Patterns of antibiotic use and risk of hospital admission because of *Clostridium difficile* infection

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ABSTRACT

Background: Previous observations have indicated that infection with *Clostridium difficile* occurs almost exclusively after exposure to antibiotics, but more recent observations have suggested that prior antibiotic exposure may be less frequent among cases of community-acquired disease.

Methods: We used 2 linked health databases to perform a matched, nested case–control study of elderly patients admitted to hospital with community-acquired *C. difficile* infection. For each of 836 cases among people 65 years of age or older, we selected 10 controls. We determined the proportion of cases that occurred without prior antibiotic exposure and estimated the risk related to exposure to different antibiotics and the duration of increased risk.

Results: Of the 836 cases, 442 (52.9%) had no exposure to antibiotics in the 45-day period before the index date, and 382 (45.7%) had no exposure in the 90-day period before the index date. Antibiotic exposure was associated with a rate ratio (RR) of 10.6 (95% confidence interval [CI] 8.9–12.8). Clindamycin (RR 31.8, 95% CI 17.6–57.6), cephalosporins (RR 14.9, 95% CI 10.9–20.3) and gatifloxacin (RR 16.7, 95% CI 8.3–33.6) were associated with the highest risk. The RR for *C. difficile* infection associated with antibiotic exposure declined from 15.4 (95% CI 12.2–19.3) by about 20 days after exposure to 3.2 (95% CI 2.0–5.0) after 45 days. Use of a proton pump inhibitor was associated with increased risk (RR 1.6, 95% CI 1.3–2.0), as were concurrent diagnoses of inflammatory bowel disease (RR 4.1, 95% CI 2.6–6.6), irritable bowel syndrome (RR 3.4, 95% CI 2.3–5.0) and renal failure (RR 1.7, 95% CI 1.2–2.2).

Interpretation: Community-acquired *C. difficile* infection occurred in a substantial proportion of individuals with no recent exposure to antibiotics. Among patients who had been exposed to antibiotics, the risk declined markedly by 45 days after discontinuation of use.

Early observations that infection with *Clostridium difficile* occurred almost exclusively after antibiotic exposure[1] gave rise to the concept that antibiotic-induced alteration of the intestinal flora was a prerequisite for its occurrence.[2] Consequently, reports that a significant proportion of patients are infected with *C. difficile* in the community without antecedent antibiotic use[3–5] have been controversial; these reports, if confirmed, could change our understanding of *C. difficile* as a human pathogen.[6]

Bartlett[7] has suggested that the role of the hospital was not clearly recognized in early epidemiologic studies of *C. difficile*. The hospital environment has many characteristics that likely contribute in important ways to the occurrence and transmission of infectious disease, in particular, clustering of susceptible hosts, environmental contamination, physical proximity of patients and multiple person-to-person contacts. In addition, antibiotic use is common in hospitals,[8] and *C. difficile* is considered by many as a primarily nosocomial disease. This perspective may have contributed to observations that *C. difficile* infection was almost always preceded by antibiotic exposure. Given the potential for an association between hospital admission and antibiotic exposure, studying *C. difficile* in the community, where the prevalence of antibiotic use is much less common, may be a way to decrease the confounding of these closely correlated exposures. Other biases have probably contributed to the almost 100% prevalence of antibiotic exposure in many reports of *C. difficile*, including ascertainment bias, given that diarrhea is a common side effect of antibiotics;[9] detection bias, because of guidelines recommending that *C. difficile* testing be limited to patients who have had a recent hospital stay or a history of antibiotic exposure;[10] and information bias, in that, among toxin-positive patients with diarrhea, the diarrhea is more likely to be attributed to *C. difficile* when there has been recent antibiotic exposure but more likely to be attributed to other causes in the absence of such a history.[11] Some studies have included prior antibiotic exposure as part of the case definition,[12–15] which would also ensure 100% antibiotic exposure in the cases.

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The primary objective of our study was to examine patterns of antibiotic exposure among people with *C. difficile* infection in the community. We wished to determine whether our previous findings from the United Kingdom[4,5] would be reproduced in a different population of high-risk patients, in a different country, with a clinically relevant case definition, that is, hospital admission because of *C. difficile* infection. A secondary objective of the study was to determine the period of risk after antibiotic administration.

