

Article details: 2019-0018	
Title	The incidence and economic burden of Clostridioides difficile in Ontario, Canada: results of a retrospective population-based study
Authors	Jennifer A. Pereira PhD, Allison McGeer MD MSc, Antigona Tomovici MD, Alex Selmani PhD, Ayman Chit PhD
Reviewer 1	Miss Nadine Chami
Institution	McMaster University, Economics, Hamilton, Ont.
General comments (author response in bold)	<p>1. In first paragraph of the methods section you mentioned that you conducted a study to obtain provincial estimates on the clinical impact of CDI described in a separate publication. I'm not sure it is necessary to include this with what is actually studied in the paper (only incidence and cost of CDI). I suggest it would be more appropriate to include the findings of this separate paper in the interpretation section (if study is already published), or in concluding remarks referring to it as future work (if still in progress). Thank you, we agree. We have removed the reference to the clinical impact manuscript in the methods section.</p> <p>2. Would it be possible to add more observed characteristics in the matching stage of the analysis? Some suggested characteristics would be number of patient visits with a primary care physician, number of inpatient/outpatient hospital visits, and emergency department (ER) visits. Unfortunately, we have access to only very limited outpatient data and therefore could not match based on the characteristics suggested. Additionally, our current criteria already limit the number of controls, such that the addition would decrease our cohort sizes considerably.</p> <p>3. Results show that costs of ACH-acquired cases were highest among the rest of the groups. Could you explain to the reader why this might be the case? Are all the hospitalization costs coming from CDI treatment/management or possibly from post-complications related to hospitalization in the 12 weeks prior to admission? It is possible that the high costs of ACH-acquired is attributed to a more severe strain resulting in more extensive treatment/management. Additionally, as explained by the reviewer, hospitalization costs may also be associated with the diagnosis for which the patient was admitted to the hospital, where they acquired CDI. We have now included this as a limitation (Interpretation, lines 101-106):</p> <p>"We did not have access to prescription data for those under 65 or not on social assistance, which will have underestimated the total costs of CDI treatment and management."</p>
Reviewer 2	Dr. Tse-Yen Yang
Institution	China Medical University Hospital, China Medical University, Molecular and Genomic Epidemiology Center
General comments (author response in bold)	The present study was tried to demonstrate that the Clostridium difficile infection (CDI) with a retrospective, population-based epidemiology study, the whole health database was generated from provincial health administrative data. The current study was shown a long-term follow up and different setting of whole provincial health data. The hospital-based and community-based CDI were existed considerably different and the detailed health policy for CDI should be leading to the interference of different, but the present study was provided that the incidence and cost burden of CDI in Ontario and present what population should exist high risk for CDI. This study was demonstrated the scientific evidence for explained the economic burden of CDI in Ontario, but these author with further conflict of interest should be notice the readers for objective judgment of this real-world data.
Reviewer 3	Dr. Preeti Kutty
Institution	Centers for Disease Control and Prevention, DHQP
General comments (author response in bold)	<p>1. Please note that Clostridium difficile is now known as Clostridioides difficile.</p> <p>Thank you – we have revised the manuscript accordingly.</p> <p>2. Line 17: Is the societal cost in Canadian dollars or US dollars? This cost is in Canadian</p>

dollars.

We have now specified this in the manuscript.

3. Paragraph 2 (lines 20-29): This is a little confusing. The first paragraph is Canadian data but the second refers to US data. Does similar information (LTCF, risk factors for CDI) exist for the Canadian population?

There is a lack of extensive Canadian data on risk factors for CDI but we have included what is available in the Background, supplemented with US literature as well.

4. Could the authors provide information regarding what CDI prevention interventions (antimicrobial stewardship, environmental cleaning policies, and enforced compliance with hand hygiene and infection prevention practices) have been in place in Ontario to prevent CDI? Or is it because there is lack of data and hence this paper? The background does not provide the exact reasons as to why this paper was written. A little more context, either here or in the Interpretation, would help the reader.

In Ontario, the Provincial Infectious Disease Advisory Committee makes recommendations and provides evidence-based guidance regarding control and prevention practices and interventions for hospitals within the province but it is ultimately up to the hospital to decide which to implement. Therefore, variation is expected, and detailed information is not available. We have revised the introduction to provide information on why this study was undertaken (lines 74-91).

