

Incidence and economic burden of *Clostridioides difficile* infection in Ontario: a retrospective population-based study

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Abstract

Background: Understanding the impact of prevention programs on *Clostridioides difficile* infection rates is important, and decisions on future program changes, including how to use vaccines currently in development, requires a detailed understanding of the epidemiologic features of *C. difficile* infection. We analyzed Ontario health administrative data to determine incidence rates and medical costs of *C. difficile* infection, based on whether acquisition and onset occurred in acute care hospitals (ACHs), long-term care facilities or the community.

Methods: We performed a retrospective analysis using individual-level data from Ontario health databases from Apr. 1, 2005, to Mar. 31, 2015, identifying rates of *C. difficile* infection requiring hospital admission per 100 000 person-years in adults aged 18 years or more for categories of acquisition and onset. We estimated health care system costs of infection 180 and 365 days after admission by matching patients with *C. difficile* infection with control patients with similar characteristics.

Results: Over the study period, 33 909 people in Ontario were admitted to hospital with *C. difficile* infection; 17 272 cases (50.9%) were associated with ACHs. The number of cases per 100 000 person-years ranged from 27.7 in 2009/10 to 37.0 in 2012/13. Annually, the highest incidence of infection was for ACH-associated/ACH-onset. Community-associated infection became more prevalent over time, rising from 19.4% of cases in 2005/06 to 29.2% in 2014/15. Infection costs were mostly due to hospital admission within 180 days after hospital discharge. Infection associated with ACHs had the highest total costs and the largest cost attributable to *C. difficile* infection (median \$38 953 for infected patients v. \$13 542 for control patients). Median costs attributable to *C. difficile* infection were \$1051 for that associated with long-term care facilities, \$13 249 for community-associated infection and \$11 917 for ACH-associated/community-onset infection.

Interpretation: Community-associated *C. difficile* infection had similar health care cost implications as hospital-associated infection. With rates of community-associated *C. difficile* infection on the rise, family physicians should be supported to prevent this infection in their patients.

In Canada, *Clostridioides difficile* infection is a leading infectious cause of morbidity and mortality.^{1,2} A Quebec study identified an increase from 35.6 to 156.3 cases per 100 000 people between 1991 and 2003.³ More recent surveillance of the 10 provinces showed a 2011 incidence rate of 535 per 100 000 admissions.⁴ *Clostridioides difficile* infection is associated with considerable costs. An Ontario study showed that acquiring this infection in hospital increased the median length of stay by 6 days.⁵ This translates to a substantial economic burden: a Canadian model estimated a total of 37 900 *C. difficile* infection episodes (in hospital and in the community) in 2012 and a total societal cost of \$2.8 million, of which 92% was in-hospital costs.¹

Although the majority of the literature on the epidemiologic features of *C. difficile* infection is based on association with acute care hospital (ACH) settings, this infection is also associated with long-term care facilities (LTCFs) owing to residents' advanced age, comorbidities and antibiotic exposure.^{6–8} In addition, rates of community-associated *C. difficile* infection appear to be increasing.^{9–11}

Understanding both changes in epidemiologic features and cost associated with this infection is important for several rea-

sons. Experience in Quebec in the early 2000s illustrated the impact of the introduction of a new and virulent strain.¹² Early detection of similar changes will permit more effective prevention. If rates of community-associated infections are truly increasing, recognition of the risk factors for disease will be important to support diagnosis and management.

In Ontario hospitals, multiple measures, including a hand hygiene program, funded infection prevention and control practitioners, regional infection control networks, antimicrobial stewardship programs and mandatory reporting of hospital *C. difficile* infections beginning in 2008, have been implemented since 2003 to prevent infection.^{13,14} Understanding the impact of such programs on *C. difficile* infection rates is important.

Competing interests: Jennifer Pereira and Allison McGeer acted as consultants to Sanofi Pasteur during the conduct of this study. Ayman Chit, Antigona Tomovici and Alex Selmani are employees of Sanofi Pasteur.

This article has been peer reviewed.

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CMAJ Open 2020. DOI:10.9778/cmajo.20190018

Finally, several vaccines to prevent *C. difficile* infection are under development. Decisions about whether and how best to use vaccines requires a detailed understanding of the epidemiologic features of *C. difficile* infection, particularly since the emergence of the virulent NAP1 strain in Ontario.

Therefore, we used linked health administrative data from Ontario to assess the incidence and economic burden of in-hospital *C. difficile* infection in the province.

Methods

We conducted a retrospective cohort study to obtain provincial estimates on the incidence and cost of *C. difficile* infection in ACH inpatients, residents of LTCFs and community-dwelling people.

Data sources

We conducted analyses using data for Ontario. The ICES houses Ontario's health administrative data on hospital and physician billings.¹⁵ Health card numbers were encrypted, converted into unique identifiers and linked to the following databases for analysis: the Ontario Health Insurance Plan physician billing claims database, which contains data for about 95% of physician visits in the province; the Canadian Institute for Health Information's Discharge Abstract Database and the National Ambulatory Care Reporting System for data related to hospital admissions and emergency department visits, respectively; and the Registered Persons Database, which contains age, sex, postal code and date of death (where applicable) for all Ontario residents eligible for health care services.¹⁶

Setting

Our study was set in Ontario (estimated 2015 population 13.7 million¹⁷) and included people admitted to hospital with *C. difficile* infection in the province. As of 2017, there were 182 acute care hospitals and 626 LTCFs.

Cases

We used administrative data to identify cases of *C. difficile* infection between Apr. 1, 2005, and Mar. 31, 2015. Affected patients 1) had an *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*, enhanced Canadian version (ICD-10-CA) diagnosis code for *C. difficile* infection (A04.7) during an inpatient hospital stay as the most responsible diagnosis, a preadmission comorbidity or a postadmission comorbidity of clinical significance, 2) were at least 18 years at diagnosis and 3) had no *C. difficile* infection diagnosis code in the previous 180 days (a second diagnosis after 180 d following discharge was considered a separate incident).

