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Importation, Antibiotics, and *Clostridium difficile* Infection in Veteran Long-Term Care

A Multilevel Case–Control Study

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Background: Although clinical factors affecting a person's susceptibility to *Clostridium difficile* infection are well-understood, little is known about what drives differences in incidence across long-term care settings.

Objective: To obtain a comprehensive picture of individual and regional factors that affect *C difficile* incidence.

Design: Multilevel longitudinal nested case–control study.

Setting: Veterans Health Administration health care regions, from 2006 through 2012.

Participants: Long-term care residents.

Measurements: Individual-level risk factors included age, number of comorbid conditions, and antibiotic exposure. Regional risk factors included importation of cases of acute care *C difficile* infection per 10 000 resident-days and antibiotic use per 1000 resident-days. The outcome was defined as a positive result on a long-term care *C difficile* test without a positive result in the prior 8 weeks.

Results: 6012 cases (incidence, 3.7 cases per 10 000 resident-days) were identified in 86 regions. Long-term care *C difficile* incidence (minimum, 0.6 case per 10 000 resident-days; maximum, 31.0 cases per 10 000 resident-days), antibiotic use (minimum, 61.0 days with therapy per 1000 resident-days; maximum, 370.2 days with therapy per 1000 resident-days), and importation (minimum, 2.9 cases per 10 000 resident-days; maximum, 341.3 cases per 10 000 resident-days) varied substantially across regions. Together, antibiotic use and importation accounted for 75% of the regional variation in *C difficile* incidence (R^2 = 0.75). Multilevel analyses showed that regional factors affected risk together with individual-level exposures (relative risk of regional antibiotic use, 1.36 per doubling [95% CI, 1.15 to 1.60]; relative risk of importation, 1.23 per doubling [CI, 1.14 to 1.33]).

Limitations: Case identification was based on laboratory criteria. Admission of residents with recent *C difficile* infection from non–Veterans Health Administration acute care sources was not considered.

Conclusion: Only 25% of the variation in regional *C difficile* incidence in long-term care remained unexplained after importation from acute care facilities and antibiotic use were accounted for, which suggests that improved infection control and antimicrobial stewardship may help reduce the incidence of *C difficile* in long-term care settings.

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Clostridium difficile infection is a diarrheal disease that is associated with antibiotic and health care exposures. It has the highest prevalence, morbidity, and mortality of any health care–associated infection (1, 2). Risk factors have been extensively studied and include age, comorbidity burden, abdominal surgery, feeding tube use, and exposure to antibiotics and antacids (3). Almost all antibiotic classes are believed to increase risk; however, the risk is greatest for antibiotics with activity against gut flora but none against *C difficile,* including cephalosporins, fluoroquinolones, and clindamycin (4, 5). Antacids, especially proton-pump inhibitors, are believed to increase risk by reducing stomach acidity, thereby allowing increased numbers of viable *C difficile* to reach the gut.

Although clinical risk factors have been extensively studied, the environmental and facility-level exposures that may drive *C difficile* transmission have not. What is known is that *C difficile* is transmitted by the fecal–oral route, and patients with symptomatic disease or asymptomatic colonization have high bacterial loads in their stool and shed infectious spores into their environs for extended periods (6, 7). Exposure of patients to ward-level disease pressure, measured as the daily number of infectious patients with recent *C difficile* present in the same ward, predicts increased risk for infection (8). In addition to disease pressure, antibiotic use in wards has been shown to increase the risk for infection together with individual-level antibiotic exposure (9). This independent effect of ward antibiotic use may be due to the higher likelihood of asymptomatic *C difficile* colonization and shedding among patients with recent antibiotic exposure (7), which creates a greater environmental *C difficile* burden.

Long-term care facilities provide services to residents requiring assistance with activities of daily living in a residential setting, skilled nursing, spinal cord injury care, and rehabilitation. In long-term care, antimicrobial use is generally high, with the point prevalence around 8%; of this, 25% to 75% may be inappropriate (10). To our knowledge, the effect of antimicrobial use on *C difficile* incidence in long-term care has never been explored. Further, long-term care residents have frequent contact with acute care facilities; therefore, importation of hospital-onset *C difficile* infection may be an important risk factor for infection in long-term care facilities (11).

EDITORS' NOTES

Context

Variation in *Clostridium difficile* incidence among long-term care facilities is not well-understood.

Contribution

In a study comparing regional Veterans Health Administration long-term care facilities there was wide variation in *C difficile* incidence that was largely explained by differences in overall use of antibiotics and the importation of *C difficile* from acute care settings rather than individual patient factors, such as age, number of comorbidities, and antibiotic use.

Implication

Approaches that focus on infection control and institutional antibiotic stewardship may be most beneficial for reducing *C difficile* incidence in long-term care facilities.

Models incorporating both individual- and facility-level risk factors can be used to distinguish risk factors that affect individual susceptibility to disease from those that that may be associated with the degree of environmental contamination and that may proxy spore ingestion (12). The objective of this study was to obtain a comprehensive picture of the individual and regional factors that drive *C difficile* infection risk across Veterans Health Administration (VHA) long-term care facilities, with an interest in the role of importation of persons with acute care–onset *C difficile* infection and regional rates of antibiotic use.

