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The Clinical Burden of *Clostridioides difficile* in Ontario, Canada

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Background. To understand the clinical burden of *Clostridioides difficile* infection (CDI), we analyzed health outcome data from Ontario, Canada for CDI associated with and manifested in acute care hospitals (ACH), long-term care facilities (LTCF), the community, or ACH-associated with community-onset.

Methods. We performed a retrospective analysis using individual-level data from Ontario databases (April 1, 2005 to March 31, 2015), identifying CDI cases ≥18 years requiring hospitalization, and stratifying into cohorts based on association and onset location. Cohort members were matched to controls on demographics and medical conditions at onset, for outcomes including 30- and 180-day all-cause mortality and rehospitalization.

Results. We stratified 22 617 individuals hospitalized with CDI during the study period: 13 152 (58.1%) ACH-associated/ACH-onset, 7116 (31.5%) community-associated/community-onset, 1847 (8.2%) ACH-associated/community-onset, and 502 (2.2%) LTCF-associated/LTCF-onset. Compared with controls, unadjusted 30-day rehospitalization rates were significantly higher ($P < .0001$) for ACH-associated/ACH-onset CDI (9.5% vs 0.4%), LTCF-associated/LTCF-onset (7.2% vs 1.1%), community-associated/community-onset (7.8% vs 0.8%), and ACH-associated/community-onset (10.9% vs 0.7%). One hundred eighty-day mortality rates were higher in the community-associated/community-onset and the LTCF-associated/LTCF-onset cohorts than controls: 66.3% vs 12.3% ($P < .0001$) and 30.9% vs 3.1% ($P < .0001$), respectively. All differences remained significant after adjusting for patient factors.

Conclusions. *Clostridioides difficile* infection is associated with higher rates of 30-day rehospitalization compared with controls. In addition, mortality rates within 180-days of hospital discharge are significantly higher for community-associated/community-onset and LTCF-associated/LTCF-onset CDI cohorts than controls. *Clostridioides difficile* infection warrants increased prevention and monitoring efforts.

Keywords. *Clostridioides difficile*; cohort; infectious disease.

Clostridioides difficile (CD) is a Gram-positive anaerobic bacterium transmitted between individuals by the transfer of spores. The primary reservoirs of CD include colonized or infected individuals, with spores commonly spread from the following multiple sources in the healthcare environment: on the hands of healthcare professionals; via contaminated surfaces, objects, and equipment; and in the feces of infected patients [1–4]. The health outcomes associated with CD infection (CDI) vary widely on a spectrum of severity, from mild diarrhea to death [5–7].

In Canada, CDI is among the primary infectious disease causes of morbidity and mortality [8] and has long been considered a hospital-acquired infection, with incidence rates of 5.35 per 1000 patient admissions [9]. However, recent literature suggests that rising incidence of CDI is associated with other settings, namely, long-term care facilities (LTCFs) and within the community [10–12]. *Clostridioides difficile* infection models have found that individuals living in long-term care facilities (LTCFs) transmit the disease at a rate of 27% of that of patients in acute care hospitals (ACHs), whereas community-dwelling residents transmit CDI at a rate of 0.1% of that of hospitalized patients [13]. However, the sheer number of individuals living in LTCFs and in community settings increases the potential for infection. Location of CDI association is likely to impact severity of disease, given that strain prevalence may be setting-dependent [14, 15]. In addition, individuals in LTCFs or in hospitals may be more vulnerable to the clinical consequences of CDI because age and underlying disease have been found to be strong risk factors for both initial illness and recurrence [16, 17]. Location of CDI onset is also likely to affect severity because detection and treatment paradigms may differ depending on whether symptoms begin in the hospital or in the community. It is important to understand to what extent the

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health outcomes experienced by individuals with CDI are attributable to the disease, how this differs by location of CDI association and onset, and whether there are specific factors that increase patient risk of poor outcomes with CDI.

Heightened surveillance and understanding of disease burden can motivate and improve prevention and disease management efforts. In this study, we used linked health administrative data from Ontario, Canada's most populous province, to estimate the medical burden of CDI based on whether the infection was associated with and manifested in ACH, LTCF, the community, or ACH-associated with community-onset.