Incidence

To calculate the incidence of *C. difficile* infection necessitating hospital admission per 100 000 person-years, the denominator included the base population aged 18–104 years. Person-years were based on postal code, Ontario Health Insurance Plan eligibility, date of death and date of last contact with the health care system.

We stratified cases into 6 cohorts depending on location of association and onset (we used hospital admission date, since the databases did not capture when laboratory testing for *C. difficile* infection was conducted) (Table 1).

Table 1: Definitions of *Clostridioides difficile* infection cohorts based on location of disease association and onset*

Cohort	Definition
ACH-associated/ACH-onset	<i>C. difficile</i> infection was coded as postadmission comorbidity of clinical significance <u>AND</u> patient did not reside in LTCF in 12 wk before admission
ACH- or LTCF-associated†/ACH-onset	<i>C. difficile</i> infection was coded as postadmission comorbidity of clinical significance <u>AND</u> patient resided in LTCF in 12 wk before admission
LTCF-associated/LTCF-onset	<i>C. difficile</i> infection was coded as most responsible diagnosis or preadmission comorbidity <u>AND</u> patient resided in LTCF with no history of hospital admission in 12 wk before admission
LTCF- or ACH-associated†/LTCF-onset	<i>C. difficile</i> infection was coded as most responsible diagnosis or preadmission comorbidity <u>AND</u> patient resided in LTCF in 12 wk before admission <u>AND</u> patient had history of hospital admission during this time
Community-associated/community-onset	<i>C. difficile</i> infection was coded as most responsible diagnosis or preadmission comorbidity <u>AND</u> patient neither resided in LTCF nor was admitted to hospital in 12 wk before admission
ACH-associated/community-onset	<i>C. difficile</i> infection was coded as most responsible diagnosis or preadmission comorbidity <u>AND</u> patient did not reside in LTCF but was admitted to hospital in 12 wk before admission

Note: ACH = acute care hospital, LTCF = long-term care facility.
 *Adapted from reference 18. Reproduced with permission.
 †Because the case involved a person who resided in an LTCF and was admitted to hospital in the 12 weeks before onset, it was not possible to determine whether the infection was acquired in an ACH or LTCF.

Table 2: Definitions of *Clostridioides difficile* infection cohort and matched control groups*

Cohort	Cohort definition	Control groups	
		Hard-match criteria	Propensity-score-match criteria
ACH-associated/ ACH-onset	ICD-10-CA diagnosis code for <i>C. difficile</i> infection (A04.7) during inpatient hospital stay, coded as postadmission comorbidity of clinical significance	<ul style="list-style-type: none"> • Age \pm 2 yr • Sex • Hospital admission date \pm 90 d • Most responsible diagnosis at hospital admission\ddagger 	<ul style="list-style-type: none"> • Urban/rural score\S • Local Health Integration Network • Elixhauser score\P
LTCF-associated/ LTCF-onset \ddagger	LTCF resident with ICD-10-CA diagnosis code for <i>C. difficile</i> infection (A04.7) during inpatient hospital stay, coded as most responsible diagnosis or preadmission comorbidity <u>AND</u> no hospital admission in 12 wk before onset	<ul style="list-style-type: none"> • Age \pm 2 yr • Sex • LTCF resident in 12 wk before matched patient's date of hospital admission \pm 90 d 	<ul style="list-style-type: none"> • Urban/rural score\S • Local Health Integration Network • Elixhauser score\P
Community-associated/ community-onset*	Community resident with ICD-10-CA diagnosis code for <i>C. difficile</i> infection (A04.7) during inpatient hospital stay, coded as most responsible diagnosis or preadmission comorbidity <u>AND</u> no hospital admission in 12 wk before onset	<ul style="list-style-type: none"> • Age \pm 2 yr • Sex • Non-LTCF resident in 12 wk before matched patient's date of hospital admission \pm 90 d • No hospital admission in 12 wk before matched patient's date of hospital admission \pm 90 d 	<ul style="list-style-type: none"> • Urban/rural score\S • Local Health Integration Network • Elixhauser score\P
ACH-associated, community-onset	ICD-10-CA diagnosis code for <i>C. difficile</i> infection (A04.7) during inpatient hospital stay, coded as most responsible diagnosis or preadmission comorbidity <u>AND</u> did not reside in LTCF in 12 wk before onset	<ul style="list-style-type: none"> • Age \pm 2 yr • Sex • Community-dwelling but admitted to hospital in 12 wk before matched patient's index date of hospital admission \pm 90 d for same most responsible diagnosis\ddagger 	<ul style="list-style-type: none"> • Urban/rural score\S • Local Health Integration Network • Elixhauser score\P

Note: ACH = acute care hospital, ICD-10-CA = *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*, enhanced Canadian version, LTCF = long-term care facility.

*Adapted from reference 19 (Oxford University Press).

\ddagger People in this control group had not necessarily been admitted to hospital at the index date.

\ddagger Matched on the first 3 digits of the ICD-10-CA code.

\S A measure of a community's rurality based on its population and population density, travel time to nearest basic referral centre and travel time to nearest advanced referral centre.²⁰

\P Comorbidity score based on ICD-10-CA coding.²¹

Cost

To estimate the health care system costs of *C. difficile* infection, we combined the 6 cohorts into 4 combined cohorts (Table 2) where possible and created control groups. Those who did not meet the definitions for any of the cohorts ($n = 972$) or could not be matched to control subjects ($n = 10\,355$) were excluded from the analysis.

Control groups

Control groups consisted of patients aged 18 years or more who resided in Ontario, were eligible for Ontario Health Insurance Plan benefits and did not have *C. difficile* infection (absence of ICD-10-CA diagnosis code A04.7) between Apr. 1, 2005, and Mar. 31, 2015. Members of the control groups were matched to cohort members at cohort members' disease onset. Each cohort member was greedy-matched to 1–3 control patients based on hard-match and propensity-score-match criteria at the time of cohort member's disease onset (Table 2).

