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Hospital-acquired *Clostridium difficile* infection: an institutional costing analysis

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SUMMARY

Background: Healthcare-acquired *Clostridium difficile* infection (HA-CDI) is a common infection and a financial burden on the healthcare system.
Aim: To estimate the hospital-based financial costs of HA-CDI by comparing time-fixed statistical models that attribute cost to the entire hospital stay to time-varying statistical models that adjust for the time between admission, diagnosis of HA-CDI, and discharge and that only attribute HA-CDI costs post diagnosis.
Methods: A retrospective cohort study was conducted (April 2008 to March 2011) using clinical and administrative costing data of inpatients (≥15 years) who were admitted to The Ottawa Hospital with stays >72 h. Two time-fixed analyses, ordinary least square regression and generalized linear regression, were contrasted with two time-dependent approaches using Kaplan–Meier survival curve.
Findings: A total of 49,888 admissions were included and 366 (0.73%) patients developed HA-CDI. Estimated total costs (Canadian dollars) from time-fixed models were as high as $74,928 per patient compared to $28,089 using a time-varying model, and these were 1.47-fold higher compared to a patient without HA-CDI (incremental cost $8,997 per patient). The overall annual institutional cost at The Ottawa Hospital associated with HA-CDI was as high as $10.07 million using time-fixed models and $1.62 million using time-varying models.
Conclusion: When calculating costs associated with HA-CDI, accounting for the time between admission, diagnosis, and discharge can substantially reduce the estimated institutional costs associated with HA-CDI.

Introduction

Clostridium difficile infection (CDI) is a common hospital-associated infection and can lead to substantial morbidity, mortality, and healthcare cost [1]. *Clostridium difficile* spores are resistant to alcohol-based sanitizers, and common bacterial reservoirs include healthcare workers, patients, and a contaminated hospital environment [2]. Hospitalized patients receiving antibiotics for an underlying infection or for surgical prophylaxis are at an increased risk for acquiring CDI because eradication of gut flora with antibiotics allows endogenous or acquired *C. difficile* to proliferate [2]. Emergent hypervirulent strains and injudicious administration of

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antibiotics has led to increased incidence and severity of CDI [3]. Within Canada, healthcare-associated CDI (HA-CDI) was reported at a rate of 3.33 per 1000 patient admissions and had a 30-day attributable mortality rate of 4% (1.74-fold greater than the 2009 reported mortality rate) in 2014 [4].

HA-CDI increases length of hospital admission and incurs additional costs from hospitalization and CDI treatment [5]. A US multi-centre cohort study reported that the mean total cost for a CDI patient was US$55,796 compared to US$28,609 for a matched control, representing nearly a two-fold cost increase [6]. A study investigating the cost associated with CDI-patient utilization of inpatient services in Australia reported an average per patient cost of A$19,743 [7]. Estimating the true cost of HA-CDI is especially difficult because patients may develop infection at any point throughout their admission. Attributing the entire length of stay to CDI may overestimate the true cost. However, few studies have accounted for HA-CDI as a time-varying variable. Challenges in adopting appropriate methodology that accounts for HA-CDI as a time-varying variable include: data limitations (e.g. lack of patient-level cost data), the inability to accurately determine the date of HA-CDI acquisition, the complexity of statistical methods required to model time-dependent exposures, and unmeasured and residual confounding due to baseline and time-dependent confounders. The risk of mortality at hospital admission is an important factor associated with both hospital costs and HA-CDI acquisition [8,9]. Accounting for baseline mortality risk is important for modelling the association between HA-CDI and hospital-based costs, but it is often difficult to estimate and not included.

Accurately estimating the financial impact of HA-CDI will allow for more efficient allocation and use of hospital resources and will reinforce the implementation of optimal policies and practices to reduce new HA-CDI infections and associated healthcare costs. The objectives of this study were to calculate the costs associated with HA-CDI using both time-varying and time-fixed methods to produce estimates that are most accurately attributed to HA-CDI in a large tertiary care institution.

