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The association of hospital prevention processes and patient risk factors with the risk of *Clostridium difficile* infection: a population-based cohort study

N Daneman,[1,2,3] A Guttmann,[1,3,4,5] X Wang,[1] X Ma,[1] D Gibson,[6] TA Stukel[1,3]

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For numbered affiliations see end of article.

Correspondence to
Dr N Daneman, Division of Infectious Diseases, Department of Medicine, Sunnybrook Health Sciences Centre, University of Toronto, 2075 Bayview, G106, Toronto, ON M4N 3M5, Canada;
nick.daneman@sunnybrook.ca

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ABSTRACT

Background *Clostridium difficile* is the most common cause of healthcare-acquired infection; the real-world impacts of some proposed *C. difficile* prevention processes are unknown.

Methods We conducted a population-based retrospective cohort study of all patients admitted to acute care hospitals between April 2011 and March 2012 in Ontario, Canada. Hospital prevention practices were determined by survey of infection control programmes; responses were linked to patient-level risk factors and *C. difficile* outcomes in Ontario administrative databases. Multivariable generalised estimating equation (GEE) regression models were used to assess the impact of selected understudied hospital prevention processes on the patient-level risk of *C. difficile* infection, accounting for patient risk factors, baseline *C. difficile* rates and structural hospital characteristics.

Results *C. difficile* infections complicated 2341 of 653 896 admissions (3.6 per 1000 admissions). Implementation of the selected *C. difficile* prevention practices was variable across the 159 hospitals with isolation of all patients at onset of diarrhoea reported by 43 (27%), auditing of antibiotic stewardship compliance by 26 (16%), auditing of cleaning practices by 115 (72%), on-site diagnostic testing by 74 (47%), vancomycin as first-line treatment by 24 (15%) and reporting rates to senior leadership by 52 (33%). None of these processes were associated with a significantly reduced risk of *C. difficile* after adjustment for baseline *C. difficile* rates, structural hospital characteristics and patient-level factors. Patient-level factors were strongly associated with *C. difficile* risk, including age, comorbidities, non-elective and medical admissions.

Conclusions In the largest study to date, selected hospital prevention strategies were not associated with a statistically significant reduction in patients' risk of *C. difficile* infection. These prevention strategies have either limited effectiveness or were ineffectively implemented during the study period.

BACKGROUND

Clostridium difficile is the most burdensome gastrointestinal infection in developed countries and among the top 10 infectious causes of death.[1] The morbidity and mortality of *C. difficile* is especially concerning because this infection is usually acquired in the process of care provision, particularly in acute care hospitals, where our sickest and most vulnerable patients receive treatment. *C. difficile* is a crucial patient safety issue, as it is the single most common cause of healthcare-associated infections.[2]

The burden of hospital-acquired *C. difficile* infections, coupled with the perceived preventability of these infections, prompted the Ontario Ministry of Health and Long-Term Care (MOHLTC) to select *C. difficile* rates as the first hospital patient safety indicator to be subject to mandatory public reporting in September 2008. Our group determined that this public reporting campaign was associated with a rapid 26% reduction in *C. difficile* cases or nearly 2000 cases prevented per year.[3] However, we lacked information on hospital-specific *C. difficile* prevention practices, and so, we could not illuminate the active ingredients in *C. difficile*-prevention efforts, nor explain the source of variability in rates of *C. difficile* across

hospitals. Just as the hospital-level factors influencing *C. difficile* risk have not been well studied, information on patient-level risk factors for *C. difficile* infection is derived primarily from single-centre studies. Understanding the broad drivers of *C. difficile* risk is growing ever more importantly in an era of hospital quality indicators, mandatory public reporting[4] and strict financial disincentives such as non-payment policies for preventable infections.[5]

Therefore, the primary goal of this population-based, Ontario-wide, retrospective cohort study was to examine the incremental influence of selected understudied hospital *C. difficile* prevention strategies on patients' risk of acquiring *C. difficile* infection during their hospital stay, after accounting for baseline *C. difficile* rates, structural hospital characteristics and patient risk factors; the secondary goal was to elucidate which patient groups are most at risk of this infection.

METHODS

General study design

We conducted a retrospective cohort study of patients admitted to acute care hospitals in Ontario, Canada's largest and most populous province (13 million residents), between 1 April 2011 and 31 March 2012. Through multivariable generalised estimating equation (GEE) binary regression analysis, we assessed the impact of patient risk factors, baseline *C. difficile* rates, structural hospital characteristics and hospital *C. difficile* prevention processes on the patient-level risk of *C. difficile* infection.

Hospital selection criteria

The study included all acute care hospitals in Ontario, which had been surveyed by the Ontario MOHLTC and Public Health Ontario (PHO) regarding *C. difficile* infection control processes.

Patient selection criteria

We included all first admissions for patients >1 year of age to these acute care hospitals in Ontario during the study year. We restricted to the first hospital admission for each patient. We also excluded admissions, which occurred within 8 weeks of discharge related to a *C. difficile* hospitalisation, so as to count only incident cases rather than relapses.

