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

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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 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 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, 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, home-care treatments, long-term care residence, physician billing claims 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 2.5

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; comorbidty 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.\(^1\)\(^5\) 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.\(^1\)\(^6\) 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.\(^3\)\(^7\) 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 V9.3 (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, 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. diffi-
and we have also demonstrated high correlation of ICD-based C. difficile rates with those measured by Ontario hospital infection-surveillance programmes. 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 MOHLC 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. 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. 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. Multiple aggregate scores of comorbidity have been associated with C. difficile risk, 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, very few previous studies have explicitly examined the impact of hospital-level factors on C. difficile risk for patients. 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. A retrospective study in the Netherlands detected an association of hospital-level class-specific antibiotic use, isolation dis-continuation policy, disinfection solution and frequency and a few other infection prevention policies with aggregate hospital-level C. difficile rates. 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.

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
Original research

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

| Patient characteristic       | No C. difficile (n=651 555) N (%) | C. difficile (n=2341) N (%) |
|------------------------------|-----------------------------------|----------------------------|
| 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%)                |

Table 2  Continued

| Hospital characteristic       | No C. difficile (n=651 555) N (%) | C. difficile (n=2341) N (%) |
|------------------------------|-----------------------------------|----------------------------|
| Admission type               |                                   |                            |
| Female sex                   | 403 609 (61.9%)                   | 1371 (58.6%)               |
| 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%)                |

*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.

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 diarrhea and 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%; 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
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

### 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

| Patient characteristic      | Adjusted OR | 95% CI       | p Value |
|-----------------------------|-------------|--------------|---------|
| 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  |

### Table 3 Continued

| Calendar month of admission | Adjusted OR | 95% CI       | p Value |
|-----------------------------|-------------|--------------|---------|
| 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 | Adjusted OR | 95% CI       | p Value |
|---------------|-------------|--------------|---------|
| 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    |

### Other hospital processes of care

| Procedure                                          | Adjusted OR | 95% CI       | p Value |
|----------------------------------------------------|-------------|--------------|---------|
| 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.
be responsible for only a minority of new C. difficile transmissions. Asymptomatic colonised patients are not targeted by current prevention strategies and may represent another major reservoir of C. difficile infection. Still, other transmission events may be occurring in the community through mechanisms that are not yet well understood. 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 institutionalised 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.

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