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Authors

Brown, Kevin A
Jones, Makoto
Daneman, Nick
et al.

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Title: Importation, Antibiotics, and *Clostridium difficile* Infection in Veteran Long-Term Care: A Multilevel Case-Control Study

Running Title: *C. difficile* Infection in Veteran Long-Term Care

Kevin A. Brown, PhD
Makoto Jones, MD
Nick Daneman, MD
Frederick R. Adler, PhD
Vanessa Stevens, PhD
Kevin E. Nechodom, BSc
Matthew B. Goetz, MD
Matthew H. Samore, MD
Jeanmarie Mayer, MD

Author Affiliations: Division of Epidemiology, University of Utah (Drs. Brown, Jones, Stevens, Samore, Mayer and Mr. Nechodom), Salt Lake City Veterans Affairs Healthcare System, (Drs. Brown, Jones, Samore, and Mayer), Dalla Lana School of Public Health, University of Toronto (Dr. Brown), Public Health Ontario (Dr. Brown), Sunnybrook Health Sciences Centre, University of Toronto (Dr. Daneman), Department of Mathematics and Department of Biology, University of Utah (Dr. Adler), Department of Pharmacotherapy, University of Utah (Dr. Stevens), Infectious Diseases Section, Department of Medicine, Greater Los Angeles Veterans Affairs Healthcare System and David Geffen School of Medicine at UCLA (Dr. Goetz)

Corresponding Author: Kevin Antoine Brown, PhD, Public Health Ontario, 480 University Ave, Toronto, Canada M5G1V2, kevin.brown@oahpp.ca

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Summary

Background: While factors impacting an individual's susceptibility to *C. 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 impact *C. difficile* infection incidence.

Design: Multilevel longitudinal nested case-control study.

Setting: Veterans Health Administration (VHA) healthcare regions, from 2006 through 2012.

Participants: Long-term care residents.

Measurements: Individual-level risk factors included age, number of comorbid conditions, and antibiotic exposure. Region-level risk factors included importation of acute care *C. difficile* cases per 10,000 resident-days and antibiotic use per 1,000 resident-days. The outcome was defined as an incident long-term care positive *C. difficile* test, without a positive test in the prior 8 weeks.

Results: 6,012 cases (incidence=3.7 per 10,000 resident-days) were identified in 86 regions. Across regions, there was substantial variation in long-term care *C. difficile* incidence (min=0.7, max=32.4), antibiotic use (min=60.9, max=370.2 per 1,000 resident-days), and importation (min=2.8, max=341.3 per 10,000 resident-days). Together, antibiotic use and importation explained 75% of the regional variation in *C. difficile* incidence (R^2=0.75). Multilevel analyses showed that region-level factors impacted risk above and beyond individual-level exposures (region antibiotic use, RR=1.45 per doubling, 95%CI: 1.24, 1.69; importation, RR=1.25 per doubling, 95%CI: 1.16, 1.34).

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

Conclusions: Only 25% of the variation in long-term care *C. difficile* infection incidence remained unexplained after accounting for importation from acute care and antibiotic use, suggesting that *C. difficile* infection control at acute care facilities and antimicrobial stewardship may help reduce long-term care *C. difficile* incidence.

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Introduction

Clostridium difficile infection is a diarrheal disease that is associated with antibiotic and healthcare exposures. *C. difficile* has the highest prevalence, morbidity, and mortality of any healthcare-associated infection (1,2). Risk factors for acquisition of *C. difficile* 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 thought to increase risk, but the magnitude of risk is especially high for antibiotics with activity against gut flora and lacking activity against *C. difficile,* which include cephalosporins, fluoroquinolones, and clindamycin (4,5). Antacids, especially proton pump inhibitors, are thought to increase risk by reducing stomach acidity, thereby allowing increased numbers of ingested *C. difficile* to reach the gut in a viable state.

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 even asymptomatic colonization have high bacterial loads in their stool and shed infectious spores into their environs for extended periods of time (6,7). Exposure of patients to inpatient care unit-level disease pressure, measured as the daily number of infectious patients with recent *C. difficile* infection present on the same inpatient care unit, predicts increased risk of *C. difficile* infection (8). In addition to disease pressure, hospital care unit antibiotic use has been shown to increase risk of acquisition, above and beyond individual-level antibiotic exposure (9). This may be due to the higher likelihood of asymptomatic *C. difficile* colonization and shedding among patients with recent antibiotic exposure (7) which thereby creates a higher 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 of antibiotic use around 8%, of which 25% to 75% may be inappropriate (10). The impact of antimicrobial use on facility *C. difficile* infection incidence in long-term care settings has never been explored. Further, long-term care residents have frequent contact with acute care facilities and, as such, importation of hospital-onset *C. difficile* cases may be an important risk factor for long-term care *C. difficile* infection incidence (11).