Administrative data sources

The study used population-based administrative databases derived from Ontario's universal single-payer healthcare system. At the Institute for Clinical Evaluative Sciences (ICES), these well-validated databases are linked through encoded healthcare numbers, and have been used extensively in prior research,[6–8] including studies of *C. difficile* infection.[3 9] Hospital admissions and *C. difficile* events were identified from the Canadian Institute for Health Information Discharge Abstract Database, which describes all hospitalisation events in the province. Multiple databases contributed to measurement of patient-level risk factors, including this hospital database and provincial databases recording same-day surgeries, emergency department visits,[10] home-care treatments, long-term care residence,[11] physician billing claims[12] and vital statistics.

Ontario hospital corporation survey of *C. difficile* prevention processes

In February 2011, the Ontario MOHLTC surveyed Ontario hospital corporations to examine the current state of *C. difficile* prevention practices and approaches. The mandatory survey, developed by the MOHLTC in conjunction with PHO, was completed by an infection control practitioner or senior manager knowledgeable about the facility's infection prevention and control activities. The survey was administered at the level of hospital corporations, given that most infection control programmes are distributed across and responsible for all sites of a hospital corporation. However, our analyses map the responses to each individual hospital within a corporation. The Sunnybrook Research Ethics Board, ICES and the MOHLTC approved linkage of the de-identified hospital survey responses to the administrative databases.

Outcome measure

The primary outcome was the diagnosis of *C. difficile* infection, as defined by International Classification of Diseases, 10th edition (ICD-10) code A047 in the hospital database. This outcome was measured at the patient level. We did not count *C. difficile* cases, which were labelled as preadmission diagnoses. Our previous work in Ontario has confirmed that hospital *C. difficile* rates measured in these databases are strongly correlated with rates reported by active infection control surveillance programmes as part of mandatory hospital reporting (Pearson's correlation coefficient 0.92).[3] Two patient-level validation studies in the USA have also confirmed that ICD codes are highly specific (>99%) for the diagnosis of *C. difficile* infection.[13 14] In a sensitivity analysis, we limited *C. difficile* outcome events to those labelled as type 2 (postadmission) diagnoses. However, we did not limit to type 2 diagnoses for our main analysis given that the majority of *C. difficile* infections are hospital acquired, and limiting to type 2 cases likely undercounts hospital-acquired cases since less than half of the cases are designated as type 2.[3]

Patient risk factors

A 1 year look-back window prior to admission was used to capture extensive patient-level factors that could potentially impact the risk of *C. difficile* infection. Demographic factors included age group and sex; comorbidity was measured through the presence

or absence of each of the 16 individual comorbidities of interest; type of admission was categorised as elective versus non-elective and separately as belonging to medical, surgical, obstetrical or other services. The calendar month of admission was recorded given that *C. difficile* infections are seasonal.[15] We identified recent healthcare exposure in the 8 weeks preceding admission, including any hospital admission, emergency department visit, same-day surgery procedure, residence in a long-term care facility, receipt of outpatient haemodialysis, outpatient chemotherapy or home-care treatment.[16] Although antibiotic treatment data are unavailable for inpatients and non-elderly outpatients, we determined whether the most responsible diagnosis for the current admission was a bacterial infection that would typically warrant antibiotic treatment. We also determined whether a bacterial infection had been diagnosed in the 8 weeks prior to admission.[1]

Structural hospital characteristics and baseline *C. difficile* rates

We measured baseline *C. difficile* rates in 2007 since current rates can be influenced by previous rates within an institution. We chose 2007 as a baseline year since mandatory public reporting was introduced in Ontario in 2008 and would be expected to have stimulated implementation of new hospital prevention processes.[3] We also measured some non-modifiable structural hospital characteristics in the administrative databases, including hospital type, since *C. difficile* rates are typically higher in academic/teaching hospitals and larger community hospitals and could confound the association between prevention practices and *C. difficile* rates.[3 17] Academic/teaching hospitals were defined based on full affiliation with the Council of Academic Hospitals of Ontario. Non-academic hospitals were subcategorised based on numbers of beds and yearly admissions as large, medium and small community hospitals. Using survey data, we also categorised the proportion of single-bedded rooms as <25% of hospital beds, 25%–35% of beds or >35% of beds.[18]