METHODS

We conducted a retrospective cohort study to obtain Ontario-based estimates on mortality and rehospitalization rates for individuals with CDI that required hospitalization, compared with controls matched on various patient factors and medical conditions at time of disease onset. This study received ethics approval by Advarra's Institutional Review Board (IRB) Services, Canada's largest central IRB.

Data Sources

We conducted analyses using data from Ontario, a Canadian province with an estimated current population of more than 13.8 million [18]. ICES, an independent research organization, holds the province's health services administrative data on hospital and physician billings [19]. Individuals' health card numbers were encrypted, converted into unique identifiers, and linked to the Ontario Health Insurance Plan physician billing claims database. These data were also linked to both the Canadian Institute for Health Information (CIHI) hospital Discharge Abstracts Database (hospital discharge data) and the National Ambulatory Care Reporting System (data on emergency department visits). We also used the Registered Persons Database, a population-based registry containing demographic information for all Ontario residents eligible for health services, to access individuals' age, sex, postal code (to distinguish between urban and rural locations), and date of death.

Study Population Cases

We used administrative data to identify individuals (1) with an *International Classification of Diseases, Tenth Revision* (ICD-10) diagnosis code for CDI (A04.7) between April 1, 2005 and March 31, 2015, (2) 18 years or older at time of diagnosis, and (3) without a diagnosis code for CDI in the previous 180 days (if a patient had a second CDI diagnosis after 180 days postdischarge, this was counted as a separate recurrent incident, whereas one occurring before that time was still considered to be part of the index case).

Where possible, the individuals identified above were then categorized into 4 cohorts depending on location of CDI association and onset (defined in Table 1, and adapted from the Centers for Disease Control and Prevention surveillance definitions [20]): ACH-associated/ACH-onset CDI, LTCF-associated/LTCF-onset CDI, community-associated/community-onset CDI, and ACH-associated/community-onset CDI. These cohorts were prespecified as of interest because they encompassed most cases, and they were also assumed to be definable within the parameters of the datasets. Those who did not meet the definitions for any of the cohorts were excluded from the analysis.

Controls

Controls were individuals who were 18 years of age or over, lived in Ontario, and without an ICD-10 diagnosis code for CDI (A04.7) between April 1, 2005 and March 31, 2015. Matching was based on hard-match and propensity-score match criteria at the time of CDI onset for cases (Table 1). Members of each cohort were greedy-matched to 1 to 3 controls based on these criteria. For each of the 4 cohorts/controls, we used calipers of width equal to 0.2 of the standard deviation of the propensity score.

The primary outcome was 30-day all-cause mortality, whereas the secondary outcomes were (1) mortality rates (90 and 180 days post-CDI admission), (2) all-cause rehospitalization (30, 90, and 180 days postdischarge), (3) index hospitalization length of stay (LOS) and intensive care unit (ICU) LOS, and (4) colectomy rates within 365 days after index date (partial, total, or radical resection of the large intestine or rectum). For the controls, LOS and ICU LOS were only calculated for individuals who are hospitalized within 90 days of index date of the paired case.

Analysis

We calculated summary statistics to characterize the CDI cohorts and controls at baseline (ie, index date) by using means and standard deviations, medians (interquartile ranges), and proportions. Categorical and continuous variables were compared using generalized estimating equations to calculate standardized differences.

Using the 4 cohorts and matched controls, the relative risk (RR) of the various outcomes (excluding LOS and ICU LOS) were determined through negative binomial generalized linear modeling. For each of the 4 cohorts, multivariable regression models were used to determine the risk factors for 30-day all-cause hospitalization, 30-day all-cause mortality, and all-cause 180-day mortality, with predictor variables including age group (45–64, 65–74, 75–84, and ≥85 years), sex, and healthcare exposure (prior hospitalization in an ACH) in previous 90 or 365 days, antibiotic exposure in previous 30 days, and comorbidities (cardiovascular disease [CVD], chronic obstructive pulmonary disease, congestive heart failure, diabetes, liver disease, renal disease, cancer, pulmonary circulation disease, valvular disease, and inflammatory bowel disease). All analyses were conducted by ICES staff rather than the study team due to privacy rules regarding access to the individual-level health data.