For all 4 sets of matches, we used calipers of width equal to 0.2 of the standard deviation of the propensity score.

Outcomes

We collected costs using ICES's GETCOST macro for 180 and 365 days after onset (hospital admission dates for cohort members) and after the index date (date of hospital admission for ACH-associated control patients, and date of matching for LTCF-associated, community-associated and ACH-associated/community-onset control patients) for hospital stays, same-day surgical procedures, emergency department visits, outpatient medications (all prescription drugs covered under the Ontario Drug benefit program for those aged ≥ 65 yr, those residing in LTCFs and those receiving social assistance), physician services, outpatient laboratory tests, complex continuing care stays and home care services. The periods were selected to capture all associated outcomes including those that do not manifest immediately. Costs were reported in 2015 Canadian dollars.

Statistical analysis

Given privacy rules regarding access to the data, all analyses were conducted by ICES staff. We used descriptive statistics to present unadjusted baseline characteristics and annual *C. difficile* infection incidence from fiscal years 2005/06 to 2014/15 and to characterize the *C. difficile* infection cohorts/control groups at baseline (i.e., index date). We estimated age-adjusted incidence rates per 100 person-years using the 2010 Ontario population as the standard.¹⁴ We compared categorical variables and continuous variables using generalized estimating equations to calculate the standardized differences.²²

Ethics approval

Ethics approval was granted by Advarra's Institutional Review Board Services, Canada's largest central review board.

Results

Between 2005/06 and 2014/15, there were 33 909 new cases of *C. difficile* infection in Ontario (Figure 1), of which 17 272 (50.9%) were ACH-associated/ACH-onset, 7216 (21.3%) were community-associated/community-onset, and 7098 (20.9%) were ACH-associated/community-onset (Table 3).

Residents of LTCFs whose infection was associated with their facility, or with either the facility or an ACH contributed a smaller proportion of cases (1.6% and 2.8%, respectively). Patients in LTCF cohorts were older than those in other cohorts (mean age 84.6 yr for LTCF-associated/LTCF-onset, and 82.1 yr for LTCF- or ACH-associated/LTCF-onset).

More than 40% of the ACH- or LTCF-associated/ACH-onset, LTCF- or ACH-associated/LTCF-onset, and ACH-associated/community-onset cohort members had used antibiotics in the 30 days before onset of the infection.

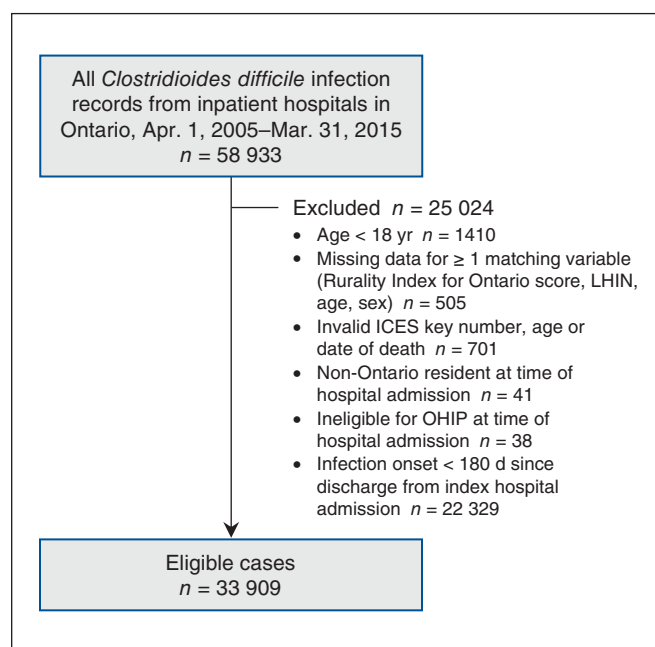


Figure 1: Flow diagram showing case inclusion. Note: LHIN = Local Health Integration Network, OHIP = Ontario Health Insurance Plan.

A higher proportion of community-associated/community-onset cohort members than other cohort members had inflammatory bowel disease (8.9% v. 3.5% for ACH-associated/ACH-onset infection).

Incidence

The overall annual number of cases of *C. difficile* infection per 100 000 person-years ranged from 27.7 (95% confidence interval 26.6–28.7) in 2009/10 to 37.0 (95% confidence interval 35.8–38.1) in 2012/13, with no obvious trends over time (Figure 2). The highest incidence was for ACH-associated/ACH-onset infection, and the second-highest was for ACH-associated/community-onset infection until 2009/10, when it was replaced with community-associated/community-onset infection.

The number of cases of ACH-associated/ACH-onset *C. difficile* infection per 100 000 person-years declined from 18.8 in 2011/12 to 15.1 in 2014/15, a decrease of 19.6% (Figure 1; Appendix 1, available at www.cmajopen.ca/content/8/1/E16/suppl/DC1). There was a decline of 69.2% in ACH- or LTCF-associated/ACH-onset cases per 100 000 person-years from 2005/06 (1.30) to 2014/15 (0.40).

The highest incidence of LTCF-associated/LTCF-onset cases per 100 000 person-years was in 2008/09, at 1.20; it declined to 0.13 in 2014/15. Community-associated/community-onset cases increased by 36.3% between 2005/06 (6.09 cases per 100 000 person-years) and 2014/15 (9.56 cases per 100 000 person-years). For ACH-associated/community-onset cases, the incidence at the study period's beginning and end was 6.8 cases per 100 000 person-years.

Comparison of cohort and control groups

Acute care hospital-associated/acute care hospital-onset infection

Compared to the control group, the infection cohort had a significantly lower proportion of LTCF residents and a longer hospital stay. Infected patients were more likely to have been admitted to hospital or have had health care exposure in the previous 12 weeks and up to 1 year prior, and were more likely to have used antibiotics in the 30 days before infection onset (Table 4). The infection cohort also had a higher prevalence of comorbidities, including cardiovascular disease and renal disease.