METHODS

Ethics Statement

Study approval was obtained from the Research Ethics Board of the Veterans Affairs Salt Lake City Health Care System. The Board waived the need for consent because there was no contact with residents, and anonymity was assured.

Study Design

We conducted a retrospective study of VHA long-term care residents across 111 health care regions from 1 January 2006 through 31 December 2012. In the VHA, health care regions act as local health care systems and usually provide both acute and long-term care services. In most of these regions, long-term care services were delivered at a single facility (n = 89), although care was distributed across 2 or more locations (n = 22) in some regions. All long-term care facilities provide 24-hour nursing care, and some also provide psychiatric, spinal cord injury, or hospice care.

This retrospective study used a multilevel, longitudinal, nested case–control design. To accurately estimate resident risk, a multilevel model that incorporated both resident-level risk factors (characteristics of specific at-risk persons) and regional risk factors (measures of the prevalence of residents who were likely to shed *C difficile* spores) was used. To allow short-term pharmaceutical exposures to be measured in an appropriate retrospective window, the analysis data set was broken down into a longitudinal resident-day format. Because the resultant data set was extensive, a nested case–control design was used.

Population

Residents were considered at risk for onset of *C difficile* infection in a long-term care facility if they resided in an inpatient VHA long-term care facility for 3 or more of the previous 28 days and did not have a positive *C difficile* test result in the prior 8 weeks. Health care regions, and eligible residents within them, were included in the risk set if there were at least 6 years of data in which long-term and acute care censuses were greater than an average of 10 eligible, at-risk persons per day for each month of the given year. Regions without acute care facilities were excluded because imported cases of *C difficile* infection from non-VHA acute care facilities were not captured and would have led to an underestimate of *C difficile* importation in those regions.

Definition of Cases and Controls

Residents were considered cases on the date of a positive *C difficile* toxin test result 3 days or more after long-term care admission and at least 8 weeks from a previous positive result (13). Positive results were identified from VHA microbiology data using natural language processing (14). Eligible controls were resident-days that did not meet the case definition and could include resident-days from persons who later became cases. A 1%, unmatched, simple random sample of eligible controls was selected for analysis.

Resident Risk Factors

The 7 resident risk factors assessed were age, sex, number of days of acute care hospitalization within the previous 4 weeks, number of comorbid conditions, and 3 pharmaceutical exposures. The value of each time-varying parameter was assessed for each day. For comorbidities, acute and long-term care facility discharge diagnosis codes (International Classification of Diseases, Ninth Revision, Clinical Modification) were used to assess the presence of 14 comorbid conditions in the preceding year as per the Charlson comorbidity index (15, 16). For a given resident, the total number of comorbid conditions was summed. The following 3 pharmaceutical exposure variables were assessed, each in a 4-week retrospective window: proton-pump inhibitors; any antibiotic except *C difficile* treatment agents (metronidazole, oral vancomycin, and fidaxomicin); and an antibiotic risk index with 4 mutually exclusive risk levels consisting of high (receipt of cephalosporins, fluoroquinolones, or clindamycin), medium (receipt of penicillins, macrolides, or sulfonamides but no high-risk agents), low (receipt of tetracyclines), or no antibiotic receipt or receipt of *C difficile* treatment agents only. This antibiotic risk index was based on a

similar index developed in an independent cohort study (17).

Pharmaceutical exposure information was drawn from administration data of the VHA electronic medical record and included all courses given during inpatient care in VHA acute or long-term care facilities. Community exposures were not considered. In addition to the 7 resident risk factors, a control variable for the duration of follow-up time, defined as the total number of days a given resident stayed in a VHA acute or long-term care facility within the past 28 days, was measured and categorized into deciles.

Health Care Regional Risk Factors

The 5 regional risk factors measured were average resident age, average resident comorbidities, proton-pump inhibitor use, antibiotic use, and importation of cases of acute care *C difficile* infection. These factors were measured from the full resident population of the regions because residents who were not at risk (that is, those recently admitted with a recent positive *C difficile* test result) were just as likely if not more likely to transmit *C difficile*. Proton-pump inhibitor use and antibiotic use (excluding the *C difficile* treatment agents previously mentioned) were measured as days with therapy per 1000 resident-days. Exposure on a given day contributed 1 unit to the numerator, regardless of the number of specific agents, dosage, or number of doses administered on that day. Importation of cases of acute care *C difficile* infection was measured as the prevalence of residents in the region who were infected with *C difficile* at an acute care facility in the previous 8 weeks per 10 000 resident-days. Acute care–onset *C difficile* infection was defined as a patient with a positive *C difficile* toxin test result 3 or more days after admission to an acute care facility.

Statistical Analysis

The incidence of *C difficile* across the VHA, and within each region, was measured using the weighted mean. In all statistical analyses, sampling weights of 1 for cases and 100 for controls corresponded to the inverse of the probability of selection, allowing analyses to produce unbiased estimates of *C difficile* incidence in the entire study population (18). The minimum, 10th percentile, median, 90th percentile, and maximum *C difficile* incidence across regions were measured. Shrunken measures of *C difficile* incidence that were robust to regression-to-the-mean bias were used for measuring robust dispersion characteristics (19) (for methods, see **Appendix**, available at annals.org).

