ORIGINAL ARTICLE

The Economic Burden of Hospital-Acquired *Clostridium difficile* Infection: A Population-Based Matched Cohort Study

Natasha Nanwa, MSc;[1,2] Jeffrey C. Kwong, MD;[3,4,5,6,7] Murray Krahn, MD;[1,2,3,5,8,9] Nick Daneman, MD;[3,8,9,10] Hong Lu, PhD;[3] Peter C. Austin, PhD;[3,9,10] Anand Govindarajan, MD;[3,11,12] Laura C. Rosella, PhD;[3,4,7] Suzanne M. Cadarette, PhD;[1,3] Beate Sander, PhD[2,3,7,9]

BACKGROUND. High-quality cost estimates for hospital-acquired *Clostridium difficile* infection (CDI) are vital evidence for healthcare policy and decision-making.

OBJECTIVE. To evaluate the costs attributable to hospital-acquired CDI from the healthcare payer perspective.

METHODS. We conducted a population-based propensity-score matched cohort study of incident hospitalized subjects diagnosed with CDI (those with the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Canada* code A04.7) from January 1, 2003, through December 31, 2010, in Ontario, Canada. Infected subjects were matched to uninfected subjects (those without the code A04.7) on age, sex, comorbidities, geography, and other variables, and followed up through December 31, 2011. We stratified results by elective and nonelective admissions. The main study outcomes were up-to-3-year costs, which were evaluated in 2014 Canadian dollars.

RESULTS. We identified 28,308 infected subjects (mean annual incidence, 27.9 per 100,000 population, 3.3 per 1,000 admissions), with a mean age of 71.5 years (range, 0–107 years), 54.0% female, and 8.0% elective admissions. For elective admission subjects, cumulative mean attributable 1-, 2-, and 3-year costs adjusted for survival (undiscounted) were $32,151 (95% CI, $28,192–$36,005), $34,843 ($29,298–$40,027), and $37,171 ($30,364–$43,415), respectively. For nonelective admission subjects, the corresponding costs were $21,909 ($21,221–$22,609), $26,074 ($25,180–$27,014), and $29,944 ($28,873–$31,086), respectively.

CONCLUSIONS. Hospital-acquired CDI is associated with substantial healthcare costs. To the best of our knowledge, this study is the first CDI costing study to present longitudinal costs. New strategies may be warranted to mitigate this costly infectious disease.

Infect Control Hosp Epidemiol 2016;37:1068–1078

Clostridium difficile was estimated to cause approximately 0.5 million infections in 2011 in the United States and was among the top 5 infectious causes of death in Ontario, Canada (annual average, 2005–2007).[1,2] Age at least 65 years, comorbidities, recent or long hospital stay, and exposure to antimicrobials increase the risk for *C. difficile* infection (CDI).[3–6] Among those infected, approximately 22% experience a recurrence or treatment failure, suggesting that CDI may behave like a chronic condition.[7,8] Up to 5% of infected individuals undergo a colectomy and more than 6% die within 3 months of diagnosis.[9–11]

The economic burden of CDI was documented in a recent systematic review, with mean attributable CDI costs ranging from $8,911 to $30,049 per hospitalized patient (2014 US dollars).[12] The review noted that most CDI cost of illness studies did not evaluate costs beyond the initial hospitalization (ie, readmissions and ongoing medical care after discharge), leading to possible underestimation of the CDI burden. High quality short- and long-term attributable cost estimates for CDI provide fundamental evidence for hospital administrators, policy decision-makers, and researchers assessing the value of existing and novel strategies to prevent, detect, and treat CDI. Our objective was to estimate short- and long-term costs attributable to hospital-acquired CDI from the healthcare payer perspective.

METHODS

Study Design, Data Sources, and Participants

Our study received ethics approval from the institutional review boards at Sunnybrook Health Sciences Centre and the University of Toronto.

Affiliations: 1. Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Canada; 2. Toronto Health Economics and Technology Assessment Collaborative, Toronto, Canada; 3. Institute for Clinical Evaluative Sciences, Toronto, Canada; 4. Dalla Lana School of Public Health, University of Toronto, Toronto, Canada; 5. University Health Network, Toronto, Canada; 6. Department of Family and Community Medicine, University of Toronto, Toronto, Canada; 7. Public Health Ontario, Toronto, Canada; 8. Department of Medicine, University of Toronto, Toronto, Canada; 9. Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Canada; 10. Sunnybrook Health Sciences Centre, Toronto, Canada; 11. Mount Sinai Hospital, Toronto, Canada; 12. Division of General Surgery, Department of Surgery, University of Toronto, Toronto, Canada.

Received January 11, 2016; accepted April 24, 2016; electronically published June 20, 2016

 0899-823X/2016/3709-0009. DOI: 10.1017/ice.2016.122

We conducted an incidence-based propensity-score matched cohort study to evaluate costs attributable to hospital-acquired CDI from the healthcare payer perspective (Ontario Ministry of Health and Long-Term Care). The study population from Ontario, Canada, was provided by the Institute for Clinical Evaluative Sciences, which houses a data repository of individually linked (via unique encoded identifiers) health service records for those eligible for publicly funded universal healthcare (~13 million, nearly the entire population of Ontario).[13]

We identified incident cases of CDI (infected subjects who were symptomatic) from January 1, 2003, through December 31, 2010, using the *International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Canada* (ICD-10-CA) code A04.7 (enterocolitis due to CDI) and followed up the cases through December 31, 2011 (see Supplementary Figure 1). We included elective and nonelective hospital admissions (differentiated by a specific field in the administrative data). The index date was the admission date of the index hospitalization.

For elective admission subjects, we assumed absence of community-associated CDI because their hospitalizations were planned. To exclude community-associated CDI among the nonelective admission group, we excluded infected subjects if (a) the length of stay (LOS) was no more than 2 days (consistent with studies that exclude those with symptom onset or a positive CDI test within 2 days of admission[14,15]); (b) CDI was the principal diagnosis and colectomy was performed within 2 days of admission; or (c) CDI was the principal diagnosis and suspected CDI, abdominal pain, cramps, or diarrhea was coded for a physician office or emergency department visit within 2 weeks prior to admission. For full exclusion criteria see Supplementary Table 1.