Methods

Study design and data sources

We performed a matched, nested case–control study among the cohort of all elderly people in the province of Quebec who had been admitted to hospital at least once between 1996 and 2004. We obtained the data for the study from 2 administrative databases: the database of the Régie de l'assurance maladie du Québec and the provincial hospital discharge summary (MED-ECHO) database.

In Quebec, everyone who is 65 years of age or older is eligible for coverage under the provincial health care fund, which is administered by the Régie de l'assurance maladie du Québec. The fund covers the costs of prescription drugs, as well as payments for inpatient and outpatient physician services and other medical services offered in private clinics or hospitals. Data in the records include information on the patient's age and sex, diagnoses, and all filled drug prescriptions and medical procedures for which physician reimbursement occurred. The data for prescription drugs include the drug name, dispensing date, dose, dosage form, treatment duration and quantity of drug dispensed. Drugs dispensed to patients during stays in hospitals or nursing homes are not included in the database. Likewise, medications dispensed in the hospital for patients in outpatient clinics, such as chemotherapy or drugs administered during dialysis, are not included. The hospital discharge summary database (MED-ECHO) provides information about patients who have been admitted to hospital, including discharge diagnosis, comorbid conditions, inpatient procedures, and dates of admission and discharge. Complete coverage for hospital stays is provided for all permanent residents of Quebec, and all dates are captured in the MED-ECHO database. We used unique patient identifiers to link the Régie de l'assurance-maladie du Québec and MED-ECHO databases. These databases have been linked in previous studies,[16] and they have been shown to be valid for pharmacoepidemiologic research.[17]

This research was approved by the research ethics board of the Montreal Chest Institute. Ethics approval for linking the databases and using the linked data for research purposes was obtained from the Commission d'accès à l'information du Québec.

Selection of cases and controls

We restricted the study population to patients 65 years of age and older so that we would have complete outpatient prescription records for all cohort members. We included only patients who had had at least 1 hospital stay during the study period (i.e., additional to the hospital stay used to identify patients for inclusion in the study). We defined the follow-up period as starting at the date of discharge from the initial hospital stay.

We identified the cases on the basis of the first hospital admission during follow-up for which *C. difficile* infection (International Classification of Diseases, 9th revision, code 008.45) was listed as the primary diagnosis. The date of admission to hospital for this stay was defined as the index date. If a patient had more than one admission for which *C. difficile* infection was listed as the primary diagnosis, we included only the first of these admissions. We excluded patients in whom *C. difficile* had been documented as a secondary diagnosis during a previous hospital stay, because we wished to study only incident *C. difficile* infection and wanted to exclude instances of relapse or recurrence. In addition, because we wished to study community-acquired *C. difficile*, we limited our study to patients who had not been admitted to any type of institution in the 90-day period before the index date (i.e., date since hospital discharge for the first stay was more than 90 days before the index date). We also excluded patients who had received a prescription for metronidazole or oral vancomycin therapy in the 90-day period before the index date, as they might have represented cases of *C. difficile* infection in which the date of onset of infection occurred before the date of hospital admission.

For each case, we randomly selected 10 controls from the study population. Controls were matched to cases in terms of index date and date of first hospital admission in the MED-ECHO database to ensure similar duration of follow-up. In addition, as for the cases, we included as controls only people who had not been admitted to hospital and who had not received a prescription for metronidazole or oral vancomycin therapy in the 90 days before the index date. For cases with admission to hospital in the period between 2 years and 90 days before the index date, we matched controls on date of the last hospital admission within 15 days and as much as possible on the number of hospital admissions during the 2-year period before the index date. Both cases and controls had to have a minimum of 1 year prior follow-up recorded in the database.