Hospital processes of care

Hospital processes of care were identified from survey responses. The primary predictors of interest in this study were prespecified to include one variable from each survey domain: infection control policies to decrease transmission, antimicrobial stewardship, environmental cleaning, diagnostic testing, treatment and leadership/culture (online supplementary table S1). Two investigators, one hospitalist and one infectious diseases specialist selected one most relevant question item from each domain based on (a) the potential to result in reduced *C. difficile* rates, (b) the likelihood that the respondents would be able to accurately gauge that hospital characteristic and (c) the expectation of variability in implementation across Ontario hospitals at the time of the survey. For example, we did not select use of contact precautions for *C. difficile* as a predictor because contact precautions are used for *C. difficile* in 100% of hospitals.[17] Instead, the infection control policy of interest was whether contact precautions are implemented immediately at the onset of diarrhoea versus at any other time point (only after patients meet qualified definitions of diarrhoea, only after physicians' order, only after advice of infection control professional or only after a positive confirmatory test result). The antimicrobial stewardship item of interest was whether the hospital reported auditing compliance of staff with antibiotic stewardship policies; similarly, the environmental cleaning predictor of interest was whether there was a system of auditing compliance of housekeeping staff with policies. With respect to *C. difficile* diagnosis, we categorised hospitals by whether testing was available on-site versus sending to off-site hospital laboratories or the public health laboratory, given that these could potentially be associated with a delayed turnaround time. We adjusted for *C. difficile* testing method given that use of sensitive PCR methods have been associated with higher detection rates of *C. difficile*.[19] With respect to *C. difficile* treatment, we categorised hospitals based on reported use of vancomycin versus metronidazole as first-line treatment; even though vancomycin is not necessarily recommended as first-line treatment in all current guidelines, it has the potential to lead to higher and faster diarrhoea resolution rates[20] and potentially decreased *C. difficile* shedding and transmission. Lastly, as a measure of leadership and culture, we categorised hospitals as to whether their infection control programme reported *C. difficile* rates to the chief executive officer or hospital board versus lower levels of the administration hierarchy.

Statistical analysis

In descriptive analyses, we calculated the prevalence of each of the six prevention processes across Ontario hospitals overall, and stratified by hospital type. The outcome was the diagnosis of *C. difficile* infection measured at the patient level. We used multivariable binary GEE regression models to assess the impact of hospital survey factors on the patient-level risk of *C. difficile* infection, accounting for baseline *C. difficile* rates, structural hospital characteristics and patient characteristics. All predictor variables were included in this model because we aimed to examine the impact of hospital prevention methods after accounting for all of these other prespecified patient-level and hospital-level characteristics; variable reduction was not required given the large number of outcome events. We incorporated GEE to account for clustering of patients within hospitals.[21] Analyses were performed using SAS statistical software V.9.3 (SAS, Cary, North Carolina, USA) and STATA. Confidentiality was maintained via encrypted health card numbers and strict safeguarding protocols at ICES.

RESULTS

Baseline patient characteristics

During the study year, 653 896 unique patients >1 years old were admitted to acute care hospital beds in Ontario. The most common categories of admission were medical (268 852, 41%), surgical (218 646, 33%) and obstetrical (133 983, 21%), and most admissions were designated as non-elective (399 958, 61%). More than one-third (248 889, 38%) of patients were elderly, ≥65 years old, and nearly two-thirds (404 980, 62%) were women.

The most common comorbid medical diagnoses were diabetes mellitus (14%), cancer (8.6%), chronic obstructive pulmonary disease (6.0%) and congestive heart failure (4.8%). Even though the population was restricted to the first hospital admission per patient in the study year, recent healthcare exposure was common in the 8 weeks prior to admission, with as many as 195 782 (30%) having been seen in the emergency room and 80 287 (12%) having received home care.

Baseline hospital characteristics

The 653 896 unique patient admissions amounted to a total of 3 798 409 patient days in hospital, which were distributed across 124 hospital corporations. All hospital corporations (124/124, 100%) responded to the mandatory survey, thereby providing information for 159 distinct hospital sites. These 159 facilities included 17 academic/teaching hospitals, 22 large community hospitals, 23 medium community hospitals and 97 small community hospitals.

There was substantial heterogeneity in the implementation of the six specific *C. difficile* prevention processes (table 1), with 17 (11%) of the hospitals reporting implementation of none of these procedures, 37 (23%) reporting one, 46 (29%) reporting two, 37 (23%) reporting three, 17 (11%) reporting four, 4 (3%) reporting five and only 1 (0.6%) reporting all six. Full responses to other survey items are listed in online supplementary table S1.

Risk of *C. difficile* infection during acute care hospitalisation in Ontario

Overall, 2341 of 653 896 admissions were associated with *C. difficile* infections for a rate of 3.6 per 1000 admissions or 6.2 per 10 000 patient days. Severe outcomes were more common among patient admissions with *C. difficile* infection as compared with admissions without *C. difficile*, including intensive care unit admissions (23.8% vs 6.5%, p<0.001), colectomy (4.4% vs 1.6%, p<0.001) and death within 30 days (23.9% vs 4.8%, p<0.001).