Table 1. Definitions of CDI Cohorts and Matched Controls

	Cohort[a]	Controls[b]	
Cohort name	Definition	Hard-Match Criteria	Propensity-Score Match Criteria
ACH-associated/ ACH-onset	**ICD-10-CA diagnosis code for CDI (A04.7) during an inpatient hospital stay, coded as a postadmit comorbidity of clinical significance[c]**	• Age ± 2 yrs • Sex • Hospitalization admission date ±90 days • Most responsible diagnosis at hospital admission[d]	• Urban/rural score[e] • LHIN[f] • Elixhauser score[g]
LTCF-associated/ LTCF-onset[h]	**LTCF resident with ICD-10-CA diagnosis code for CDI (A04.7) during an inpatient hospital stay, coded as the most responsible diagnosis or a preadmit comorbidity of significance[i] AND no hospitalization in the 12 prior weeks before onset**	• Age ± 2 yrs • Sex • LTCF resident in the 12 wks before the matched cohort's date of hospitalization ±90 days	• Urban/rural score • LHIN • Elixhauser score
Community-associated/ community-onset[h]	**Community resident with ICD-10-CA diagnosis code for CDI (A04.7) during an inpatient hospital stay, coded as the most responsible diagnosis or a preadmit comorbidity AND no hospitalization or stay in an LTCF in the 12 weeks before onset**	• Age ± 2 yrs • Sex • Non-LTCF resident in the 12 wks before the matched cohort's date of hospitalization ±90 days • No hospitalization in the 12 wks before the matched cohort's date of hospitalization ±90 days	• Urban/rural score • LHIN • Elixhauser score
ACH-associated, community-onset	**ICD-10-CA diagnosis code for CDI (A04.7) during an inpatient hospital stay, coded as the most responsible diagnosis or a preadmit comorbidity of significance AND hospitalization in the 12 weeks before onset AND did not reside in an LTCF in the 12 weeks before onset**	• Age ± 2 yrs • Sex • Community-dwelling but hospitalized in the 12 wks before the matched cohort's index date of hospitalization ±90 days for same most responsible diagnosis[d]	• Urban/rural score • LHIN • Elixhauser score

Abbreviations: ACH, acute care hospital; CDI, *Clostridioides difficile* infection; ICD-10, *International Classification of Diseases, Tenth Revision*; ICD-10-CM, ICD-10-*Clinical Modification*; LHIN, Local Health Integration Network; LTCF, long-term care facility.

[a]Adapted from the Centers for Disease Control and Prevention surveillance definitions [20] and reproduced with permission.

[b]Controls did not have an ICD-10-CA code for CDI (A04.7) during the study period.

[c]A "postadmit comorbidity of significance" is a condition that arises postadmission, has been assigned an ICD-10-CA code, and affects the resource consumption or length of stay (LOS) of the patient.

[d]The "most responsible diagnosis" is the one most significant diagnosis or condition that causes a patient's hospital stay; matched on first 3 digits of ICD-10-CA code.

[e]A measure of a community's rurality based on its population and population density, travel time to nearest basic referral center, and travel time to nearest advanced referral center.

[f]Ontario comprises 14 LHINs that function as health authorities responsible for regional administration of public health services including hospitals and LTCFs.

[g]Comorbidity score based on ICD-10 coding [21].

[h]Individuals in this control group had not necessarily been hospitalized at index date.

[i]A "preadmit comorbidity of significance" is a condition that existed before admission, has been assigned an ICD-10-CA code, and affects the resource consumption or LOS of the patient.

RESULTS

There were 33 909 new cases of hospitalized CDI in Ontario between April 1, 2005 and March 31, 2015. Of these, 32 972 met our criteria for 1 of the 4 cohorts and 22 617 were able to be matched with controls: 13 152 (58.1%) were ACH-associated/ ACH-onset, 7116 (31.5%) were community-associated/ community-onset, 1847 (8.2%) were ACH-associated cases that manifested in the community, and 502 (2.2%) were LTCF-associated/LTCF-onset.

Baseline Characteristics

Acute-Care Hospital (ACH)-Associated/ACH-Onset Clostridioides difficile Infection.

There were multiple significant baseline differences between the cohort and their controls: the cohort had a lower percentage of LTCF residents, a longer LOS, and were more likely to have been hospitalized in the last 12 weeks and up to 1 year prior. They were also more likely to have used antibiotics in the 30 days before onset and to have renal disease (Table 2).

Long-Term Care Facility (LTCF)-Associated/LTCF-Onset Clostridioides difficile Infection.

