The Incidence and Economic Burden of Clostridium Difficile in Ontario, Canada: Results of a Retrospective Population-Based Study

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Abstract:	Background: To characterize recent Clostridium difficile infection (CDI) epidemiology in Ontario, Canada, we analyzed provincial health administrative data to determine incidence rates and medical costs, based on whether acquisition and onset occurred in acute-care hospitals (ACH), long-term care facilities (LTCF) or the community. Methods: We performed a retrospective analysis using individual-level data from Ontario health databases from 2005 to 2014, identifying CDI requiring hospitalization in adults ≥ 18 years per 100,000 person-years (PYs) for six categories of acquisition and onset. We estimated costs of CDI for 180 and 365 days post-admission by matching CDI cases with non-CDI controls with similar patient characteristics. Results: Between 2005 and 2014, 33,909 individuals in Ontario were hospitalized with CDI; 17,272 (50.9%) were ACH-acquired. The total number of cases per 100,000 PYs ranged from 27.7 (95% CI:26.6-28.7) in 2009 to 37.0 (95% CI:35.8-38.1) in 2012. Annually, the highest incidence of CDI was ACH-acquired/ACH-onset; community-acquired CDI became more prevalent over time, rising from 19.4% in 2005 to 29.2% of cases in 2014. CDI costs were mostly due to hospitalization incurred 180 days post-index CDI hospital discharge. ACH-acquired CDI had the highest total costs and the largest CDI-attributable cost (median: $38,953 for the cohort vs. $13,542 for the controls). Median costs attributable to CDI were $1051 for LTCF-acquired, $13,249 for community-acquired, and $11,917 for ACH-acquired/community-onset CDI.

	Interpretation: Community-acquired CDI has similar health care cost implications as hospital-acquired CDI. With community-acquired CDI on the rise, family physicians should be supported and motivated to prevent CDI in their patients.

The Incidence and Economic Burden of Clostridium Difficile in Ontario, Canada:

Results of a Retrospective Population-Based Study

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Competing interests: JP and AM acted as consultants to Sanofi Pasteur for the conduct of this study. AC, AT and AS are employees of Sanofi Pasteur.

Contributions: JAP, MT and AC conceived and designed the study. AM and AS contributed to the study design and analysis plan. All authors interpreted the data, and JAP drafted the manuscript, with the support of the other authors. All of the authors critically revised the manuscript for important intellectual content, approved the final version to be published and agreed to be accountable for all aspects of the work.

Abstract

Background: To characterize recent *Clostridium difficile* infection (CDI) epidemiology in Ontario, Canada, we analyzed provincial health administrative data to determine incidence rates and medical costs, based on whether acquisition and onset occurred in acute-care hospitals (ACH), long-term care facilities (LTCF) or the community.

Methods: We performed a retrospective analysis using individual-level data from Ontario health databases from 2005 to 2014, identifying CDI requiring hospitalization in adults ≥ 18 years per 100,000 person-years (PYs) for six categories of acquisition and onset. We estimated costs of CDI for 180 and 365 days post-admission by matching CDI cases with non-CDI controls with similar patient characteristics.

Results: Between 2005 and 2014, 33,909 individuals in Ontario were hospitalized with CDI; 17,272 (50.9%) were ACH-acquired. The total number of cases per 100,000 PYs ranged from 27.7 (95% CI:26.6-28.7) in 2009 to 37.0 (95% CI:35.8-38.1) in 2012. Annually, the highest incidence of CDI was ACH-acquired/ACH-onset; community-acquired CDI became more prevalent over time, rising from 19.4% in 2005 to 29.2% of cases in 2014. CDI costs were mostly due to hospitalization incurred 180 days post-index CDI hospital discharge. ACH-acquired CDI had the highest total costs and the largest CDI-attributable cost (median: $38,953 for the cohort vs. $13,542 for the controls). Median costs attributable to CDI were $1051 for LTCF-acquired, $13,249 for community-acquired, and $11,917 for ACH-acquired/community-onset CDI.

Interpretation: Community-acquired CDI has similar health care cost implications as hospital-acquired CDI. With community-acquired CDI on the rise, family physicians should be supported and motivated to prevent CDI in their patients.

THE INCIDENCE AND BURDEN OF CLOSTRIDIUM DIFFICILE IN ONTARIO

Background

Clostridium difficile (CD) is a spore-forming bacterium that has historically caused infection primarily in elderly, hospitalized patients with exposure to antibiotics.[1-4] In Canada, CD infection (CDI) is a leading infectious disease cause of morbidity and mortality, with increases in incidence over the last two decades.[5,6] A retrospective study in Quebec identified a growth from 35.6 to 156.3 cases per 100,000 people between 1991 and 2003.[7] More recent surveillance of ten provinces found a 2011 incidence rate of 535 per 100,000 patient admissions.[8] CDI is associated with considerable costs; a study of Ontario hospital data demonstrated that acquiring CDI in hospital increased the median length of stay (LOS) by six days.[9] This translates to a significant economic burden; a Canadian model estimated a total of 37,900 CDI episodes (hospitalized and community-dwelling) in 2012, and a total societal cost of $281,000,000 of which 92% was in-hospital costs.[5]

While the majority of literature on CDI epidemiology is based on acquisition in acute-care hospital (ACH) settings, this infection is also associated with long-term care facilities (LTCFs), due to the residents' advanced age, presence of comorbidities, and antibiotics exposure.[10,11] Additionally, recent data indicates that community-acquired CDI is on the rise.[12,13] Possible shifting epidemiology will have important implications on efforts to prevent and diagnose CDI early. Healthcare system costs will likely vary depending on where CDI is acquired and where symptoms manifest since this dictates what type of medical care is sought. Therefore, we used linked health administrative data from Ontario to establish the incidence and economic burden of hospitalized CDI in Canada's most populous province, stratifying cases by acquisition and onset.

Methods

We conducted a retrospective cohort study to obtain provincial estimates on the incidence, cost and clinical impact (described in a separate publication) of CDI requiring hospitalization in ACH in-patients, LTCF residents and community-dwelling individuals. Ethics approval was granted by Institutional Review Board (IRB) Services.

Data sources

Analyses were conducted using data from Ontario, Canada which has an estimated current population of 13.8 million.[14] The Institute for Clinical Evaluative Sciences (IC/ES) houses Ontario's health administrative data on hospital and physician billings.[15] Health card numbers are encrypted, converted into unique identifiers and linked to the Ontario Health Insurance Plan (OHIP) physician billing claims database which contains data for approximately 95% of physician-based visits in Ontario. These data are also linked to both the Canadian Institute for Health Information (CIHI) hospital Discharge Abstracts Database and the National Ambulatory Care Reporting System for data related to patients' hospital admissions and emergency department (ED) visits, respectively. The Registered Persons Database (RPDB) is a population-based registry containing demographic information (age, sex, postal code, and date of death [where applicable]) for all Ontario residents eligible for health services.