Long-term care facility-associated/long-term care facility-onset infection

Compared to the control group, the infection cohort had a significantly longer hospital stay, and higher rates of renal disease, health care exposure in the previous year and antibiotic use in the previous 30 days (Table 4).

Community-associated/community-onset infection

There were multiple significant baseline differences between the cohort and control groups (Table 4). The former had a longer hospital stay, and a higher proportion of patients had had health care exposure in the previous year and antibiotic

Table 3: Baseline characteristics of *Clostridioides difficile* infection cohorts in Ontario, 2005/06–2014/15, stratified by association and onset*

Characteristic	No. (%) of patients†						
	ACH- associated/ ACH-onset n = 17 272	ACH- or LTCF- associated/ ACH-onset n = 842	LTCF- associated/ LTCF-onset n = 544	LTCF- or ACH- associated/ LTCF-onset n = 937	Community- associated/ community- onset n = 7216	ACH- associated/ community- onset n = 7098	All n = 33 909
Patient days, mean ± SD	49.00 ± 64.69	33.66 ± 46.46	13.89 ± 19.53	13.44 ± 14.68	20.63 ± 34.27	21.54 ± 38.35	35.29 ± 54.37
Age at index date, yr, mean ± SD	72.22 ± 15.29	81.43 ± 9.67	84.57 ± 8.48	82.14 ± 9.99	70.07 ± 17.78	71.48 ± 15.77	72.31 ± 15.90
Age group, yr							
18–44	1005 (5.8)	1–5‡	1–5‡	4–8‡	728 (10.1)	486 (6.8)	2227 (6.6)
45–64	3516 (20.4)	46–50‡	7–11‡	45–49‡	1578 (21.9)	1485 (20.9)	6687 (19.7)
65–74	3576 (20.7)	118 (14.0)	48 (8.8)	116 (12.4)	1330 (18.4)	1474 (20.8)	6662 (19.6)
75–84	5458 (31.6)	296 (35.2)	174 (32.0)	337 (36.0)	1946 (27.0)	2197 (31.0)	10 408 (30.7)
≥ 85	3717 (21.5)	377 (44.8)	310 (57.0)	431 (46.0)	1634 (22.6)	1456 (20.5)	7925 (23.4)
Sex							
Female	8735 (50.6)	504 (59.9)	356 (65.4)	585 (62.4)	4305 (59.7)	3880 (54.7)	18 365 (54.2)
Male	8537 (49.4)	338 (40.1)	188 (34.6)	352 (37.6)	2911 (40.3)	3218 (45.3)	15 544 (45.8)
Admitted within 90 d before onset	5909 (34.2)	481 (57.1)	13 (2.4)	937 (100.0)	132 (1.8)	7098 (100.0)	14 570 (43.0)
Antibiotic use in 30 d before onset*	4216 (24.4)	342 (40.6)	147 (27.0)	512 (54.6)	1570 (21.8)	3212 (45.3)	9999 (29.5)
Comorbidities							
Cardiovascular disease	10 771 (62.4)	663 (78.7)	378 (69.5)	794 (84.7)	3935 (54.5)	5045 (71.1)	21 586 (63.7)
Chronic obstructive pulmonary disease	2057 (11.9)	114 (13.5)	77 (14.2)	148 (15.8)	771 (10.7)	1104 (15.6)	4271 (12.6)
Congestive heart failure	3076 (17.8)	205 (24.3)	108 (19.9)	286 (30.5)	998 (13.8)	1567 (22.1)	6240 (18.4)
Diabetes	1590 (9.2)	100 (11.9)	60 (11.0)	92 (9.8)	583 (8.1)	775 (10.9)	3200 (9.4)
Renal disease	3682 (21.3)	212 (25.2)	98 (18.0)	270 (28.8)	1277 (17.7)	1839 (25.9)	7378 (21.8)
Liver disease	1311 (7.6)	52 (6.2)	26 (4.8)	55 (5.9)	474 (6.6)	686 (9.7)	2604 (7.7)
Cancer	3249 (18.8)	76 (9.0)	28 (5.1)	84 (9.0)	924 (12.8)	1668 (23.5)	6029 (17.8)
Pulmonary circulation disease	634 (3.7)	44 (5.2)	20 (3.7)	46 (4.9)	197 (2.7)	405 (5.7)	1346 (4.0)
Valvular disease	986 (5.7)	53 (6.3)	16 (2.9)	73 (7.8)	242 (3.4)	462 (6.5)	1832 (5.4)
Inflammatory bowel disease	605 (3.5)	16 (1.9)	14 (2.6)	35 (3.7)	640 (8.9)	537 (7.6)	1847 (5.4)
Hospital characteristics							
Location							
Urban	16 726 (96.8)	823 (97.7)	524 (96.3)	916 (97.8)	6802 (94.3)	6624 (93.3)	32 415 (95.6)
Rural	546 (3.2)	19 (2.3)	20 (3.7)	21 (2.2)	414 (5.7)	474 (6.7)	1494 (4.4)
No. of beds							
< 100	1682 (9.7)	79 (9.4)	87 (16.0)	114 (12.2)	1155 (16.0)	1232 (17.4)	4349 (12.8)
100–299	7026 (40.7)	409 (48.6)	279 (51.3)	430 (45.9)	3118 (43.2)	3037 (42.8)	14 299 (42.2)
300–499	6395 (37.0)	282 (33.5)	144 (26.5)	312 (33.3)	2221 (30.8)	2130 (30.0)	11 484 (33.9)
≥ 500	2169 (12.6)	72 (8.6)	34 (6.3)	81 (8.6)	722 (10.0)	699 (9.8)	3777 (11.1)

Note: ACH = acute care hospital, LTCF = long-term care facility, SD = standard deviation.

*We excluded 22 329 cases from analysis because they occurred within 180 days of the index hospital admission date.

†Except where noted otherwise.

‡Exact counts suppressed for privacy reasons.

