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Association Between Antibiotic Use and Hospital-onset *Clostridioides difficile* Infection in US Acute Care Hospitals, 2006–2012: An Ecologic Analysis

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Background. Unnecessary antibiotic use (AU) contributes to increased rates of *Clostridioides difficile* infection (CDI). The impact of antibiotic restriction on hospital-onset CDI (HO-CDI) has not been assessed in a large group of US acute care hospitals (ACHs).

Methods. We examined cross-sectional and temporal associations between rates of hospital-level AU and HO-CDI using data from 549 ACHs. HO-CDI was defined as a discharge with a secondary *International Classification of Diseases, Ninth Revision, Clinical Modification* code for CDI (008.45), and treatment with metronidazole or oral vancomycin > 3 days after admission. Analyses were performed using multivariable generalized estimating equation models adjusting for patient and hospital characteristics.

Results. During 2006–2012, the unadjusted annual rates of HO-CDI and total AU were 7.3 per 10 000 patient-days (PD) (95% confidence interval [CI], 7.1–7.5) and 811 days of therapy (DOT)/1000 PD (95% CI, 803–820), respectively. In the cross-sectional analysis, for every 50 DOT/1000 PD increase in total AU, there was a 4.4% increase in HO-CDI. For every 10 DOT/1000 PD increase in use of third- and fourth-generation cephalosporins or carbapenems, there was a 2.1% and 2.9% increase in HO-CDI, respectively. In the time-series analysis, the 6 ACHs with a ≥30% decrease in total AU had a 33% decrease in HO-CDI (rate ratio, 0.67 [95% CI, .47–.96]); ACHs with a ≥20% decrease in fluoroquinolone or third- and fourth-generation cephalosporin use had a corresponding decrease in HO-CDI of 8% and 13%, respectively.

Conclusions. At an ecologic level, reductions in total AU, use of fluoroquinolones, and use of third- and fourth-generation cephalosporins were each associated with decreased HO-CDI rates.

Keywords. *Clostridioides difficile* infection; *Clostridium difficile* infection; hospital-onset CDI; antibiotic use; antimicrobial stewardship.

Overuse of antibiotics is a threat to patient safety, contributing to increased antibiotic resistance and rates of *Clostridioides difficile* infection (CDI) [1, 2]. CDI remains the most prevalent healthcare-associated infection in the United States [2]. Although direct patient exposure to antibiotics is a primary risk factor for CDI, recent studies indicate that the influence of antibiotic use (AU) on risk of CDI may operate not only at the individual patient level (or patient use of antibiotics), but also at aggregate levels (ie, ward-level or hospital-level AU). For example, the healthcare facility–level rate of AU may affect shedding of *C. difficile* spores by colonized patients, which in turn may impact the risk of acquisition and development of CDI in other patients receiving care at the same facility [3]. Several single-institution studies have shown immediate and prolonged influence of changes in hospital-level AU on incidence of hospital-onset CDI (HO-CDI) [4, 5]. In addition, hospitals implementing antibiotic stewardship programs restricting use of high-risk antibiotics, such as cephalosporins and fluoroquinolones, have reported corresponding reductions in CDI incidence [6, 7]. Similar to the small-scale interventions at the hospital level, national policy to restrict high-risk antibiotics in Scotland and England resulted in rapid country-wide decline in CDI, particularly among the cases caused by epidemic multidrug-resistant ribotypes [5, 8, 9].

In this study, our objective was to examine cross-sectional associations between levels of AU and incidence of HO-CDI in US acute care hospitals (ACHs). To strengthen our understanding of these ecologic relationships, we then examined temporal trends in monthly rates of AU and HO-CDI in ACHs that experienced reductions or increases in AU over time.

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METHODS

We conducted an ecologic analysis using data from >500 ACHs in the United States contributing to the Truven Health MarketScan Hospital Drug Database (HDD) between 2006 and 2012. For this study, we included hospital discharge records for patients ≥18 years old, capturing discharge-specific diagnostic and procedure codes, demographic information, inpatient drug usage, and facility descriptors. Previously, the HDD was used to estimate national trends in inpatient AU and was found to be approximately representative of ACHs in the United States [10].