Models incorporating both individual- and facility-level risk factors can be used to distinguish risk factors that impact individual susceptibility to disease from factors 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 region-level factors that drive *C. difficile* infection risk across Veterans Health Administration (VHA) long-term care, with a specific interest in the role of importation of acute care facility onset *C. difficile* infection and regional rates of antibiotic use.

Methods

Ethics Statement

Study approval was obtained from the research ethics board of the Salt Lake City Veterans Affairs Health Care System. The board waived the need for consent because there was no contact with residents and their anonymity was assured.

Study Design

A retrospective study of VHA long-term care residents across 111 healthcare regions in the 7-year period from January 1, 2006 through December 31, 2012 was conducted. In VHA, healthcare regions act as local healthcare systems and usually provide both acute and long-term care services. In most of these regions, long-term care services were delivered in a single facility (n=89), though in some regions care was distributed across 2 or more locations (n=22). All long-term care facilities provide 24-hour nursing care and some additionally provide psychiatric care, spinal cord injury care, or hospice care.

This retrospective study employed a multilevel longitudinal nested case-control design. To accurately estimate resident risk, a multilevel model was used, which incorporated both resident-level risk factors (characteristics of specific at-risk individuals), as well as region-level risk factors (measures of the prevalence of residents that were likely to shed *C. difficile* spores). To allow short-term pharmaceutical exposures to be measured in an appropriate retrospective window, the analysis dataset was broken down into a longitudinal, resident-day format. Since the resultant dataset was extensive, a nested case-control design was used.

Population

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

Definition of Cases and Controls

A resident was considered a case on the date of a positive *C. difficile* toxin test ≥3 days after their long-term care admission and occurring at least 8 weeks from a previous positive test (13). Positive *C. difficile* tests 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 individuals that 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 consisted of age, sex, days of acute care hospitalization within the previous 4 weeks, number of comorbid conditions, 3 pharmaceutical exposures, and days of follow-up time within the previous 4 weeks. The value of each time-varying variable was assessed for each day. For comorbidity count, acute and long-term care facility discharge diagnosis codes (ICD-9-CM) were used to assess the presence of 14 comorbidities in the preceding year, as per Charlson (15,16). For a given resident, the total number of comorbidities was summed. Three pharmaceutical exposure variables were assessed, each in a 4-week retrospective window: (i) proton pump inhibitors, (ii) any antibiotic, but excluding *C. difficile* treatment agents (metronidazole, oral vancomycin and fidaxomicin), and (iii) an antibiotic risk index with 4 mutually exclusive levels consisting of: high-risk (receipt of cephalosporins, fluoroquinolones, or clindamycin), medium-risk (receipt of penicillins, macrolides, or sulfonamides but no high-risk agents), or low-risk (receipt of tetracyclines), or no antibiotic receipt or receipt of *C. difficile* treatment agents only, based on a similar risk index developed in an independent cohort study (17).

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

Healthcare Region Risk Factors

The five regional risk factors measured were average resident age, average resident comorbidity count, proton pump inhibitor use, antibiotic use, and importation of acute care *C. difficile* cases. These five region-level risk factors were measured from the full resident population of the regions, because residents who were not at risk (i.e.: recently admitted residents with a recent positive *C. difficile* test) were just as likely or more likely to transmit *C. difficile*. Proton pump inhibitor use and antibiotic use (excluding the *C. difficile* treatment agents mentioned above) were each measured as days of therapy (DOT) per 1,000 resident-days. Exposure on a given day contributed one unit to the numerator, regardless of the number of specific agents, dosage, or number of doses administered on that day. Importation of acute care *C. difficile* cases was measured as the prevalence of residents in the region that had an acute care onset *C. difficile* infection in the previous 8 weeks, per 10,000 resident-days. Acute care onset *C. difficile* infection was defined as a resident with a positive *C. difficile* toxin test ≥3 days after their long-term care admission from an acute care facility.

Statistical Analyses

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, 10^{th} percentile (p10), 90^{th} percentile (p90), and maximum *C. difficile* infection 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) (see appendix for methods).

The association between each of the 7 resident-level and 5 region-level predictors, and *C. difficile* infection risk was assessed using 13 weighted Poisson generalized estimating equation (GEE) regression models that controlled for duration of follow-up time, and 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 13 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, where clusters corresponded to regions (21). In order to provide an intuitive measurement of the global model fit for the regional models, we also measured the proportion of region-level variance in incidence explained (R^2) by dividing 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 region-level model was also built to obtain adjusted estimates, which included all 5 region-level covariates.