Patient risk factors for *C. difficile* infection

As compared with patients without *C. difficile* infection, those with this infection were more likely to be older, admitted non-electively and to medical services (table 2). Those with *C. difficile* also had significantly higher rates of comorbidities, greater exposure to healthcare settings in the previous 8 weeks and more frequent confirmed diagnoses of bacterial infection in the preceding 8 weeks or as the most responsible diagnosis for the current admission (table 2). Multivariable logistic regression analysis confirmed that age, comorbidities and medical non-elective admissions were strongly predictive of increased risk of *C. difficile* infection (table 3). These findings were consistent in a sensitivity analysis limited to *C. difficile* cases labelled as postadmission diagnoses (data not shown).

Hospital risk factors for *C. difficile* infection

The prevalence of hospital structural characteristics and prevention processes among patients with and without *C. difficile* infection are displayed in table 2. Multivariable adjustment accounting for patient and hospital factors confirmed an increased risk of *C. difficile* in hospital types other than small community hospitals (table 3). Use of PCR methods was associated with significantly higher risk of *C. difficile* (adjusted OR 1.40, 95% CI 1.03 to 1.91, p=0.03) (table 3). However, none of the six prespecified selected hospital prevention processes were associated with a significantly lower risk of *C. difficile* (table 3). These findings were consistent in a sensitivity analysis limited to *C. difficile* cases labelled as postadmission (type 2) diagnoses (data not shown).

DISCUSSION

Our analysis of more than 650 000 patients admitted to Ontario's 159 acute care hospitals has documented wide variability in reported implementation of the selected understudied *C. difficile* infection-prevention processes, and found that none of these hospital processes were strongly associated with a patient's risk of acquiring *C. difficile*. Our findings confirm that patient-level risk factors are crucial drivers of *C. difficile* infection. *C. difficile* risk is most strongly associated with older age, non-elective and medical admissions and specific medical comorbidities, including inflammatory bowel disease, peptic ulcer disease, liver disease, immunocompromise, peripheral vascular disease, congestive heart failure, hemiparesis/paraplegia and dementia.

Our study is strengthened by a population-based assessment of *C. difficile* risk in a large jurisdiction. It is the largest study of patient-level and hospital-level risk factors, with rare access to both complete patient-level data for 650 000 patients and complete hospital-level survey data for 159 hospitals. Nevertheless, an observational study using retrospective administrative data may be subject to some important limitations. The presence of *C. difficile* may have been misclassified in some cases, but the literature suggests very high specificity of the ICD diagnostic code for *C.*

Table 1 *Clostridium difficile* prevention processes across Ontario acute care hospitals

General domain	Specific item	All hospitals N=159	Academic/ teaching N=17	Large community N=22	Medium community N=23	Small community N=97
Infection control	Isolation at onset of diarrhoea	43 (27%)	10 (59%)	6 (27%)	3 (13%)	24 (25%)
Antibiotic stewardship	Audit of antibiotic use	26 (16%)	6 (35%)	6 (27%)	4 (17%)	10 (10%)
Environmental cleaning	Audit of cleaning practices	115 (72%)	15 (88%)	20 (91%)	18 (78%)	62 (64%)
Diagnosis	On-site diagnostic testing	74 (47%)	11 (65%)	15 (68%)	13 (57%)	35 (36%)
Treatment	Vancomycin as first-line treatment	24 (15%)	4 (24%)	0 (0%)	2 (9%)	18 (19%)
Leadership	Reporting to senior leadership	52 (33%)	6 (35%)	6 (27%)	5 (22%)	35 (36%)

difficile,[13 14] and we have also demonstrated high correlation of ICD-based *C. difficile* rates with those measured by Ontario hospital infection-surveillance programmes.[3] The survey results were self-reported by hospital infection control programmes, and so, there could have been misclassification of exposure variables related to variable stringency of interpretation regarding the implementation of prevention processes across the different hospitals. Although we selected processes that we felt were easier to gauge in comparison to other processes, even these items were open to some subjectivity in interpretation. The dates of implementation of hospital processes were not collected in the MOHLTC survey, and so, it is possible that high *C. difficile* rates may have driven process implementation, thereby obscuring any benefit of these processes. We sought to account for this by adjusting for 2007 hospital *C. difficile* rates (the year prior to mandatory public reporting), but this approach may be imperfect. Antibiotics are the most important risk factor for *C. difficile*, and inpatient drug use is not available in the Ontario administrative databases; therefore, our results may have been subject to indication bias. However, we designed our model to be based on risk factors present and definable on hospital admission, and so, a diagnosis of bacterial infection served as an appropriate surrogate.[22] Lastly, strain type was not available for a study of this size; so, we cannot determine whether there were hospital variations in the prevalence of more virulent *C. difficile* strains, such as the epidemic NAP1/ribotype 027 strain.