Assessment of exposure to antibiotics

Using the Régie de l'assurance maladie du Québec database, we identified all prescriptions for antibiotics and gastric acid suppressant agents, including proton pump inhibitors and histamine$_2$-receptor antagonists, as well as prescriptions for other antacids written during the 2-year period before the index date. We classified patients as having current exposure to a drug if they had received a prescription for the drug in the 45-day period before the index date and were otherwise not exposed. We defined the risk of antibiotic exposure for each agent separately and for antibiotics as a group. We evaluated the following classes of antibiotics: cephalosporins, macrolides, penicillins and tetracyclines. We examined clindamycin and trimethoprim–sulfamethoxazole individually, and did the same for each of the following commonly used quinolone agents: levofloxacin, gatifloxacin, moxifloxacin and ciprofloxacin. We classified all other antibiotics as "other." Because we excluded patients with exposure to metronidazole and oral vancomycin therapy in the 90 days before the index date, we were unable to evaluate metronidazole as a possible risk factor.

Definition of covariates

We used both databases to identify any comorbid gastrointestinal illnesses diagnosed in the 2 years before the index date, including inflammatory bowel disease, irritable bowel syndrome, peptic ulcer disease, gastroesophageal reflux disease, diverticular disease and gastrointestinal malignant disease. Other comorbid illnesses identified were chronic obstructive pulmonary disease, coronary artery disease, congestive heart failure, renal failure, diabetes mellitus, cerebrovascular accident and cancer (including solid tumours and hematologic malignant disease). We also determined the number of hospital admissions in the period from 90 days to 2 years before the index date.

Statistical analysis

We determined the number of cases fulfilling our inclusion criteria as a function of calendar time and time from the last hospital admission. We based all analyses on conditional logistic regression to estimate the odds ratio as an approximation of the rate ratio for the risk factors under study. We estimated the adjusted rate ratios of community-acquired *C. difficile* infection for current use of antibiotics, proton pump inhibitors and histamine$_2$-receptor antagonists, after adjustment for sex, comorbidity and hospital stays. Antibiotics were analyzed as a group and separately by drugs and classes. We also used time strata to evaluate the adjusted risk of *C. difficile*-associated diarrhea as a function of time from the last antibiotic prescription received. We considered *p* values less than 0.005 to be significant.

Results

For the 8-year study period, we identified 5673 hospital admissions in the MED-ECHO database for which *C. difficile*-associated diarrhea was listed as the primary diagnosis. Of these, 836 cases met our definition of community-acquired *C. difficile* infection: no hospital stay in the 90 days before the index admission, no presc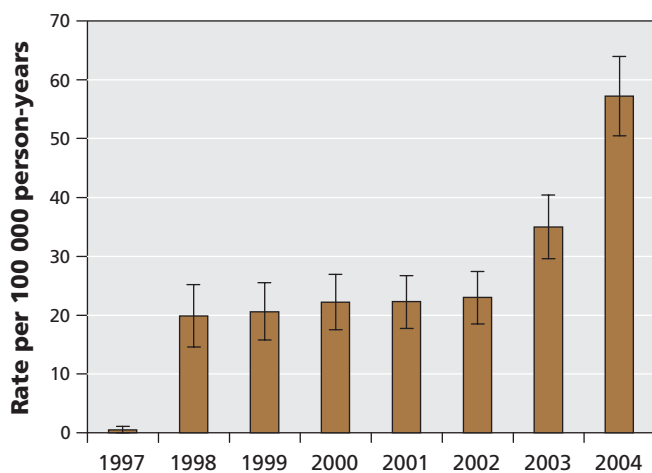ription for metronidazole or oral vancomycin in the 90 days before the index admission and no record of *C. difficile* infection as a secondary diagnosis during a previous hospital stay. The rate of community-acquired cases diagnosed per 100 000 patient-years per calendar year was fairly stable between 1998 to 2002 and then rose significantly during 2003 and 2004 (Figure 1), similar to the pattern observed for patients in hospital.[18] Most hospital admissions for incident *C. difficile* infection occurred within 90 days after a recent hospital stay (Figure 2), which confirms the importance of hospital admission as a risk factor for this disease.

People who met the case definition were older than controls, were more likely to be female and had had more encounters with physicians in the 2-year period before diagnosis (Table 1). Certain comorbidities, particularly the gastrointestinal disorders inflammatory bowel disease and irritable bowel syndrome, were more common among the cases. Renal failure was the only other comorbid illness that was significantly associated with *C. difficile* infection.