In order to distinguish the direct and indirect effects of antibiotic use on resident *C. difficile* risk, we fit two weighted Poisson GEE regression models for the association between region-level antibiotic use and *C. difficile* incidence to residents with and without direct antibiotic exposure in the previous 28-days.

A multilevel weighted Poisson GEE model was built 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, comorbidity count, and pharmaceutical exposures in the previous 28 days (antibiotic use and PPI use), comorbidity burden, importation of acute care *C. difficile* cases and region antibiotic use. As such, the model included a total of 8 covariates, and accounted for region-level clustering.

Sensitivity Analyses

To better capture the region-level effects of low, medium, and high risk antibiotics and capture them in a single variable, we measured a region-level antibiotic risk index that was measured as DOT per 1,000 resident-days, but where days of therapy for high-risk antibiotics were given a weight of 2, medium-risk antibiotics, a weight of 1, and low-risk antibiotics, a weight of 0. This weighting scheme was adapted from 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 region-level clustering.

Data extraction and statistical software

Datasets were builit using SQL Server Management Studio. Analyses were conducted using SAS and R software, 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 through the United States Centers for Disease Control and the Veterans Health Administration. The funders had no role in the design and conduct of the study; the collection, management, analysis, and interpretation of the data; the preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

Results

Population and Nested Case-Control Sample Characteristics

86 regions met the inclusion criteria. In total, the population included 47,342 person-years of follow-up, of which 44,759 years met the criteria for being at risk for *C. difficile* infection. Per region, at-risk follow-up varied from 80 to 2,176 person-years (median=447 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 controls selected per region varied between 282 and 8,148, and the achieved sampling rate was stable across regions, varying from 0.9% to 1.1%.

Outcome

There were 6,012 cases of long-term care onset *C. difficile* infection, representing 5,499 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 at-risk resident-days. Across the 86 care regions, the median region-level incidence of *C. difficile* infection was 3.2 per 10,000 at-risk resident-days and there was a substantial variation in incidence across regions (min=0.6, p10=1.2, median=3.2, p90=8.3, max=31.0, range=48.31-fold, interdecile range [IDR]=6.96-fold). The dispersion of the shrunken incidence measurements remained elevated (min=0.7, p10=1.3, median=3.2, p90=7.9, max=29.9, range=40.11-fold, IDR=6.11-fold).

Resident Risk Factors

Residents with a history of acute care hospitalization in the previous 28 days had a 4.49-fold increase in the risk of developing *C. difficile* (95%CI: 4.25, 4.74, Table 1). Residents who received antibiotics in the previous 28 days were 7.07-fold more likely to develop a *C. difficile* infection (95%CI: 6.63, 7.54), and there was a positive gradient across levels of the antibiotic risk index.

Healthcare Region Risk Factors

In unadjusted analyses, the strongest predictors of region *C. difficile* incidence were region antibiotic use (Figure 1, panel A, and Table 2, unadjusted incidence rate ratio [IRR]=2.86 per doubling of antibiotic use, 95%CI: 2.34, 3.49, R^2=0.63) and importation of acute care *C. difficile* cases (Figure 1, panel B, unadjusted IRR=1.59 per doubling of importation, 95%CI: 1.43, 1.78, R^2=0.50). These two factors also showed dramatic variation across regions: antibiotic use varied over 6-fold (min=70.0, p10=92.1, median=137.0, p90=248.3, max=370.2, range=6.07-fold, IDR=2.70-fold) and importation of acute care *C. difficile* cases varied over 100-fold (min=2.9, p10=17.3, median=47.7, p90=123.2, max=341.3, range=118.79-fold, IDR=7.11-fold).

The remaining 3 region-level risk factors yielded weaker associations with region-level *C. difficile* incidence. In the adjusted analysis that included all 5 region-level covariates, antibiotic use and importation of acute care *C. difficile* cases remained significantly associated with increased region-level *C. difficile* incidence, but the remaining three region-level covariates were not significant. Dropping the three non-significant region-level covariates yielded a parsimonious model that was statistically equivalent (score χ^2_{3df}=1.3 p=0.72) to the 5-covariate model. This parsimonious model included just antibiotic use and importation of acute care cases (R^2=0.75, Figure 1, panel C).