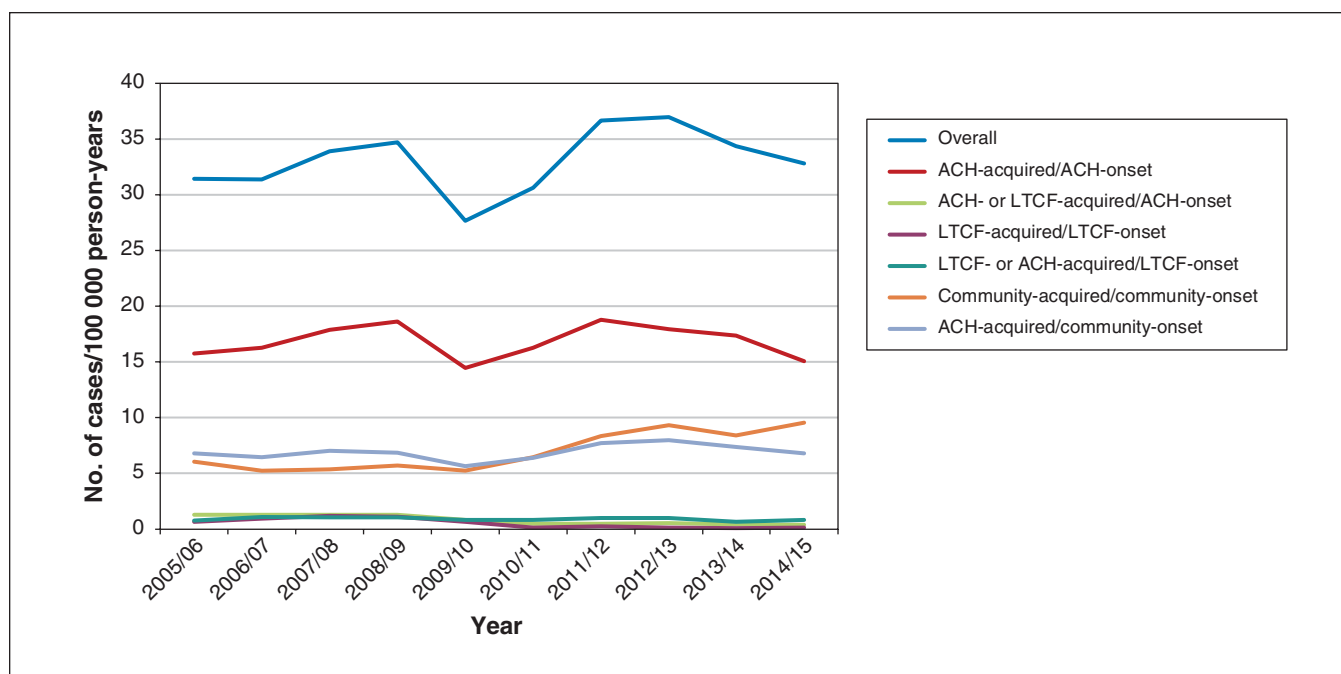


Figure 2: Number of cases of *Clostridioides difficile* infection per 100 000 person-years based on association and onset, 2005/06–2014/15. Note: ACH = acute care hospital, LTCF = long-term care facility.

use in the previous 30 days. The infection cohort also had a higher prevalence of cardiovascular disease and renal disease.

Acute care hospital–associated/community-onset infection
Compared to the control group, those in the infection cohort had a significantly longer hospital stay, a higher rate of renal disease and a lower rate of cancer (Table 4).

Cost

For each cohort, costs were incurred primarily in the first 180 days after admission (Table 5), mainly owing to the hospital stay, followed by physician services, outpatient medications and emergency department visits. *Clostridioides difficile* infection associated with ACHs had the highest median cost for inpatient hospital stays (\$36 370 v. \$8270 for control patients), as well as the highest median overall cost compared to control patients (\$48 593 v. \$13 542). However, large differences in median cost between the infection cohort and control patients were also seen with community-associated infection (\$20 258 v. \$1144). The median cost of outpatient medications was highest in the LTCF group, although the infection cohort had a lower cost than the control group (\$318 v. \$1646).

Interpretation

In the last 15 years, Ontario hospitals have filled in important gaps toward improving antimicrobial stewardship, as well as stringent hand hygiene and cleaning practices.^{13,14,23} Our findings suggest that it is too early to assess the impact of these changes. Although the overall *C. difficile* infection rate appears to have declined between 2012 and March 2015, it follows an

increase from 2005. Our data do confirm that community-associated *C. difficile* infection is increasing in incidence. This increase, and the considerable associated costs, have important implications for prevention strategies and practices.

Our data are compatible with those from other jurisdictions.^{24–26} A report from the sentinel hospitals of the Canadian Nosocomial Infection Surveillance Program also documented an increase in rates of hospital-associated *C. difficile* infection in central Canada from 2009 to 2012, followed by a decrease from 2012 to 2015. Those authors attributed the decline to improved infection control and prevention practices, and a regression in the NAP1 strain, which is associated with health care facility outbreaks.²⁷

We observed low rates of LTCF-associated *C. difficile* infection, similar to a study of LTCFs in Alberta in 2012/13, which also showed infected patients to be older (≥ 85 yr) and female, likely owing to their higher prevalence in these facilities.⁶ The authors of a US study that also showed an annual decline in *C. difficile* infection rates in 10 LTCFs attributed the decline to the decreased use of fluoroquinolone.²⁸

Conversely, we observed a 36% increase in the incidence of community-associated infection; similar increases have been observed in other North American studies.^{5,29–31} This trend may be due to increased exposure of community-dwelling people to outpatient health care settings, as well as greater clinician awareness of *C. difficile* infection as a potential cause of diarrhea, leading to more stool tests and diagnoses.