The patient risk factors identified in our population-based study are consistent with those in previous single-centre studies.[23–27] Increased age is among the most well established predictors of *C. difficile* risk, and could relate to increased frailty, immune senescence and high rates of hospital contact and antibiotic exposure, but may also be driven by an age-related reduction in the protective diversity of the gut microbiome.[28] Multiple aggregate scores of comorbidity have been associated with *C. difficile* risk,[24 25 27] and we have more specifically delineated the types of individual comorbidities most strongly linked with *C. difficile*. The most important comorbidities appear to be those associated with bowel inflammation (inflammatory bowel disease), need for gastric acid suppression (peptic ulcer disease), decreased intestinal blood supply (congestive heart failure, peripheral vascular disease), immunocompromise or greater likelihood of being confined to bed (hemiparesis/paraplegia, dementia). Our model is limited to patient-level characteristics definable on admission to hospital, and therefore has the potential to identify high-risk patients for targeted surveillance and prevention efforts. Our model is derived from population-wide data sources, and so has the potential to improve patient-level risk adjustment to improve inter-hospital comparisons and performance measurement.

Although *C. difficile* prevention guidelines have been widely published and endorsed by professional societies,[29] very few previous studies have explicitly examined the impact of hospital-level factors on *C. difficile* risk for patients.[30 31] A population-based study in Quebec examined hospital factors associated with increased *C. difficile* incidence during pre-epidemic and epidemic periods in that province. This study was large, but the investigators did not have information on hospital-specific *C. difficile* prevention processes; so, they were only able to examine structural hospital characteristics such as geographical location, size and academic category.[30] A retrospective study in the Netherlands detected an association of hospital-level class-specific antibiotic use, isolation discontinuation policy, disinfection solution and frequency and a few other infection prevention policies with aggregate hospital-level *C. difficile* rates.[31] However, their study was conducted during a time-limited outbreak, included only 23 voluntarily participating hospitals from a total of 98 in the country and could not account for patient-level risk factors.[31]

We studied putative prevention factors across six domains of hospital *C. difficile* prevention, but none were associated with a significant reduction in patient risk of *C. difficile* infection. A meaningful impact of these prevention processes could have been missed in our study if, for example, higher rates of infection have also prompted some hospitals to be more likely to implement these processes. It is also possible that these self-reported *C. difficile* infection prevention

Table 2 Baseline characteristics among patient admissions with versus without *Clostridium difficile* infection

	No *C. difficile* (n=651 555) N (%)	*C. difficile* (n=2341) N (%)
Patient characteristic		
Age group (years)		
1–10	26 063 (4.0%)	28 (1.2%)
11–17	18 523 (2.8%)	23 (1.0%)
18–44	210 095 (32.2%)	189 (8.1%)
45–64	149 632 (23.0%)	454 (19.4%)
65–74	90 108 (13.8%)	389 (16.6%)
75–84	96 533 (14.8%)	674 (28.8%)
≥85	60 601 (9.3%)	584 (24.9%)
Female sex	403 609 (61.9%)	1371 (58.6%)
Admission type		
Medical	266 943 (41.0%)	1909 (81.5%)
Surgical	218 267 (33.5%)	379 (16.2%)
Obstetrical or other	166 345 (25.5%)	53 (2.3%)
Elective admission	253 736 (38.9%)	202 (8.6%)
Infection as most responsible diagnosis	48 847 (7.5%)	262 (11.2%)
Previous diagnoses		
Myocardial infarction	27 173 (4.2%)	155 (6.6%)
Congestive heart failure	30 741 (4.7%)	346 (14.8%)
Peripheral vascular disease	9782 (1.5%)	102 (4.4%)
Cerebrovascular disease	20 431 (3.1%)	144 (6.2%)
Dementia	20 015 (3.1%)	241 (10.3%)
Chronic obstructive pulmonary disease	38 879 (6.0%)	286 (12.2%)
Rheumatological disease	3951 (0.6%)	35 (1.5%)
Peptic ulcer disease	4450 (0.7%)	57 (2.4%)
Diabetes mellitus	91 592 (14.1%)	572 (24.4%)
Hemiparesis/paraplegia	55 749 (8.6%)	294 (12.6%)
Renal disease	7290 (1.1%)	88 (3.8%)
Malignancy	3955 (0.6%)	48 (2.1%)
Liver disease	15 616 (2.4%)	200 (8.5%)
Inflammatory bowel disease	4913 (0.8%)	43 (1.8%)
HIV or other immunocompromise	4934 (0.8%)	66 (2.8%)
Healthcare exposure in preceding 8 weeks		
Hospital admission*	9571 (1.5%)	139 (5.9%)
Emergency department visit	194 621 (29.9%)	1161 (49.6%)
Past gastrointestinal procedure	17 499 (2.7%)	104 (4.4%)
Same-day surgery procedure	36 206 (5.6%)	152 (6.5%)
Nursing home stay	1851 (0.3%)	27 (1.2%)
Haemodialysis	4192 (0.6%)	53 (2.3%)
Chemotherapy	11 060 (1.7%)	73 (3.1%)
Homecare treatment	79 564 (12.2%)	723 (30.9%)
Recent diagnosis of infection	196 828 (30.2%)	1190 (50.8%)
Calendar month of admission		
January	49 975 (7.7%)	164 (7.0%)
February	47 838 (7.3%)	169 (7.2%)
March	50 275 (7.7%)	156 (6.7%)
April	66 767 (10.2%)	353 (15.1%)
May	63 047 (9.7%)	256 (10.9%)
June	59 250 (9.1%)	231 (9.9%)
July	54 464 (8.4%)	198 (8.5%)
August	52 474 (8.1%)	204 (8.7%)
September	52 995 (8.1%)	138 (5.9%)
October	52 780 (8.1%)	164 (7.0%)
November	51 594 (7.9%)	157 (6.7%)
December	50 096 (7.7%)	151 (6.5%)
Hospital characteristic		
Hospital type		
Academic/teaching	207 942 (31.9%)	746 (31.9%)
Large community	248 377 (38.1%)	869 (37.1%)
Medium community	118 463 (18.2%)	497 (21.2%)
Small community	76 773 (11.8%)	229 (9.8%)
Proportion of beds in single-bed rooms		
<25%	193 195 (29.7%)	638 (27.3%)
25%–35%	81 843 (12.6%)	324 (13.8%)
>35%	245 677 (37.7%)	890 (38.0%)
Not available	130 840 (20.1%)	489 (20.9%)
Hospital processes of care		
Immediate isolation for patients with diarrhoea	222 265 (34.1%)	735 (31.4%)
Audit of compliance for antibiotic stewardship	195 921 (30.1%)	748 (32.0%)
Audit of compliance of environmental cleaning	562 104 (86.3%)	2102 (89.8%)
Reporting to CEO or hospital board	217 603 (33.4%)	739 (31.6%)
On-site *C. difficile* diagnostic testing	428 694 (65.8%)	1482 (63.3%)
Use of vancomycin as first-line treatment	73 284 (11.2%)	288 (12.3%)