AU was examined through annual and monthly rates of AU measured by days of therapy (DOT) per 1000 patient-days (PD) for total AU and for 7 antibiotic classes: fluoroquinolones, third- and fourth-generation cephalosporins, piperacillin-tazobactam, carbapenems, β-lactam/β-lactamase inhibitor combinations (excluding piperacillin-tazobactam), clindamycin, and penicillins. These classes of antibiotics were chosen based on frequency of their use [10] and suspected risk for CDI [11–13]. Piperacillin-tazobactam and penicillins were investigated separately because they were reported to have antimicrobial activity against *C. difficile* [14, 15]. Previous studies showed that substitution of piperacillin-tazobactam for third-generation cephalosporins could be associated with reductions in the incidence of CDI [13].

HO-CDI was defined as a hospital discharge with a secondary *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) diagnosis code for CDI (008.45) plus inpatient treatment with metronidazole or oral vancomycin initiated on day 3 or later during hospitalization. The HO-CDI rate was calculated as the number of HO-CDI case patients divided by the number of PD per year (or month) and was reported per 10 000 PD. Several hospital characteristics (urban vs rural location, bed size, teaching status, and census division) were included. In addition, we calculated and included the hospital-level annual/monthly average proportion of patients aged ≥65, average Gagne comorbidity score [16], proportion of discharges with a surgical diagnosis-related group (DRG), community-onset CDI (CO-CDI) rate, and patient case mix index. Case mix index represents the average DRG weight for a hospital and is calculated as the sum of the weights of a facility's DRGs divided by the number of admissions during year/month [17]. CO-CDI was defined as a discharge with a primary *ICD-9-CM* code for CDI plus inpatient treatment with metronidazole or oral vancomycin initiated at any time during hospitalization plus no hospitalization at the same hospital in the previous 28 days [18]. CO-CDI rate was calculated as the number of CO-CDI case patients per 100 discharges per year/month.

Analysis

Bivariate relationships between AU and HO-CDI were explored by describing mean unadjusted rates of AU among 3 categories of hospitals: low, average, or high HO-CDI intensity. Grouping of hospitals into the 3 categories was based on results of a multivariable generalized linear mixed model incorporating a random intercept for each ACH [19] and adjusting for hospital and patient characteristics. ACHs with significantly lower/higher intercepts compared to the overall weighted average were categorized into the respective high/low HO-CDI intensity groups; hospitals with intercepts not statistically different from the overall weighted average were classified as average HO-CDI intensity.

Cross-sectional associations between annual rates of AU and HO-CDI were examined using multivariable generalized estimating equation (GEE) models. Rate ratios for HO-CDI associated with total AU (total AU model) and with the use of 7 antibiotic classes (class-specific AU model) were estimated. The correlation between fluoroquinolone use and HO-CDI changed near the higher end of fluoroquinolone use and, therefore, we performed a sensitivity analysis fitting 2 separate models: one for hospitals with low-to-average fluoroquinolone use (defined by those ACHs in the first, second, and third quartiles of fluoroquinolone use, which corresponds to ≤207 DOT/1000 PD) and the second for ACHs with high fluoroquinolone use (defined by those ACHs in the fourth quartile of fluoroquinolone use, which corresponds to >207 DOT/1000 PD).

Temporal trends in HO-CDI and AU rates were assessed through analysis of monthly rates of HO-CDI, total AU, and use of antibiotic classes for which significant cross-sectional associations with HO-CDI were observed. To be included in time series, a hospital had to have, as a minimum, 2 consecutive years of data. AU changes were categorized as follows: up to 10% increase/decrease, ≥10% increase/decrease, ≥20% increase/decrease, and ≥30% increase/decrease. Individual hospitals may have data included in multiple time series because the categories were not mutually exclusive and hospital-specific change in AU may vary in direction and magnitude from year to year.

Cross-sectional and longitudinal analyses utilized GEE models adjusting for ACH-level clustering, autocorrelation, hospital and patient characteristics, and offset by PD. A normal distribution was assumed for AU models and negative binomial distribution for HO-CDI models.

All analyses were conducted using SAS version 9.4 statistical software (SAS Institute, Cary, North Carolina). The α level was set to .05 for all statistical analyses.