Study population cases

Administrative data were used to identify cases in Ontario between April 1, 2005 and March 31, 2015. Cases had to i) have an ICD-10-CM diagnosis code for CDI (A04.7) during an in-patient hospital stay, as most responsible diagnosis, a pre-admit comorbidity, or a post-admit comorbidity of clinical significance;

ii) be at least 18 years at time of diagnosis; and iii) have no diagnosis code for CDI in the previous 180 days (a second diagnosis after 180 days post-discharge was considered a separate incidence).

i. CDI incidence

To calculate the outcome of number of cases requiring hospitalization per 100,000 person-years (PYs) from April 1, 2005 to March 31, 2015, the denominator included the base population that was ≥18 years but < 105 years, from RPDB data. PYs were based on postal code, OHIP eligibility, date of death, and date of last contact with healthcare system (individuals not seen in the healthcare system for more than seven years were considered to have moved).

Cases were stratified into six groups depending on location of CDI acquisition and onset (hospital admission date was used, since the databases did not capture when true onset occurred; **Table 1**).

Table 1: Definitions of CDI case groups based on location of disease acquisition and onset~

i. ACH-acquired/ ACH-onset CDI	CDI was coded as a post-admit comorbidity of clinical significance **AND** patient did not reside in a LTCF in the 12 weeks prior to admission
ii. ACH- or LTCF-acquired*/ ACH-onset CDI	CDI was coded as a post-admit comorbidity of clinical significance **AND** patient resided in a LTCF in the 12 weeks prior to admission
iii. LTCF-acquired/ LTCF-onset CDI	CDI was coded as the most responsible diagnosis or a pre-admit comorbidity **AND** patient resided in a LTCF with no history of hospitalization in the 12 weeks prior to admission
iv. LTCF- or ACH-acquired*/ LTCF-onset CDI	CDI was coded as the most responsible diagnosis or a pre-admit comorbidity **AND** patient resided in a LTCF in the 12 weeks prior to admission AND had a history of hospitalization during this time
v. Community-acquired/ Community-onset CDI	CDI was coded as the most responsible diagnosis or a pre-admit comorbidity **AND** patient neither resided in a LTCF nor was hospitalized in the 12 weeks prior to admission
vi. ACH-acquired/ Community-onset CDI	CDI was coded as the most responsible diagnosis or a pre-admit comorbidity **AND** patient did not reside in a LTCF but was hospitalized in the 12 weeks prior to admission

~Adapted from the Centers for Disease Control and Prevention (CDC) surveillance definitions[16]

*Because the case involved an individual who resided in a LTCF and was hospitalized in the 12 weeks prior to onset, it was not possible to determine whether CDI was required in an ACH or LTCF

ii. Cost of CDI

Individuals that met the above inclusion criteria were categorized into four cohorts, with each member matched to one to three controls based on hard-match and propensity-score match criteria at the time of CDI disease onset in the cases (**Table 2**).

Table 2: Definitions of CDI cohorts and matched controls

	Cohort	Control	
	Definition	**Hard-match criteria**	**Propensity-score match criteria**
ACH-acquired	ICD-10 diagnosis code for CDI (A04.7) during an in-patient hospital stay, coded as a post-admit comorbidity of clinical significance	Age ± 2yrs Sex Hospitalization admission date ±90 days Most responsible diagnosis**	Urban/rural score LHIN Elixhauser score
LTCF-acquired*	LTCF resident with ICD-10 diagnosis code for CDI (A04.7) during an in-patient hospital stay, coded as the most responsible diagnosis or a pre-admit comorbidity AND no hospitalization in the 12 prior weeks prior to onset	Age ± 2yrs Sex LTCF resident in the 12 wks prior to the matched cohort's date of hospitalization ±90 days	Urban/rural score LHIN Elixhauser score
Community-acquired*	Community resident with ICD-10 diagnosis code for CDI (A04.7) during an in-patient hospital stay, coded as the most responsible diagnosis or a pre-admit comorbidity AND no hospitalization in the 12 weeks prior to onset	Age ± 2yrs Sex Non-LTCF resident in the 12 wks prior to the matched cohort's date of hospitalization ±90 days	Urban/rural score LHIN Elixhauser score
ACH-acquired, community-onset	ICD-10-CM diagnosis code for CDI (A04.7) during an in-patient hospital stay, coded as the most responsible diagnosis or a pre-admit comorbidity AND did not reside in a LTCF in the 12 weeks prior to onset	Age ± 2yrs Sex Community-dwelling but hospitalized in the 12 wks prior to the matched cohort's index date of hospitalization ±90 days for same Most Responsible Diagnosis**	Urban/rural score LHIN Elixhauser score

*Individuals in this control group had not necessarily been hospitalized at index date
**Matched on first 3 digits of ICD-10 code

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

Outcomes: costs were collected for 180 and 365 days post-onset (hospital admission dates for cases) and post-index date (date of hospitalization for ACH-acquired controls, and the date matching began for LTCF-acquired, community-acquired and ACH-acquired/community-onset controls) for hospitalizations, same-day surgery procedures, ED visits, outpatient medications (for those aged ≥65 years or on social assistance), physician services, outpatient laboratory tests, complex continuing care admissions, and home-care services (standardized to 2015).

Analysis

We used simple descriptive statistics to present the unadjusted baseline characteristics of the cases annually from April 1st 2005 to March 31st 2006 (year 2005) to April 1st 2014 to March 31st 2015 (year 2014).

Summary statistics were calculated and compared for each CDI cohort/control matched group. We used descriptive summary statistics to characterize the cohort at baseline (i.e., index date). We estimated age-adjusted incidence rates per 100 PY using the 2015 Ontario population as the standard.[17] Categorical variables were compared using McNemar test, and continuous variables were evaluated using paired t-test.

Given privacy rules regarding access to the individualized data, all data derivation, calculations and analyses were conducted by IC/ES staff.

Results

Between April 1, 2005 and March 31, 2015, 33,909 individuals were diagnosed with CDI in Ontario (**Table 3**). Of these, 17,272 (50.9%) were ACH-acquired/ACH-onset, 7,216 (21.3%) were community-acquired/community-onset, and 7,098 (20.9%) were ACH-acquired/community-onset. LTCF residents who acquired the infection in the facility or either in the facility or ACH contributed a smaller percentage of cases (1.6% and 2.8%, respectively). As expected, patients in LTCF groups were older (mean age: 84.6 years for LTCF-acquired/LTCF-onset and 82.1 years for LTCF- or ACH-acquired/LTCF-onset), while more than 25% of cases from each of the other groups were 65 years or younger. More than 40% of cases in the ACH- or LTCF-acquired/ACH-onset, LTCF- or ACH-acquired/LTCF-onset, and ACH-acquired/community-onset groups had used antibiotics in the 30 days prior to onset. A higher percentage of community-acquired/community-onset cases had IBD compared to the other groups (8.9% vs. 3.5% for ACH-acquired/ACH-onset CDI).