*The study involved only the first hospital admission per patient in the study year, but patients enrolled in the first 8 weeks of the study period could have been hospitalised at the end of the preceding year.
CEO, chief executive officer.

practices do not adequately reflect actual *C. difficile* practices, or that there may have been variability across institutions in what survey respondents considered to be adequate implementation of a particular process. For example, a meta-analysis suggests that antimicrobial stewardship can reduce *C. difficile* incidence by 50%[32]; the lack of association between antibiotic stewardship and reduced *C. difficile* infections in this study may reflect low rates of stewardship auditing (reported by only 16% of hospitals) and that many of these auditing efforts or stewardship programmes themselves were likely still early in their evolution or implementation at the time of this study.[33]

Our findings, though, do raise the possibility that some current best practices may be suboptimal approaches to preventing this challenging infection. Most prevention practices focus on detecting and isolating symptomatic patients with *C. difficile* diarrhoea and

Table 3 Multivariable binary generalised estimating equations (GEE) regression modelling the impact of patient and hospital-level predictors on the patient-level risk of *Clostridium difficile* infection

	Adjusted OR	95% CI	p Value
Patient characteristic			
Age group (years)			
1–10	0.15	0.07 to 0.31	<0.001
11–17	0.19	0.10 to 0.39	<0.001
18–44	0.52	0.44 to 0.62	<0.001
45–64	0.61	0.54 to 0.69	<0.001
65–74	0.77	0.68 to 0.87	<0.001
75–84	1.00	1.00	1.00
≥85	1.12	1.00 to 1.26	0.05
Female sex	1.28	1.18 to 1.40	<0.001
Admission type			
Medical	2.30	2.01 to 2.64	<0.001
Obstetrical	0.04	0.015 to 0.091	<0.001
Surgical	1.00	1.00	1.00
Other	2.52	1.29 to 4.92	0.007
Elective admission	0.55	0.46 to 0.65	<0.001
Infection as most responsible diagnosis	0.90	0.78 to 1.02	0.10
Previous diagnoses			
Myocardial infarction	0.85	0.72 to 1.01	0.06
Congestive heart failure	1.41	1.24 to 1.59	<0.001
Peripheral vascular disease	2.11	1.72 to 2.58	<0.001
Cerebrovascular disease	0.93	0.77 to 1.12	0.42
Dementia	1.39	1.20 to 1.60	<0.001
Chronic obstructive pulmonary disease	1.17	1.03 to 1.33	0.014
Rheumatological disease	1.55	1.10 to 2.18	0.012
Peptic ulcer disease	2.05	1.57 to 2.68	<0.001
Diabetes mellitus	1.03	0.93 to 1.14	0.57
Hemiparesis/paraplegia	2.04	1.49 to 2.79	<0.001
Renal disease	1.44	1.23 to 1.69	<0.001
Malignancy	1.18	1.03 to 1.35	0.020
Liver disease	2.05	1.64 to 2.56	<0.001
HIV	1.56	0.50 to 4.91	0.45
Inflammatory bowel disease	2.43	1.78 to 3.32	<0.001
Other immunocompromise	2.19	1.67 to 2.88	<0.001
Healthcare exposure in preceding 8 weeks			
Hospital admission	1.64	1.31 to 2.05	<0.001
Emergency department visit	0.80	0.53 to 1.21	0.29
Past gastrointestinal procedure	1.15	0.91 to 1.46	0.24
Same-day surgery procedure	1.07	0.88 to 1.30	0.49
Nursing home stay	1.08	0.73 to 1.60	0.71
Haemodialysis	1.29	0.96 to 1.75	0.09
Chemotherapy	0.89	0.68 to 1.15	0.37
Homecare treatment	1.37	1.25 to 1.52	<0.001
Recent diagnosis of infection	1.56	1.02 to 2.38	0.038
Calendar month of admission			
January	0.93	0.75 to 1.14	0.49
February	1.03	0.84 to 1.26	0.80
March	0.90	0.73 to 1.11	0.31
April	1.08	0.90 to 1.29	0.42