RESULTS

Between 2006 and 2012, about 300 of 549 ACHs contributed data in any given year. The mean HO-CDI rate across all years was 7.3 per 10 000 PD (95% confidence interval [CI], 7.1–7.5) and varied by census division, teaching status, urban vs rural location, proportion of surgical discharges, and bed size (Table 1). The unadjusted rates of third- and fourth-generation cephalosporins, piperacillin-tazobactam, β-lactam/β-lactamase inhibitor combination, and carbapenem use were higher among

Table 1. Characteristics of Acute Care Hospitals (N = 549) Included in the Study

Characteristic	ACHs, No.	Mean Unadjusted HO-CDI Rate (95% CI)[a]
Year		
2006	380	6.9 (6.3–7.4)
2007	335	7.2 (6.6–7.8)
2008	310	7.4 (6.9–8.0)
2009	364	6.9 (6.4–7.4)
2010	323	7.2 (6.7–7.8)
2011	304	7.1 (6.5–7.6)
2012	299	8.4 (7.8–9.1)
All years	549	7.3 (7.1–7.5)
US Census Division		
Southwest Central	58	4.6 (4.3–5.0)
Southeast Central	51	4.8 (4.3–5.3)
Northwest Central	26	5.2 (4.5–5.9)
Pacific	39	7.2 (6.3–8.2)
South Atlantic	159	7.4 (7.1–7.8)
Mid-Atlantic	95	7.9 (7.5–8.4)
Mountain	26	8.1 (7.3–8.9)
Northeast Central	81	9.1 (8.4–9.8)
New England	14	11.8 (9.7–13.9)
Teaching status		
Teaching	121	8.4 (8.0–8.9)
Nonteaching	428	6.8 (6.6–7.1)
Location		
Rural	88	5.9 (5.4–6.5)
Urban	461	7.5 (7.3–7.7)
Proportion of medical discharges >/≤ mean across 7 y[b]		
>70%	381	7.3 (7.0–7.6)
≤70%	374	7.3 (7.0–7.6)
Proportion of surgical discharges >/≤ mean across 7 y[b]		
>25%	210	7.7 (7.3–8.0)
≤25%	429	7.1 (6.9–7.4)
Bed size, No.		
<300	362	7.0 (6.7–7.2)
≥300	187	7.8 (7.5–8.2)

Abbreviations: ACH, acute care hospital; CI, confidence interval; HO-CDI, hospital-onset *Clostridioides difficile* infection; y, years.

[a]HO-CDI rate is the number of HO-CDI cases per 10 000 patient-days.

[b]Hospitals' proportions of medical and surgical discharges may change from year to year and, therefore, the numbers of hospitals in each category do not add up to 549.

ACHs in the high HO-CDI intensity category compared with those in average and low HO-CDI intensity (Table 2).

In the cross-sectional multivariable analysis, total AU was significantly associated with HO-CDI, with a 4.4% increase in HO-CDI rate for every 50 DOT/1000 PD increase in total AU (rate ratio [RR], 1.044 [95% CI, 1.031–1.058]; $P < .001$; Figure 1; Supplementary Table 1). In the class-specific AU model, third- and fourth-generation cephalosporin and carbapenem use were independently associated with HO-CDI, with respective 2.1% and 2.9% increases in HO-CDI rate for every 10 DOT/1000 PD increase in use. In the fluoroquinolone-specific models, ACHs utilizing ≤207 DOT fluoroquinolones/1000 PD showed a 1.1% increase in HO-CDI for every 10 DOT/1000 PD increase in fluoroquinolone use. For ACHs with a higher utilization of fluoroquinolones, no association was observed between fluoroquinolone use and HO-CDI.

Evaluation of temporal trends in AU identified 338 hospitals that decreased their total AU 0%–10% and experienced a significant 3% decrease in annual HO-CDI rates (Table 3). Likewise, hospitals with ≥10% or ≥20% decreases in total AU observed significant 13% and 22% declines in HO-CDI, respectively. Six hospitals with ≥30% decrease in total AU observed a 33% decrease in HO-CDI (Figure 2). Twenty percent or larger increases in total AU corresponded with increases in HO-CDI; however, those trends were not statistically significant (Supplementary Figure 1; Table 3). Evaluation of trends in fluoroquinolone use showed that decreases in fluoroquinolone use corresponded with significant decreases in HO-CDI; specifically, hospitals that decreased fluoroquinolone use by ≥20% or ≥30% experienced 8% and 19% decreases, respectively, in HO-CDI rates (Table 3; Supplementary Figure 2). For third- and fourth-generation cephalosporins, any decrease corresponded with decreases in HO-CDI. However, only ≥20% decrease in use of third- and fourth-generation cephalosporins corresponded with a significant 13% decrease in HO-CDI (Table 3; Supplementary Figure 3). Neither increases nor decreases in carbapenem use corresponded with significant trends in HO-CDI (Table 3; Supplementary Figure 4).