Compared with the controls, this CDI cohort had a significantly longer hospital LOS, as well as higher rates of renal disease, hospitalization in the previous year, and antibiotic use in the previous 30 days.

Community-Associated/Community-Onset Clostridioides difficile Infection.

The cohort had a longer hospital stay than their matched controls. In addition, a higher percentage of the cohort had CVD, renal disease, hospitalization in the previous year, and used antibiotics in the previous 30 days.

Acute-Care Hospital-Associated/Community-Onset Clostridioides difficile Infection.

Compared with the controls, the cohort had a significantly longer hospital stay, as well as a higher rate of renal disease and a lower rate of cancer.

Table 2. Baseline Characteristics of CDI Cohorts and Matched Controls, Stratified by Association and Onset (April 1, 2005 to March 31, 2015)[a]

	ACH-Associated/ACH-Onset CDI		LTCF-Associated/LTCF-Onset CDI		Community-Associated/Community-Onset CDI		ACH-Associated/ Community-Onset CDI	
Characteristic	CDI Cohort	Non-CDI Cohort	CDI Cohort	Non-CDI Cohort	CDI Cohort	Non-CDI Cohort	CDI Cohort	Non-CDI Cohort
All patients (total)	N = 13 152	N = 33 058	N = 502	N = 1407	N = 7116	N = 21 127	N = 1847	N = 3817
LOS (days): median (IQR)	**29 (16–57)**	**6 (3–13)**	**10 (5–18)**	**0 (0)**	**10 (5–22)**	**0 (0)**	**14 (6–28)**	**7 (3–15)**
Age Group								
18–44	428 (3.3%)	943 (2.9%)	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%)
Sex: Male	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%)
Hospitalized in previous 12 weeks	4,149 (31.5%)	7,831 (23.7%)	0(0%)	0(0%)	0(0%)	0(0%)	1,847 (100.0%)	3,817 (100.0%)
Hospitalized in 90 days prior to onset	4,246 (32.3%)	8,043 (24.3%)	11 (2.2%)	16 (1.1%)	125 (1.8%)	101 (0.5%)	1,847 (100.0%)	3,817 (100.0%)
Hospitalized in year prior to onset	6,513 (49.5%)	13,429 (40.6%)	217 (43.2%)	403 (28.6%)	2,303 (32.4%)	3,631 (17.2%)	1,847 (100.0%)	3,817 (100.0%)
Comorbidities								
CVD	**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%)**
COPD	1498 (11.4%)	3597 (10.9%)	69 (13.7%)	147 (10.4%)	**748 (10.5%)**	**1728 (8.2%)**	**310 (16.8%)**	**522 (13.7%)**
CHF	**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 diseases	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 days 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								
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%)**
Number of Beds								
<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%)**

Abbreviations: ACH, acute care hospital; CDI, *Clostridioides difficile* infection; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; IQR, interquartile range; LOS, length of stay; LTCF, long-term care facility.

[a]Bold values denote the statistical significance of the standardized difference ($P \leq .05$) between the CDI cohort and their matched controls.

Clinical Outcomes

Acute-Care Hospital (ACH)-Associated/ACH-Onset Clostridioides difficile Infection.

Compared with controls, patients whose CDI was associated with staying in-hospital while admitted for a separate health issue had significantly worse unadjusted outcomes including a median total LOS that was 3.9 times longer, as well as higher rates of colectomies, and all-cause rehospitalization at 30, 90, and 180 days ($P < .0001$ for all comparisons) (Table 3). Mortality rates were 6.0% lower for the cohort than the control at 30 days postdischarge and similar at 180 days.

After adjusting for risk factors, significant results were still observed: the magnitude of the RR for rehospitalization decreased with time from 21.04 (95% confidence interval [CI], 17.67–25.05) at 30 days to 14.28 (95% CI, 12.92–15.78) at 180 days, compared with controls (Table 4).

Long-Term Care Facility (LTCF)-Associated/LTCF-Onset Clostridioides difficile Infection.

The LTCF-associated cohort had a significantly longer median hospital LOS than their controls as well as higher rates of clinical outcomes including mortality and rehospitalization ($P < .0001$ for all comparisons) (Table 3). These differences remained significant after adjusting for patient factors (Table 4).

Community-Associated/Community-Onset Clostridioides difficile Infection.