Methods:

1. Consider providing demographics of these facilities such as bed-size, type of facility. It was only later in text that the caveat about the CDI testing is mentioned. It would be preferred that this be mentioned earlier.

We have access to bed-size data and have included that in Table 4. We have also moved the limitation about CDI testing to the Methods section (lines 132-134):

“Cases were stratified into six cohorts depending on location of association and onset (we used hospital admission date, since the databases did not capture when laboratory testing for CDI was conducted; Table 1).”

2. Page 3, Line 34: The authors mention that the ‘clinical impact’ is described in a separate publication. Has this been published? If yes, please add the reference. If no, how is that paper different from this? What do the authors mean by ‘clinical impact’? The manuscript regarding clinical impact has been submitted elsewhere but is not yet published. This manuscript describes the impact of CDI on mortality and re-hospitalization, and although it shares the same methodology with this paper, there is no overlap in study results.

3. Page 3, Line 43: the text ‘ed’ seems to stand alone. Please correct this **We have corrected this error.**

4. Page 3, Line 44: Could the authors expand on what ‘physician-based visits’ mean? Are these outpatient visits? **We have revised this to “physician visits”.**

5. Page 3, Line 53: Why did the data stop at 2015? Is it possible to obtain newer data? **Unfortunately, it is not possible to obtain and include more recent data in our analysis.**

6. Page 3, line 54: Did the change from ICD-9 to ICD-10-CM diagnosis codes affect the analyses? **No. Ontario switched from using ICD-9 to ICD-10 in 2002. We used ICD-10 diagnoses codes for the analyses.,**

7. Page 4, Table 1: The term ‘acquired’ has a different connotation these days, especially in the age of Whole Genome Sequencing. This will lead to the reader misunderstanding the groups. The better term would be ‘associated’. Additionally, the reference used here mentions the word ‘associated’. Please change. **We agree and have made the change to “associated”.**

8. Page 4, Table 1, group VI- were the authors able to differential or tease out the outpatient visits? Healthcare exposure referred only to prior hospitalization in an acute-care

hospital. **We have now added a footnote to Table 1 to state this:**
“**Healthcare exposure refers to prior hospitalization in an ACH.**”

We have also included this as a limitation (Interpretation, lines 95-97):

“We did not have access to outpatient data, and could not include this in our definition of “previous healthcare exposure” so could not assess whether recent exposure to outpatient healthcare settings were associated with CDI.”

9. Page 6, Line 6: Was the 2015 Ontario population used in the 2005 estimates? That is a large gap of 10 years Thank you for pointing out this typo. The 2010 Ontario population was used for all estimates, chosen because it was in the middle of our study period. **We have corrected this sentence (lines 182).**

Results

1. Page 6, Line 16: Are these 33,909 unique individuals or are these CDI cases? Did the databases provide information on recurrent CDI? If yes, were the recurrent CDI cases removed for the analyses? Please modify the text to reflect what was provided by the databases. **There are 33,909 cases; these are not necessarily unique individuals. We classified recurrence as a second code for CDI within 180 days of the first code, and these were removed from the analysis because they were considered to be from the same index episode of CDI. There were 22,329 such cases. We have added the following sentence to the footnote for Table 3:**

“22,329 cases were excluded from analysis because they occurred within 180 days of the index hospitalization date”

2. Page 6, Line 31: The data available is until March 2015. The text ‘recent years’ indicates more recently. **We have revised the text to state “end of the study period” rather than “recent years”.**

3. Cost of CDI – the actual information starts much lower on Page 7. Please move the tile to where appropriate **We have made this change.**

4. Is the cost information in US or Canadian dollars? **This cost is in Canadian dollars and we have specified this in the Cost of CDI subsection of the Methods section, in the Results section as well as Table 5.**

5. Tables

a. What happened to Tables 2 and 3? They are missing and are not mentioned in the text. Was additional data provided? **We are not sure why the reviewer was unable to view Table 2 and 3. Table 2 was on page 5 (referred to in the Methods section) and Table 3 was page 8/9 of our original submission (referred to in the Results section).**

b. Please standardize all the tables – appropriate terminologies, acronym expansion, appropriate superscripts for the significant values, footnotes for all the tables, titles for all the tables (including the years the data was analyzed from), the province and the country where the data is from. **We have made these changes.**

c. It was very confusing to read the tables.

d. Table 4: Some of the percentages of the shaded cells are very similar. Were these significantly different (e.g., ACH-acquired CDI for age group 75-85; Community-acquired CDI for age groups 45-64 and 75-84 years)?