The risk for *C difficile* infection associated with each of the 7 resident-level and 5 regional predictors was assessed by using 12 weighted Poisson generalized estimating equation (GEE) regression models that controlled for duration of follow-up time, with clusters that corresponded to region. Duration of follow-up time was included as a control covariate in each model. Within clusters, the independence covariance structure was used, yielding sandwich variance estimators. For each of the 12 models, the marginal standardization approach was used to obtain absolute estimates of incidence for each exposure group (20). Confidence intervals for absolute estimates of incidence were measured using 1000 cluster bootstrap resamples in which clusters corresponded to regions (21). To provide an intuitive measurement of the global model fit for the regional models, we also measured the proportion of regional variance in incidence (R^2); we divided the sum-squared residuals around the Poisson GEE model-based incidence estimates (log scale) by the sum-squared residuals around the mean incidence. An analogous multivariate regional model was also built to obtain adjusted estimates, which included all 5 regional covariates.

To distinguish the direct and indirect effects of antibiotic use on resident risk for *C difficile* infection, we fit 2 weighted Poisson GEE regression models for the association between regional antibiotic use and *C difficile* incidence to residents with and without direct antibiotic exposure in the previous 28 days.

We built a multilevel weighted Poisson GEE model that controlled for duration of follow-up time and included individual-level factors of age, sex, days of acute care hospitalization within the previous 28 days, comorbidities, pharmaceutical exposures in the previous 28 days (antibiotic use and proton-pump inhibitor use), comorbidity burden, importation of cases of acute care *C difficile* infection, and regional antibiotic use. As such, the model included a total of 8 covariates and accounted for regional clustering.

Sensitivity Analysis

To better capture the regional effects of low-, medium-, and high-risk antibiotics and capture them in a single variable, we measured a regional antibiotic risk index in days with therapy per 1000 resident-days. Days with therapy for high-, medium-, and low-risk antibiotics were given weights of 2, 1, and 0, respectively. This weighting scheme was an adaptation of a similar risk scale from a meta-analysis of antibiotic exposures (4). This variable was included in a Poisson GEE model that controlled for follow-up time and regional clustering.

Data Extraction and Statistical Software

Data sets were built using Microsoft SQL Server Management Studio 2014. Analyses were conducted with SAS, version 9.3 (SAS Institute), and R software, version 3.1 (R Foundation for Statistical Computing), by using the GLIMMIX procedure for generalized linear mixed models and the GENMOD procedure for the GEE models.

Role of the Funding Source

This study was funded by Centers for Disease Control and Prevention and the VHA. The funders had no role in the design or conduct of the study; the collection, management, analysis, or interpretation of the data; the preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

Table 1. Resident-Level Risk Factors for *Clostridium difficile* Infection

Risk Factor	Cases, *n (%)*	Controls, *n (%)*	IRR* (95% CI)	Incidence Rate* (Per 10 000 Resident-Days)
Sex				
Female	130 (2.2)	5287 (3.2)	Reference	2.3 (1.8–3.0)
Male	5882 (97.8)	158 154 (96.8)	1.52 (1.23–1.87)	3.5 (3.0–4.0)
Age				
<60 y	902 (15.0)	27 716 (17.0)	Reference	3.0 (2.6–3.5)
60 to 69 y	1664 (27.7)	42 366 (25.9)	1.23 (1.14–1.34)	3.7 (3.1–4.3)
70 to 79 y	1398 (23.3)	36 105 (22.1)	1.23 (1.13–1.34)	3.7 (3.1–4.2)
≥80 y	2048 (34.1)	57 254 (35.0)	1.17 (1.08–1.27)	3.5 (3.0–4.0)
Hospitalization in the prior 28 d				
None	2921 (48.6)	133 844 (81.9)	Reference	2.2 (1.9–2.5)
Any	3091 (51.4)	29 597 (18.1)	4.49 (4.25–4.74)	9.9 (8.8–11.0)
1 to 7 d	1343 (22.3)	16 037 (9.8)	3.65 (3.41–3.91)	8.0 (7.0–9.2)
8 to 14 d	1102 (18.3)	9454 (5.8)	4.95 (4.59–5.34)	10.9 (9.5–12.3)
15 to 28 d	646 (10.7)	4106 (2.5)	6.92 (6.33–7.56)	15.2 (13.3–17.4)
Charlson comorbidities				
None	1246 (20.7)	67 874 (41.5)	Reference	1.8 (1.5–2.1)
1 to 2	2613 (43.5)	58 708 (35.9)	2.28 (2.13–2.44)	4.1 (3.6–4.7)
≥3	2153 (35.8)	36 859 (22.6)	3.04 (2.83–3.26)	5.5 (4.8–6.2)
Pharmaceutical exposures in the previous 28 d				
Proton-pump inhibitor				
None	2214 (36.8)	83 443 (51.1)	Reference	2.5 (2.2–2.9)
Any	3798 (63.2)	79 998 (48.9)	1.76 (1.67–1.86)	4.5 (3.9–5.1)
Antibiotic risk class				
None	1165 (19.4)	105 234 (64.4)	Reference	1.1 (1.0–1.3)
Any	4847 (80.6)	58 207 (35.6)	7.07 (6.63–7.54)	7.8 (6.9–8.8)
Low- or no-risk agents†	27 (0.4)	1949 (1.2)	1.26 (0.86–1.85)	1.4 (0.9–2.0)
Medium-risk agents‡	974 (16.2)	19 368 (11.9)	4.40 (4.04–4.79)	4.9 (4.3–5.5)
High-risk agents§	3846 (64.0)	36 890 (22.6)	8.79 (8.23–9.39)	9.7 (8.6–11.0)