Compared with controls, the cohort had a 10-day longer median LOS and higher rates of 30-, 90-, and 180-day mortality, rehospitalization, and colectomies within 1 year after disease onset ($P < .0001$ for all comparisons) (Table 3). Adjusted risks of the mortality and rehospitalization outcomes were also significantly higher for patients with CDI than their controls (Table 4).

Acute-Care Hospital-Associated/Community-Onset Clostridioides difficile Infection.

Patients whose CDI was hospital-associated but whose disease onset occurred after discharge into the community had significantly longer mean LOS (difference = 7 days) and higher rates of rehospitalization than their controls ($P < .0001$ for all comparisons) (Table 3). However, this cohort had significantly lower mortality rates compared with their controls (34.5% vs 46.1% at 30 days postdischarge). After adjusting for risk factors, the differences were still significant for mortality (RR = 0.75 and 95% CI = 0.70–0.80 at 30 days) and rehospitalization outcomes (Table 4).

Risk Factors

Acute-Care Hospital (ACH)-Associated/ACH-Onset Clostridioides difficile Infection.

Those in the CDI cohort who died within 30 or 180 days of discharge were significantly more likely than their controls to have used antibiotics in the 30 days before onset (30.8% vs 23.9% and 28.8% vs 23.4%, respectively) (Supplemental Table 1a). Compared with their controls of the same age group, significantly more cohort members 45–64 years of age were rehospitalized within 30 days postdischarge (23.8% vs 10.6%).

In adjusted models for risk factors for rehospitalization and mortality in the CDI cohort (Supplementary Table 1b), we found that greater age was significantly associated with higher odds of mortality (RR for 30-day postadmission all-cause mortality: 0.14 [95% CI, 0.10–0.20] for 18–49 years vs 85 years and older) but lower odds of rehospitalization. Recent antibiotic use and healthcare exposure remained significant predictors of mortality, as did both renal disease and liver disease, but the odds of mortality decreased in individuals with inflammatory bowel disease.

Long-Term Care Facility (LTCF)-Associated/LTCF-Onset Clostridioides difficile Infection.

Of those who died at 30-days or 180-days, there was a significantly higher percentage of those who used antibiotics in the 30 days before onset (29.1% vs <5% [actual number unavailable], and 45.0% vs 31.8%, respectively) (Supplemental Table 2a) or had healthcare exposure in the previous 365 days (45.7% vs 33.9% and 45.0% vs 31.8%, respectively). However, there were no significant risk factors identified in the adjusted analysis (Supplementary Table 2b), apart from females having a lower odds of being hospitalized within 30 days of discharge, compared with males (RR = 0.45; 95% CI, 0.22–0.90).

Community-Associated/Community-Onset Clostridioides difficile Infection.

Of those rehospitalized within 180 days of discharge, 22.4% of those with CDI were 45–64 years old compared with 10.9% of controls (Supplementary Table 3a). Compared with the controls, those in the cohort who died within 30 and 180 days of discharge were significantly more likely to have used antibiotics in the 30 days before onset (25.8% vs 12.1% and 22.8% vs 9.6%, respectively).

In the adjusted analysis (Supplementary Table 3b), those at a younger age have significantly lower odds of mortality than those 85 years and over (RR = 0.09 and 95% CI = 0.06–0.13 for 180-day mortality). In addition, healthcare exposure in previous year, being male, and having cancer and liver disease were all associated with significantly higher odds of 30-day and 180-day mortality.

Acute-Care Hospital-Associated/Community-Onset Clostridioides difficile Infection.

Of those rehospitalized within 30 days of discharge, those with CDI were significantly more likely to be 45–64 years (34.2% vs 11.5%) and to have used antibiotics in the 30 days before CDI onset (44.1% vs 34.6%) (Supplementary Table 4a). Those in the cohort who died at 30 and 180 days were significantly more likely to have used antibiotics in the 30 days before CDI onset than the controls (51.2% vs 36.9% and 49.4% vs 36.5%, respectively).