CDI incidence

The annual number of CDI cases increased from 2005 (3030) to 2008 (3481) then declined in 2009 (2816), peaked in 2012 (3919) and has been declining again in the most recent years. Overall, there have been small fluctuations in the number of CDI cases per 100,000 PYs, ranging from 27.7 in 2009 to a peak of 37.0 in 2012 **(Figure 1)**. The highest incidence of CDI was from ACH-acquired/ACH-onset cases. The ACH-acquired/community-onset group contributed the second highest CDI incidence rate until 2009, when it was replaced with the community-acquired/community-onset group.

For ACH-acquired/ACH-onset cases, the number of cases per 100,000 PYs declined by 19.6% in recent years (15.1 in 2014) from a ten-year high of 18.8 in 2011 **(Figure 1; Supplemental Table 1)**. There was a 67% decline in ACH- or LTCF-acquired/ACH-onset cases per 100,000 PYs from 1.30 in 2005 to 0.40 in 2014. LTCF-acquired/LTCF-onset cases peaked in 2008 with 1.20 cases per 100,000 PYs but have declined in recent years to 0.13 cases per 100,000 PYs in 2014. Community-acquired/community-onset cases have shown a fairly consistent upwards trend, rising by 36.3% since 2005, with 9.56 cases per 100,000 PYs in 2014. For ACH-acquired cases with community-onset, incidence at the beginning and end of the study period was 6.8 cases per 100,000 PYs with considerable variation in between.

Figure 1: CDI cases based on acquisition and onset (2015 to 2014)

Cost of CDI

ACH-acquired CDI: There were several statistically significant differences between the CDI cohort and their matched controls (**Table 4**). Compared to the controls, the cohort had a lower percentage of individuals 75 years and older, LTCF residents, and individuals from rural Ontario. The CDI cohort had a longer hospital stay, and was more likely to have been hospitalized or have some healthcare exposure both in the recent past (within 12 weeks) and up to one year prior, and were also more likely to have used antibiotics in the 30 days before onset. The CDI cohort also had a higher prevalence of several comorbidities including CVD, CHF and renal disease.

LTCF-acquired CDI: The CDI cohort and its matched controls had similar baseline characteristics. However, the CDI cohort had a significantly longer hospital stay, a higher rate of healthcare exposure in the previous year, as well as antibiotic use in the 30 days prior to onset. Additionally, renal disease was more prevalent in the CDI cohort.

Community-acquired CDI: There were multiple significant baseline differences between the CDI and non-CDI cohort, with the former having a longer hospital stay, and a higher percentage having healthcare exposure in the previous year and antibiotic use in the previous 30 days, as well as a higher prevalence of most comorbidities.

ACH-acquired/community-onset CDI: Those in the CDI cohort had a significantly longer hospital stay, higher rates of several comorbidities including renal disease, but a lower rate of cancer.

Across all four matched groups, the bulk of the costs were incurred in the first 180 days post-admission rather than spread throughout the first year **(Table 5)**. The majority of the costs were due to the inpatient hospitalization, followed by physician services, outpatient medications, and ER visits.

Those who acquired CDI in hospital had the highest inpatient hospitalization cost (median: $36,370 vs. $8,270 for matched controls) as well as the highest overall cost compared to the control group (median: $48,593 vs. $13,542). However, large differences in cost between disease cohort and matched controls were also seen with community-acquired CDI (median: $20,258 vs $1,144). Costs related to ED visits were lowest in the ACH-acquired/ACH-onset group (median: $611) across all CDI-cohorts and the differential between the median costs of CDI group and control was also the smallest. The cost of outpatient medications was highest in the LTCF group, although the CDI cohort had a lower mean cost than the non-CDI cohort (median: $318 vs. $1,646).

Table 3: Baseline characteristics of CDI cases, stratified by acquisition and onset

Characteristics	ACH-acquired/ ACH-onset	ACH- or LTCF-acquired/ ACH-onset	LTCF-acquired/ LTCF-onset	LTCF- or ACH-acquired/ LTCF-onset	Community-acquired/ Community-onset	ACH-acquired Community-onset	CDI (all)
All patients (total)	**N=17,272**	**N=842**	**N=544**	**N=937**	**N=7,216**	**N=7,098**	**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							
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, n(%)							
18-44	1,005 (5.8%)	*1 – 5	*1 – 5	*4 – 8	728 (10.1%)	486 (6.8%)	2,227 (6.6%)
45-64	3,516 (20.4%)	*46 – 50	*7 – 11	*45 – 49	1,578 (21.9%)	1,485 (20.9%)	6,687 (19.7%)
65-74	3,576 (20.7%)	118 (14.0%)	48 (8.8%)	116 (12.4%)	1,330 (18.4%)	1,474 (20.8%)	6,662 (19.6%)
75-84	5,458 (31.6%)	296 (35.2%)	174 (32.0%)	337 (36.0%)	1,946 (27.0%)	2,197 (31.0%)	10,408 (30.7%)
85+	3,717 (21.5%)	377 (44.8%)	310 (57.0%)	431 (46.0%)	1,634 (22.6%)	1,456 (20.5%)	7,925 (23.4%)
Sex, n(%)							
Female	8,735 (50.6%)	504 (59.9%)	356 (65.4%)	585 (62.4%)	4,305 (59.7%)	3,880 (54.7%)	18,365 (54.2%)
Male	8,537 (49.4%)	338 (40.1%)	188 (34.6%)	352 (37.6%)	2,911 (40.3%)	3,218 (45.3%)	15,544 (45.8%)
Healthcare exposure in 90 days prior to onset, n(%)	**5,909 (34.2%)**	**481 (57.1%)**	**13 (2.4%)**	**937 (100.0%)**	**132 (1.8%)**	**7,098 (100.0%)**	**14,570 (43.0%)**
Antibiotic use in 30 days prior to onset, n(%)	**4,216 (24.4%)**	**342 (40.6%)**	**147 (27.0%)**	**512 (54.6%)**	**1,570 (21.8%)**	**3,212 (45.3%)**	**9,999 (29.5%)**
Comorbidities							
CVD, n(%)	**10,771 (62.4%)**	**663 (78.7%)**	**378 (69.5%)**	**794 (84.7%)**	**3,935 (54.5%)**	**5,045 (71.1%)**	**21,586 (63.7%)**
COPD, n(%)	**2,057 (11.9%)**	**114 (13.5%)**	**77 (14.2%)**	**148 (15.8%)**	**771 (10.7%)**	**1,104 (15.6%)**	**4,271 (12.6%)**
CHF, n(%)	**3,076 (17.8%)**	**205 (24.3%)**	**108 (19.9%)**	**286 (30.5%)**	**998 (13.8%)**	**1,567 (22.1%)**	**6,240 (18.4%)**
Diabetes, n(%)	**1,590 (9.2%)**	**100 (11.9%)**	**60 (11.0%)**	**92 (9.8%)**	**583 (8.1%)**	**775 (10.9%)**	**3,200 (9.4%)**
Renal disease, n(%)	**3,682 (21.3%)**	**212 (25.2%)**	**98 (18.0%)**	**270 (28.8%)**	**1,277 (17.7%)**	**1,839 (25.9%)**	**7,378 (21.8%)**
Liver disease, n(%)	**1,311 (7.6%)**	**52 (6.2%)**	**26 (4.8%)**	**55 (5.9%)**	**474 (6.6%)**	**686 (9.7%)**	**2,604 (7.7%)**