IRR = incidence rate ratio.
* Adjusted for days of follow-up in prior 28 d.
† Only tetracycline exposure in the previous 28 d.
‡ Penicillin, macrolide, or sulfonamide exposures, but no high-risk agent exposures.
§ Carbapenem, monobactam, cephalosporin, fluoroquinolone, or clindamycin exposures, regardless of other antibiotic exposures.

RESULTS

Population and Nested Case–Control Sample Characteristics

Eighty-six regions met the inclusion criteria. The total population included 47 342 person-years of follow-up, 44 759 of which met the criteria for being at risk for *C difficile* infection. Per region, at-risk follow-up varied from 80 to 2176 person-years (median, 447 person-years). The 1% sampling of controls yielded a selection of 163 441 controls from across the 86 regions and represented 55 504 unique residents. The number of controls selected per region varied between 282 and 8148. The achieved sampling rate for controls was stable across regions and varied from 0.9 to 1.1 controls per 100 at-risk patient-days.

Outcome

The 6012 cases of long-term care–onset *C difficile* infection represented 5499 unique residents. The sampling ratio was 27 controls for each case, and the incidence rate of *C difficile* infection was 3.7 cases per 10 000 resident-days. Across the 86 care regions, the median regional incidence of *C difficile* infection was 3.2 cases per 10 000 resident-days and there was a substantial variation in incidence across regions (minimum, 0.6 case per 10 000 resident-days; maximum, 31.0 cases per 10 000 resident-days; range, 48.31-fold) (see Appendix Table 1, available at www.annals.org, for additional regional attributes). The dispersion of the shrunken incidence measurements remained elevated (minimum, 0.7 case per 10 000 resident-days; maximum, 29.9 cases per 10 000 resident-days; range, 40.11-fold).