Table 3. Comparison of Outcomes Between CDI Cohorts and Their Matched Controls (April 1, 2005 to March 31, 2015)[a]

	ACH-Associated/ ACH-Onset[b]		LTCF-Associated/ LTCF-Onset		Community-Associated/ Community-Onset		ACH-Associated/ Community-Onset	
Outcomes	CDI Cohort	Non-CDI Controls	CDI Cohort	Non-CDI Controls	CDI Cohort	Non-CDI Controls	CDI Cohort	Non-CDI Controls
Number of individuals	N = 13 152	N = 33 058	N = 502	N = 1407	N = 7116	N = 21 127	N = 1847	N = 3817
LOS (days): median (IQR)	**29 (16–57)**	**6 (3–13)**	**10 (5–18)**	**0 (0–0)**	**10 (5–22)**	**0 (0–0)**	**14 (6–28)**	**7 (3–15)**
Mortality rate 30-day post-admission date: n (%)	-	-	**234 (46.6%)**	**59 (4.2%)**	**1253 (17.6%)**	**199 (0.9%)**	**637 (34.5%)**	**1758 (46.1%)**
Mortality rate 90-days post-admission date: n (%)	-	-	**298 (59.4%)**	**106 (7.5%)**	**1901 (26.7%)**	**384 (1.8%)**	**915 (49.5%)**	**2224 (58.3%)**
Mortality rate 180-day post-admission date: n (%)	-	-	**333 (66.3%)**	**173 (12.3%)**	**2197 (30.9%)**	**653 (3.1%)**	**1024 (55.4%)**	**2392 (62.7%)**
Mortality rate 30-day post-discharge date: n (%)	**4764 (36.2%)**	**12 737 (38.5%)**	-	-	-	-	-	-
Mortality rate 90-day postdischarge date: n (%)	5507 (41.9%)	14 152 (42.8%)	-	-	-	-	-	-
Mortality rate 180-day post-discharge date: n (%)	6009 (45.7%)	15 077 (45.6%)	-	-	-	-	-	-
CDI recurrence 181–365 days: n (%)	**101 (0.8%)**	**6 (0.0%)**	[c]	**0 (0.0%)**	[c]	[c]	[c]	[c]
All-cause 30-day rehospitalization: n (%)	**1256 (9.5%)**	**141 (0.4%)**	**36 (7.2%)**	**15 (1.1%)**	**554 (7.8%)**	**175 (0.8%)**	**202 (10.9%)**	**26 (0.7%)**
All-cause 90-day rehospitalization: n (%)	**2283 (17.4%)**	**302 (0.9%)**	**58 (11.6%)**	**40 (2.8%)**	**1067 (15.0%)**	**494 (2.3%)**	**359 (19.4%)**	**54 (1.4%)**
All-cause 180-day rehospitalization: n (%)	**3070 (23.3%)**	**510 (1.5%)**	**74 (14.7%)**	**107 (7.6%)**	**1528 (21.5%)**	**1322 (6.3%)**	**478 (25.9%)**	**88 (2.3%)**
Colectomy 365-day postdiagnosis: n (%)	**47 (0.4%)**	**13 (0.0%)**	0 (0.0%)	[c]	95 (1.3%)	70 (0.3%)	[c]	[c]

Abbreviations: ACH, acute care hospital; CDI, *Clostridioides difficile* infection; IQR, interquartile range; LOS, length of stay.

[a]Bold values denote the statistical significance of the standardized difference ($P \leq .05$) between the CDI cohort and their matched controls.

[b]ACH-acquired/ACH-onset mortality was estimated from date of discharge rather than date of admission given that the patient did not have CDI at admission.

[c]Exact counts were low and therefore withheld from analysis to protect patient privacy.

Table 4. Comparison of Adjusted Outcomes Between CDI Cohorts and Their Matched Controls (April 1, 2005 to March 31, 2015)[a]

Cohort	ACH-Associated/ ACH-Onset	LTCF-Associated/ LTCF-Onset	Community-Associated/ Community-Associated	ACH-Associated/ Community-Onset
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
Mortality rate 30 days postadmission date	-	**10.78 (8.20–14.18)**	**17.36 (14.87–20.26)**	**0.75 (0.70–0.80)**
Mortality rate 90 days postadmission date	-	**7.80 (6.39–9.51)**	**14.00 (12.51–15.67)**	**0.86 (0.82–0.90)**
Mortality rate 180 days postadmission date	-	**5.49 (4.71–6.41)**	**9.47 (8.66–10.34)**	**0.89 (0.86–0.93)**
Mortality rate 30 days postdischarge date	**0.92 (0.90–0.95)**	-	-	-
Mortality rate 90 days postdischarge date	**0.96 (0.94–0.98)**	-	-	-
Mortality rate 180 days postdischarge date	0.99 (0.97–1.00)	-	-	-
All-cause 30-day rehospitalization	**21.04 (17.67–25.05)**	-	**8.37 (6.98–10.03)**	**15.24 (9.80–23.69)**
All-cause 90-day rehospitalization	**17.97 (15.91–20.28)**	**3.38 (2.16–5.3)**	**5.59 (5.08–6.37)**	**13.20 (9.76–17.86)**
All-cause 180-day rehospitalization	**14.28 (12.92–15.78)**	**1.62 (1.18–2.23)**	**2.99 (2.77–3.23)**	**10.75 (8.44–13.68)**