Only 394 (47.1%) of the 836 cases and 639 (7.6%) of the controls had been exposed to antibiotics in the 45-day period before the index admission. Using 90 days as an alternate definition of current exposure, 454 (54.3%) of the cases and 1137 (13.6%) of the controls had been exposed to any antibiotic before diagnosis. On multivariable analysis, all antibiotic classes other than tetracyclines, trimethoprim–sulfamethoxazole and antibiotics classified as "other" were associated with increased risk, but the highest risks were observed with clindamycin and cephalosporins and one of the quinolones (gatifloxacin). The adjusted rate ratios for each medication or class evaluated are shown in Figure 3.

To date, the at-risk period for *C. difficile* infection related to prior antibiotic exposure has not been well defined. On the basis of our results, the period of maximum risk related to antibi-
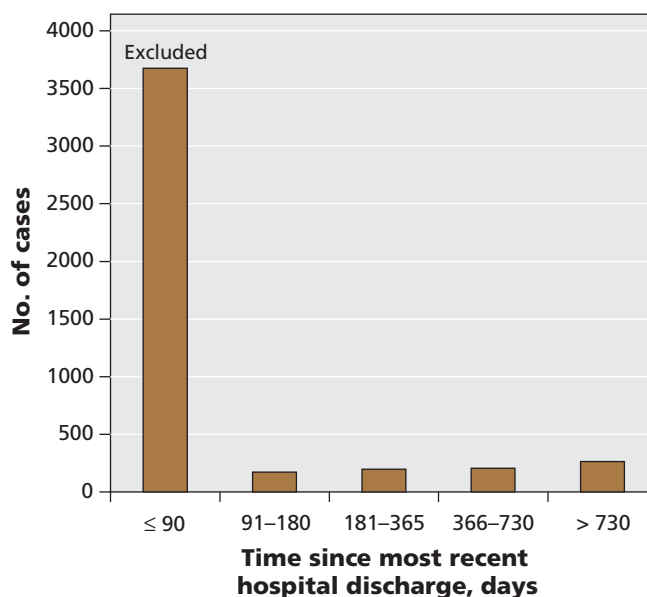

Figure 1: Population rates of community-acquired *Clostridium difficile*-associated diarrhea among people 65 years and older who required hospital admission in Quebec. Error bars = 95% confidence intervals.

Figure 2: Distribution of community-acquired *Clostridium difficile*-associated diarrhea as a function of time from hospital admission in the 2 years before the index admission.

otic exposure appears to be within 30 days after the start of antibiotic use, with a significant decrease after 45 days (Figure 4).

We also performed a sensitivity analysis in which community-acquired *C. difficile* was defined as greater than 180 days between the current and previous hospital admission. In that analysis, 665 of the 836 cases met the definition, and only 326 (49%) of these 665 cases were exposed to antibiotics in the 45 days beforehand.

Interpretation

In this population-based study, we determined the period of risk of *C. difficile* infection that might be related to antibiotic exposure and found that about 50% of patients had no history of antibiotic exposure in the 45 days before admission because of *C. difficile* infection. We also demonstrated that a significant proportion of hospital admissions because of incident *C. difficile* infection occurred within 90 days after discharge from hospital, confirming the importance of the hospital experience in the epidemiology of this disease.

Using a large sample of patients identified from the community, we have again documented that antibiotic use is not a prerequisite to the development of *C. difficile* infection.[4,5] A number of smaller studies have reported similar observations.[3,19–22] Substantially lower rates of prior antibiotic exposure in community-acquired *C. difficile* infection support the tenet that there may be significant confounding of the association between antibiotics and *C. difficile* infection with hospital admission.[7]

Clindamycin, cephalosporins and gatifloxacin were the antibiotics associated with the highest risk in this study. Recent studies of nosocomial *C. difficile* infection in the same province[23,24] demonstrated no significant increase in risk asso-

Table 1: Characteristics of 836 elderly patients with community-acquired *Clostridium difficile* infection and 8360 controls