Methods

Study population

This study was conducted at The Ottawa Hospital (TOH), a 1050-bed tertiary care teaching hospital located in Ottawa, Ontario, Canada, serving a population of ~1.5 million. It is comprised of three inpatient acute care campuses — the General and Civic Campuses, and the University of Ottawa Heart Institute. We used clinical and administrative databases to determine HA-CDI cases and outcomes for all eligible hospital admissions at the two largest campuses (General and the Civic). The unit of analysis for the study was the hospital inpatient encounter. Each encounter refers to an admission to the hospital.

All inpatients treated at the General and Civic campuses were eligible for this study if they were admitted after April 1st, 2008 and discharged before March 31st, 2011. Admissions with a hospital stay of <72 h, those aged <15 years, and those with child-related care (i.e. admissions to obstetric service) were excluded. This study excluded patients from the University of Ottawa Heart Institute.

Data sources

Data were gathered from two sources: The Ottawa Hospital Data Warehouse and The Ottawa Hospital Case Costing system. The Data Warehouse is a relational database that links clinical, laboratory, and administrative data using common identification keys. Cost data were extracted from TOH's case costing system, which uses standardized methods established and approved by the Ontario Case Costing system [10]. The Case Costing system was designed to derive patient-specific hospital costs by allocating total hospital costs to each patient. Total hospital costs are attributed to each patient as direct and indirect costs based on services that a patient receives during a hospital stay.

Measurements and definitions

The primary outcome was direct costs and the secondary outcome was total hospital cost per case. Direct costs are defined as any hospital costs attributable to treating patients while in hospital. Examples of direct costs include costs for nursing, medical supplies, surgical supplies, laboratory testing, medications, isolation, personal protective equipment, and operations. Indirect costs are defined as costs that do not contribute directly to providing patient care, such as those arising from essential auxiliary support (e.g. administration or overhead expenses). Direct costs — rather than total costs — were analysed due to the presence of a small number of extreme outliers representing unusually high indirect costs. We extrapolated total costs from the direct costs (rather than use the measured indirect costs) for our analysis at the patient level. Whereas, on an aggregate level, the use of indirect costs would likely be acceptable, it is possible that accounting for errors when assessing individual cases would lead to spurious results. Total hospital costs for patients with HA-CDI were calculated using the ratio of direct to indirect costs at TOH. During the study period at TOH, the ratio of direct to indirect costs was 7:3. Direct costs were therefore multiplied by a factor of 1.428 to derive total costs. All costs were adjusted to 2010 Canadian dollars by using the healthcare component from the Canadian consumer price index [11].

HA-CDI was defined as a positive *C. difficile* toxin assay from liquid stool obtained from a patient ≥72 h after admission [9]. *C. difficile* cases were identified in the Data Warehouse using a text-searching technique for *C. difficile* toxin tests in electronic laboratory reports. Previously established logical rules were followed to define each encounter based on whether the patient developed CDI during admission [9]. Cases were classified as healthcare-associated if a positive *C. difficile* test was collected from a patient >72 h after admission. Positive results within 72 h of admission were classified as community-acquired and excluded from analyses. We excluded relapsed CDI cases, defined as cases occurring within eight weeks of a previous CDI episode [12].

HA-CDI was analysed in two different ways: (i) as a dichotomous variable comparing HA-CDI cases to non-HA-CDI cases in the time-fixed analyses; (ii) as a continuous time-to-event variable that accounted for the length of time from admission to HA-CDI detection, and time from HA-CDI detection until hospital discharge.

Baseline mortality risk for each admission was measured using a score that predicts the likelihood of dying during a

hospital stay, calculated using a regression model that was previously validated at TOH [13]. The mortality likelihood model uses the following covariates: age at admission, gender, admitting hospital service (medical, surgical or intensive unit care), acuity of admission (elective or emergent), comorbidity (by Charlson index score), and severity of acute disease. Severity of acute disease was represented by the Laboratory-based Acute Physiology Score (LAPS), which is a continuous variable calculated by summarizing the results of 14 laboratory tests performed within the first 24 h of admission.