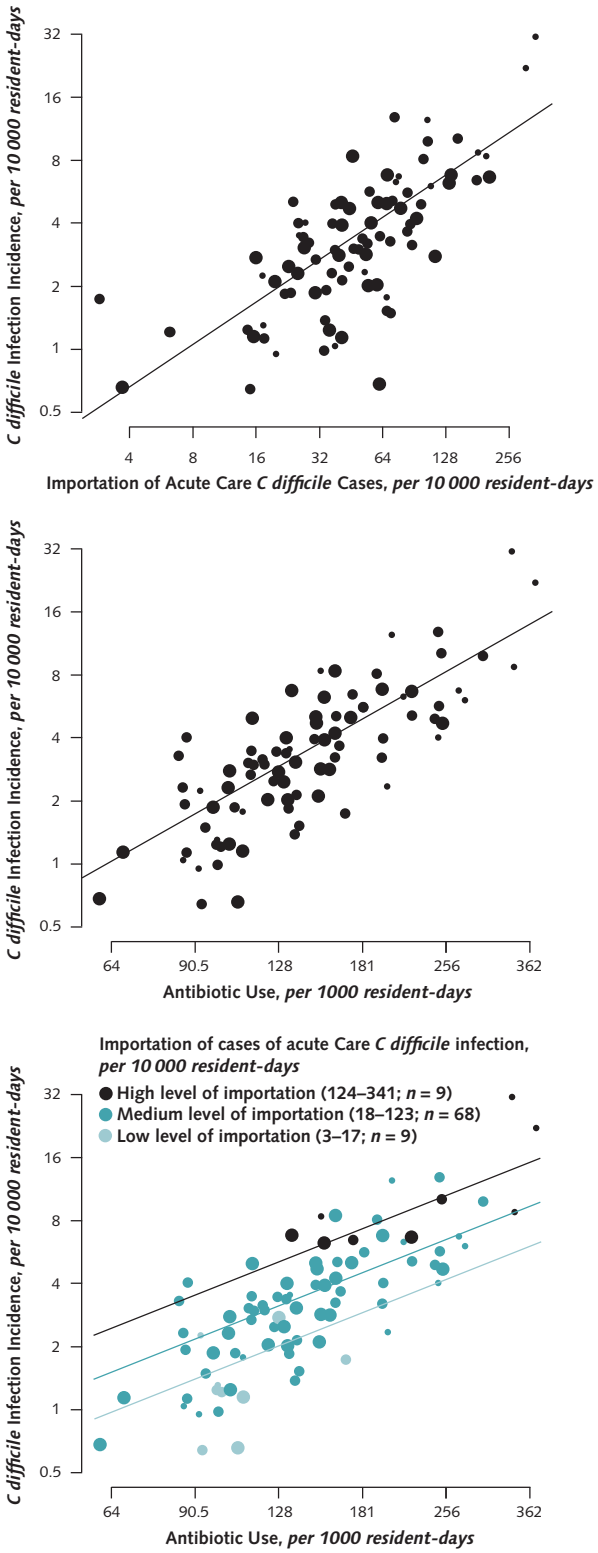
Resident Risk Factors

Residents with a history of acute care hospitalization in the previous 28 days were at increased risk for *C difficile* infection (incidence rate ratio [IRR], 4.49 [95% CI, 4.25 to 4.74]) (Table 1). Those who received antibiotics in the previous 28 days were more likely to become infected (IRR, 7.07 [CI, 6.63 to 7.54]), and there was a positive gradient across levels of the antibiotic risk index.

Health Care Region Risk Factors

In unadjusted analyses, the strongest predictors of regional *C difficile* incidence were regional antibiotic use (unadjusted IRR, 2.86 per doubling [CI, 2.34 to 3.49]; R^2 = 0.63) (Figure 1, *middle*, and Table 2) and importation of cases of acute care *C difficile* infection

Figure 1. The association between the incidence of long-term care–onset *Clostridium difficile* infection and importation of cases of acute care *C difficile* infection (*top*), antibiotic use (*middle*), and both of these variables (*bottom*).



Data represent 86 Veterans Health Administration health care regions from 2006 to 2012. Point size represents the duration of follow-up, in resident-days, within each region: small points, fewer than 100 000; medium points, 100 000 to 199 999; and large points, 200 000 or more. In the bottom panel, increased importation is represented by a shift to a higher regression line.

Table 2. Predictors of Region-Level *Clostridium difficile* Incidence*

Variable	Unadjusted IRR (95% CI)	Adjusted† IRR (95% CI)
Average patient age, per 1-y increase	0.90 (0.85–0.95)	0.97 (0.93–1.02)
Average comorbidity count, per increase of 0.1	1.14 (1.10–1.19)	0.99 (0.95–1.03)
Proton-pump inhibitor use per 1000 resident-days, per increase of 100	1.26 (1.05–1.51)	1.02 (0.91–1.14)
Antibiotic use per 1000 resident-days, per doubling	2.86 (2.34–3.49)	2.08 (1.63–2.64)
Importation of cases of acute care *C difficile* infection per 10 000 patient-days, per doubling	1.59 (1.43–1.78)	1.29 (1.18–1.41)

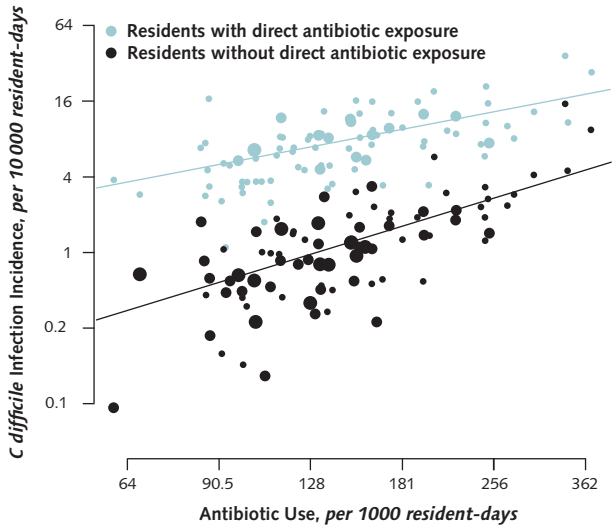
IRR = incidence rate ratio.
* Data from 86 Veterans Health Administration health care regions.
† The adjusted model included all 5 region-level covariates.

(unadjusted IRR, 1.59 per doubling [CI, 1.43 to 1.78]; R^2 = 0.50) (**Figure 1**, *top*). These 2 factors also showed dramatic variation across regions. Antibiotic use varied more than 6-fold (minimum, 61.0 days with therapy per 1000 resident-days; maximum, 370.2 days with therapy per 1000 resident-days; range, 6.07-fold), and importation of cases of acute care *C difficile* infection varied more than 100-fold (minimum, 2.9 cases per 10 000 resident-days; maximum, 341.3 cases per 10 000 resident-days; range, 118.79-fold).

The remaining 3 regional risk factors yielded weaker associations with regional *C difficile* incidence. In the adjusted analysis that included all 5 regional covariates, antibiotic use and importation of cases of acute care *C difficile* infection remained significantly associated with increased regional *C difficile* incidence but the remaining 3 covariates were not significant. Removing these 3 covariates yielded a parsimonious model that was statistically equivalent (chi-square distribution-based *P* value for removal of the 3 covariates equal to 0.72) to the 5-covariate model. This parsimonious model included only antibiotic use and importation of cases of acute care *C difficile* infection (R^2 = 0.75) (**Figure 1**, *bottom*).