Characteristic	No. (%) of patients*		Rate ratio†	
	Cases n = 836	Controls n = 8360	Unadjusted	Adjusted‡ (95% CI)
Demographic characteristics				
Age, mean (SD)	79.8 (6.8)	77.5 (6.3)		1.4§ (1.3–1.5)¶
Follow-up, yr, mean (SD)	3.8 (2.2)	3.8 (2.2)		
Sex, female	554 (66.3)	4944 (59.1)	1.4	1.3 (1.0–1.4)
Use of health care system				
No. of physician visits in previous 2 yr, mean (SD)	12.8 (25.0)	9.2 (18.8)		
No. of hospital admissions in previous 2 yr, mean (SD)	1.4 (1.5)	1.3 (1.4)		2.2 (2.0–2.4)¶
No. of days in hospital in previous 2 yr, mean (SD)	18.5 (33.8)	11.0 (23.5)		
Concurrent medical conditions				
Inflammatory bowel disease	41 (4.9)	88 (1.1)	4.7	4.1 (2.6–6.6)¶
Irritable bowel syndrome	86 (10.3)	117 (1.4)	5.5	3.4 (2.3–5.0)¶
Peptic ulcer disease	35 (4.2)	269 (3.2)	1.3	1.1 (0.7–1.7)
Gastroesophageal reflux disease	74 (8.9)	536 (6.4)	1.4	1.0 (0.7–1.4)
Diverticular disease	96 (11.5)	636 (7.6)	1.6	1.2 (0.9–1.5)
Chronic obstructive pulmonary disease	325 (38.9)	2381 (28.5)	1.6	1.1 (0.9–1.3)
Coronary artery disease	217 (21.0)	1333 (15.9)	1.4	1.3 (0.9–1.4)
Congestive heart failure	175 (20.9)	668 (8.0)	1.4	0.9 (0.7–1.2)
Renal failure	50 (6.0)	128 (1.5)	1.8	1.7 (1.3–2.2)¶
Diabetes mellitus	171 (20.4)	1146 (13.7)	1.2	1.2 (1.0–1.5)
Cerebrovascular accident	163 (19.5)	745 (8.9)	1.4	1.2 (1.0–1.5)
Colon cancer	25 (3.0)	126 (1.5)	1.3	1.2 (0.7–1.9)
Other gastrointestinal malignant disease	18 (2.2)	114 (1.4)	1.4	1.2 (0.8–1.8)
Hematologic malignant disease	27 (3.2)	80 (1.0)	1.7	1.5 (0.9–2.4)
Other malignant disease	223 (26.7)	1768 (21.1)	1.0	1.0 (0.8–1.2)

Note: SD = standard deviation.
*Unless indicated otherwise.
†Rate ratios greater than 1 imply that the rate of hospital admission because of *Clostridium difficile*-associated diarrhea was greater among patients with the particular exposure than among those without.
‡Adjusted for all variables in this table (except number of physician visits and number of days in hospital) and exposure to antibiotics, proton pump inhibitors and histamine$_2$-receptor antagonists.
§Per 5 years.
¶$p < 0.005$.

ciated with clindamycin. Clindamycin and cephalosporins are frequently associated with gastrointestinal side effects and have previously been labelled high-risk drugs associated with *C. difficile*-associated diarrhea.[2] These features are likely to increase ascertainment bias, since patients with gastrointestinal symptoms, particularly those who have received reputedly high-risk antibiotics, are more likely to be tested. The antibiotic associated with the highest risk for *C. difficile*-associated diarrhea has not been consistent among studies, and almost all antibiotics have been associated with an increased risk of *C. difficile* infection, irrespective of their spectrum of activity on either the normal flora or *C. difficile*. The inconsistency among studies of results implicating particular antibiotics, as well as the nonspecificity of the drugs, support the hypothesis that some of the risk attributed to antibiotics may be confounded.