Information on sex (female vs male), age (continuous), hospital campus (Civic vs General), in-hospital deaths, and the Charlson index (categorized into four levels 0, 1–2, 3–4, ≥5) was collected. A list of the most common chronic conditions was also extracted and included myocardial infarction, congestive heart failure, diabetes, and cancer. Admissions data included length of stay in the hospital and length of time from admission to HA-CDI diagnosis (days).

Statistical analysis

Descriptive statistics were generated for the study cohort stratified by HA-CDI status. Variables that were normally distributed are described using means and standard deviations (SD). Variables with skewed distributions are described using median and interquartile range (IQR). Categorical variables are described using frequency and percentage.

Time-fixed analysis

Time-fixed analyses were conducted using two different linear regression models. The first was the ordinary least square (OLS) regression model that estimated the effect of HA-CDI on direct costs under the assumption that the errors are normally distributed. The OLS regression coefficient was used to determine the mean log-cost for patients with HA-CDI and those without HA-CDI. The cost difference in dollars was calculated by exponentiating the log-cost for each group providing the geometric mean of costs. To address the possibility of retransformation bias (especially in the case when error terms are not log-normal) a smearing factor adjustment was used [14]. We calculated a group-specific smearing factor for those with HA-CDI (1.56509) and without HA-CDI (1.53991) and multiplied them by the geometric mean costs to generate the estimated direct costs for those with and without HA-CDI.

The second was a generalized linear model (GLM) to analyse the effect of HA-CDI on the direct costs using a gamma-family and log-link function as it allows the development of models with an outcome variable that is non-normally distributed. The advantage of the GLM approach over the OLS is that it directly incorporates the logarithmic scale of cost measurement into the model. Therefore, unlike OLS, it does not suffer from any retransformation bias when converting estimates on the original scale by exponentiating the estimated regression coefficient. To obtain the estimated mean costs for the group with HA-CDI and the group without HA-CDI in dollars, we retransformed the regression coefficients via exponentiation by holding baseline mortality risk constant at its median.

In both analyses the models were adjusted for baseline mortality risk at its median to account for any potential confounding related to the severity of illness of the patient.

Time-varying analyses

Time varying analyses were conducted using a method to account for the time-dependent nature of the infection. Kaplan–Meier survival curve was used to describe the costs to hospital discharge while accounting for the time-to-event nature of HA-CDI (i.e. admission to CDI diagnosis, CDI detection to discharge). To estimate the mean direct costs, the area under the estimated survival curve (AUC) was calculated using the Reimann sum estimation method [15].

To control for baseline mortality risk in the Kaplan–Meier curve, the cohort was stratified by quartile of baseline mortality risk. This enabled estimation of the mean costs for each stratum by calculation of the AUC using the Riemann sum estimation method. One thousand bootstrap samples were taken from the original cohort to report 2.5th and 97.5th percentiles of the estimated mean.

All statistical analyses were performed with SAS 9.2 (SAS Institute, Cary, NC, USA).

Results

Patient demographic characteristics

Descriptive statistics for the patient cohort are presented in Table I. During the three-year study period there were 49,888 inpatient admissions. Of those, 360 admissions were classified as HA-CDI cases, representing 0.73% of the total number of admissions. Among HA-CDI cases, the median (IQR) number of days from admission to HA-CDI diagnosis (i.e. interval between admission and a positive test) was 13 (7–29 days). The median (IQR) length of stay (LOS) for CDI cases was 36 days (20–62) and eight days (5–15) for non-CDI cases. In both the HA-CDI and non-HA-CDI groups, ~50% of admissions were among female patients. HA-CDI patients were older (median: 71.3 vs 64.5 years) and had a greater baseline mortality risk score (median: 0.12 vs 0.04). The prevalence of in-hospital mortality was 24.2% among HA-CDI patients and 6.8% among non-HA-CDI patients.