When measured in residents with and without direct antibiotic exposure separately, a strong dose-response relationship between region antibiotic use and *C. difficile* incidence was observed in both groups (Figure 2). This association was stronger in residents without direct exposure (IRR=2.81 per doubling, 95%CI: 2.20, 3.58, R^2=0.49), than among residents with direct exposure (IRR=1.90 per doubling, 95%CI: 1.55, 2.33, R^2=0.39). Antibiotic users were at greater relative risk, but lower absolute risk, in low antibiotic use regions as compared to high antibiotic use regions (Figure 2).

Multilevel Model

The multilevel model of risk (Table 3), which included 5 individual-level covariates, in addition to region antibiotic use and region importation of acute care *C. difficile* cases, demonstrated that antibiotic-use had both a direct, resident-level impact on risk (IRR=4.81, 95%CI: 4.37, 5.28), in addition to an indirect impact on risk via region antibiotic use (IRR=1.36 per doubling, 95%CI: 1.15, 1.60). Importation of acute care *C. difficile* cases also continued to impact risk in this model (IRR=1.23, 95%CI: 1.14, 1.33).

Sensitivity Analyses

In order to distinguish the role of low- and high-risk antibiotics in driving region-level *C. difficile* infection risk, we conducted a sensitivity analysis that used a region-level antibiotic risk index having larger weights for high-risk antibiotics. In this model, the antibiotic risk index yielded a fit that was very similar to antibiotic use (unadjusted IRR=2.71 per doubling, 95%CI=2.26, 3.25, R^2=0.58). The antibiotic risk index was strongly correlated

with total antibiotic use (R^2=0.96). Additional sensitivity analyses are presented in the appendix.

Conclusions

In this comprehensive nested case-control study of *C. difficile* infection risk across long-term care facilities in 86 VHA healthcare regions, (i) region rates of *C. difficile* infection varied 40-fold, (ii) region antibiotic use varied over 6-fold and importation of acute care *C. difficile* cases varied over 100-fold, (iii) region antibiotic use and importation of acute care *C. difficile* cases explained 75% of the variability in region long-term care onset of *C. difficile* infection incidence, and (iv) region antibiotic prescribing impacted resident risk above and beyond individual receipt of antibiotics.

The median daily point prevalence of antibiotic use in long-term care was 14%, which is double that of previous 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 drove risk more 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 reductions of total antibiotic usage as a primary target.

Furthermore, important herd effects of antibiotic use were identified. Residents with direct antibiotic receipt, as well as those without direct receipt, were both more likely to develop *C. difficile* infection in regions with higher levels of antibiotic use. Such herd-effects of antibiotic prescribing on *C. difficile* infection were hypothesized nearly two decades ago (23) and since then, only two studies have empirically analyzed the indirect effects of antibiotic use on *C. difficile* incidence with contradictory findings (9,24). This study identified that the direct effects of antibiotic use were heterogeneous: antibiotic users were at greater relative risk, but lower absolute risk, in low antibiotic use regions as compared to high antibiotic use regions. This may help to explain the substantially larger relative risks of antibiotics observed in community (4) as compared to acute care settings (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 increased prevalence of residents with asymptomatic *C. difficile* colonization, who, when exposed to antibiotics, become more effective *C. difficile* shedders (7). This research supports efforts in many countries to institute regional and care-system-wide antibiotic stewardship initiatives that aim to reduce unnecessary prescribing (25), and also suggests that the scope of antibiotic reporting also consider long-term care antibiotic use as intrinsic to regional stewardship programs.

Previous studies have measured prevalence of colonization with *C. difficile* on admission to acute care hospitals (26,27) and noted that an important proportion of *C. difficile* infections in long-term care appeared 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). However, the impact of importation on rates of long-term care onset *C. difficile* has never been assessed. In this study, the

prevalence of residents with acute care onset *C. difficile* infection in the previous 8-weeks was, on average, 45.5 per 10,000 resident-days and varied over a 100-fold range. The importation of residents with acute care onset *C. difficile* acted in concert with antibiotic use in predicting long-term care onset *C. difficile* 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 a number of limitations. First, our outcome considered only laboratory-identified *C. difficile*, which do not necessarily correspond with clinical infections. This is especially a concern given heterogeneity in testing practices across regions. However, one study has shown that over 90% of laboratory-identified *C. difficile* cases in the VHA were clinically confirmed (31). Second, our study only included importation from VHA acute care facilities and did not consider *C. difficile* cases from all sources. As such, this study may have underestimated the role of importation. Furthermore, this study only considered importation in a 56-day window from a positive *C. difficile* test. Third, we had no molecular information on the strains of *C. difficile* that infected residents and therefore the risk levels incurred by antibiotics represented averages across the strains in each region. Our results may not be representative or generalizable to other countries where strain distributions differ. Finally, this study did not incorporate outpatient pharmaceutical exposures and considered only a brief antibiotic exposure assessment window, both factors that sensitivity analyses suggested could have led to an underestimation of antibiotic effects.