We matched each infected subject to 1 uninfected subject (those without the ICD-10-CA code A04.7) on both the propensity score and a limited set of baseline covariates. For the elective admission group, we identified a sample of uninfected elective admission subjects. The propensity score was estimated using a logistic regression model to regress exposure status (infected versus uninfected) on the following variables: rurality; neighborhood income quintile; comorbidities within 2 years prior to the index date; hospital facility; healthcare utilization (emergency department visit, hospital admission, same-day surgery, or long-term care stay) within 12 weeks prior to the index date; and a record of an infection that may have led to an antibiotic prescription within 12 weeks prior to the index date. We chose 12 weeks because the onset of CDI symptoms can occur up to 3 months after hospital discharge or antibiotic cessation.[4–6] See Supplementary Table 2 for details on each propensity score variable. In addition to matching on the propensity score, subjects were hard matched on sex, birth year plus or minus 3 years, index date plus or minus 30 days, and the first 3 digits of the intervention code (first elective procedure performed within 2 days of the hospital admission).

For the nonelective admission group, we identified uninfected subjects from a random sample of nonelectively admitted subjects with a LOS at least 3 days. The matching procedure was similar to the elective admission group, except the intervention code for an elective procedure was not applicable.

To determine the impact of CDI on costs near the time of death, we rematched infected subjects who died during the observation period to uninfected subjects who also died (randomly selected), ensuring similarity between infected and uninfected subjects. Variables included in the propensity score model were rurality, neighborhood income quintile, and comorbidities assessed 3 months prior to the death date, along with hard matching on birth year plus or minus 3 years, sex, and date (3 months prior to the death date) plus or minus 30 days.

For both sets of matches, we used nearest neighbor matching without replacement on the logit of the propensity score, using calipers of width equal to 0.2 of the standard deviation of the logit of the propensity score.[16] To assess balance, we calculated standardized differences between infected and uninfected subjects for each variable included in the propensity score, with standardized differences less than 0.1 indicating good balance.[17]

Outcomes

We evaluated the following clinical outcomes: LOS, colectomy within 1 year after the index hospital admission date (identified using intervention codes outlined in Supplementary Table 3), and mortality. Cost outcomes included costs unadjusted for survival (during the index hospitalization and 30 days, 180 days, and 1 year after the index hospital admission date) and costs adjusted for survival (1, 2, and 3 years after the index hospital admission date). Costs captured the following publicly funded healthcare services: (1) inpatient hospitalizations, (2) same-day surgery procedures, (3) emergency department visits, (4) outpatient medications (for those aged ≥65 years or on social assistance), (5) physician services, (6) nonphysician services (eg, physiotherapy), (7) outpatient laboratory tests, (8) rehabilitation services, (9) complex continuing care admissions, (10) homecare services, (11) long-term care admissions, (12) dialysis clinic visits, (13) cancer clinic visits, and (14) assistive devices.[18] Index hospitalization costs included only hospital costs because physician services could not be disaggregated by inpatient versus outpatient services.

Analysis

Using the matched samples, we determined the relative risk and 95% CIs of colectomy and all-cause mortality.[19,20] We also estimated 3-year survival curves for infected subjects and matched uninfected subjects.

We evaluated attributable LOS and cumulative costs unadjusted for survival by calculating the mean difference between matched pairs. We used bootstrapping to calculate 95% CIs for the mean difference.[21]

To estimate cumulative attributable 1-, 2-, and 3-year costs adjusted for survival, we used the phase-of-care approach,

https://doi.org/10.1017/ice.2016.122 Published online by Cambridge University Press

assigning an infected subject's observation time to distinct phases reflecting the course of the disease from diagnosis to death.[22–25] We defined 3 phases (acute infection, continuing care, and final care) and used clinical judgment and the shape of the cost functions (observed when costs were graphed) to determine phase length. We measured costs in 30-day periods and determined attributable phase-specific costs by calculating the mean difference between matched pairs.[23] We combined phase-specific costs with crude monthly probabilities of death, derived from infected subjects, to obtain predicted cumulative attributable mean 1-, 2-, and 3-year costs.[22,23] We reported undiscounted and discounted costs (discount rate, 5% annually).[26] We used bootstrapping to calculate 95% CIs for mean attributable phase-specific costs.[21] We derived the 95% CIs for the predicted 1-, 2-, and 3- year costs by combining the lower and upper limits of the CIs for the phase-specific costs with the crude monthly probabilities of death.[23]

We stratified mean attributable costs by healthcare service (eg, physician visits, emergency department visits), sex, age group, year of diagnosis, those who underwent colectomy attributable to CDI during the index hospitalization (see Supplementary Table 4), and survivorship, defined as short-term (died <1 year after the index date) versus long-term (died >1 year after the index date or survived the entire observation period) survivors.

All costs were evaluated in 2014 Canadian dollars ($1 Canadian = $0.9054146 US[27]) and analyses were conducted at the Institute for Clinical Evaluative Sciences.

Sensitivity Analysis

CDI can be coded as a preadmission comorbidity, indicated by the hospitalization data field "diagnosis type." Although the accuracy of this field is poor,[28] it is possible that some of the infected subjects in our study had community-associated CDI or subjects may not have been incident cases. We therefore conducted a sensitivity analysis excluding these subjects to assess the impact on mean attributable costs. We also varied the phase length of the acute infection and final care phases by 1 to 12 months to assess the effect on predicted 1-year costs. We chose 1 month to capture a short episode of CDI and 12 months because it is commonly used in similar studies.[22,23]

RESULTS

Study Cohort

We identified 28,308 subjects infected with hospital-acquired CDI (Table 1). The crude mean annual incidence rate was 27.9 per 100,000 population (3.3 per 1,000 admissions). The mean (range) age of incident infected subjects was 71.5 (0–107) years; 54.0% were female, and 8.0% were elective admissions. Compared with elective admission subjects, nonelective admission subjects were more likely to be female, be older, and have more comorbidities (very high users of the healthcare system), along with greater healthcare utilization and possible antibiotic exposure within 12 weeks prior to the index hospitalization. They were also more likely to die.