Abbreviations: ACH, acute care hospital; CDI, *Clostridioides difficile* infection; CI, confidence interval; LTCF, long-term care facility; RR, relative risk.

[a]Bold values denote statistically significant differences ($P \leq .05$) between the CDI cohort and their matched controls.

[b]ACH-acquired/ACH-onset mortality was estimated from date of discharge rather than date of admission given that the patient did not have CDI at admission.

In the adjusted analysis, all adult age groups were significantly more likely to be rehospitalized than those 85 years and older, and the association was strongest in those 45–64 years (Supplementary Table 4b). For 30-day and 180-day mortality, all age groups had significantly lower odds than those 85 years and older, with the association strengthening with decreasing age.

DISCUSSION

The clinical burden of hospitalized CDI in Ontario is considerable, manifesting as both in-hospital and postdischarge outcomes. Our study demonstrates that compared with those without CDI but with similar demographics and medical history, individuals with this infection had poorer outcomes, including significantly longer hospital stays, higher rates of all-cause rehospitalization, and, for those whose CDI was associated with their LTCF or the community, higher rates of all-cause mortality. For each of the 4 CDI cohorts, the odds of 30-day and 180-day all-cause mortality increased with age. Factors identified with higher odds of 30-day all-cause rehospitalization with ACH-associated/ACH-onset CDI included being a younger adult and having healthcare exposure in the previous year. Individuals with liver disease, cancer, or healthcare exposure in the prior year were associated with 30-day all-cause rehospitalization and 30-day and 180-day all-cause postadmission mortality for those with community-associated/community-onset CDI.

In prior studies, 30-day mortality rates in individuals with CDI have varied widely, from 2% to 42% [22–24]. In our 4 cohorts, LTCF-associated CDI was associated with highest mortality rates (46.6% at 30 days postadmission), as well as largest attributable risk, compared with matched controls. A significantly higher percentage of the cohort had been in a healthcare setting in the previous year and had used antibiotics in the previous 30 days, indicating that they may have had recent illnesses that left them vulnerable to CDI and death. A study of CDI outcomes in LTCFs in Alberta, Canada found that 22.2% of affected residents died within 30 days of their diagnosis [12]. This is significantly less than what we observed (46.6%), and the difference cannot be explained by a comparison of available patient demographics and medical history. However, it is possible that cases in our population were more frail or had a higher prevalence of previously identified risk factors for mortality including antibiotic exposure, hypoalbuminemia, or infection with ribotype 027 [25].

We observed higher rates of all outcomes in the community-associated CDI cohort than their matched controls. Our results corroborate a study of community-associated CDI in Ontario between 2003 and 2010, which also found increased mortality rates in 30 days (11.8%) and 180 days (19.6%) compared with noninfected controls [26]. We also observed a median hospital stay of 10 days longer for cohorts versus controls; 20% were hospitalized again in the following 6 months. Although our study excluded CDI that did not require hospitalization, community-associated CDI that does is clearly quite severe. Although this CDI had the lowest mortality rate of the 4 cohorts, with less than one third of individuals dying at 180 days, the rates are not insignificant. Those whose CDI was associated with their hospital

stay but were discharged into the community where their disease manifested had very severe outcomes, with more than one quarter requiring rehospitalization after discharge for their CDI stay, and half dying in the 6 months postadmission. Mortality rates and rates of clinical events such as rehospitalizations were even higher than they were for those who were diagnosed in-hospital during their index stay. This may imply that those for whom CDI is not diagnosed quickly during their index stay may have more clinically severe disease. However, a higher percentage of ACH-associated/community-onset cases had antibiotic exposure in the previous 30 days compared with ACH-associated/ACH-onset cases (46.8% vs 25.0%), which may have contributed to the severity of their CDI and higher outcome rates. In addition, those whose CDI manifested in the community may have had a more clinically detrimental illness for which they were admitted to hospital than those whose CDI was diagnosed during their index hospital stay. Further research is needed to investigate this finding.