Cancer, n(%)	**3,249 (18.8%)**	**76 (9.0%)**	**28 (5.1%)**	**84 (9.0%)**	**924 (12.8%)**	**1,668 (23.5%)**	**6,029 (17.8%)**
Pulmonary circulatory disorder, n(%)	**634 (3.7%)**	**44 (5.2%)**	**20 (3.7%)**	**46 (4.9%)**	**197 (2.7%)**	**405 (5.7%)**	**1,346 (4.0%)**
Valvular disease, n(%)	**986 (5.7%)**	**53 (6.3%)**	**16 (2.9%)**	**73 (7.8%)**	**242 (3.4%)**	**462 (6.5%)**	**1,832 (5.4%)**
Inflammatory bowel disease, n(%)	**605 (3.5%)**	**16 (1.9%)**	**14 (2.6%)**	**35 (3.7%)**	**640 (8.9%)**	**537 (7.6%)**	**1,847 (5.4%)**
Hospital characteristics							
Hospital location, n(%)							
Urban	16,726 (96.8%)	823 (97.7%)	524 (96.3%)	916 (97.8%)	6,802 (94.3%)	6,624 (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%)	1,494 (4.4%)
Number of beds, n(%)							
<100	1,682 (9.7%)	79 (9.4%)	87 (16.0%)	114 (12.2%)	1,155 (16.0%)	1,232 (17.4%)	4,349 (12.8%)
100-299	7,026 (40.7%)	409 (48.6%)	279 (51.3%)	430 (45.9%)	3,118 (43.2%)	3,037 (42.8%)	14,299 (42.2%)
300-499	6,395 (37.0%)	282 (33.5%)	144 (26.5%)	312 (33.3%)	2,221 (30.8%)	2,130 (30.0%)	11,484 (33.9%)
>=500	2,169 (12.6%)	72 (8.6%)	34 (6.3%)	81 (8.6%)	722 (10.0%)	699 (9.8%)	3,777 (11.1%)

Table 4: Baseline characteristics of CDI cohorts and matched controls, stratified by acquisition and onset*

	ACH-acquired CDI		LTCF-acquired CDI		Community-acquired CDI		ACH-acquired, community-onset CDI	
	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=1,407**	**N=7,116**	**N=21,127**	**N=1,847**	**N=3,817**
Patient days: mean ± SD	47.3 ± 59.7	12.11 ± 22.8	13.8 ± 17.8	0.96 ± 4.2	20.7 ± 34.4	0.85 ± 6.2	23.8 ± 33.4	13.8 ± 24.2
Age group								
18-44	428 (3.3%)	943 (2.9%)	0(0%)	0(0%)	718 (10.1%)	2,106 (10.0%)	61 (3.3%)	112 (2.9%)
45-64	2,238 (17.0%)	5,263 (15.9%)	8 (1.6%)	18 (1.3%)	1,552 (21.8%)	4,491 (21.3%)	346 (18.7%)	621 (16.3%)
65-74	2,677 (20.4%)	6,561 (19.8%)	41 (8.2%)	99 (7.0%)	1,315 (18.5%)	3,899 (18.5%)	436 (23.6%)	851 (22.3%)
75-84	4,558 (34.7%)	11,584 (35.0%)	166 (33.1%)	469 (33.3%)	1,930 (27.1%)	5,578 (26.4%)	628 (34.0%)	1,393 (36.5%)
85+	3,251 (24.7%)	8,707 (26.3%)	287 (57.2%)	821 (58.4%)	1,601 (22.5%)	5,053 (23.9%)	376 (20.4%)	840 (22.0%)
Sex: Male	6,418 (48.8%)	16,015 (48.4%)	168 (33.5%)	455 (32.3%)	2,876 (40.4%)	8,533 (40.4%)	913 (49.4%)	1,897 (49.7%)
LTCF resident	***660 (5.0%)***	***3,088 (9.3%)***	***502 (100.0%)***	***1,407 (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%)***
Healthcare exposure 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%)***
Healthcare exposure 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	8,287 (63.0%)	19,476 (58.9%)	343 (68.3%)	925 (65.7%)	3,854 (54.2%)	9,542 (45.2%)	1,400 (75.8%)	2,795 (73.2%)
COPD	1,498 (11.4%)	3,597 (10.9%)	69 (13.7%)	147 (10.4%)	748 (10.5%)	1,728 (8.2%)	310 (16.8%)	522 (13.7%)
CHF	2,289 (17.4%)	5,001 (15.1%)	93 (18.5%)	235 (16.7%)	954 (13.4%)	2,305 (10.9%)	459 (24.9%)	900 (23.6%)
Diabetes	1,204 (9.2%)	2,864 (8.7%)	57 (11.4%)	131 (9.3%)	569 (8.0%)	1,503 (7.1%)	194 (10.5%)	408 (10.7%)
Renal disease	2,572 (19.6%)	4,358 (13.2%)	83 (16.5%)	154 (10.9%)	1,232 (17.3%)	2,273 (10.8%)	512 (27.7%)	817 (21.4%)
Liver disease	684 (5.2%)	1,359 (4.1%)	20 (4.0%)	37 (2.6%)	433 (6.1%)	1,501 (7.1%)	139 (7.5%)	261 (6.8%)