Crude costs analysis

Summary statistics for observed direct costs and total costs are presented in Table II. The median (IQR) direct cost (Canadian dollars) per patient with HA-CDI was $32,954 (17,068–63,735) and $7,816 (4,735–13,992) per patient without HA-CDI. The median (IQR) total hospital cost per patient with HA-CDI was $47,075 (24,382–91,045) and $11,165 (6,764–19,987) per patient without HA-CDI.

Time-fixed analyses

The results from the time-fixed analyses are presented in Table III. The estimated mean direct cost from the OLS analyses was $47,505 for an HA-CDI patient and $13,086 for a non-HA-CDI patient, a difference of $34,419. The estimated direct cost from the GLM was similar where an HA-CDI patient cost $48,025 and a non-HA-CDI patient $12,887, making a difference of $35,138. Using the ratio of direct to indirect costs (1.428), the OLS model estimated that the total hospital cost for an HA-CDI patient was $67,837 and $18,686 for a non-HA-CDI patient, a difference of $49,150. In the GLM model the estimated total

Table I
Characteristics of the study cohort by HA-CDI status ($N = 49,888$)

Characteristics	HA-CDI: yes ($n = 360$)	HA-CDI: no ($n = 49,528$)
Age (mean, SD)	71.3 (16.10)	65 (17.80)
Female (no., %)	180 (50.00)	25,345 (51.17)
Campus (no., %)		
Civic	184 (51.11)	21,477 (43.36)
General	176 (48.89)	28,051 (56.64)
Predicted baseline mortality risk (median, IQR)	0.12 (0.04–0.27)	0.04 (0.01–0.14)
Length of stay in hospital (days) (median, IQR)	36 (20–62)	8 (5–15)
CDI detection from admission (days) (median, IQR)	13 (7–26)	NA
In-hospital deaths (no., %)	87 (24.17)	3367 (6.80)
Charlson index (no., %)		
0	71 (19.72)	15,016 (30.32)
1–2	93 (25.83)	13,548 (27.35)
3–4	78 (21.67)	7989 (16.13)
≥5	118 (32.78)	12,975 (26.20)
Most common conditions (no., %)		
Moderate or severe liver disease	103 (28.61)	740 (1.49)
Hemiplegia or paraplegia	83 (23.06)	1488 (3.00)
Congestive heart failure	67 (18.61)	5218 (10.54)
Diabetes with complications	61 (16.94)	7657 (15.46)
Chronic obstructive pulmonary disease	55 (15.28)	5476 (11.06)
Primary cancer	46 (12.78)	13,660 (27.58)
Cerebrovascular disease	36 (10.00)	4702 (9.49)
Peripheral vascular disease	35 (9.72)	3310 (6.68)
Dementia	35 (9.72)	2585 (5.22)
HIV/AIDS	29 (8.06)	266 (0.54)
Myocardial infarction	18 (5.00)	2507 (5.06)
Mild liver disease	18 (5.00)	1273 (2.57)
Diabetes without complications	18 (5.00)	8804 (17.78)
Renal disease	16 (4.44)	4065 (8.21)
Metastatic cancer	12 (3.33)	5984 (12.08)
Peptic ulcer disease	9 (2.50)	1005 (2.03)
Connective tissue/rheumatic disease	5 (1.39)	609 (1.23)

HA-CDI, healthcare-associated *Clostridium difficile* infection.