May	0.96	0.79 to 1.15	0.64
June	1.03	0.85 to 1.24	0.78
July	1.00	1.00	1.00
August	1.06	0.87 to 1.29	0.59
September	0.75	0.60 to 0.93	0.01
October	0.90	0.73 to 1.11	0.32
November	0.87	0.70 to 1.07	0.18
December	0.85	0.69 to 1.06	0.15
Hospital characteristic			
Hospital type			
Academic/teaching	2.13	1.55 to 2.93	<0.001
Large community	1.83	1.38 to 2.42	<0.001
Medium community	1.77	1.38 to 2.36	<0.001
Small community	1.00	1.00	1.00
Proportion of beds in single-bed rooms			
<25%	1.00	1.00	1.00
25%–35%	1.16	0.86 to 1.55	0.34
>35%	1.16	0.92 to 1.47	0.21
Not available	1.13	0.82 to 1.55	0.45
Baseline *C. difficile* rates in fiscal year 2007	1.02	1.01 to 1.03	0.010
Testing method for *C. difficile*			
Standard culture followed by cytotoxin assay	0.90	0.66 to 1.22	0.49
PCR	1.40	1.03 to 1.91	0.03
Toxin A/B testing by commercial enzyme assay	0.92	0.66 to 1.30	0.65
Other	1.00	1.00	1.00
Hospital processes of care			
Immediate isolation for patients with diarrhoea	0.93	0.66 to 1.22	0.56
Audit of compliance for antibiotic stewardship	1.17	0.92 to 1.50	0.20
Audit of compliance of environmental cleaning	1.29	0.99 to 1.67	0.06
Reporting to CEO or hospital board	0.97	0.77 to 1.21	0.78
On-site *C. difficile* diagnostic testing	0.87	0.68 to 1.10	0.24
Use of vancomycin as first-line treatment	1.19	0.87 to 1.63	0.28

CEO, chief executive officer.

cleaning and decontaminating their micro-environment to prevent transmission to other hospitalised patients. Yet, emerging research, including whole genome sequencing studies, now suggests that symptomatic patients may

be responsible for only a minority of new *C. difficile* transmissions.[34 35] Asymptomatic colonised patients are not targeted by current prevention strategies and may represent another major reservoir of *C. difficile* infection.[36 37] Still, other transmission events may be occurring in the community through mechanisms that are not yet well understood.[38] Our data also suggest that patient-level risk factors may be more important than hospital-level processes in driving patient-level risk of infection. If current prevention efforts have limited yield in preventing *C. difficile*, this would call into question the fairness of hospital rankings, which use *C. difficile* rates as a quality indicator, and on funding withdrawal for admissions complicated by this infection.

CONCLUSIONS

In summary, our population-wide study has confirmed the importance of patient-level risk factors, such as age, comorbidity and admission type, in predicting a patient's risk of *C. difficile* infection. However, a range of selected understudied hospital-level prevention strategies appears to have either limited effectiveness or were ineffectively implemented at the time of this study. Given the limitations of an observational study design and the fact that we could not study well-established prevention measures that were already instituted in all hospitals, we would not recommend withdrawing these processes or diverting resources away from *C. difficile* infection prevention programmes. However, our findings do suggest the need to improve implementation of *C. difficile* prevention practices, assess the system-wide benefits of putative prevention processes and to uncover other innovative means of *C. difficile* prevention.