A strong dose–response relationship between regional antibiotic use and *C difficile* incidence was observed in residents with and without direct antibiotic exposure when measured separately (**Figure 2**). This association was stronger in those without direct exposure (IRR, 2.81 per doubling [CI, 2.20 to 3.58]; R^2 = 0.49) than in those with direct exposure (IRR, 1.90 per doubling [CI, 1.55 to 2.33]; R^2 = 0.39). Antibiotic users were at greater relative risk, but lower absolute risk, in

Figure 2. The association between antibiotic use and incidence of long-term care–onset *Clostridium difficile* infection among residents with and without direct antibiotic use.



Data represent 86 Veterans Health Administration regions from 2006 to 2012. Point size represents the duration of follow-up, in resident-days, within each unit: small points, fewer than 100 000; medium points, 100 000 to 199 999; large points, 200 000 or more.

regions with low antibiotic use than in regions with high antibiotic use (Figure 2).

Multilevel Model

The multilevel model of risk (Table 3), which included 5 individual-level covariates (in addition to regional antibiotic use and regional importation of cases of acute care *C difficile* infection), showed that antibiotic use had a direct resident-level effect on risk (IRR, 4.81 [CI, 4.37 to 5.28]) and an indirect effect on risk by regional antibiotic use (IRR, 1.36 per doubling [CI, 1.15 to 1.60]). Importation of cases of acute care *C difficile* infection also continued to affect risk in this model (IRR, 1.23 [CI, 1.14 to 1.33]).

Sensitivity Analysis

To distinguish the role of low- and high-risk antibiotics in driving regional *C difficile* infection risk, we conducted a sensitivity analysis that used a regional antibiotic risk index with larger weights for high-risk antibiotics. In this model, the antibiotic risk index yielded a fit that was very similar to total antibiotic use (unadjusted IRR, 2.71 per doubling [CI, 2.26 to 3.25]; $R^2 = 0.58$). This index was strongly correlated with total antibiotic use ($R^2 = 0.96$). Additional sensitivity analyses are presented in the Appendix and Appendix Table 2 (available at www.annals.org).

DISCUSSION

In this comprehensive, nested case–control study of the risk for *C difficile* infection across long-term care facilities in 86 VHA health care regions, regional rates of *C difficile* infection varied 40-fold. Regional antibiotic use varied more than 6-fold, and importation of cases of acute care *C difficile* infection varied more than 100-fold. Regional antibiotic use and importation accounted for 75% of the regional variability in the incidence of long-term care–onset *C difficile* infection. Regional differences in the prescription of antibiotics affected resident risk in addition to individual receipt of antibiotics, which suggests that antibiotic users were at increased risk for both acquiring and spreading *C difficile*.

The median daily point prevalence of antibiotic use in long-term care was 14%, which was double that of previously reported estimates of antibiotic use (10, 22). Antibiotic use was the primary driver of differences in *C difficile* rates across VHA long-term care facilities, and total antibiotic use predicted risk more accurately than the specific mix of high- and low-risk antibiotics dispensed. Antimicrobial stewardship initiatives geared toward *C difficile* reduction in long-term care could consider the reduction of total antibiotic use as a primary target.

Further, important herd effects of antibiotic use were identified. Residents with and without direct antibiotic receipt were more likely to develop *C difficile* infection in regions with greater levels of antibiotic use. Such herd effects of antibiotic prescribing on *C difficile* infection were hypothesized nearly 2 decades ago (23); since then, only 2 studies have empirically analyzed the indirect effects of antibiotic use on *C difficile* incidence and have yielded contradictory findings (9, 24). Our study found that the direct effects of antibiotic use were heterogeneous: Antibiotic users were at greater relative risk, but lower absolute risk, in regions with low antibiotic use than in those with high antibiotic use. This may help to explain the substantially larger relative risks

Table 3. Summary of Resident- and Region-Level Risk Factors for *Clostridium difficile* Infection

Risk Factor	IRR* (95% CI)
Resident level	
Male sex	1.41 (1.14–1.76)
Age	
<60 y	Reference
60 to 69 y	1.23 (1.12–1.34)
70 to 79 y	1.31 (1.19–1.45)
≥80 y	1.49 (1.34–1.65)
Acute care hospitalization in the prior 28 d	1.85 (1.71–2.01)
Charlson comorbidities	
None	Reference
1 to 2	1.28 (1.17–1.39)
≥3	1.50 (1.37–1.63)
Pharmaceutical exposures in the previous 28 d	
Antibiotic	4.81 (4.37–5.28)
Proton-pump inhibitor	1.29 (1.21–1.38)
Region level	
Antibiotic use, per doubling	1.36 (1.15–1.60)
Importation of cases of acute care *C difficile* infection, per doubling	1.23 (1.14–1.33)

IRR = incidence rate ratio.
* This model included adjustment for days of follow-up in the prior 28 d.

for antibiotics observed in the community (4) than in the acute care setting (5).

This study provides evidence that antibiotic use drives *C difficile* transmission within long-term care facilities. The mechanism of transmission may be that in facilities with high antibiotic use, there is an increased prevalence of residents with asymptomatic *C difficile* colonization who, when exposed to antibiotics, become more effective at shedding *C difficile* spores (7). This research supports efforts in many countries to institute regional and health care system–wide antibiotic stewardship initiatives that aim to reduce unnecessary prescribing (25); further, this research suggests that the scope of antibiotic reporting should include long-term care antibiotic use as intrinsic to regional stewardship programs.