DISCUSSION

This retrospective ecologic investigation is the largest to date examining the association between rates of AU and HO-CDI in ACHs in the United States. It showed that higher levels of total inpatient AU, third- and fourth-generation cephalosporin use and carbapenem use were significantly and independently associated with higher rates of HO-CDI, and that temporal changes in AU correlated with changes in HO-CDI. These findings support the evidence that effective antibiotic stewardship programs can have a major impact on HO-CDI in the United States.

Exposure to antibiotics has been well documented as the most important modifiable patient-level risk factor for development of CDI. Our study was not designed to further examine the risk of CDI among individuals exposed to antibiotics, but rather to examine the relationship between antibiotic exposure and risk of CDI at the population level, specifically populations of hospitalized patients. The rate of CDI in a hospital is determined not only by the risk of disease among individual patients who carry the organism, but also by the risk of creating new carriers through transmission from patients who are infected or colonized with *C. difficile* to those who are not. Antibiotics are also likely to affect the risk of acquiring colonization, the risk of progressing from colonization to disease, and also the level of contagiousness of carriers, even those that are asymptomatic [20–23]. For example, one recent study found ward-level

Table 2. Unadjusted Hospital-onset *Clostridioides difficile* Infection (HO-CDI)[a] and Antibiotic Use in Acute Care Hospitals (N = 549) with Low, Average, and High HO-CDI Intensity, 2006–2012[b]

	HO-CDI Intensity[c]		
Characteristic	Low	Average	High
No. (%) of hospitals	41 (7)	440 (80)	68 (12)
PD/y, mean	76 366	58 634	81 956
Unadjusted HO-CDI rate (per 10 000 PD)	2.97	10.09	18.05
Antibiotic use, DOT/1000 PD, mean			
Total antibiotic	568	831	852
Fluoroquinolone	114	171	155
Third-/fourth-generation cephalosporin	76	106	108
Piperacillin-tazobactam	58	78	83
Carbapenem	19	30	35
Clindamycin	16	24	20
βL/βLI combination (excluding piperacillin-tazobactam)	19	22	27
Penicillin	19	22	20
Other antibiotic use[d]	247	378	403

Abbreviations: βL/βLI, β-lactam/β-lactamase inhibitor; DOT, days of therapy; HO-CDI, hospital-onset *Clostridioides difficile* infection; PD, patient-days.

[a]HO-CDI was defined as a discharge with a secondary *International Classification of Diseases, Ninth Revision, Clinical Modification* diagnosis code for *Clostridioides difficile* (CDI) (008.45) and inpatient treatment with metronidazole or oral vancomycin initiated on a third day or later after admission and measured as a rate per 10 000 PD.

[b]The mean rates of antibiotic use and HO-CDI were obtained from the Truven Health MarketScan Hospital and Drug Database.

[c]Five hundred forty-nine acute care hospitals were grouped into the categories of average, high, or low HO-CDI intensity based on the results of a multivariate analysis using generalized linear mixed model with random intercept and annual trend, adjusting for hospital-level characteristics: urban vs rural, bed size, teaching status, census division, case mix category, community-onset CDI rate, proportion of patients aged ≥65 years, average Gagne comorbidity score, and proportion of surgical patients.

[d]Majority of other antibiotics included vancomycin, metronidazole, and first- and second-generation cephalosporins.