Patients whose *C. difficile* infection was associated with hospital admission had the highest median 180-day health care costs. The costs of community-associated and LTCF-associated infection were considerably lower, although still substantial. The control patients for both groups had much

Table 4: Baseline characteristics of *Clostridioides difficile* infection cohorts and matched control patients, stratified by association and onset*

Characteristic	No. (%) of patients†‡							
	ACH-associated/ACH-onset		LTCF-associated/LTCF-onset		Community-associated/ community-onset		ACH-associated/ community-onset	
	Cohort n = 13 152	Control group n = 33 058	Cohort n = 502	Control group n = 1407	Cohort n = 7116	Control group n = 21 127	Cohort n = 1847	Control group n = 3817
Patient days, mean ± SD	4730 ± 59.70	12.11 ± 22.80	13.80 ± 17.80	0.96 ± 4.20	20.70 ± 34.40	0.85 ± 6.20	23.80 ± 33.40	13.80 ± 24.20
Age group, yr								
18–44	428 (3.3)	943 (2.9)	0 (0.0)	0 (0.0)	718 (10.1)	2106 (10.0)	61 (3.3)	112 (2.9)
45–64	2238 (17.0)	5263 (15.9)	8 (1.6)	18 (1.3)	1552 (21.8)	4491 (21.3)	346 (18.7)	621 (16.3)
65–74	2677 (20.4)	6561 (19.8)	41 (8.2)	99 (7.0)	1315 (18.5)	3899 (18.5)	436 (23.6)	851 (22.3)
75–84	4558 (34.7)	11 584 (35.0)	166 (33.1)	469 (33.3)	1930 (27.1)	5578 (26.4)	628 (34.0)	1393 (36.5)
≥ 85	3251 (24.7)	8707 (26.3)	287 (57.2)	821 (58.4)	1601 (22.5)	5053 (23.9)	376 (20.4)	840 (22.0)
Male sex	6418 (48.8)	16 015 (48.4)	168 (33.5)	455 (32.3)	2876 (40.4)	8533 (40.4)	913 (49.4)	1897 (49.7)
LTCF resident	660 (5.0)	3088 (9.3)	502 (100.0)	1407 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Admitted in previous 12 wk	4149 (31.5)	7831 (23.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1847 (100.0)	3817 (100.0)
Admitted within 90 d before onset	4246 (32.3)	8043 (24.3)	11 (2.2)	16 (1.1)	125 (1.8)	101 (0.5)	1847 (100.0)	3817 (100.0)
Admitted in year before onset	6513 (49.5)	13 429 (40.6)	217 (43.2)	403 (28.6)	2303 (32.4)	3631 (17.2)	1847 (100.0)	3817 (100.0)
Comorbidities								
Cardiovascular disease	8287 (63.0)	19 476 (58.9)	343 (68.3)	925 (65.7)	3854 (54.2)	9542 (45.2)	1400 (75.8)	2795 (73.2)
Chronic obstructive pulmonary disease	1498 (11.4)	3597 (10.9)	69 (13.7)	147 (10.4)	748 (10.5)	1728 (8.2)	310 (16.8)	522 (13.7)
Congestive heart failure	2289 (17.4)	5001 (15.1)	93 (18.5)	235 (16.7)	954 (13.4)	2305 (10.9)	459 (24.9)	900 (23.6)
Diabetes	1204 (9.2)	2864 (8.7)	57 (11.4)	131 (9.3)	569 (8.0)	1503 (7.1)	194 (10.5)	408 (10.7)
Renal disease	2572 (19.6)	4358 (13.2)	83 (16.5)	154 (10.9)	1232 (17.3)	2273 (10.8)	512 (27.7)	817 (21.4)
Liver disease	684 (5.2)	1359 (4.1)	20 (4.0)	37 (2.6)	433 (6.1)	1501 (7.1)	139 (7.5)	261 (6.8)
Cancer	2115 (16.1)	5550 (16.8)	22 (4.4)	69 (4.9)	887 (12.5)	2243 (10.6)	444 (24.0)	1118 (29.3)
Pulmonary circulation disease	408 (3.1)	867 (2.6)	16 (3.2)	24 (1.7)	179 (2.5)	419 (2.0)	99 (5.4)	228 (6.0)
Valvular disease	696 (5.3)	1540 (4.7)	10 (2.0)	49 (3.5)	232 (3.3)	704 (3.3)	135 (7.3)	280 (7.3)
Inflammatory bowel disease	414 (3.1)	727 (2.2)	14 (2.8)	27 (1.9)	634 (8.9)	311 (1.5)	127 (6.9)	156 (4.1)
Antibiotic use 30 d before onset	3283 (25.0)	6146 (18.6)	141 (28.1)	58 (4.1)	1552 (21.8)	949 (4.5)	865 (46.8)	1278 (33.5)
Hospital location								
Not admitted	0 (0.0)	0 (0.0)	0 (0.0)	1252 (89.0)	0 (0.0)	19 475 (92.2)	0 (0.0)	0 (0.0)
Rural	449 (3.4)	2694 (8.1)	20 (4.0)	7 (0.5)	405 (5.7)	127 (0.6)	124 (6.7)	360 (9.4)
Urban	12 703 (96.6)	30 364 (91.9)	482 (96.0)	148 (10.5)	6711 (94.3)	1525 (7.2)	1723 (93.3)	3457 (90.6)
No. of beds								
Not admitted	0 (0.0)	0 (0.0)	0 (0.0)	1252 (89.0)	0 (0.0)	19 475 (92.2)	0 (0.0)	0 (0.0)
< 100	1380 (10.5)	6813 (20.6)	84 (16.7)	18 (1.3)	1138 (16.0)	318 (1.5)	308 (16.7)	832 (21.8)
100–299	5652 (43.0)	14 739 (44.6)	259 (51.6)	81 (5.8)	3084 (43.3)	674 (3.2)	817 (44.2)	1634 (42.8)
300–499	4665 (35.5)	10 178 (30.8)	130 (25.9)	43 (3.1)	2187 (30.7)	484 (2.3)	554 (30.0)	1106 (29.0)
≥ 500	1455 (11.1)	1328 (4.0)	29 (5.8)	13 (0.9)	707 (9.9)	176 (0.8)	168 (9.1)	245 (6.4)

Note: ACH = acute care hospital, LTCF = long-term care facility, SD = standard deviation.