Author affiliations
[1]Institute for Clinical Evaluative Sciences, Toronto, Ontario, Canada
[2]Division of Infectious Diseases, Department of Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada
[3]Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada
[4]Division of Paediatric Medicine, Hospital for Sick Children, Toronto, Ontario, Canada
[5]Department of Paediatrics, University of Toronto, Toronto, Ontario, Canada
[6]Health Analytics Branch, Ontario Ministry of Health and Long-Term Care, Toronto, Ontario, Canada

Twitter Follow Debbie Gibson at @debbieandrockie

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Supplemental Table 1: Full Survey Responses Across 159 Acute Care Hospitals	
Survey Domains and Individual Items	**Survey Responses n/N (%)**
Infection Control Policies to Decrease Transmission	
Time point at which contact precautions are generally initiated	
Onset of diarrhea (not qualified)	43 (27.0%)
Onset of diarrhea not due to another underlying cause (eg, laxative)	89 (56.0%)
After 3 episodes of diarrhea	9 (5.7%)
After receipt of positive laboratory result	<6 (0.6%)
After advice of IPAC professional	11 (6.9%)
Other	6 (3.8%)
Individuals with authority to initiate contact precautions/isolation	
Front-line staff	158 (99.4%)
IPAC staff	151 (95.0%)
Unit manager	142 (89.3%)
Physician	151 (95.0%)
Other	12 (7.5%)
Isolation procedures for patients with suspected CDI	
Always placed in a single room	60 (37.7%)
Placed in a single room or cohorted if single room not available	88 (55.3%)
Remains in current room until case is confirmed	<6 (2.5%)
Other	7 (4.4%)
Policy in place to monitor/audit compliance with contact precautions	64 (40.3%)
Compliance results reported back to hospital staff	54 (30.4%)
Antimicrobial Stewardship	
Implemented antimicrobial stewardship for high risk antibiotics	48 (30.2%)
Hospital has antibiotic management committee or stewardship team	37 (23.3%)
IPAC team has internal support from a pharmacist	125 (78.6%)
System in place for auditing compliance with antibiotic stewardship	26 (16.4%)
Antibiotic compliance results reported back to staff	15 (9.4%)
Environmental cleaning	
Hospital disinfectant used for environmental cleaning on daily basis	
Quaternary ammonium	88 (55.3%)
Accelerated hydrogen peroxide	105 (66.0%)
Bleach	15 (9.4%)
Other	17 (10.7%)
Don’t know	<6 (2.5%)
Hospital disinfectant used for CDI room or during CDI outbreak	
Quaternary ammonium	33 (20.8%)
Accelerated hydrogen peroxide	119 (74.8%)

Bleach	37 (23.3%)
Other	41 (25.8%)
Don’t know	<6 (1.9%)
Frequency of CDI room cleaning	
Once daily	6 (3.8%)
Twice daily	146 (91.8%)
As needed, or other	7 (4.4%)
How often is CDI equipment cleaned	
Once daily	29 (18.2%)
Twice daily	80 (50.3%)
As needed	34 (21.4%)
Other	16 (10.1%)
Housekeeping staff receive training on disinfection procedures	158 (99.4%)
Auditing system to monitoring compliance to these procedures	115 (72.3%)
Cleaning compliance results reported back to staff	112 (70.4%)
Memory aids to health care providers regarding hand hygiene	159 (100%)
Memory aids for family members regarding hand hygiene	155 (97.5%)
Hand hygiene compliance rates reported back to staff	154 (96.9%)
Diagnostic testing	
Laboratory location for CDI testing	
Onsite hospital laboratory	74 (46.5%)
Offsite hospital laboratory	68 (42.8%)
Public health laboratory	66 (41.5%)
Testing Method for CDI	
Standard culture followed by cytotoxin neutralization assay	19 (11.9%)
Polymerase chain reaction	26 (16.4%)
Toxin A/B testing by commercial enzyme immunoassay kits	125 (78.6%)
Other	8 (5.0%)
Average Turn Around Time	
Within 24 hours	85 (53.5%)
Between 24-48 hours	58 (36.5%)
Greater than 48 hours	15 (9.4%)
Treatment	
Algorithms or care pathways for treatment of patients with CDI	108 (67.9%)
Vancomycin is first line treatment for patients with CDI	24 (15.1%)
Leadership and Culture	
Highest level of administration to which IPAC reports	
Senior administration (CEO or board)	52 (32.7%)
Senior management (eg, Director of nursing or inpateint services)	86 (54.1%)
Quality manager/committee/program	7 (4.4%)
Other	14 (8.8%)
Frequency of IPAC committee meetings	

Monthly or 12 times/year	29 (18.2%)
Less than monthly (5-11 times/year)	68 (42.8%)
Quarterly (every 3 months, 4 times/year)	57 (35.8%)
Bi-annually, as needed or rarely	<6 (3.2%)
Amount of paid educational time for IPAC staff	
None	6 (3.8%)
<1 work day / year	10 (6.3%)
1-5 work days / year	86 (5.4%)
>5 work days / year	44 (27.7%)
Unknown	13 (8.2%)
Infection control materials located in area accessible to all staff	153 (96.2%)
Frequency of Reviewing CDI data to review trends/identify clusters	
Rarely	12 (7.5%)
Regularly – every few months	9 (5.7%)
Regularly – every week or month	29 (18.2%)
Each time a case is identified	109 (68.6%)

IPAC – Infection prevention and control; CEO – Chief executive officer; CDI – *Clostridium difficile* infection