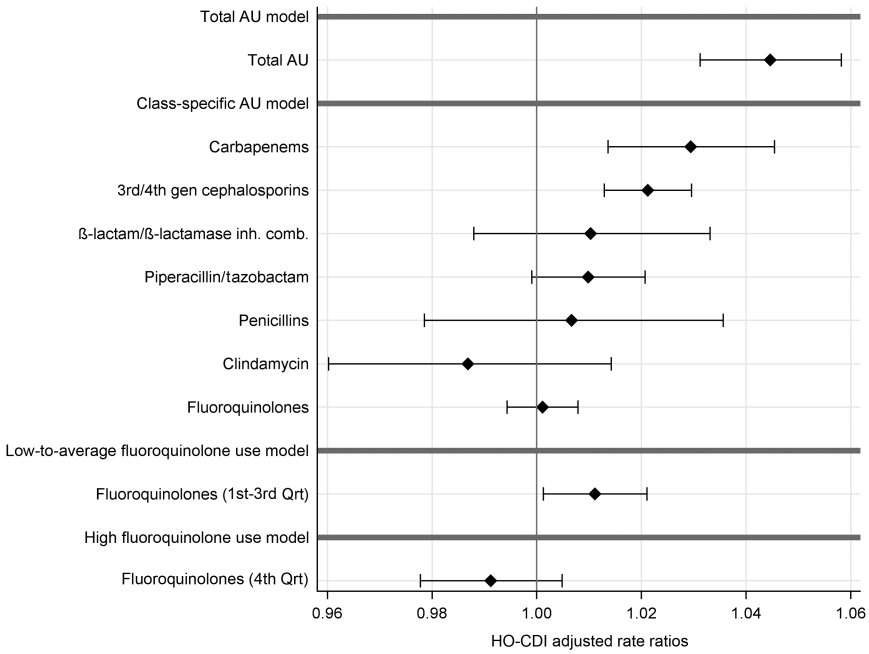

Figure 1. Adjusted rate ratios and 95% confidence intervals for the association between hospital-onset *Clostridioides difficile* infection (HO-CDI) and antibiotic use. Adjusted rate ratios in the total antibiotic use (AU) model were estimated for an increase of 50 days of therapy (DOT)/1000 patient-days (PD) and in all other models for an increase of 10 DOT/1000 PD. Across all models, HO-CDI rate ratios were estimated using generalized estimating equation models that assumed negative binomial distribution of HO-CDI, autoregressive correlation of repeated measurements within acute care hospitals (ACHs), offset by PD and adjusted for patient (case mix category, community-onset CDI rate, proportion of patients aged ≥65 years, average Gagne comorbidity score, and proportion of surgical patients) and hospital (urban vs rural, bed size, teaching status, census division) characteristics. Total AU model included overall AU and hospital-level adjustors. Class-specific AU model included 7 antibiotic classes and hospital-level adjustors. Rate ratio for fluoroquinolone use in ACHs with low-to-average fluoroquinolone use (mean fluoroquinolone use, ≤207 DOT/1000 PD [1st–3rd qrt]) and with high fluoroquinolone use (mean fluoroquinolone use, >207 DOT/1000 PD [4th qrt]) were estimated using the same adjustors as in the class-specific model. Abbreviations: inh. comb., inhibitor combination; Qrt, quartile.

Table 3. Analysis of Trends in Rates of Antibiotic Use and Hospital-onset *Clostridioides difficile* Infection in Hospitals With Various Degrees of Change in Antibiotic Use