It was surprising that mortality rates for ACH-associated CDI appeared significantly lower than matched controls. Because those with ACH-associated CDI have more clinically severe disease, as evidenced by their increased LOS and their higher rates of rehospitalization, this seems especially puzzling. There is no evidence in the literature to indicate that CDI has a protective effect on individuals with respect to death, and therefore we assume that this is likely a difference specific to this dataset and a result of the limitations of our matching criteria. We matched the first 3 digits of the case's ICD-10 diagnosis code to ensure that differences in burden could likely be attributed to CDI rather than the primary reason for hospitalization. This specific matching criteria has been used in a previous Canadian study [26]. However, the matched controls may have had more severe primary diagnoses than the CDI cohort, resulting in their higher mortality rates. In addition, compared with the ACH-associated CDI cohort, a higher percentage of their matched controls were LTCF residents, and individuals may have been more frail and therefore at greater risk for mortality [27].

We determined risk factors for all-cause rehospitalization and all-cause mortality for each of the 4 cohorts. Although many of the factors we identified—increasing age, healthcare exposure in previous year, antibiotic use, and cancer and liver disease—have previously been associated with increased risk of poor outcomes [28–30], others, such as the effect of inflammatory bowel disease, will require further validation. Being able to identify patients with CDI who are most at risk for severe outcomes may prove an important tool in reducing the clinical burden of this disease.

Our study is not without its limitations. Of those with ACH-associated CDI, 5% were LTCF resident, and therefore they may have been infected in their facility and not during hospitalization. Although, we attempted to use robust matching criteria to match CDI cohorts to controls, we noted many differences with respect to patient factors and certain comorbidities that may have affected rates of outcomes in our unadjusted analysis. The health administrative databases do not identify the date of positive CDI diagnoses, only whether they were diagnosed during a hospitalization; therefore, it was not possible to determine mortality rates from the exact date of diagnosis, so instead we measured mortality rates after admission and after discharge (where applicable). We used ICD-10 codes to identify cases of CDI, and therefore coding errors will impact our estimations of incidence. However, a Canadian study found that the ICD-9/ICD-10, with Canadian Enhancements (ICD-10-CA) codes for CDI have high sensitivity (88%) and specificity (100%) so we expect that impact to be minimal [31]. In addition, the Canadian Institute of Health Information conducts annual testing on a sample of charts from Canadian hospitals to assess the accuracy of diagnosis type coding, by way of comparison to the corresponding hospital charts. In 2015/2016 (the most recent year such data are currently available), there was 93% agreement for most responsible diagnosis, 83% for preadmit comorbidity, and 84% for postadmit comorbidity for several diseases including CDI [32]. We did not have access to outpatient data, and we could not include this in our definition of "previous healthcare exposure", so we could not assess whether recent exposure to outpatient healthcare settings were associated with CDI. In Ontario, CDI is tested by enzyme immunoassay, nucleic acid amplification test, and cytotoxicity assay, in addition to other visualization or histological diagnoses. Testing type was not available, nor did we have access to strain type data; these inclusions could provide more insight into whether the cohorts included cases of colonization or only true disease, as well as which strains were most responsible for mortality and other severe outcomes of CDI. Data on strain type may have also helped with validation of our assumption that all ICD-10 codes for CDI that were 180 days or more from a prior code represented a new case. Finally, data were not available for those Ontario residents diagnosed with CDI outside of Ontario or admitted and/or readmitted to hospitals outside of Ontario.

CONCLUSIONS

Our study provides important data on the clinical burden of CDI in Ontario, informing a stronger understanding of how the changing epidemiology of this infectious disease has impacted the health of affected individuals. Given that one third of cases occur outside of hospital settings, there is strong justification for prevention and early identification of CDI in the community and LTCFs. We have identified that CDI is associated with poor patient outcomes from infections associated with all settings, making it important (1) to identify those considered at high-risk for CDI and (2) to focus on prevention efforts to control the spread of this infection.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader,

the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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