The strengths of our study include use of a community-based population of high-risk patients for whom there was complete data about medication exposure and hospital admission. We also used a clinically relevant case definition. By restricting the population to community-based patients, we controlled for factors associated with hospital admission. We controlled for confounding by severity of illness both by matching and by adjustment in the analysis. We studied a high-risk population and included incident cases only. Antibiotic exposure among patients who have had a previous episode of *C. difficile* infection may be modified by the first event, and physi-

cians may be less likely to use antibiotics considered to present a high risk. Therefore, the exclusion of cases with recurrent disease decreased the risk of bias in the antibiotic estimates.
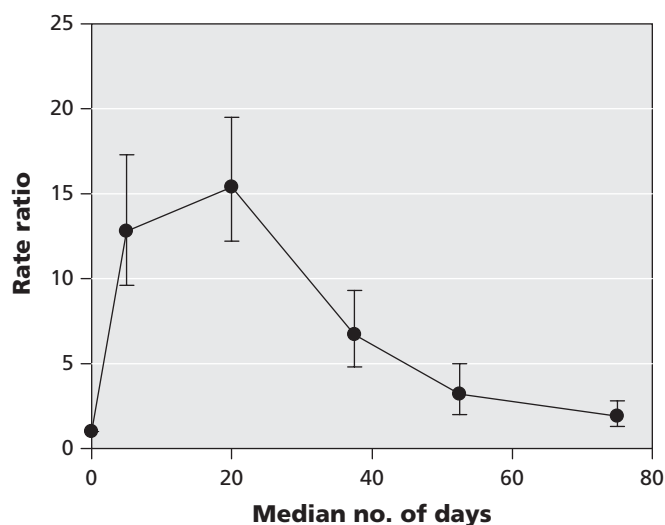

Figure 4: Risk of hospital admission because of *Clostridium difficile* infection as a function of time from most recent antibiotic prescription. Values shown are rate ratios for patients with *C. difficile* infection (*n* = 836) relative to those without *C. difficile* infection (*n* = 8360).

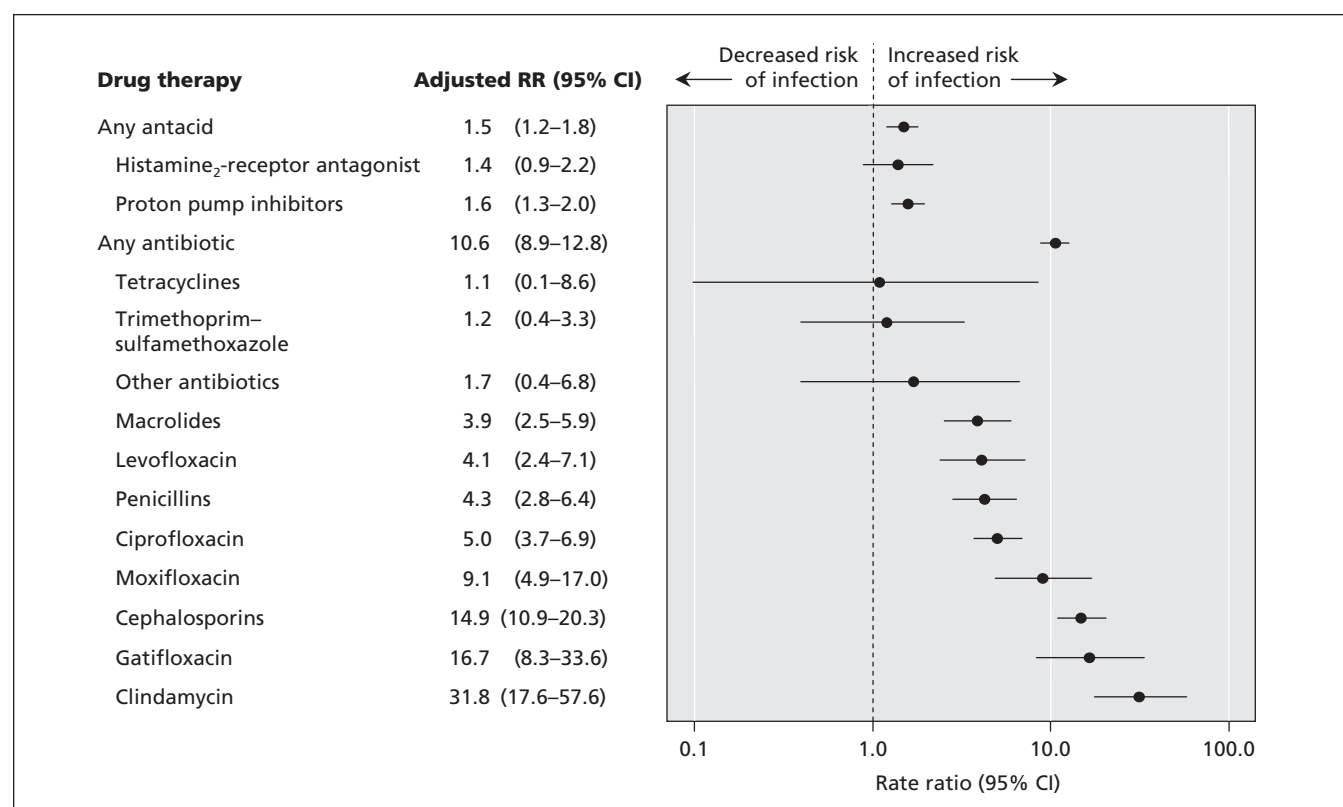| Drug therapy	Adjusted RR (95% CI)
Any antacid	1.5 (1.2–1.8)
Histamine$_2$-receptor antagonist	1.4 (0.9–2.2)
Proton pump inhibitors	1.6 (1.3–2.0)
Any antibiotic	10.6 (8.9–12.8)
Tetracyclines	1.1 (0.1–8.6)
Trimethoprim–sulfamethoxazole	1.2 (0.4–3.3)
Other antibiotics	1.7 (0.4–6.8)
Macrolides	3.9 (2.5–5.9)
Levofloxacin	4.1 (2.4–7.1)
Penicillins	4.3 (2.8–6.4)
Ciprofloxacin	5.0 (3.7–6.9)
Moxifloxacin	9.1 (4.9–17.0)
Cephalosporins	14.9 (10.9–20.3)
Gatifloxacin	16.7 (8.3–33.6)
Clindamycin	31.8 (17.6–57.6)