Matching Results

After propensity-score matching, 1,471 (65.3%) of infected subjects in the elective admission group were matched to uninfected subjects, while 24,015 (92.2%) of infected subjects in the nonelective admission group were matched to uninfected subjects. Unmatched infected subjects in both groups had more comorbidities than matched infected subjects.

During the study period (January 2003 to December 2011), 43.8% (n = 645) and 65.3% (n = 15,692) of the matched infected subjects in the elective admission and nonelective admission groups, respectively, died.

Among those who died, 97.7% (n = 630) in the elective admission group and 98.3% (n = 15,433) in the nonelective admission group were successfully matched to comparable uninfected subjects that died.

After the matches were conducted, nearly all standardized differences for the baseline covariates were 0.1 or less (Supplementary Tables 5 and 6).

Outcomes

Hospital-acquired CDI was associated with worse clinical outcomes among infected subjects compared with matched uninfected subjects (Tables 2 and 3). The mean attributable LOS was 23.5 days (95% CI, 21.6–25.5 days; median, 13.0 days) for elective admission subjects and 22.7 days (22.1–23.3 days; 13.0 days) for nonelective admission subjects. The relative risk for colectomy was 1.08 (95% CI, 1.00–1.17) for elective admission subjects and 1.88 (1.68–2.11) for nonelective admission subjects. The relative risks for mortality during the index hospitalization and 1 year post–index hospital admission date were 4.14 (95% CI, 2.90–5.90) and 2.01 (1.71–2.35) for elective admission subjects and 2.35 (2.24–2.46) and 2.03 (1.97–2.08) for nonelective admission subjects. Infected subjects also experienced lower survival over 3 years than matched uninfected subjects (Figure 1).

Cumulative costs unadjusted for survival were higher among infected subjects compared with matched uninfected subjects (Tables 2 and 3). For elective admission subjects, cumulative mean attributable 30-day, 180-day, and 1-year costs unadjusted for survival were $20,905 (95% CI, $19,572–$22,290), $44,696 ($40,892–$48,625), and $48,029 ($43,315–$52,871), respectively, whereas for nonelective admission subjects, corresponding costs were $12,350 ($11,974–$12,660), $35,457 ($34,561–$36,329), and $40,889 ($39,768–$42,010), respectively.

Costs exhibited a "U" shaped function from index hospital admission date to death (Figure 2). We defined acute infection to be up to 6 months and final care to be up to 3 months. The continuing care phase ranged from 0 to 110 months.

https://doi.org/10.1017/ice.2016.122 Published online by Cambridge University Press

TABLE 1. Selected Characteristics of Infected Subjects Before Matching

Variable	Elective admission subjects (n = 2,254)	Nonelective admission subjects (n = 26,054)
Age[a]		
Mean (SD)	63.4 (20.2) years	72.2 (17.1) years
Median (range)	69 (0–98) years	77 (0–107) years
Female sex, %	46.5	54.6
Age group, %		
Children (≤18 years)	6.5	1.7
Adults (19-64 years)	33.4	22.4
Older adults (≥65 years)	60.1	75.8
CDI as principal diagnosis, %[b]	2.6	18.8
Crude annual incidence rate, per 100,000 population (per 1,000 admissions)[c]		
2003	1.8 (0.2)	20.9 (2.4)
2004	2.5 (0.3)	26.4 (3.0)
2005	2.5 (0.3)	28.6 (3.2)
2006	2.1 (0.2)	23.2 (2.7)
2007	2.5 (0.3)	29.7 (3.6)
2008	2.4 (0.3)	28.5 (3.5)
2009	2.0 (0.2)	23.4 (2.9)
2010	2.0 (0.2)	24.3 (3.0)
Neighborhood income quintile, %[a]		
1 (lowest)	20.5	24.2
2	21.7	21.8
3	18.2	19.2
4	20.8	17.7
5 (highest)	18.8	17.1
Rurality, %[a]		
Major urban	63.9	66.4
Non-major urban	26.2	25.5
Rural	9.9	8.1
Very high users of the healthcare system, %[d]	54.9	58.0
Healthcare utilization, %[e]	64.8	75.5
Record of an infection that may have led to an antibiotic prescription, %[e]	26.3	44.3
Length of stay of index hospitalization		
Mean (SD)	33.8 (43.1) days	34.8 (46.4) days
Median (interquartile range, range)	20 (11-38, 1–791)	21 (10-42, 3–1,572)
Attributable colectomy, %[f,g]	1.3	0.9
1-year colectomy, %[h]	13.9	3.3
All-cause mortality, %		
Index hospitalization	10.6	21.1
30 day[h]	5.3	14.4
180 day[h]	19.1	38.2
1 year (short-term survivors)[h]	25.5	44.7
End of study period[h]	46.1	65.8

NOTE. CDI, *Clostridium difficile* infection.
[a]At the index hospital admission date.
[b]Most responsible diagnosis (accounting for the greatest proportion of the length of hospital stay) for the index hospitalization.
[c]Not standardized to a specific year.
[d]Highest resource utilization band presented to summarize comorbidities that were measured within 2 years prior to the index hospital admission date (see Supplementary Tables 2 and 5).
[e]Within the 12 weeks prior to the index hospital admission date.
[f]During the index hospitalization.
[g]See Supplementary Table 4 for how a colectomy was attributed to CDI.
[h]After index hospital admission date.

https://doi.org/10.1017/ice.2016.122 Published online by Cambridge University Press

TABLE 2. Clinical and Cost Outcomes Attributable to Hospital-Acquired CDI Among Elective Admission Subjects