Table II
Crude cost analysis by HA-CDI status

Cost type ($)	HA-CDI: Yes	HA-CDI: No	Difference
Direct cost			
Median (IQR)	32,954.00 (17,068.00–63,735.00)	7,816.00 (4,735.00–13,992.00)	25,138.00 (12,333.00–49,743.00)
Mean (SD)	53,582.00 (66,388.00)	13,290.00 (19,181.00)	40,292.00 (47,207.00)
Total cost[a]			
Median (IQR)	47,058.31 (24,373.10–91,013.58)	11,161.25 (6,761.58–19,980.58)	35,897.06 (17,611.52–71,033.00)
Mean (SD)	76,515.10 (94,802.06)	18,978.12 (27,390.47)	57,536.98 (67,411.60)

HA-CDI, healthcare-associated *Clostridium difficile* infection; IQR, interquartile range; SD, standard deviation.
[a] Total costs were obtained by using the ratio of direct to indirect (1.428) costs during the study period.

hospital cost was $68,579 for an HA-CDI patient and $18,402 for a non-HA-CDI patient, a difference of $50,177.

Time-varying analyses

The results from the Kaplan–Meier analyses are reported in Table IV. The time-fixed Kaplan–Meier analysis shows that the mean direct cost of an HA-CDI patient was $52,471 and a non-HA-CDI patient was $13,282, making a difference of $39,189. The time-varying Kaplan–Meier analysis estimated that the mean direct cost of an HA-CDI patient was $19,670 and a non-HA-CDI patient was $13,370, making a mean difference of $6,300. Using the ratio of direct to total costs, it was estimated that the mean total hospital cost of an HA-CDI patient was

Table III
Mean costs time-fixed analyses by HA-CDI status

Cost type ($)	HA-CDI: yes		HA-CDI: no		Difference	
	Estimate	95% CI	Estimate	95% CI	Estimate	95% CI
OLS model						
Direct	47,505.00	(43,628.00–51,728.00)	13,086.00	(12,980.00–13,194.00)	34,419.00	(30,648.00–38,534.00)
Total[a]	67,837.14	(62,300.78–73,867.58)	18,686.81	(18,535.44–18,841.03)	49,150.33	(43,765.34–55,026.55)
GLM model						
Direct	48,025.00	(44,006.00–52,411.00)	12,887.00	(12,768.00–12,985.00)	35,138.00	(31,238.00–39,426.00)
Total[a]	68,579.70	(62,840.57–74,842.91)	18,402.64	(18,232.70–18,542.58)	50,177.06	(44,607.86–56,300.33)

HA-CDI, healthcare-associated *Clostridium difficile* infection; OLS, ordinary least square regression; GLM, generalized linear model.
[a] Total costs were obtained by using the ratio of direct to indirect (1.428) costs during the study period.

$28,088 and non-HA-CDI patient was $19,092, making the incremental total cost per patient $8,996.

Table V presents the results from the Kaplan–Meier survival curve, stratified by the baseline risk of mortality accounting for the time-varying nature of CDI. In general, the difference in mean estimated direct costs increased as the risk of baseline mortality increased, with the exception that patients with CDI in the second quartile showed higher cost than the patients in the third quartile.

Total annual cost of HA-CDI

The estimated number of annual cases of HA-CDI at TOH is 180, and Table VI presents the results summarizing all total hospital costs associated with HA-CDI and non-HA-CDI patients to estimate the range of projected annual cost in millions. Projected annual costs range from as low as 1.62 million using the time-varying Kaplan–Meier method to 10.36 million using crude cost estimates.

Discussion

At TOH, there are ~180 HA-CDI cases per year. HA-CDI patients had an average length of stay of 36 days and the average number of days until CDI diagnosis was 13 days. Using detailed individual-level data, four different costing analyses were conducted to explore the variation in cost estimates associated with HA-CDI. HA-CDI cases are known to cost more than non-HA-CDI cases; however, it is important to understand what factors are specifically attributable to CDI and what costs can be attributed to hospital admissions before onset of HA-CDI. This has important implications for resource allocation and hospital administration.

An incremental cost associated with HA-CDI was estimated at $8,996 per patient when accounting for time variation. By contrast, time-fixed analyses generated cost estimates of $55,962 per patient, which is about six times higher than the time-varying estimates. Time-fixed models yield biased estimates due to treating HA-CDI as a time-fixed variable even though the time of onset of HA-CDI varies among patients. At our institution, the annual cost of HA-CDI is about $1.62 million, compared to projected annual costs of about $8.85 to $10.07 million from time-fixed models.