Figure 3: Adjusted rate ratios (RRs) of *Clostridium difficile* infection among patients exposed to antibiotics and gastric suppressive therapy in the 45 days before the index date compared with patients not exposed in that period. Adjustments were made for the variables in Table 1 and for the agents listed in the above figure. CI = 95% confidence interval.

Our study has limitations. The study population was restricted to a specific population of elderly patients with at least 1 prior hospital admission in the previous 8 years. Because the case definition was restricted to patients with severe infection, the risk factors observed may differ from those for the general population and for patients with less severe disease.

The information obtained from administrative databases also has limitations. Two previous studies[25,26] examining a diagnosis of *C. difficile* infection based on codes from the International Classification of Diseases, 9th revision, showed that the definition had high specificity (over 99%) but lower sensitivity, which could result in case misclassification and might have affected some of the risk estimates that we obtained. We did not obtain any confirmatory laboratory data, as this information was not available in the database; however, it is unlikely that patients who had been admitted to hospital would be recorded as having *C. difficile* infection in the absence of testing. The drug database might not have taken into consideration administration of antibiotics or other drugs from physician samples, but this was deemed unlikely to be significant. It is also possible that patients who were classified as having been exposed to antibiotics because a prescription was dispensed did not actually take the medication. Some of the patients defined as having community-acquired infection may have been residing in long-term care institutions, but such cases probably represented less than 5% of the elderly population[27] and were unlikely to substantially affect the estimates.

Similarly, the assignment of comorbid diagnoses using administrative databases has limitations, and previous research with such databases has shown that many of the diagnoses of comorbidity have high specificity, with sensitivity varying greatly by condition.[16,28] This might have led to misclassification in our study, and since these misclassifications were likely nondifferential, our estimates of relative risk were likely underestimated. We believe, however, that the extent of such information bias was minimal. Therefore, the associations that we found were likely real, especially given that they have been documented in previous research, including studies that we conducted using another validated research database.[4,5]

Community-acquired *C. difficile* infections were common and developed without prior exposure to antibiotics in the study population. Testing for *C. difficile* should be considered in community patients with diarrhea in whom a history of antibiotic exposure cannot be elicited.

This article has been peer reviewed.

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