Variable	n matched pairs	Infected subjects	Uninfected subjects	Attributable outcome (95% CI)
Clinical outcomes[a]				
Mean length of stay, days[b]	1,471	31.7 Median = 19.0 IQR = 11–38 Range = 1–318	8.2 Median = 6.0 IQR = 3–9 Range = 1–205	23.5 (21.6–25.5) Median = 13.0
1-year colectomy, RR[c,d]	1,471	16.5%	15.3%	1.08 (1.00–1.17)
All-cause mortality, RR				
Index hospitalization[e]	1,471	10.1%	2.4%	4.14 (2.90–5.90)
30 days[c]	1,471	4.6%	2.6%	1.79 (1.22–2.63)
180 days[c]	1,471	18.0%	7.3%	2.48 (2.02–3.04)
1 year[c]	1,471	24.0%	12.0%	2.01 (1.71-2.35)
Mean cost outcomes unadjusted for survival[a]				
Index hospitalization costs[e]	1,471	$52,244 Median = $32,739	$14,962 Median = $10,620	$37,282 ($34,187–$40,616) Median = $22,119
30-day cumulative costs[c]	1,471	$40,806	$19,901	$20,905 ($19,572–$22,290)
180-day cumulative costs[c]	1,471	Median = $35,862 $76,980	Median = $16,023 $32,284	Median = $19,838 $44,696 ($40,892–$48,625)
1-year cumulative costs[c]	1,471	Median = $51,337 $89,474	Median = $23,146 $41,446	Median = $28,191 $48,029 ($43,315–$52,871)
		Median = $58,088	Median = $27,662	Median = $30,425
Mean cost outcomes by phase[f]				
Acute infection costs[a,g]	1,282	$13,609	$5,794	$7,815 ($7,066–$8,581)
Continuing care costs[a,h]	1,150	$1,636	$717	$919 ($602–$1,193)
Final care costs[i,j]	630	$23,991	$10,286	$13,705 ($11,444–$15,754)
Mean cost outcomes adjusted for survival[c,k]				
1-year cumulative costs	1,471	NA	NA	$32,151 ($28,192–$36,005)
2-year cumulative costs				
Undiscounted	1,471	NA	NA	$34,843 ($29,298–$40,027)
Discounted 5%	1,471	NA	NA	$33,101 ($27,833–$38,025)
3-year cumulative costs				
Undiscounted	1,471	NA	NA	$37,171 ($30,364–$43,415)
Discounted 5%	1,471	NA	NA	$35,313 ($28,846–$41,244)

NOTE. CDI, *Clostridium difficile* infection; IQR, interquartile range; NA, not applicable; RR, relative risk.
[a]Index date was the index hospital admission date.
[b]Index hospital admission date to index hospital discharge date.
[c]After index hospital admission date.
[d]See Supplementary Table 3 for intervention codes used to identify a colectomy procedure.
[e]During the index hospitalization.
[f]Costs standardized to 30 days.
[g]Phase length up to 6 months.
[h]Phase length varied between 1 and 110 months.
[i]Costs derived from the re-match of infected subjects who died during the observation period to uninfected subjects who also died.
[j]Phase length up to 3 months.
[k]Phase-specific costs combined with crude monthly probabilities of death derived from the matched infected subjects.

https://doi.org/10.1017/ice.2016.122 Published online by Cambridge University Press

TABLE 3. Clinical and Cost Outcomes Attributable to Hospital-Acquired CDI Among Nonelective Admission Subjects

Variable	n matched pairs	Infected subjects	Uninfected subjects	Attributable outcome (95% CI)
Clinical outcomes[a]				
Mean length of stay, days[b]	24,015	34.6 Median = 20.0 IQR = 10–42 Range = 3–1,572	12.0 Median = 7.0 IQR = 4–13 Range = 3–808	22.7 (22.1-23.3) Median = 13.0
1-year colectomy, RR[c,d]	24,015	3.4%	1.8%	1.88 (1.68–2.11)
All-cause mortality, RR				
Index hospitalization[e]	24,015	20.6%	8.8%	2.35 (2.24-2.46)
30 days[c]	24,015	14.0%	10.0%	1.40 (1.34–1.47)
180 days[c]	24,015	37.6%	17.3%	2.17 (2.10–2.24)
1 year[c]	24,015	44.0%	21.7%	2.03 (1.97–2.08)
Mean cost outcomes unadjusted for survival[a]				
Index hospitalization costs[e]	24,015	$37,679	$11,746	$25,933 ($25,134–$26,799)
		Median = $18,603	Median = $6,689	Median = $11,915
30-day cumulative costs[c]	24,015	$27,044	$14,695	$12,350 ($11,974–$12,660)
		Median = $21,691	Median = $10,573	Median = $11,118
180-day cumulative costs[c]	24,015	$60,937	$25,480	$35,457 ($34,561–$36,329)
		Median = $41,179	Median = $16,561	Median = $24,618
1-year cumulative costs[c]	24,015	$74,772	$33,882	$40,889 ($39,768–$42,010)
		Median = $50,019	Median = $21,364	Median = $28,655
Mean cost outcomes by phase[f]				
Acute infection costs[a,g]	16,882	$12,486	$4,973	$7,513 ($7,304–$7,719)
Continuing care costs[a,h]	14,099	$2,704	$861	$1,843 ($1,761–$1,938)
Final care costs[i,j]	15,433	$20,330	$10,367	$9,963 ($9,614–$10,291)
Mean cost outcomes adjusted for survival[c,k]				
1-year cumulative costs	24,015	NA	NA	$21,909 ($21,221–$22,609)
2-year cumulative costs				
Undiscounted	24,015	NA	NA	$26,074 ($25,180–$27,014)
Discounted 5%	24,015	NA	NA	$24,770 ($23,921–$25,663)
3-year cumulative costs				
Undiscounted	24,015	NA	NA	$29,944 ($28,873–$31,086)
Discounted 5%	24,015	NA	NA	$28,447 ($27,429–$29,532)

NOTE. CDI, *Clostridium difficile* infection; IQR, interquartile range; NA, not applicable; RR, relative risk.
[a]Index date was the index hospital admission date.
[b]Index hospital admission date to index hospital discharge date.
[c]After index hospital admission date.
[d]See Supplementary Table 3 for intervention codes used to identify a colectomy procedure.
[e]During the index hospitalization.
[f]Costs standardized to 30 days.
[g]Phase length up to 6 months.
[h]Phase length varied between 1 and 110 months.
[i]Costs derived from the re-match of infected subjects who died during the observation period to uninfected subjects who also died.
[j]Phase length up to 3 months.
[k]Phase-specific costs combined with crude monthly probabilities of death derived from the matched infected subjects.

https://doi.org/10.1017/ice.2016.122 Published online by Cambridge University Press