*Adapted from reference 19 (Oxford University Press).

†Shaded cells denote the statistical significance ($p \leq 0.05$) of the standardized difference between the infection cohort and matched control patients.

‡Except where noted otherwise.

Table 5: Impact of hospital admission for *Clostridioides difficile* infection on costs (adjusted to 2015 Canadian dollars) 180 and 365 days after admission stratified by association and onset

Item†	Cost, \$*							
	ACH-associated		LTCF-associated		Community-associated		ACH-associated/community-onset	
	Cohort	Control group	Cohort	Control group	Cohort	Control group	Cohort	Control group
180 d after admission								
Inpatient hospital stays								
Median (IQR)	36 370 (19 700–72 050)	8270 (4977–15 118)	10 512 (5605–17 358)	0 (0–0)	13 249 (6106–28 465)	0 (0–0)	19 948 (10 793–40 147)	8031 (4815–16 231)
Mean ± SD	60 634.46 ± 71 778.71	15 040.39 ± 26 077.94	16 204.58 ± 24 121.61	1686.52 ± 6180.19	26 078.24 ± 39 508.03	1521.96 ± 7627.97	34 061.46 ± 45 162.54	16 579.24 ± 29 053.97
Emergency department visits								
Median (IQR)	611 (0–902)	559 (0–789)	668 (0–829)	0 (0–126)	635 (167–958)	0 (0–0)	619 (0–915)	548 (0–752)
Mean ± SD	666.89 ± 766.98	518.66 ± 495.71	617.35 ± 640.14	181.46 ± 420.58	708.21 ± 677.24	150.72 ± 423.95	724.86 ± 851.88	500.98 ± 478.89
Outpatient medications‡								
Median (IQR)	192 (0–1038)	146 (0–936)	318 (42–1583)	1646 (957–2434)	278 (0–1224)	332 (0–986)	64 (0–1114)	13 (0–683)
Mean ± SD	842.03 ± 2378.90	732.77 ± 1717.44	968.89 ± 1267.01	1781.81 ± 1152.34	1008.56 ± 2414.25	789.91 ± 2695.40	923.58 ± 2092.82	669.52 ± 1941.53
Physician services								
Median (IQR)	4579 (2592–8324)	1788 (951–3234)	1430 (832–2478)	679 (515–988)	2338 (1322–4465)	310 (76–849)	2808 (1412–5433)	1586 (828–2802)
Mean ± SD	6827.81 ± 6945.65	577.23 ± 2830.52	2064.48 ± 2598.27	929.47 ± 1013.78	3667.64 ± 4133.96	776.38 ± 1437.33	4191.95 ± 4453.04	2367.13 ± 2772.78
Total costs								
Median (IQR)	48 593 (27 707–92 417)	13 542 (8372–23 576)	13 951 (8756–23 048)	2995 (1942–4622)	20 258 (10 658–41 263)	1144 (300–3234)	28 486 (16 058–53 697)	13 557 (8100–25 203)
Mean ± SD	74 496.36 ± 78 111.95	21 833.49 ± 30 088.58	20 760.15 ± 27 362.89	5355.20 ± 9468.88	35 458.34 ± 45 345.38	4264.40 ± 11 330.13	44 738.49 ± 51 144.10	23 616.52 ± 33 062.58
365 d after admission								
Inpatient hospital stays								
Median (IQR)	38 832 (21 256–76 985)	8391 (4999–15 430)	10 829 (5605–18 865)	0 (0–0)	15 218 (6959–32 952)	0 (0–0)	21 765 (11 468–46 265)	8159 (4862–16 938)
Mean ± SD	67 121.13 ± 90 699.65	15 446.71 ± 28 373.96	17 669.40 ± 32 455.65	2881.96 ± 8133.05	29 809.12 ± 47 241.81	3164.33 ± 11 986.56	39 015.27 ± 53 837.57	17 185.72 ± 32 413.07
Emergency department visits								
Median (IQR)	678 (0–1151)	588 (0–814)	692 (0–913)	0 (0–533)	723 (388–1211)	0 (0–357)	678 (0–1 228)	578 (0–794)
Mean ± SD	867.96 ± 1118.86	577.73 ± 620.81	704.63 ± 735.94	330.35 ± 591.97	942.05 ± 987.16	307.38 ± 693.48	990.25 ± 1457.78	561.37 ± 610.01
Outpatient medications‡								
Median (IQR)	396 (0–2153)	215 (0–1709)	332 (42–2729)	3030 (1588–4666)	518 (0–2432)	685 (0–1980)	96 (0–2084)	25 (0–1078)
Mean ± SD	1674.50 ± 4784.24	1331.64 ± 3036.82	1645.95 ± 2354.53	3347.08 ± 2305.86	1940.65 ± 4352.58	1579.82 ± 5241.77	1675.95 ± 3684.43	1166.97 ± 3654.67
Physician services								
Median (IQR)	5298 (2969–9701)	2128 (1079–3807)	1729 (886–2943)	1366 (1007–1969)	3077 (1668–5733)	743 (231–1877)	3307 (1615–6535)	1798 (914–3327)
Mean ± SD	7918.96 ± 8131.04	2967.15 ± 3144.92	2488.54 ± 3377.68	1711.19 ± 1539.40	4738.46 ± 5187.00	1538.04 ± 2393.55	5244.60 ± 5815.23	2726.24 ± 3317.25
Total costs								
Median (IQR)	54 169 (30 873–102 711)	15 168 (9182–26 004)	15 565 (9750–25 649)	6232 (3732–9912)	25 245 (12 873–51 066)	2616 (721–7833)	33 342 (17 487–65 334)	14 837 (8710–28 267)
Mean ± SD	86 882.61 ± 101 953.16	24 224.39 ± 34 851.75	24 114.74 ± 38 520.25	9942.79 ± 16 397.21	44 047.52 ± 58 622.89	8564.23 ± 19 207.29	54 170.54 ± 65 160.54	26 175.76 ± 39 323.83

Note: ACH = acute care hospital, IQR = interquartile range, LTCF = long-term care facility, SD = standard deviation.