Change in Annual Antibiotic Use	No. of ACHs	Mean Annual AU[a], Baseline Year	Mean Annual AU, Subsequent Year	Adjusted Trend in AU (95% CI)[b]	Mean Annual HO-CDI[c], Baseline Year	Mean Annual HO-CDI, Subsequent Year	Adjusted Trend in HO-CDI (95% CI)[d]
Total AU							
≥30% increase	9	639	1000	277 (216–337)	8.1	10.7	1.03 (.91–1.17)
≥20% increase	19	769	1036	184 (139–229)	7.0	8.8	1.16 (.97–1.39)
≥10% increase	106	804	942	80 (65–94)	7.7	8.3	0.96 (.89–1.04)
0%–10% increase	383	796	825	13 (9–17)	7.6	7.9	1.02 (.99–1.05)
0%–10% decrease	338	817	790	–10 (–15 to –6)	8.8	8.2	0.97 (.94–.99)
≥10% decrease	58	952	814	–84 (–107 to –61)	9.3	8.4	0.87 (.82–.92)
≥20% decrease	11	962	706	–218 (–278 to –157)	7.7	6.3	0.78 (.64–.96)
≥30% decrease	6	953	603	–268 (–361 to –175)	8.2	6.6	0.67 (.47–.96)
Fluoroquinolone use							
≥30% increase	16	195	273	53 (43–62)	6.5	8.3	0.89 (.71–1.14)
≥20% increase	49	191	245	30 (22–39)	8.0	8.4	1.01 (.91–1.13)
≥10% increase	117	182	216	18 (13–23)	8.2	8.3	0.96 (.90–1.02)
0%–10% increase	275	158	165	–1.5 (–3.5 to .5)	9.8	10.4	0.97 (.93–1.01)
0%–10% decrease	346	157	149	–7 (–8 to –5)	8.1	8.2	0.99 (.97–1.02)
≥10% decrease	212	192	163	–16 (–18 to –13)	9.3	9.4	1.00 (.96–1.05)
≥20% decrease	67	221	173	–26 (–32 to –21)	9.3	8.5	0.92 (.86–.98)
≥30% decrease	22	243	176	–43 (–60 to –25)	9.2	8.5	0.81 (.71–.92)
Third-/fourth-generation cephalosporin use							
≥30% increase	51	135	183	36 (29–43)	7.5	9.1	1.12 (1.02–1.23)
≥20% increase	106	122	158	23 (19–27)	7.9	8.6	1.02 (.96–1.09)
≥10% increase	261	110	133	13 (11–15)	8.2	8.9	1.04 (.99–1.08)
0%–10% increase	315	86	91	1 (–.02 to 2)	7.9	8.2	1.00 (.98–1.03)
0%–10% decrease	268	98	93	–2 (–3 to –1)	8.2	7.9	0.97 (.93–1.01)
≥10% decrease	164	130	109	–9 (–12 to –6)	8.8	8.5	0.98 (.94–1.03)
≥20% decrease	66	152	119	–19 (–25 to –12)	9.7	9.0	0.87 (.81–.93)
≥30% decrease	26	164	121	–35 (–42 to –29)	9.6	9.2	0.88 (.75–1.03)
Carbapenem use							
≥30% increase	160	37	54	11 (9–12)	8.0	8.4	1.05 (.99–1.11)
≥20% increase	242	36	49	9 (8–10)	7.9	8.1	1.02 (.98–1.06)
≥10% increase	329	31	41	6 (5–7)	7.7	7.7	1.03 (.99–1.06)
0%–10% increase	235	22	23	0 (–.9 to .5)	8.2	8.3	1.01 (.98–1.05)
0%–10% decrease	214	23	22	–1 (–2 to –1)	8.2	8.3	0.96 (.93–.99)
≥10% decrease	237	40	31	–3 (–4 to –2)	8.6	8.7	0.97 (.93–1.01)
≥20% decrease	147	50	38	–6 (–8 to –3)	9.3	9.5	0.99 (.94–1.04)
≥30% decrease	78	57	39	–8 (–12 to –3)	9.9	10.2	0.97 (.90–1.04)

Abbreviations: ACHs, acute care hospitals; AU, antibiotic use; CI, confidence interval; HO-CDI, hospital-onset *Clostridioides difficile* infection.

[a]Mean annual AU is a rate calculated as days of therapy per 1000 patient-days (PD).

[b]Trends in AU were estimated using generalized estimating equation (GEE) models applying normal distribution of AU as outcome, autoregressive correlation structure, offset by PD, and adjusting for patient and hospital characteristics: urban vs rural, bed size, teaching status, census division, case mix index category, community-onset CDI rate, proportion of patients aged ≥65 years, average Gagne comorbidity score, and proportion of patients with infectious disease diagnosis code.

[c]Mean annual HO-CDI is a rate calculated as number of HO-CDI cases per 10 000 PD.

[d]Trends in HO-CDI were estimated using GEE models applying negative binomial distribution and instead of proportion of patients with infectious disease diagnosis, controlled for proportion of patients having surgery.

antibiotic prescribing to be a risk factor for CDI independent of risk from antibiotics in individual patients [24]. Another study demonstrated increased risk of CDI among patients admitted to a room where the previous occupant received antibiotics but did not have CDI [3]. Our ecologic analysis supports the evidence that the level of antibiotic consumption by ACHs is predictive of incidence of CDI in the facility.