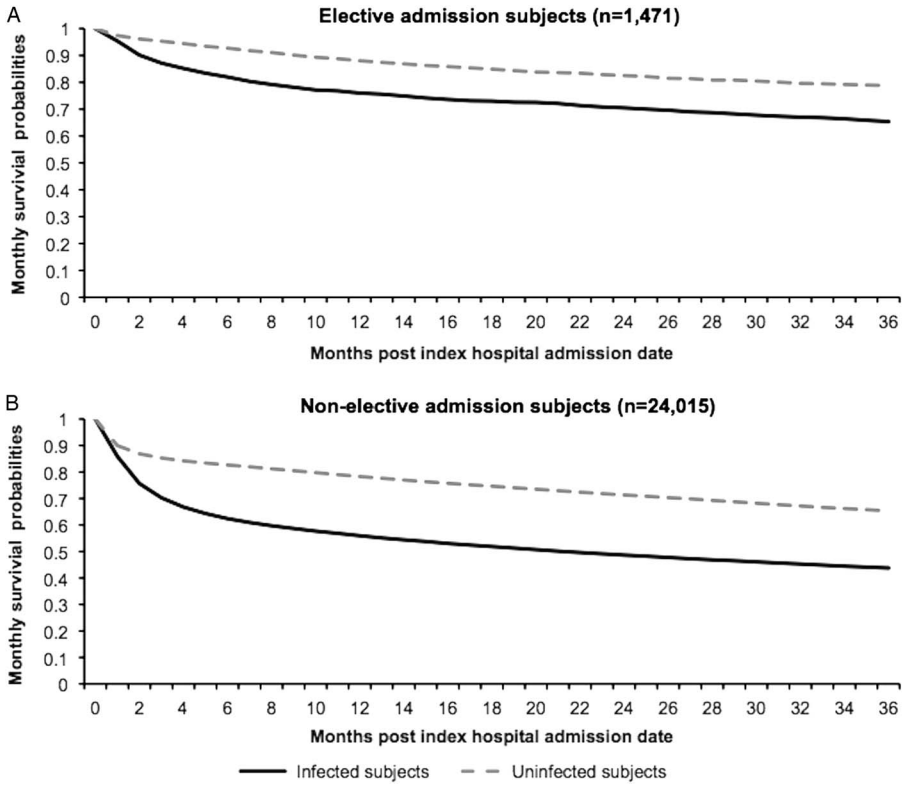

FIGURE 1. Survival curves for infected subjects and their matched uninfected subjects, 3 years after the index hospital admission date.

Phase-specific costs were higher among infected subjects than uninfected subjects. For elective admission subjects, cumulative mean attributable 1-, 2-, and 3-year costs adjusted for survival were $32,151 (95% CI, $28,192–$36,005), $34,843 ($29,298–$40,027), and $37,171 ($30,364–$43,415), respectively, whereas for nonelective admission subjects, corresponding attributable costs were $21,909 ($21,221–$22,609), $26,074 ($25,180–$27,014), and $29,944 ($28,873–$31,086), respectively (Tables 2 and 3).

The largest cost components among the acute infection and final care phases were inpatient hospitalization and physician services (Figure 3). For the continuing care phase, the largest cost components were inpatient hospitalization and complex continuing care admissions.

In the stratified analyses, costs were generally higher for males, those infected after 2008, those who underwent a CDI-attributed colectomy, and short-term survivors (Supplementary Table 7).

Sensitivity Analysis

Cost results were sensitive to excluding those with a CDI diagnosis characterized as a preadmission comorbidity (5,641 [22.1%]; 3% to 14% higher costs, Supplementary Table 8). Costs were more sensitive to varying the length of acute infection (baseline 6 months) and final care (baseline 3 months) from 1 to 12 months, where mean attributable 1-year costs ranged from $27,516 to $43,730 (baseline $32,151) in the elective admission group and $18,775 to $28,411 (baseline $21,909) in the nonelective admission group (Supplementary Table 8).

DISCUSSION

Our findings suggest that hospital-acquired CDI prolongs hospital stay, substantially increases the risks for mortality and colectomy, and leads to greater short- and long-term healthcare costs compared with rigorously matched uninfected subjects. Attributable costs were greatest during the index hospitalization and decreased over time; however, higher costs persisted. To the best of our knowledge, this study is the first CDI costing study to present longitudinal costs, demonstrating that attributable costs accrue beyond 6 months after the index hospital admission date, and that costs, when graphed, follow a "U" shaped function, similar to cancer and heart failure.[24,29] For comparison, the mean 1-year costs ($21,909 to $32,151) attributable to hospital-acquired CDI were within the range for mean 1-year costs attributable to cancer ($5,115 to $59,582,[23,30] converted to 2014 Canadian dollars[31,32]).

Higher costs were found among (a) those who underwent a colectomy, because additional resources are needed to manage complications; (b) short-term survivors, indicating that CDI burden is proximal to the index hospitalization; and (c) those infected after 2008, which could be owing to a more virulent strain of CDI circulating in Ontario during that period.[33]

https://doi.org/10.1017/ice.2016.122 Published online by Cambridge University Press