Cancer	2,115 (16.1%)	5,550 (16.8%)	22 (4.4%)	69 (4.9%)	887 (12.5%)	2,243 (10.6%)	444 (24.0%)	1,118 (29.3%)
Pulmonary circulatory disorder	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%)	1,540 (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 prior to onset	***3,283 (25.0%)***	***6,146 (18.6%)***	***141 (28.1%)***	***58 (4.1%)***	***1,552 (21.8%)***	***949 (4.5%)***	***865 (46.8%)***	***1,278 (33.5%)***
Hospital location								
Rural	449 (3.4%)	2,694 (8.1%)	0 (0.0%)	1,252 (89.0%)	0 (0.0%)	19,475 (92.2%)	124 (6.7%)	360 (9.4%)
Urban	12,703 (96.6%)	30,364 (91.9%)	20 (4.0%)	7 (0.5%)	405 (5.7%)	127 (0.6%)	1,723 (93.3%)	3,457 (90.6%)
Number of beds			482 (96.0%)	148 (10.5%)	6,711 (94.3%)	1,525 (7.2%)		
<100	1,380 (10.5%)	6,813 (20.6%)					308 (16.7%)	832 (21.8%)
100 – 299	5,652 (43.0%)	14,739 (44.6%)	0 (0.0%)	1,252 (89.0%)	0 (0.0%)	19,475 (92.2%)	817 (44.2%)	1,634 (42.8%)
300 – 499	4,665 (35.5%)	10,178 (30.8%)	84 (16.7%)	18 (1.3%)	1,138 (16.0%)	318 (1.5%)	554 (30.0%)	1,106 (29.0%)
≥500	1,455 (11.1%)	1,328 (4.0%)	259 (51.6%)	81 (5.8%)	3,084 (43.3%)	674 (3.2%)	168 (9.1%)	245 (6.4%)

*Shaded cells denote statistically significant differences (p-value ≤ 0.05) between the CDI cohort and their matched controls

Table 5: Impact of CDI on costs (adjusted to 2015 CDN)*

	ACH-acquired CDI		LTCF-acquired CDI		Community-acquired CDI		ACH-acquired, community-onset CDI	
Cohort	**CDI cohort**	**Non-CDI cohort**	**CDI cohort**	**Non-CDI cohort**	**CDI cohort**	**Non-CDI cohort**	**CDI cohort**	**Non-CDI cohort**
180 days post-admission								
Inpatient hospitalization								
Median (IQR)	36,370 (19,700-72,050)	8,270 (4,977-15,118)	10,512 (5,605-17,358)	0 (0-0)	13,249 (6,106-28,465)	0 (0-0)	19,948 (10,793-40,147)	8,031 (4,815-16,231)
ED 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)
Outpatient medications								
Median (IQR)	192 (0-1,038)	146 (0-936)	318 (42-1,583)	1,646 (957-2,434)	278 (0-1,224)	332 (0-986)	64 (0-1,114)	13 (0-683)
Physician services								
Median (IQR)	4,579 (2,592-8,324)	1,788 (951-3,234)	1,430 (832-2,478)	679 (515-988)	2,338 (1,322-4,465)	310 (76-849)	2,808 (1,412-5,433)	1,586 (828-2,802)
Total costs								
Median (IQR)	48,593 (27,707-92,417)	13,542 (8,372-23,576)	13,951 (8,756-23,048)	2,995 (1,942-4,622)	20,258 (10,658-41,263)	1,144 (300-3,234)	28,486 (16,058-53,697)	13,557 (8,100-25,203)
365 days post-admission								
Inpatient hospitalization								
Median (IQR)	38,832 (21,256-76,985)	8,391 (4,999-15,430)	10,829 (5,605-18,865)	0 (0-0)	15,218 (6,959-32,952)	0 (0-0)	21,765 (11,468-46,265)	8,159 (4,862-16,938)
ED visits								
Median (IQR)	678 (0-1,151)	588 (0-814)	692 (0-913)	0 (0-533)	723 (388-1,211)	0 (0-357)	678 (0-1,228)	578 (0-794)
Outpatient medications								
Median (IQR)	396 (0-2,153)	215 (0-1,709)	332 (42-2,729)	3,030 (1,588-4,666)	518 (0-2,432)	685 (0-1,980)	96 (0-2,084)	25 (0-1,078)
Physician services								
Median (IQR)	5,298 (2,969-9,701)	2,128 (1,079-3,807)	1,729 (886-2,943)	1,366 (1,007-1,969)	3,077 (1,668-5,733)	743 (231-1,877)	3,307 (1,615-6,535)	1,798 (914-3,327)
Total costs								
Median (IQR)	54,169 (30,873-102,711)	15,168 (9,182-26,004)	15,565 (9,750-25,649)	6,232 (3,732-9,912)	25,245 (12,873-51,066)	2,616 (721-7,833)	33,342 (17,487-65,334)	14,837 (8,710-28,267)

*Costs for other services such as home-care and same day surgeries were excluded from Table but included in the Total costs

Interpretation

Our study demonstrates that the overall rate of CDI in Ontario has been declining since 2012, primarily driven by a decrease in ACH-acquired CDI. However, community-acquired cases of CDI have been on the rise. CDI-attributable costs in ACH-acquired cases were higher than for LTCF-acquired or community-acquired cases, but across all groups, the biggest contributor came from hospitalization. Rates in LTCF residents were relatively low (less than 1 case per 100,000 PYs), indicating that facilities are likely implementing infection control programs and antibiotic stewardship to reduce outbreak risks. We observed a temporary decline in CDI incidence rates in 2009, likely a consequence of a provincial requirement beginning in 2008 that hospitals publicly report their CDI rates.[18]

Our findings are supported by epidemiological data from the U.S. and Europe suggesting that the incidence of CDI has declined in recent years.[19-21] We observed a 36% increase in community-acquired infection, corroborating recent US studies[22,23] as well as a large Canadian study which found that 43.0% of CDI cases in 2012 were community-acquired.[5] This trend may be due to increased community-dwelling patient exposure to outpatient healthcare settings as well as greater clinician awareness of CDI as a potential cause of diarrhea, leading to more stool tests and diagnoses. As with prior population-based US studies,[23,24] we found that compared to those with ACH-acquired CDI, those with community-acquired CDI were typically younger, female and had lower rates of comorbidities. The rise in community-acquired CDI and the considerable attributable costs have important implications for infection prevention and control strategies. Community-acquired CDI's impact is not insignificant: a past study of patients afflicted found that 40% required hospitalization, 20% suffered from a severe infection, and 28% had a recurrence.[23] Early identification of patients at high risk is crucial to ensure timely treatment. We have also found consistent incidence rates in those with ACH-acquired/community-onset CDI, highlighting the need for careful monitoring of those with risk factors for CDI (such as being elderly and having recently been prescribed antibiotics) who were recently discharged from hospital. 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 those with persistent diarrhea as potential cases, and those with risk factors as most susceptible.