Our findings are consistent with previous studies reporting associations between use of certain antibiotic classes, such as fluoroquinolones and third- and fourth-generation cephalosporins and carbapenems, and CDI risk [9]. It has been suggested that fluoroquinolone use in healthcare settings may have been responsible for the emergence and spread of a toxigenic *C. difficile* strain, designated polymerase chain reaction (PCR) ribotype 027, which produces elevated levels of toxins A and B and is highly resistant to fluoroquinolones [25–27]. In England where the PCR ribotype 027 strain was common, restricting fluoroquinolone prescribing may have been at

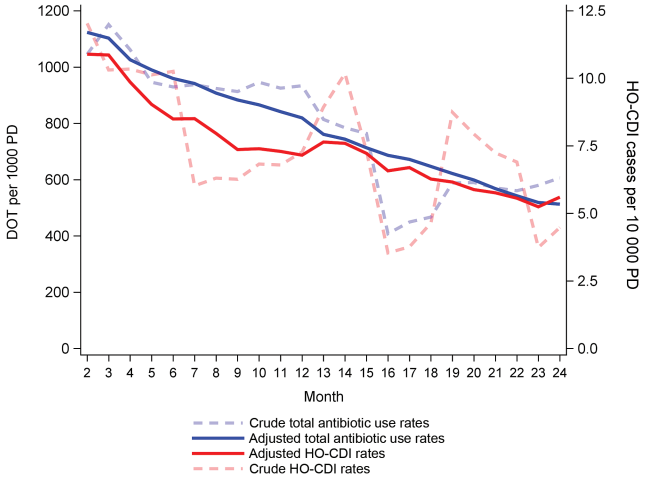

Figure 2. Temporal trends in hospital-onset *Clostridioides difficile* infection (HO-CDI) and total antibiotic use rates in hospitals with ≥30% decrease in total antibiotic use. Adjusted and unadjusted monthly rates of HO-CDI and total antibiotic use within the period of ≥30% decrease in total annual antibiotic use. Abbreviations: DOT, days of therapy; PD, patient-days.

least partially responsible for the 80% decline in incidence of CDI and near extinction of the PCR ribotype 027 strain [8]. In our study, the association with fluoroquinolone use was moderate, and only reached statistical significance among hospitals with low to average-level use (≤207 DOT/1000 PD). Although the cause for these unique findings requires further investigation, the prevalence of the PCR ribotype 027 strain was lower in the United States during our study period in comparison to the United Kingdom at the peak of its outbreak, possibly blunting an association with fluoroquinolone use. There may also be a "saturation effect" where fluoroquinolone-associated CDI risk rises until reaching a certain threshold of use beyond which risk plateaus. Of note, rates of fluoroquinolone use in the US hospitals appear to be substantially higher than those reported in the United Kingdom; US hospitals with high levels of use may have exceeded a threshold where the fluoroquinolone-associated CDI risk has been maximized [10].

In addition to cross-sectional associations between AU and HO-CDI, we observed correlation between temporal changes in AU overtime and HO-CDI rate, where significant decreases in total AU, third- and fourth-generation cephalosporin use, or fluoroquinolone use concurred with significant decreases in HO-CDI. The relationship between temporal increases in AU and changes in HO-CDI was not as evident, with exception of large increases in third- and fourth-generation cephalosporin use. In our study, the largest reduction in HO-CDI (33%) was observed among hospitals that decreased their total annual antibiotic consumption by 30%. Although achieving a 30% decrease in total AU within a hospital may represent a challenge, such reduction may be feasible in many hospitals based on findings of a recent study suggesting that AU can be improved in 37.2% of the most common prescription scenarios [28].

An alternative to targeting total AU may be to focus stewardship efforts on high-risk antibiotic classes, particularly fluoroquinolones and third- and fourth-generation cephalosporins [29]. In our study, hospitals achieving a 30% reduction of fluoroquinolones observed a 19% reduction in HO-CDI. Similarly, a 30% reduction in third- and fourth-generation cephalosporin use was associated with a 12% reduction in HO-CDI. Although we did not determine effects of reducing specific classes of antibiotics independent of changes in other antibiotics, given the fact that fluoroquinolones and third- and fourth generation cephalosporins, on average, represent about 18% and 13% of total AU respectively [10], targeted reductions in the use of these antibiotic classes is likely to have a disproportionate effect on HO-CDI compared to their relative effect on total AU. These findings are also consistent with a substantial body of evidence that stewardship efforts focusing on fluoroquinolones and cephalosporins can be effective [30]. In Germany, where cephalosporins and fluoroquinolones are also among the most frequently prescribed antibiotics, reducing their use by 50% was associated with a roughly 50% reduction in the incidence of CDI [31]. In England, dramatic reductions in *C. difficile* infection were observed between 2005 and 2009 after reducing fluoroquinolone and cephalosporin use nationally [8]. Of note, overall rates of AU in England remained stable during this time; fluoroquinolone and cephalosporin use was largely replaced with penicillin-based antibiotics.