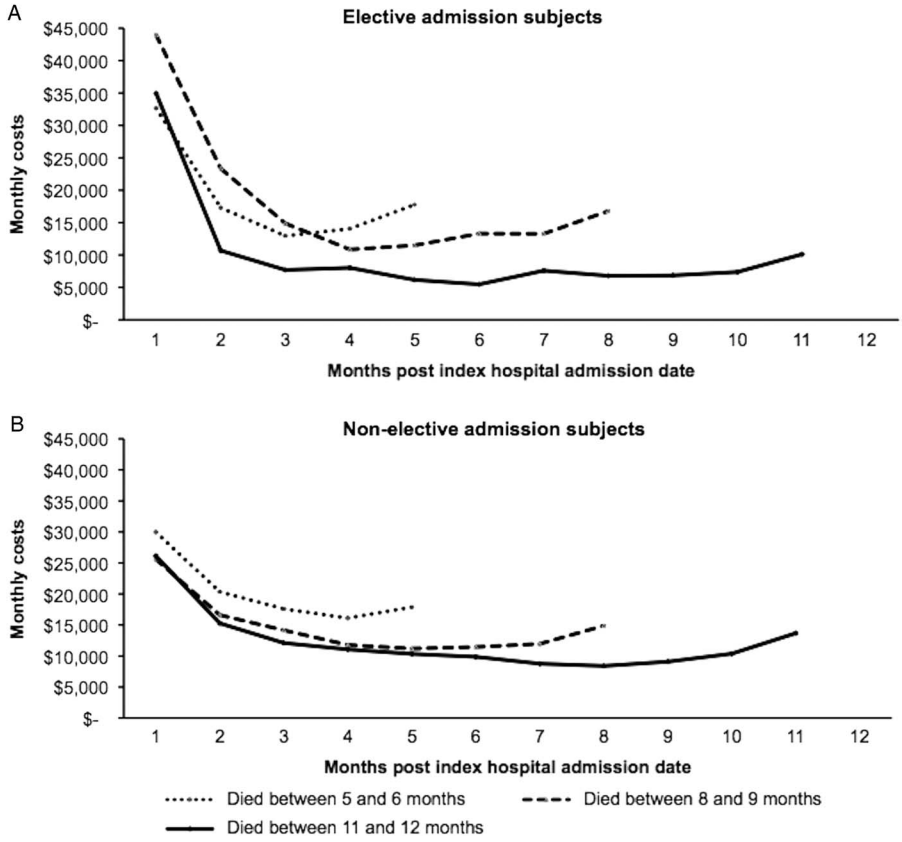

FIGURE 2. Costs (unadjusted for survival) of short-term survivors (infected subjects). Among elective admission infected subjects, 21 died between 5 and 6 months, 15 died between 8 and 9 months, and 12 died between 11 and 12 months and among nonelective admission infected subjects, 466 died between 5 and 6 months, 251 died between 8 and 9 months, and 214 died between 11 and 12 months.

Our findings were generally consistent with previous studies. Death during the index hospitalization among infected elective admission subjects and 30-day mortality among infected nonelective admission subjects were within the range reported in comparable patient groups (eg, infected surgical[34,35] and hospitalized[36,37] patients). Moreover, attributable 180-day and 1-year mortality among the nonelective admissions group were similar to the results found in a Canadian study by Pepin et al,[38] who compared hospitalized patients with and without CDI. In terms of economic burden, among elective admission subjects, results were similar to Zerey et al,[35] who evaluated charges in surgical subjects from the United States (median attributable LOS, 14 days; 4-fold higher hospitalization charges for those with CDI versus those without CDI). Among nonelective admission subjects, results differed from Dubberke et al,[39] who evaluated costs in nonsurgical subjects from the United States (median attributable LOS, 6 days; 50% to 80% higher hospitalization and 180-day costs for those with CDI versus those without CDI). The differences in results could be due to Dubberke et al[39] defining nonsurgical subjects as those without operating room costs and basing results on cases from 2003 only, whereas we included those with emergency interventions and subjects from 2003 to 2010.

Our study has some limitations. First, we did not validate the ICD-10-CA code used to identify CDI-infected subjects, because we did not have access to CDI-specific laboratory data. However, a Canadian validation study comparing the ICD-9/ICD-10-CA code against the reference standard of CDI stool toxin in an ulcerative colitis population reported 88% sensitivity and 100% specificity.[40] The lower sensitivity suggests that we may have underestimated the true number of infected subjects, but it is uncertain whether we under- or overestimated outcomes, because we do not know if those not identified had more or less severe disease than those included in this study. Second, our exclusion criteria might have excluded hospital-acquired CDI with community onset. Despite this, we feel our strict criteria provided a probable sample of hospital-acquired cases. In addition, although we were unable to match all patients who met our CDI definition, the matched infected subjects were generally a good representation of the groups before matching (Supplementary Table 5). However, the unmatched infected subjects had more comorbidities; therefore, we may have underestimated attributable outcomes. Third, we were unable to isolate the costs of CDI recurrences because we did not have access to CDI-specific laboratory data to define those; it is likely that the

https://doi.org/10.1017/ice.2016.122 Published online by Cambridge University Press

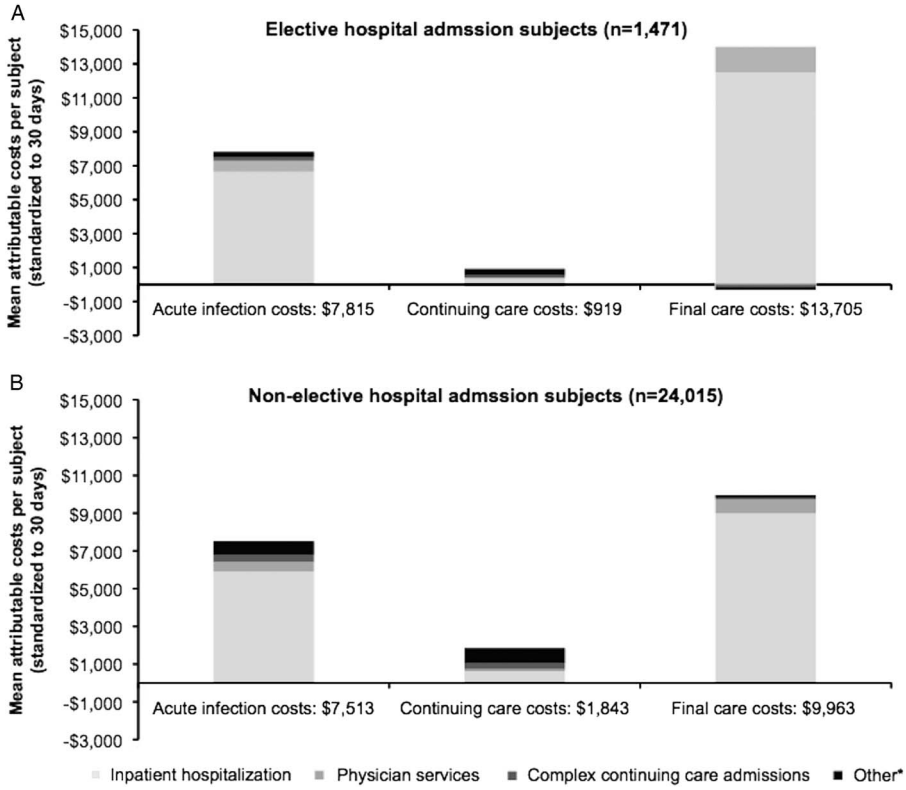

FIGURE 3. Phase-specific costs stratified by healthcare services. *"Other" includes same-day surgery procedures, emergency department visits, outpatient medications, nonphysician services, outpatient laboratory tests, rehabilitation services, home care services, long-term care admissions, dialysis clinic visits, cancer clinic visits, and assisted devices.