LTCF cases contributed only a small amount to overall cases throughout the study period, with rates declining 80% from 2005 to 2014. This trend was also observed in a US study of 10 LTCFs, which noted an annual decline of 17.5% in CDI rates between 2011 and 2015, and speculated that this may be attributed to the decreased use of floroquinolone during this period.[25] Improvements in antimicrobial strategies employed at the facilities may also have led to the decreased rates. Similar to our findings, a 2012 study of LTCFs in Alberta, Canada found that CDI cases were older (85 years and above) and female, likely due to these being the average resident demographics in such facilities.[26]

Individuals who acquired CDI in-hospital had the highest median 180-day healthcare costs, while the costs of community-acquired and LTCF-acquired cases were considerably lower although still significant. The matched controls for both groups had much lower costs, mainly due to many not having been hospitalized, and therefore not incurring those costs for the healthcare system. It is challenging to compare our costing results to previous literature, given that other studies use a variety of timeframes, and typically focus on ACH-acquired CDI only. Several systematic reviews have been conducted which reflect this variation but also validate our ACH-acquired costs; estimated CDI-attributable costs have ranged from $2,992 to $34,157 USD[27-29] and $10,861 to $36,960[30] CDN.

Our study is not without limitations. Although we strived to include a range of explanatory factors in our analysis, and also match CDI cohorts to controls with similar demographics and medical history, we did

observe key differences, and unidentified confounding factors may have also impacted our costing results. The health administrative databases do not include laboratory test results or prescriptions, so these could not be included in our case criteria. However, previous studies have shown that ICD-10 codes for CDI have decent sensitivity and excellent specificity.[31] Data were not available for Ontario residents diagnosed or admitted to hospitals outside the province. However, only a small number of patients are likely to be affected by this limitation. Given that only hospital costs and some physician costs are included in the databases and treatment costs are unavailable, we were unable to estimate the total cost of CDI to the healthcare system. Finally, any incidence trends identified may have been confounded by changes in infection control practices within one or more hospital.

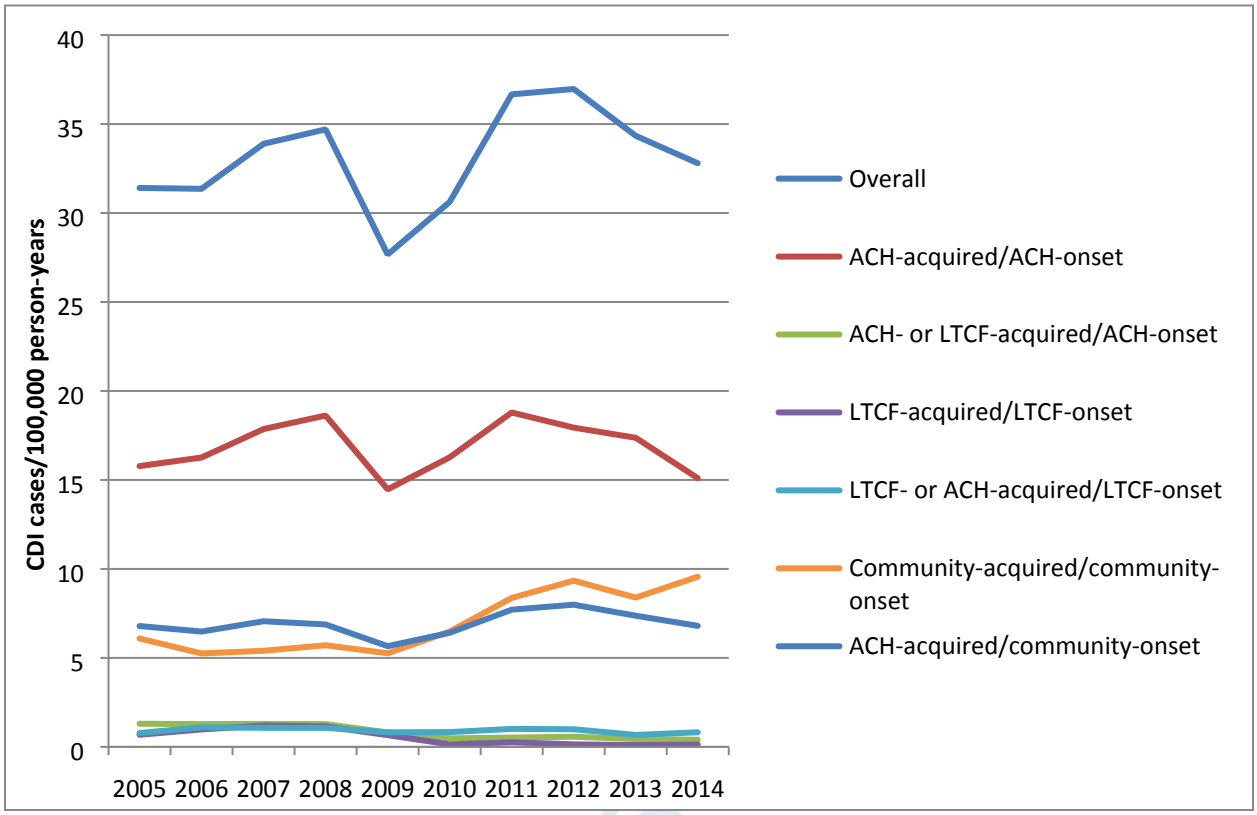
We have provided important data on the incidence and cost burden of CDI in Ontario, using comprehensive provincial health administrative databases. Increases in incidence in community-dwelling individuals present a need to strengthen efforts to identify those at risk for this infectious disease, particularly those who have been prescribed antibiotics, or had recent healthcare exposure, including but not limited to hospitalization.