In the United States, trends in inpatient AU between 2006 and 2012 suggest that fluoroquinolone use decreased significantly during that time [10]. As no major national reductions in CDI rates accompanied this change, it is possible that any potential benefit may have been offset by significant increases in use of third- and fourth-generation cephalosporins during the same period or that fluoroquinolone use remained in the previously described, hypothetical range of "high-use" saturation effect [10]. A more effective national antibiotic stewardship strategy for reducing CDI rates may be encouraging not only continued reduction of fluoroquinolone use, but also a shift toward replacing cephalosporin use with penicillin-based agents, such as β-lactam/β-lactamase inhibitors. Several investigators have provided evidence suggesting that replacing fluoroquinolones and cephalosporins with penicillins, even if total AU remains unchanged, may be an effective approach to CDI reduction [5].

The mechanism for CDI reduction following such a switch in antibiotic class is unclear. One hypothesis is that penicillin-based antibiotics, which have activity against *C. difficile*, may change the epidemiology of *C. difficile* colonization and spread. Data from animal models suggest that administering antibiotics to which *C. difficile* is resistant can induce a "super shedder" state in colonized mice, whereas antibiotics active against *C. difficile* can suppress *C. difficile* concentration in

stool while on the drug [14, 32, 33]. Human studies suggest that piperacillin-tazobactam treatment can inhibit acquisition of *C. difficile* colonization and possibly lead to loss of colonization, while treatment with a cephalosporin is associated with increased risk of acquiring colonization [14, 34]. Taken together, these studies suggest that replacing fluoroquinolones and cephalosporins with penicillin-based antibiotics could change the epidemiology of *C. difficile* within a hospital by decreasing risk of colonization, risk of progression from colonization to disease, and risk of shedding, which together could translate into reduced spread and reduced CDI rates.

There are several limitations to this investigation. Our analysis relied on the use of administrative data and is therefore subject to certain limitations [35]. However, there are no other data sources currently available containing a large number of hospitals and the necessary data such as AU data, discharge data, and patient characteristic data to conduct such a study. Several studies have also suggested that using *ICD-9* codes alone as compared to using toxin assay results may lead to overestimation of incidence of HO-CDI [36]. This study addressed the limitation by using a combination of *ICD-9* codes and date of CDI treatment initiation. As a result, the mean CDI incidence rate in our study (7.3 per 10 000 patient-days) was similar to the rates reported previously. For example, in 2015 the states of California and New York reported crude HO-CDI rates of 8.1 and 7.9 per 10 000 patient-days, respectively [37, 38]. Next, we did not have data on hospital infection control and diagnostic practices that might have been implemented across participating hospitals and could confound the observed associations. Information on the use of diagnostic tests was not available from the hospitals in this data source. Since 2008, nucleic acid amplification tests (NAATs), with markedly increased sensitivity over toxin enzyme immunoassays (EIAs), have become available and increasingly used, with the possibility that changes in individual HO-CDI rates resulted from switching between NAAT and EIA test platforms [39]. Changes in diagnostic practices may have influenced our findings in at least 2 ways. First, changes in HO-CDI related to changes from EIA to NAAT may have obscured potential associations between increased AU and HO-CDI. Second, there could be a potentially confounding association between HO-CDI rates, implementation of antibiotic stewardship, and overall diagnostic practices, including test ordering practices [40]. Finally, we did not assess for interactions between antibiotic classes. Nationally, there has been a decreasing trend of fluoroquinolone use with an increase in use of cephalosporins and carbapenems [10]. On a facility level, it is unclear whether decreasing multiple high-risk antibiotic classes concurrently would have a synergistic impact on reducing HO-CDI rates.

In conclusion, our study suggests that facility-level AU in US ACHs is strongly associated with HO-CDI rates. Furthermore, reductions in AU, either overall or focused reductions in use of fluoroquinolones and third- and fourth-generation cephalosporins, can reduce facility-level rates of HO-CDI.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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