higher long-term attributable costs observed in our study are driven at least in part by recurrences. Other reasons for the long-term burden could be the need for continued medical care after CDI due to the frailty of these subjects. Last, we were unable to ascertain the timing of disease onset because we did not have access to CDI-specific laboratory data, which could have led to time-dependent bias, overestimating attributable LOS and therefore costs.[41] However, because we matched on a broad range of covariates, we may have minimized this bias.[17]

Strengths of our study include the availability of linked datasets enabling us to exclude possible community-associated CDI, the ability to match on a broad range of baseline covariates using propensity methods to reduce bias, and the comprehensiveness of our cost analysis that included all publicly funded healthcare services and an adjustment for survival.

Other jurisdictions can utilize our actual estimates (where costs can be converted to a preferred currency and/or year) or the relative results (eg, largest cost components, populations with higher costs, percent increase in costs due to CDI) to understand the burden of hospital-acquired CDI in their respective settings. Our results are based on a large population-based sample, thereby increasing the generalizability of our results, and costs were evaluated beyond a hospital stay, providing a more complete estimate of the economic burden. Therefore, our results can be used to support decisions on prevention and treatment strategies (eg, modification of antibiotic stewardship programs, addition of a CDI-safe antibiotic to the hospital formulary).

In conclusion, our study describes the attributable economic burden of hospital-acquired CDI, highlighting the need to explore and employ strategies that mitigate this costly infectious disease, along with the importance of examining the long-term impact of acute infectious diseases.

ACKNOWLEDGMENTS

Financial support. Canadian Institutes of Health Research (operating grant MOP 130553); and the Institute for Clinical Evaluative Sciences and Public Health Ontario, which are funded by annual grants from the Ontario Ministry of Health and Long-Term Care.

Potential conflicts of interest. N.N. reports that she received stipend support throughout her PhD graduate work from the University of Toronto, Pfizer Canada, the Ontario Graduate Scholarship program, and a Canadian Institutes of Health Research operating grant that funded this current study. J.C.K. reports that he is supported by a Canadian Institutes of Health Research New Investigator Award and a Clinician Scientist Award from the University of Toronto's Department of Family and Community Medicine. P.C.A. reports that he is supported in part by a Career Investigator Award from the Heart and Stroke Foundation of Canada. N.D. reports that he is supported by a Canadian Institutes of Health Research Clinician Scientist Award. All other authors report no conflicts of interest relevant to this article.

https://doi.org/10.1017/ice.2016.122 Published online by Cambridge University Press

Disclaimer. The Canadian Institutes of Health Research, University of Toronto, Pfizer Canada, the Ontario Graduate Scholarship program, and the Heart and Stroke Foundation did not participate in: the design or concept of the study; the acquisition, analysis, or interpretation of the data; and the drafting or reviewing of the manuscript. The opinions, results, and conclusions reported in this article do not necessarily represent the views of the Institute for Clinical Evaluative Sciences, Public Health Ontario, or the Ontario Ministry of Health and Long-Term Care. Parts of this material are based on data and information compiled and provided by the Canadian Institute of Health Information. However, the analyses, conclusions, opinions, and statements expressed herein are those of the authors, and not necessarily those of the Canadian Institute of Health Information.

Address correspondence to Natasha Nanwa, MSc, Leslie Dan Faculty of Pharmacy, University of Toronto, 144 College St, 6th Fl, Rm 658, Toronto, Ontario, M5S 3M2, Canada (natasha.nanwa@mail.utoronto.ca).

SUPPLEMENTARY MATERIAL

To view supplementary material for this article, please visit http://dx.doi.org/10.1017/ice.2016.122