In order to assess the impact of CDI direct costs, while controlling for the effect of baseline mortality risk, a stratified analysis was conducted using quartiles of baseline risk. Patients with CDI in the second quartile of the baseline risk of mortality were observed to have direct costs of $22,405 whereas those in the third quartile had direct costs of $21,345. Variability in costs was high in the CDI patients in the second quartile, as evidenced by the wide 95% bootstrap confidence interval estimates (between $1,906 and $34,660), which may explain this finding. Overall, the direct costs associated with CDI (incremental effect $ = CDI present $ − CDI absent $) increased regardless of stratum, and the estimated incremental cost increase was similar across the four strata, ranging between $6,562 and $9,969 after controlling the time-varying nature of CDI.

HA-CDI is one of the more common healthcare-associated infections and imposes a financial burden to the healthcare system [16,17]. However, these cost estimates may be biased as many previous studies did not account for the time-varying nature of HA-CDI. Accounting for the time-varying nature of HA-CDI is important because the onset of HA-CDI varies between patients and may occur at any point during hospitalization. Accurate cost estimates for HA-CDI can help policy makers and funders with the allocation of limited health resources, and help researchers to develop and investigate more cost-effective prevention strategies and more robustly evaluate the cost-effectiveness of infection control interventions [6]. In addition, it will be possible to apply these cost estimates

Table IV
Direct cost estimates (Can$) using Kaplan–Meier curve

Cost type	HA-CDI: yes	HA-CDI: no	Difference
Kaplan–Meier time-fixed			
Direct			
Median	32,954.00	7,816.00	25,138.00
Mean	52,471.00	13,282.00	39,189.00
Total[a]			
Median	47,058.31	11,161.25	35,897.06
Mean	74,928.59	18,966.70	55,961.89
Kaplan–Meier time-varying			
Direct			
Median	11,520.00	7,846.00	3,674.00
Mean	19,670.00	13,370.00	6,300.00
Total[a]			
Median	16,450.56	11,204.09	5,246.47
Mean	28,088.76	19,092.36	8,996.40

HA-CDI, healthcare-associated *Clostridium difficile* infection.
[a] Total costs were obtained by using the ratio of direct to indirect (1.428) costs during the study period.

Table V
Direct cost estimates using Kaplan–Meier curve stratified by the baseline risk of mortality

Baseline mortality risk quartile (Kaplan–Meier time-varying)	HA-CDI: yes Can$ (95% CI)[a]	HA-CDI: no Can$ (95% CI)[a]	Difference Can$
Quartile			
1st	15,572 (10,560–20,385)	9,010 (8,804–9,231)	6,562
2nd	22,405 (1,906–34,660)	12,436 (12,120–12,731)	9,969
3rd	21,348 (15,143–27,920)	13,823 (13,496–14,167)	7,525
4th	25,432 (20,183–32,897)	18,182 (17,709–18,568)	7,270

HA-CDI, healthcare-associated *Clostridium difficile* infection; CI, confidence interval.
[a] 95% bootstrap confidence interval constructed from 1000 samples.

to other hospital-based complications with a defined specific onset date. For example, one will be able to apply this time-varying method to other types of healthcare-associated infections, procedure complications, and adverse drug events.

Previous studies have addressed time-dependent biases when analysing different healthcare-associated infections. A study by Nelson *et al.* investigating hospital-acquired (HA) MRSA infection also found that attributing costs to the entire length of stay for an HA-MRSA patient will inflate costs, compared to attributing costs only from diagnosis to discharge [18]. A study by Puchter *et al.* investigated the economic burden of vancomycin-resistant enterococci (VRE), another type of hospital-acquired infection. Authors compared hospital costs from patients with VRE infections (cases) and patients with vancomycin-susceptible enterococci (VSE) infections (controls) to specifically investigate the costs of vancomycin resistance. This study found that the costs of VRE cases and VSE controls were similar before the onset of infection, but that costs after onset of infection were significantly higher among patients with VRE infections than VSE infections [19].