*Shaded cells denote the statistical significance ($p \leq 0.05$) of the standardized difference between the infection cohort and matched control patients.

†Costs for other services such as home care and same-day surgical procedures were excluded from the table but included in the total costs.

‡Includes any prescription drugs purchased for outpatient use through the Ontario Drug Benefit plan. Costs are based on the total amount paid to the pharmacy (including pharmacy fees) from Ontario Ministry of Health and Long-Term Care.

lower costs, mainly because many were not admitted to hospital. It is challenging to compare our costing results to those of previous studies, given that other investigators used a variety of time frames and typically focused on ACH-associated *C. difficile* infection only. Several systematic reviews have been conducted that reflect this variation but also validate our ACH-associated costs; estimated costs attributable to *C. difficile* infection have ranged from \$10 861 to \$36 960.^{32–35}

The impact of community-associated *C. difficile* infection is not insignificant: up to 40% of patients require hospital admission, 20% experience a severe infection, and 28% have a recurrence.³⁰ The continued education of physicians who may be the first point of health care contact for those with *C. difficile* infection (family physicians and emergency department physicians) is critical to identify patients at high risk quickly in order to permit successful treatment of the infection and to contain and limit transmission. Careful monitoring for *C. difficile* infection may include diagnostic testing of older patients with diarrhea who have recently been exposed to antibiotics and asking patients about recent hospital admissions and health care exposure. A 2018 Canadian analysis of isolates in community-acquired cases of *C. difficile* infection showed that all patients had been admitted in the previous year,³⁶ which indicates that many, and perhaps all, community-associated cases actually have nosocomial origins.

Limitations

Although we strove to match infected patients to control patients with similar demographic characteristics and medical history in each association/onset group, infected patients had higher rates of several comorbidities, which may have contributed to their higher incurred health care costs, owing to both unrelated hospital admissions and difficulty recovering from *C. difficile* infection because of frailty.

Given that the health administrative databases did not include the actual date of symptom onset or laboratory test confirmation of *C. difficile* infection, we modified the Centers for Disease Control and Prevention case definitions;¹⁸ our adaptations have not been validated, and therefore a small proportion of cases may have been misclassified by location of association. Since we used ICD-10-CA codes to identify cases, any coding errors will have under- or overestimated the number of cases. However, we expect that this impact is minimal given that a Canadian study showed high sensitivity (88%) and specificity (100%) associated with the *International Classification of Diseases, 9th Revision/ICD-10-CA* code for *C. difficile* infection.³⁷

We did not have access to outpatient data and could not include this information in our definition of “previous health care exposure,” so we could not assess whether recent exposure to outpatient health care settings was associated with *C. difficile* infection. We assumed that all ICD-10-CA codes for *C. difficile* infection within 180 days were from the same case and that codes 181 days or more from a prior code represented a new case; however, we did not have data on strain type to validate our assumptions.

We did not have access to prescription data for patients less than 65 years of age and those not receiving social assistance,

which will have underestimated the total costs of *C. difficile* infection treatment and management. Data were not available for Ontario residents in whom *C. difficile* infection was diagnosed or who were admitted to hospitals outside the province. Given that only hospital costs and certain physician and drug costs are included in the databases, we were unable to estimate the total cost of *C. difficile* infection to the health care system.

Although the analysis included data up to March 2015 only, there have not been any substantial changes in antimicrobial stewardship or hospital reporting requirements since then, nor have there been changes in circulating strains of *C. difficile*. Finally, any incidence trends identified may have been confounded by changes in infection control practices within 1 or more hospital.

Conclusion

We have reported on the incidence and cost burden of *C. difficile* infection in Ontario using comprehensive provincial health administrative databases. Increases in incidence among community-dwelling people present a need to strengthen efforts to identify those at risk for this infectious disease, particularly those who have been prescribed antibiotics or have had recent health care exposure, including but not limited to hospital admission.

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Contributors: Jennifer Pereira, Antigona Tomovici and Ayman Chit conceived and designed the study. Allison McGeer and Alex Selmani contributed to the study design and analysis plan. Jennifer Pereira drafted the manuscript. All of the authors interpreted the data, revised the manuscript critically for important intellectual content, approved the final version to be published and agreed to be accountable for all aspects of the work.

Funding: The study was funded by Sanofi Pasteur through the provision of salaries to Antigona Tomovici, Alex Selmani and Ayman Chit, and consulting fees to Jennifer Pereira and Allison McGeer, as well as research material.

Acknowledgement: The authors gratefully acknowledge Dr. Shudong Li for carrying out analyses at ICES.

Disclaimer: The authors had full control of study design, data collection and analysis, decision to publish and preparation of the manuscript. This study made use of deidentified data from the ICES Data Repository, which is managed by ICES with support from its funders and partners: Canada's Strategy for Patient-Oriented Research (SPOR), the Ontario SPOR SUPPORT Unit, the Canadian Institutes of Health Research and the Government of Ontario. The opinions, results and conclusions reported are those of the authors. No endorsement by ICES or any of its funders or partners is intended or should be inferred. Parts of this material are based on data and information compiled and provided by the Canadian Institute for Health Information (CIHI). However, the analyses, conclusions, opinions and statements expressed herein are those of the authors and not necessarily those of CIHI. Parts of this material are based on data and information provided by Cancer Care Ontario (CCO). The opinions, results, view and conclusions reported in this paper are those of the authors and do not necessarily reflect those of CCO. No endorsement by CCO is intended or should be inferred.

Supplemental information: For reviewer comments and the original submission of this manuscript, please see www.cmajopen.ca/content/8/1/E16/suppl/DC1.