REFERENCES

1. Lessa FC, Mu Y, Bamberg WM, et al. Burden of *Clostridium difficile* infection in the United States. *N Engl J Med* 2015;372:825–834.
2. 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:e44103.
3. Badger VO, Ledeboer NA, Graham MB, Edmiston CE Jr. *Clostridium difficile*: epidemiology, pathogenesis, management, and prevention of a recalcitrant healthcare-associated pathogen. *JPEN J Parenter Enteral Nutr* 2012;36:645–662.
4. Dubberke ER, McMullen KM, Mayfield JL, et al. Hospital-associated *Clostridium difficile* infection: is it necessary to track community-onset disease? *Infect Control Hosp Epidemiol* 2009;30:332–337.
5. Dubberke ER, Reske KA, Yan Y, Olsen MA, McDonald LC, Fraser VJ. *Clostridium difficile*–associated disease in a setting of endemicity: identification of novel risk factors. *Clin Infect Dis* 2007;45:1543–1549.
6. Hensgens MP, Goorhuis A, Dekkers OM, Kuijper EJ. Time interval of increased risk for *Clostridium difficile* infection after exposure to antibiotics. *J Antimicrob Chemother* 2012;67:742–748.
7. Vardakas KZ, Polyzos KA, Patouni K, Rafailidis PI, Samonis G, Falagas ME. Treatment failure and recurrence of *Clostridium difficile* infection following treatment with vancomycin or metronidazole: a systematic review of the evidence. *Int J Antimicrob Agents* 2012;40:1–8.
8. Musher DM, Nuila F, Logan N. The long-term outcome of treatment of *Clostridium difficile* colitis. *Clin Infect Dis* 2007;45:523–524.
9. Halabi WJ, Nguyen VQ, Carmichael JC, Pigazzi A, Stamos MJ, Mills S. *Clostridium difficile* colitis in the United States: a decade of trends, outcomes, risk factors for colectomy, and mortality after colectomy. *J Am Coll Surg* 2013;217:802–812.
10. Ananthakrishnan AN, McGinley EL, Saeian K, Binion DG. Temporal trends in disease outcomes related to *Clostridium difficile* infection in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2011;17:976–983.
11. Karas JA, Enoch DA, Aliyu SH. A review of mortality due to *Clostridium difficile* infection. *J Infect* 2010;61:1–8.
12. Nanwa N, Kendzerska T, Krahn M, et al. The economic impact of *Clostridium difficile* infection: a systematic review. *Am J Gastroenterol* 2015;110:511–519.
13. Institute for Clinical Evaluative Sciences (ICES). ICES data. ICES website. http://www.ices.on.ca/Data-and-Privacy/ICES-data. Published 2014. Accessed August 29, 2014.
14. Wilcox MH, Cunniffe JG, Trundle C, Redpath C. Financial burden of hospital-acquired *Clostridium difficile* infection. *J Hosp Infect* 1996;34:23–30.
15. Campbell R, Dean B, Nathanson B, Haidar T, Strauss M, Thomas S. Length of stay and hospital costs among high-risk patients with hospital-origin *Clostridium difficile*-associated diarrhea. *J Med Econ* 2013;16:440–448.
16. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm Stat* 2011;10:150–161.
17. Austin PC. An introduction to propensity score methods for reducing the effects of confounding in observational studies. *Multivariate Behav Res* 2011;46:399–424.
18. Wodchis WP, Bushmeneva K, Nikitovic M, McKillop I. *Guidelines on Person-Level Costing Using Administrative Databases in Ontario* Working Paper Series. Vol. 1 Toronto: Health System Performance Research Network, 2013.
19. Austin PC. A tutorial and case study in propensity score analysis: an application to estimating the effect of in-hospital smoking cessation counseling on mortality. *Multivariate Behav Res* 2011;46:119–151.
20. Agresti A, Min Y. Effects and non-effects of paired identical observations in comparing proportions with binary matched-pairs data. *Stat Med* 2004;23:65–75.
21. Austin PC, Small DS. The use of bootstrapping when using propensity-score matching without replacement: a simulation study. *Stat Med* 2014;33:4306–4319.
22. Brown ML, Riley GF, Potosky AL, Etzioni RD. Obtaining long-term disease specific costs of care: application to Medicare enrollees diagnosed with colorectal cancer. *Med Care* 1999;37:1249–1259.
23. Yabroff KR, Lamont EB, Mariotto A, et al. Cost of care for elderly cancer patients in the United States. *J Natl Cancer Inst* 2008;100:630–641.
24. Riley GF, Potosky AL, Lubitz JD, Kessler LG. Medicare payments from diagnosis to death for elderly cancer patients by stage at diagnosis. *Med Care* 1995;33:828–841.
25. Krajden M, Kuo M, Zagorski B, Alvarez M, Yu A, Krahn M. Health care costs associated with hepatitis C: a longitudinal cohort study. *Can J Gastroenterol* 2010;24:717–726.
26. Canadian Agency for Drugs and Technologies in Health (CADTH). Guidelines for the economic evaluation of health technologies. CADTH website. http://www.cadth.ca/media/pdf/186_Economic Guidelines_e.pdf. Published 2006. Accessed June 9, 2015.
27. Bank of Canada. Annual average exchange rates. Bank of Canada website. http://www.bankofcanada.ca/rates/exchange/annual-average-exchange-rates/. Published 2014. Accessed June 9, 2015.
28. Juurlink DPC, Croxford R, Chong A, Austin P, Tu J, Laupacis A. *Canadian Institute for Health Information Discharge Abstract Database: A Validation Study*. Toronto: Institute for Clinical Evaluative Sciences, 2006.

29. Wijeysundera HC, Machado M, Wang X, et al. Cost-effectiveness of specialized multidisciplinary heart failure clinics in Ontario, Canada. *Value Health* 2010;13:915–921.
30. Thein H-H, Isaranuwatchai W, Campitelli MA, et al. Health care costs associated with hepatocellular carcinoma: a population-based study. *Hepatology* 2013;58:1375–1384.
31. The Organisation for Economic Co-operation and Development (OECD). PPPs and exchange rates. OECD website. http://stats.oecd.org/Index.aspx?datasetcode=SNA_TABLE4. Published 2014. Accessed July 14, 2014.
32. Bank of Canada. Inflation Calculator. Bank of Canada website. http://www.bankofcanada.ca/rates/related/inflation-calculator/. Published 2014. Accessed July 14, 2014.
33. Pillai DR, Longtin J, Low DE. Surveillance data on outbreaks of *Clostridium difficile* infection in Ontario, Canada, in 2008-2009. *Clin Infect Dis* 2010;50:1685–1686.
34. Yasunaga H, Horiguchi H, Hashimoto H, Matsuda S, Fushimi K. The burden of *Clostridium difficile*-associated disease following digestive tract surgery in Japan. *J Hosp Infect* 2012;82:175–180.
35. Zerey M, Paton BL, Lincourt AE, Gersin KS, Kercher KW, Heniford BT. The burden of *Clostridium difficile* in surgical patients in the United States. *Surg Infect (Larchmt)* 2007;8:557–566.
36. Hensgens MPM, Goorhuis A, Dekkers OM, van Benthem BHB, Kuijper EJ. All-cause and disease-specific mortality in hospitalized patients with *Clostridium difficile* infection: a multicenter cohort study. *Clin Infect Dis* 2013;56:1108–1116.
37. Bhangu S, Bhangu A, Nightingale P, Michael A. Mortality and risk stratification in patients with *Clostridium difficile*-associated diarrhoea. *Colorectal Dis* 2010;12:241–246.
38. Pepin J, Valiquette L, Cossette B. Mortality attributable to nosocomial *Clostridium difficile*-associated disease during an epidemic caused by a hypervirulent strain in Quebec. *CMAJ* 2005;173:1037–1042.
39. Dubberke ER, Reske KA, Olsen MA, McDonald LC, Fraser VJ. Short- and long-term attributable costs of *Clostridium difficile*-associated disease in nonsurgical inpatients. *Clin Infect Dis* 2008;46:497–504.
40. 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.
41. Mitchell BG, Gardner A, Barnett AG, Hiller JE, Graves N. The prolongation of length of stay because of *Clostridium difficile* infection. *Am J Infect Control* 2014;42:164–167.

https://doi.org/10.1017/ice.2016.122 Published online by Cambridge University Press