US, would use more Canadian findings and studies that compare more in terms of incidence of CDI, recurrence of episodes, and healthcare systems **Author's response: As suggested, we have added to the introduction.** 2. I disagree about "hospital discharge data do not include many community-associated cases and cannot distinguish onset in the community versus occurrence in hospital". Hospital data could distinguish between HCFA and community acquired CDI if previous exposure to healthcare is included in the definition of recurrence. **Author's response: First, CDI cases occurring in the community and never admitted to a hospital are not included in the hospital datasets. Therefore, hospital datasets do not include most of the community associated CDI.** **Second, while the reviewer is correct that knowing about previous health care exposure is helpful, this alone cannot separate out the different subtypes of CDI: Most of the community-onset CDI cases are not in hospital when the samples are collected. From a hospital data set, there is no way of distinguishing whether the sample collection occurred during the hospitalization, or previously in the community.** **In addition, there is no date of diagnosis in the hospital datasets and hence impossible to determine the timing of CDI diagnosis in the hospital.** **Hence, from a hospital dataset alone, it is impossible to determine whether a particular case is community associated CDI, healthcare facility (HCF) onset HCF-associated CDI or community-onset HCF-associated CDI** 3. Methods: 2006 Canadian population was used for the age-standardized rates. It's probably more appropriate to use the province population as Manitoba is much less populated than other provinces mainly Quebec and Ontario. **Author's response: Our provincial population is not very different from the Canadian average. More importantly for the purpose of cross-comparison of rates among different studies, age standardized rates are reported based on the Canadian population.** 4. Results: the presentation of the results is confusing and very hard to follow. Absolute frequencies should be presented before rates and variations and sub-

	groups. All the results section should be rewritten to read easily and flow. **Author's response: As suggested by the editor, we have included the number of patients and events in the revised tables.** 5. I would present rates and proportions in tables with precise values along with confidence intervals instead of Figure 2. **Author's response: We would prefer to keep the pictorial graphic presentation for this analysis. We report in the text for results: "the proportion of CDI cases that were community-associated increased an average of 4.76%/year (95%CI 2.8, 6.8) over the duration of the study"** **In addition, as suggested by the reviewer, we have added a supplementary table B to provide the precise values for each with the confidence intervals** 6. Tables: In the absence of a descriptive Table 1, the frequency for covariates categories should be indicated so the reader would assess the distributions. **Author's response: We are including a descriptive Table 1 in the revised manuscript.**