References

1. Bartlett JG, Gerding DN. Clinical recognition and diagnosis of Clostridium difficile infection. Clin Infect Dis. 2008;46(Suppl 1):12-8.
2. Dubberke ER, Reske KA, Olsen MA et al. Evaluation of Clostridium difficile-associated disease pressure as a risk factor for C. difficile-associated disease. Arch Intern Med. 2007;167:1092–1097.
3. Karmali S, Laffin M, de Gara C. CAGS clinical practice committee report: the science of clostridium difficile and surgery. Can J Surg. 2013;56:367–71.
4. Kelly CP, Pothoulakis C, LaMont JT. *Clostridium difficile* colitis. N Engl J Med 1994;330:257–62.
5. Levy AR, Szabo SM, Lozano-Ortega G, Lloyd-Smith E, Leung V, Lawrence R, Romney MG. Incidence and costs of *Clostridium difficile* infections in Canada. Open Forum Infect Dis. 2015 Jun 3;2(3):ofv076.
6. Kwong JC, Ratnasingham S, Campitelli MA, et al. The impact of infection on population health: results of the Ontario burden of infectious diseases study. PLoS ONE. 2012;7(9): e44103.
7. Pépin J, Valiquette L, Alary ME et al. *Clostridium difficile*-associated diarrhea in a region of Quebec from 1991 to 2003: a changing pattern of disease severity. CMAJ. 2004;171:466-472.
8. The Canadian Nosocomial Infection Surveillance Program (CNISP). Healthcare-Associated-Clostridium difficile Infection (HA-CDI) 2007-2011. Public Health Agency of Canada. http://www.phac-aspc.gc.ca/nois-sinp/projects/cdad-eng.php. Accessed 04-04-2016.
9. Forster A, Taljaard M, Oake N, Wilson K, Roth V, and van Walraven C. The effect of hospital-acquired infection with Clostridium difficile on length of stay in hospital. CMAJ. 2011; DOI:10.1503/cmaj.110543.
10. Simor AE. Diagnosis, management and prevention of *Clostridium difficile* infection in long-term care facilities: a review. JAGS. 2010;58:1556-1564.
11. Hunter JC, Mu Y, Dumyati GK et al. Burden of nursing home-onset *Clostridium difficile* infection in the United States: estimates of incidence and patient outcomes. Open Forum Infect Dis. 2016;3(1): doi:10.1093/ofid/ofv196
12. Gupta A, Khanna S. Community-acquired *Clostridium difficile* infection: an increasing public health threat. Infection and Drug Resistance. 2014;7:63-72.

13. Lessa FC, Mu Y, Bamberg WM. Burden of *Clostridium difficile* infection in the United States. N Engl J Med. 2015; 372:825-834.
14. Statistics Canada. Estimates of population, Canada, provinces, territories. http://www5.statcan.gc.ca/cansim/a26?lang=eng&id=510005 2015. (Accessed 04-02-2017)
15. ICES. Types of ICES data. http://www.ices.on.ca/Data-and-Privacy/ICES-data/Types-of-ICES-Data Accessed 04-05-2016.
16. McDonald LC, Coignard B, Dubberke E, et al. The Ad Hoc Clostridium difficile Surveillance Working Group. Recommendations for surveillance of Clostridium difficile–associated disease. Infect Control Hosp Epidemiol. 2007;28(2):140–145.
17. Statistics Canada. Table 17-10-0005-01 Population estimates on July 1st, by age and sex.
18. Daneman N, Stukel T, Ma X, Vermeulen M, Guttman A. Impact of Mandatory Public Reporting of Hospital Rates of Clostridium difficile in Ontario, Canada. PLoS Med. 2012 Jul;9(7): e1001268.
19. Wilcox, MH, Shetty, N, Fawley, WN et al. Changing epidemiology of *Clostridium difficile* infection following the introduction of a national ribotyping-based surveillance scheme in England. Clin Infect Dis. 2013;55:1056–1063
20. Giancola SE et al. Prevalence of the *Clostridium difficile* BI/NAP1/027 strain across the United States Veterans Health Administration. Clin Microbiol Infect 2017 Nov 21; [e-pub]. (http://dx.doi.org/10.1016/j.cmi.2017.11.011)
21. Hensgens MP, Goorhuis A, Notermans DW, van Benthem BH, Kuijper EJ. Decrease of hypervirulent Clostridium difficile PCR ribotype 027 in the Netherlands. Euro Surveill: Bulletin Europeen sur les Maladies Transmissibles Z European Communicable Disease Bulletin. 2009;14(45).
22. Young-Xu Y, Kuntz JL, Gerding DN et al. *Clostridium difficile* infection among Veterans Health Administration patients. Infection Control & Hospital Epidemiology. 2015;36:1038-45.
23. Khanna S, Pardi DS, Aronson SL, et al. The epidemiology of community-acquired Clostridium difficile infection: a population-based study. Am J Gastroenterol. 2012;107(1):89-95.
24. Olsen MA, Young-Xu Y, Stwalley D, et al. The burden of *clostridium difficile* infection: estimates of the incidence of CDI from U.S. Administrative databases. BMC Infectious Diseases. 2016;16:177.
25. Guh AY, Mu Y, Baggs J, et al. Trends in incidence of long-term-care facility onset Clostridium difficile infections in 10 US geographic locations during 2011-2015. Am J Infect Control. 2018;17:31295-6.
26. Lindeman C, Leal J, Rusk A, et al. Clostridium difficile infection in Alberta's long-term care facilities. Can J Infect Control. 2017;32(2):87-92.
27. Gabriel L, Beriot-Mathiot A. Hospitalization stay and costs attributable to Clostridium difficile infection: a critical review. J Hosp Infection. 2014;88(1):12-21.
28. Ghantoji SS, Sail K, Lairson DR, DuPont HL, Garey KW. Economic healthcare costs of *Clostridium difficile* infection: a systematic review. J Hosp Infection. 2010;74(4):309-18.
29. Zhang D, Prabhu VS, Marcella SW. Attributable healthcare resource utilization and costs for patients with primary and recurrent *Clostridium difficile* infection in the United States. Clinical Infectious Diseases. 2018 Apr 17;66(9):1326-1332.
30. Nanwa N, Kendzerska T, Krahn M. The economic impact of Clostridium difficile infection: a systematic review. Am J Gastroenterol. 2015;110(4):511-9.
31. Negron M, Barkema H, Rioux K, et al. Accuracy of ICD-9 and ICD-10 codes for Clostridium difficile among ulcerative colitis patients. Am J Gastroenterol. 2011;106:S481.