This study has limitations that should be taken into consideration with interpretation and application. The study's time horizon was the encounter. Therefore, costs incurred by other parts of the healthcare system and other societal costs, such as the lost productivity associated with HA-CDI, could not be assessed. This analysis used 72 h after admission as the case definition for diagnosing CDI, as per the national surveillance protocol [4]. This may have overestimated the incidence of HA-CDI compared to longer cut-offs. Community onset healthcare-associated cases (i.e. tests positive within 72 h with a prior hospitalization within eight weeks) were excluded as a conservative precaution but we cannot confirm with certainty that CDI was not attributable to the previous admission. Additionally, patients may develop HA-CDI following an encounter and not return to The Ottawa Hospital (e.g. if the symptoms are self-limiting, if they are treated by an outpatient physician, or if they are treated at another hospital). Thus, we chose the encounter as the unit of analysis and only included patients with a positive *C. difficile* test $\geq$72 h after admission to TOH. We did not examine whether the death rate among patients with CDI in hospitals would influence hospital costs for patients with CDI and without CDI. Our results should therefore be considered conservative estimates of the overall costs to the hospital and not the healthcare system. This study compared OLS models, GLM models, and stratified KM analyses. There are, however, other modelling approaches, including the nested g-formula and the Aalen additive approach, which are innovative methods that may provide more accurate cost estimates for time-dependent outcomes. Consideration should be given to applying these methods in future studies [20,21].

In addition, one of the most important and challenging components of estimating costs associated with HA-CDI is the influence of time-dependent confounding factors. More than 40 risk factors for CDI have been identified in the literature, including some that would be considered time-dependent factors, such as antibiotic use (especially cumulative antibiotic use) and receipt of invasive procedures [22]. A critical time-dependent factor associated with HA-CDI is the cumulative exposure to antibiotics [23,24], which is likely to be higher among patients who deteriorate more after admission – compared to those who remain CDI-free – and who are therefore associated with higher costs even when removing the effect of CDI. However, adjusting for time-dependent antibiotic exposure is complex, as antibiotics present varying effects on the risk of developing CDI based on the duration, dose, and type of antibiotics used. The lack of adjustment for time-dependent confounding may therefore result in overestimates of the hospital costs associated with CDI.

Table VI
Estimated total mean annual inpatient costs (Can$)

	Adjust for baseline mortality risk	Adjust for time-varying	Total cost for CDI patient	Total costs for non-CDI patient	Difference	Projected annual costs (difference × 180)[a] in millions
Crude	No	No	76,515.10	18,978.12	57,536.98	10.36
OLS	Yes	No	67,837.14	18,686.81	49,150.33	8.85
GLM	Yes	No	68,579.70	18,402.64	50,177.06	9.03
KM						
Time-fixed	No	No	74,928.59	11,161.25	55,961.89	10.07
Time-varying	No	Yes	28,088.76	19,092.36	8,996.40	1.62

CDI, *Clostridium difficile* infection.
[a] It is estimated that there are 180 CDI cases per year at The Ottawa Hospital.

Our study was a database analysis that set out to determine costs associated with HA-CDI. Detailed information about specific patient-level variables that may influence cost, such as surgeries and postoperative complications, and use of laboratory (and other) investigations and medications, were not available in this database. We are thus unable to comment in detail on these factors; however, the design of future studies should take more detailed individual-level factors into consideration.

In summary, HA-CDI is a serious infection and burden in healthcare settings. Although the cost of an illness is not the sole determinant to assess the effectiveness of infection prevention and control intervention programmes from the hospital perspective, obtaining cost estimates that include the time-varying nature of HA-CDI is essential. This provides greater accuracy when predicting the cost that can be saved when each HA-CDI case is prevented. More accurate estimates on the incremental cost associated with HA-CDI can support the choices of hospital decision-makers.

Conflict of interest statement
None declared.

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