Why are some of the text and numbers bolded? **We have revised Table 4 so that shaded cells denote statistical significance, and removed the bolding. We agree that some of the percentages of the shaded cells are similar, and the statistical significance is likely the result of large sample sizes rather than indicative of true clinical significance. We have revised the Results section to only mention those differences that are likely to be clinical significant.**

e. Table 5: for clarity, provide the explanations for outpatient medications in the text – how was this defined? Did the authors look at all medications or just antibiotics? If only antibiotics – did the authors assess for high-risk antibiotics. **We have added the following footnote to Table 5:**

“Outpatient medication costs include any prescription drugs purchased for outpatient use through the Ontario Drug Benefit (ODB) plan. The ODB is provincially funded, and is available to individuals who are 65 years and older, those residing in

LTCFs, and/or those who are on social assistance. Costs are based on the total amount paid to the pharmacy (including pharmacy fees) from Ontario's Ministry of Health and Long-term Care."

Interpretation section

1. Please reorder the text here. There are mixed messages and lacks clarity. Some of the results are re-stated without expanding on why and how. **We have revised this section for better clarity and consistent messaging.**

2. Page 13, Line 5: the text should include March 2015 as the end. Otherwise, it misleads the reader. **Thank you. We have made this change.**

3. Page 13, Line 11: The authors state this but does not provide any evidence or information as to why they think this is likely in Ontario. Hence the importance of the background information. **We have revised the Interpretations section to include more information and background, where available.**

4. Page 13, Line 13: are hospitals in Ontario affected by a pay-for-performance measure as it is in the US? Why did the rates decline? Was this decline seen elsewhere in Canada? Hospitals in Ontario are not subject to a pay-for-performance measure, but public reporting of CDI rates is a motivator for facilities to improve their practices. **We have added the following sentence (Interpretation, lines 20-25):**

"A report from the sentinel hospitals of the Canadian Nosocomial Infection Surveillance Program also documented an increase in hospital-associated CDI rates in central Canada from 2009-2012, followed by a decrease from 2012-2015. These authors attributed the decline to improved infection control and prevention practices, and to a regression in the NAP1 strain, which is associated with healthcare facility outbreaks.²³"

5. Page 13, Line 28-31: provide evidence as to why early identification patients is crucial. How would one do 'careful monitoring' for community-onset CDI? **We have added the following sentences (Interpretation, lines 42-47):**

"The continued education of physicians who may be the first point of healthcare contact for those with CDI (family physicians and ED physicians) is critical to quickly identify high-risk patients for both successful treatment of CDI and to contain and limit transmission. Careful monitoring may include diagnostic testing of patients with diarrhea who are older, and have recently been exposed to antibiotics, and asking patients about recent hospitalizations and healthcare exposure. A 2018 Canadian analysis of isolates in community-acquired CDI cases found that all were hospitalized in the previous year, indicating that many, and perhaps all community-associated cases actually have nosocomial origins.³³"

6. Page 13, line 36-43: What happened in Ontario, which resulted in the decline of CDI cases in LTCF? Can the authors provide some insight rather than speculations, perhaps published literature? **We do not have a definitive answer regarding the decline in CDI rates in LTCFs, and – similar to our references paper on rates in Alberta LTCFs – we can only speculate regarding what may have changed (better infection control practices or reduced antibiotic use). We are not aware of any literature that helps to understand this change.**

7. Page 14, Line 4-7: Please move this up to the methods **We have made this change.**

8. Page 14, line 12-13: Please provide references for this statement. Is it truly changes in infection control practices? Or did something else change, like diagnostic testing practices? **Please see above.**