Previous studies have measured the prevalence of colonization with *C difficile* on admission to acute care hospitals (26, 27) and noted that a substantial proportion of persons with *C difficile* infection in long-term care seemed to have acquired the bacteria in acute care facilities (11, 28, 29). Importation has been shown to be an important predictor of facility-level methicillin-resistant *Staphylococcus aureus* colonization (30). To our knowledge, however, its effect on rates of onset of *C difficile* infection in long-term care has never been assessed. In this study, the median regional prevalence of residents with acute care–onset infection in the previous 8 weeks was 47.7 cases per 10 000 resident-days and varied more than 100-fold across regions. The importation of patients with acute care–onset infection acted in concert with antibiotic use in predicting long-term care infection rates. Our results suggest that infection prevention and control teams may need to take special measures in long-term care facilities that receive residents from hospitals with elevated rates of *C difficile* infection.

Our study has several limitations. First, our outcome considered only laboratory-identified *C difficile*, which does not necessarily correspond with clinical infections. This is concerning given heterogeneity in testing practices across regions. However, it has been shown that more than 90% of laboratory-identified cases of *C difficile* infection in the VHA were clinically confirmed (31). Second, our study included importation from only VHA acute care facilities and did not consider cases of *C difficile* infection from all sources. As such, this study may have underestimated the role of importation. Further, our study only considered importation in a 56-day window from a positive *C difficile* test result. Third, we had no molecular information on the strains of *C difficile* that infected residents; therefore, the risk levels incurred by antibiotics represented averages across the strains in each region. Our results may not be representative of or generalizable to other countries in which strain distributions differ. Finally, this study did not incorporate outpatient pharmaceutical exposures and considered only a brief antibiotic exposure assessment window. These are factors that sensitivity analyses suggested could have led to an underestimation of antibiotic effects.

To our knowledge, this study of long-term care–onset *C difficile* infection is the largest and most comprehensive to date. It provides a detailed portrait of risk, including both individual and regional factors. We found that variation in regional antimicrobial use was strongly associated with variation in the *C difficile* incidence in long-term care settings. In regions with high rates of *C difficile* in long-term care, coordinated antimicrobial stewardship initiatives that reduce inappropriate prescribing have the potential to substantially reduce rates of *C difficile* infection.

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Appendix

Robust Measures of Dispersion

Because measurement error can inflate estimates of the range and IDR, we also calculated the minimum, 10th percentile, median, 90th percentile, and maximum on the predicted regional incidence rates from a generalized linear mixed model that included only the fixed-effect intercept and random intercepts for regions. These calculations provided estimates of range and IDR that were shrunken toward the ensemble mean in proportion to the degree of potential measurement error and thus robust against regression-to-the-mean bias (19).

Methods for Additional Sensitivity Analysis

We conducted different sensitivity analyses to explore the robustness of the regional estimates from the main adjusted multilevel model. Each sensitivity analysis consisted of a slight modification to the variable specification or the source population of the main multilevel model (Table 3).

The first sensitivity analysis considered the effects of regional antibiotic use and importation of cases of *C difficile* infection on the risk for infection in a more causally relevant 8-week retrospective window. To do this, we built a region-day data set that included 1 observation for each day of the study period per region. For each region-day, importation of cases of *C difficile* infection and antibiotic use within the region on that given day were measured. We then calculated the mean regional importation and antibiotic use across a 56-day retrospective window, and this variable was merged into the nested case–control data set by matching on region and day. These 2 time-varying region variables were then used in the multilevel analyses rather than the time-fixed versions that were used in the main analysis.

The second sensitivity analysis explored the effect of including only residents who were present in a VHA acute or long-term care facility in each of the prior 28 days because they had the most accurate assessment of pharmaceutical exposures.

The third sensitivity analysis included an additional covariate that identified patients whose most recent antibiotic exposure was in a 5- to 12-week retrospective window.

To investigate whether the sample size for the nested case–control study was sufficiently large, the fourth sensitivity analysis included the same variables as the main analysis (Table 3), except that a 5% control sample was used rather than a 1% control sample.

To identify whether importation from other non-VHA acute care sources may affect the analysis results, the fifth sensitivity analysis included the same variables as the main analysis (Table 3), except this analysis was limited to only regions in which at least 10% of the resident population had contact with a VHA acute care facility in the prior 28 days. This subset of regions was likely to have more accurate identification of importation because the resident population was so closely tied to VHA acute care facilities.

Results for Additional Sensitivity Analysis

Sensitivity Analysis 1

When the 2 region risk factors were considered as time-varying covariates within the multilevel model, the dose–response association between each variable and increased *C difficile* incidence remained (Appendix Table 2) (IRR for mean regional antibiotic use in past 56 days, 1.61 per doubling [CI, 1.39 to 1.87]; IRR for mean importation of cases of acute care *C difficile* infection in the last 56 days, 1.14 per doubling [CI, 1.10 to 1.18]).