Figure 1: CDI cases based on acquisition and onset (2015 to 2014)



Supplemental Table 1: Incidence of CDI based on location of acquisition and onset (2005 to 2014)

Characteristic	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Overall										
# of hospitalized CDI cases	3030	3068	3354	3481	2816	3161	3836	3919	3687	3557
CDI cases/100,000 PYs (CI)	31.41 (30.29 - 32.53)	31.36 (30.25 - 32.47)	33.89 (32.74 - 35.04)	34.70 (33.55 - 35.86)	27.67 (26.64 - 28.69)	30.62 (29.55 - 31.68)	36.67 (35.51 - 37.83)	36.97 (35.81 - 38.13)	34.34 (33.23 - 35.45)	32.80 (31.73 - 33.88)
CDI cases/1000 hospital-days (CI)	0.52 (0.50 - 0.54)	0.55 (0.53 - 0.57)	0.58 (0.56 - 0.60)	0.59 (0.57 - 0.61)	0.49 (0.47 - 0.50)	0.55 (0.53 - 0.57)	0.66 (0.64 - 0.68)	0.68 (0.65 - 0.70)	0.63 (0.61 - 0.66)	0.61 (0.59 - 0.63)
ACH-acquired/ACH-onset										
# of hospitalized CDI cases	1522	1591	1768	1868	1473	1680	1966	1902	1865	1637
CDI cases/100,000 PYs	15.78	16.26	17.86	18.62	14.47	16.27	18.79	17.94	17.37	15.10
(95% CI)	(14.99 - 16.57)	(15.46 - 17.06)	(17.03 - 18.70)	(17.78 - 19.47)	(13.73 - 15.21)	(15.49 - 17.05)	(17.96 - 19.62)	(17.14 - 18.75)	(16.58 - 18.16)	(14.37 - 15.83)
CDI cases/1000 hospital-days	0.26	0.28	0.31	0.32	0.25	0.29	0.34	0.33	0.32	0.28
(95% CI)	(0.25 - 0.27)	(0 .27 - 0.30)	(0.29 - 0.32)	(0.30 - 0.33)	(0.24 - 0.27)	(0.28 - 0.31)	(0.32 - 0.35)	(0.31 - 0.34)	(0.31 - 0.34)	(0.27 - 0.29)
ACH- or LTCF-acquired/ACH-onset										
# of hospitalized CDI cases	125	125	128	128	82	50	54	60	47	43
CDI cases/100,000 PYs	1.30	1.28	1.29	1.28	0.81	0.48	0.52	0.57	0.44	0.40
(95% CI)	(1.07 - 1.52)	(1.05 - 1.50)	(1.07 - 1.52)	(1.06 - 1.50)	(0.63 - 0.98)	(0.35 - 0.62)	(0.38 - 0.65)	(0.42 - 0.71)	(0.31 - 0.56)	(0.28 - 0.52)
LTCF-acquired/LTCF-onset										
# of hospitalized CDI cases	66	96	119	115	67	14	27	15	11	14
CDI cases/100,000 PYs	0.68	0.98	1.20	1.15	0.66	0.14	0.26	0.14	0.10	0.13
(95% CI)	(0.52 - 0.85)	(0.79 - 1.18)	(0.99 - 1.42)	(0.94 - 1.36)	(0.50 - 0.82)	(0.06 - 0.21)	(0.16 - 0.36)	(0.07 - 0.21)	(0.04 - 0.16)	(0.06 - 0.20)
LTCF- or ACH-acquired/LTCF-onset										
# of hospitalized CDI cases	75	108	106	107	83	86	106	105	72	89
CDI cases/100,000 PYs	0.78	1.10	1.07	1.07	0.82	0.83	1.01	0.99	0.67	0.82
(95% CI)	(0.60 - 0.95)	(0.90 - 1.31)	(0.87 - 1.27)	(0.86 - 1.27)	(0.64 - 0.99)	(0.66 - 1.01)	(0.82 - 1.21)	(0.80 - 1.18)	(0.52 - 0.83)	(0.65 - 0.99)
CDI cases/1000 hospital-days	0.01	0.02	0.02	0.02	0.01	0.02	0.02	0.02	0.01	0.02
(95% CI)	(0.01 - 0.02)	(0.02 - 0.02)	(0.01 - 0.02)	(0.01 - 0.02)	(0.01 - 0.02)	(0.01 - 0.02)	(0.01 - 0.02)	(0.01 - 0.02)	(0.01 - 0.02)	(0.01 - 0.02)
Community-acquired/community-onset										
# of hospitalized CDI cases	587	514	534	573	535	669	876	990	901	1037
CDI cases/100,000 PYs	6.09	5.25	5.40	5.71	5.26	6.48	8.37	9.34	8.39	9.56
(95% CI)	(5.59 - 6.58)	(4.80 - 5.71)	(4.94 - 5.85)	(5.24 - 6.18)	(4.81 - 5.70)	(5.99 - 6.97)	(7.82 - 8.93)	(8.76 - 9.92)	(7.84 - 8.94)	(8.98 - 10.15)
ACH-acquired/community-onset										
# of hospitalized CDI cases	655	634	699	690	576	662	807	847	791	737
CDI cases/100,000 PYs	6.79	6.48	7.06	6.88	5.66	6.41	7.71	7.99	7.37	6.80
(95% CI)	(6.27 - 7.31)	(5.98 - 6.99)	(6.54 - 7.59)	(6.37 - 7.39)	(5.20 - 6.12)	(5.92 - 6.90)	(7.18 - 8.25)	(7.45 - 8.53)	(6.85 - 7.88)	(6.31 - 7.29)
CDI cases/1000 hospital-days	0.11	0.11	0.12	0.12	0.10	0.12	0.14	0.15	0.14	0.13
(95% CI)	(0.10 - 0.12)	(0.10 - 0.12)	(0.11 - 0.13)	(0.11 - 0.13)	(0.09 - 0.11)	(0.11 - 0.12)	(0.13 - 0.15)	(0.14 - 0.16)	(0.13 - 0.15)	(0.12 - 0.13)

ACH-onset CDI was calculated using patient-days at hospital as the denominator. The denominator of LTCF-onset CDI was the number of PYs living in LTCF for residents. The denominator for community-onset CDI was the number of PYs for individuals living in the community (not in LTCFs).

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Page 1 (title page)
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Page 2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Page 3, Paragraphs 1-2
Objectives	3	State specific objectives, including any prespecified hypotheses	Page 3, Paragraph 2
Methods			
Study design	4	Present key elements of study design early in the paper	Page 3, Methods section, Paragraph 1
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Page 3, Methods section, Paragraph 3 to Page 5, Paragraph 2
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Page 3, Methods section, Paragraph 3; Table 1 (Page 4)
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Table 2 (Page 5)
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Page 5, Paragraph 2
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Page 3 (Methods section: Data Sources)
Bias	9	Describe any efforts to address potential sources of bias	N/A
Study size	10	Explain how the study size was arrived at	N/A (incidence study)
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	N/A
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Page 5-6 (Analysis section)
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	N/A
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A

		(*e*) Describe any sensitivity analyses	N/A
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	N/A
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Table 3 (Page 8); Table 4 (Page 10)
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	N/A
Outcome data	15*	Report numbers of outcome events or summary measures over time	Page 6, (Sub-section: CDI incidence)

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Pages 6-12 N/A N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	Page 13, Paragraph 1
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Page 14, Paragraph 1
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Page 13, Paragraphs 2 and 3
Generalisability	21	Discuss the generalisability (external validity) of the study results	Page 13
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Page 1

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.