Sensitivity Analysis 2

When the analysis sample for the main multilevel model was restricted to residents with complete 28-day follow-up, the estimated association between direct antibiotic use and the risk for *C difficile* infection and regional antibiotic use and the risk for *C difficile* infection both increased substantially.

Sensitivity Analysis 3

When a variable capturing the effect that antibiotic exposure had in the previous 5 to 12 weeks was added to the main multilevel model, the estimated association for direct antibiotic use in the previous 4-week period increased and the regional antibiotic use remained unchanged.

Sensitivity Analysis 4

The estimates from this sensitivity analysis were almost identical to our main analysis, suggesting that our 1% control sample size was sufficient.

Sensitivity Analysis 5

Across regions, the proportion of residents who had acute care contact in the prior 28 days varied from 5.2% to 62.4%. In 77 regions, an average of at least 10% of the residents had recent contact in the prior 28 days with VHA acute care. The analysis results (not shown) were almost identical to the main analysis. In this model, the effect of importation of cases of acute care *C difficile* infection was identical (IRR, 1.23 per doubling [CI, 1.13 to 1.34]; results not shown in Appendix Table 2).

Appendix Table 1. Region-Level Distribution of *Clostridium difficile* Incidence, Antibiotic Use, and Importation of Cases of Acute Care *C difficile* Infection (n = 86)

Variable	Minimum	p10	Median	p90	Maximum	Range	IDR
C difficile incidence per 10 000 resident-days	0.6	1.2	3.2	8.3	31.0	48.31	6.96
Shrunken *C difficile* incidence per 10 000 resident-days	0.7	1.3	3.2	7.9	29.9	40.11	6.11
Antibiotic use per 1000 resident-days	61.0	92.1	137.0	248.3	370.2	6.07	2.70
Importation of cases of acute care *C difficile* infection, per 10 000 resident-days	2.9	17.3	47.7	123.2	341.3	118.79	7.11

IDR = interdecile range; p10 = 10th percentile; p90 = 90th percentile.

Appendix Table 2. Summary of Sensitivity Analyses for Adjusted Predictors of *Clostridium difficile* Infection*

Risk Factor	Sensitivity Analysis 1: Time-Varying Region-Level Exposures	Sensitivity Analysis 2: Subset of Residents With 28-d Follow-up	Sensitivity Analysis 3: 12-wk Antibiotic Exposure Window	Sensitivity Analysis 4: Larger 5% Control Sample Size
Resident level				
Male sex	1.41 (1.13–1.75)	1.44 (1.11–1.87)	1.42 (1.14–1.77)	1.42 (1.14–1.76)
Age				
<60 y	Reference	Reference	Reference	Reference
60 to 69 y	1.26 (1.16–1.38)	1.17 (1.06–1.29)	1.23 (1.13–1.35)	1.24 (1.14–1.34)
70 to 79 y	1.31 (1.19–1.45)	1.23 (1.10–1.38)	1.32 (1.19–1.45)	1.33 (1.21–1.47)
≥80 y	1.49 (1.34–1.64)	1.35 (1.22–1.50)	1.49 (1.35–1.65)	1.50 (1.36–1.66)
Hospitalization at an acute care facility in the previous 28 d	1.91 (1.76–2.07)	2.09 (1.92–2.26)	1.86 (1.71–2.02)	1.87 (1.71–2.03)
Charlson comorbidities				
None	Reference	Reference	Reference	Reference
1 to 2	1.29 (1.19–1.40)	1.53 (1.36–1.72)	1.22 (1.13–1.33)	1.27 (1.17–1.37)
≥3	1.50 (1.38–1.64)	1.73 (1.54–1.94)	1.42 (1.30–1.55)	1.48 (1.35–1.61)
Antibiotic use				
None†	Reference	Reference	Reference	Reference
Antibiotic use in the previous 4 wk	4.71 (4.28–5.17)	5.04 (4.50–5.64)	6.91 (6.08–7.85)	4.78 (4.35–5.25)
Antibiotic use in the previous 5–12 wk	NA	NA	2.34 (2.08–2.63)	NA
Proton-pump inhibitor use in previous 4 wk	1.28 (1.20–1.37)	1.22 (1.13–1.32)	1.28 (1.19–1.36)	1.28 (1.20–1.37)
Region level				
Antibiotic use, per doubling	NA	1.45 (1.23–1.72)	1.35 (1.14–1.59)	1.36 (1.16–1.61)
Importation of cases of acute care *C difficile* infection, per doubling	NA	1.22 (1.13–1.32)	1.23 (1.14–1.33)	1.23 (1.14–1.33)
Region-level exposures in the previous 56-d period				
Antibiotic use, per doubling	1.61 (1.39–1.87)	NA	NA	NA
Importation of cases of acute care *C difficile* infection, per doubling	1.14 (1.10–1.18)	NA	NA	NA

NA = not applicable.
* All numbers represent incidence rate ratios and 95% CIs from multilevel Poisson generalized estimating equation models that included adjustment for days of follow-up.
† For sensitivity analysis 3, the referent group included residents with no antibiotic exposure in the previous 84 d. For all other sensitivity analyses, the referent category included residents with no antibiotic exposure in the previous 28 d only.