This study of long-term care *C. difficile* infection is the largest and most comprehensive to date, and provides a detailed portrait of risk, including both individual and regional factors. We found that variation in region antimicrobial use was strongly associated with variation in the *C. difficile* infection incidence in long-term care. 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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Study conception and design: Brown, Adler, Mayer, Jones, Samore. Acquisition of the data: Brown, Mayer, Jones, Samore, Nechodom. Analysis or interpretation of the data: All authors. Drafting of the manuscript: Brown. Critical revision of the manuscript: All authors. Administrative, technical, or material support: Jones, Samore, Nechodom. Study supervision: Brown, Mayer, Jones, Samore.

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Figure legends

Figure 1. The association between the incidence of long-term care onset *C. difficile* infection and importation of acute care *C. difficile* cases (panel A), antibiotic use (panel B), and both of these variables (panel C), across 86 VHA healthcare regions, 2006 to 2012. Point-size represents the duration of follow-up in resident-days within each region: (small point) less than 100,000, (medium point) 100,000 to 199,999, (large point) 200,000 or more. For panel C, regression lines represent the estimated association between antibiotic use and *C. difficile* infection incidence at the 5th (lowest line), 50th (middle line), and 95th (highest line) percentiles of importation.

Figure 2. The association between antibiotic use and the incidence of long-term care onset *C. difficile* infection among residents with and without direct antibiotic use across 86 VHA regions, 2006 to 2012. Point-size represents the duration of follow-up, in resident-days, within each unit: (small point) less than 100,000, (medium point) 100,000 to 199,999, (large point) 200,000 or more.

Appendix

Robust Measures of Dispersion

Because measurement error can inflate estimates of the range and interdecile range, we also calculated the minimum, p10, p90, and maximum on the predicted region-level incidence rates from a generalized linear mixed model that included only the intercept fixed effect and random intercepts for regions. These estimates provided estimates of range and interdecile range 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 Analyses

We conducted different sensitivity analyses in order to explore the robustness of the region-level estimates from the main adjusted multilevel model, presented in Table 3. Each sensitivity analysis consisted of a slight modification to the variable specification or the source population of the main multilevel model presented in Table 3.

- The first sensitivity analysis considered the impacts of region antibiotic use and importation of *C. difficile* cases on *C. difficile* risk in a more causally relevant 8-week retrospective window. To do this we built a region-day dataset that included, for each region, one observation for each day of the study period. For each region-day, importation of *C. difficile* cases and antibiotic use within the region on that given day were measured. We then calculated the mean region-level importation and antibiotic use across a 56-day retrospective window and this was merged into the nested case control dataset, matching on region and day. These two 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 impact 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 exposure assessment for pharmaceutical exposures.
- The third sensitivity analysis included an additional covariate that identified patients whose most recent antibiotic exposure was in a 5-12 week retrospective window.
- In order 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 presented in Table 3, except that a 5% control sample was used rather than a 1% control sample.
- In order to identify whether importation from, other, non-VHA acute care sources may impact the analysis results, the fifth sensitivity analysis included the same variables as the main analysis presented in Table 3, except this analysis was limited to only those regions in which at least 10% of the resident population had VHA acute care contact in the prior 28 days. This subset of regions was likely to have more accurate identification

of importation because in these regions the resident population was so closely tied to VHA acute care facilities.

Results for Additional Sensitivity Analyses

- Sensitivity analysis 1: When the two region risk factors were considered as time-varying covariates within the multilevel model described above, the dose-response association between each variable and increased *C. difficile* incidence remained present (Appendix Table, IRR for mean region-level antibiotic use in last 56 days, per doubling=1.61, 95%CI: 1.39, 1.87, IRR for mean importation of acute care *C. difficile* cases in last 56 days, per doubling=1.14, 95%CI: 1.10, 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 for between direct antibiotic use and region-level antibiotic use actually increased substantially.
- Sensitivity analysis 3: When a variable capturing the impact antibiotic exposure in the previous 5-12 weeks was added to the main multilevel model, the estimated association for direct antibiotic use in the previous 4-week period increased, while region-level antibiotic use remained unchanged.
- Sensitivity analysis 4: The estimates from this sensitivity analysis were almost exactly identical to our main analysis, suggesting that our 1% control sample size was sufficient.
- Sensitivity analysis 5: Across regions, the proportion of residents that had acute care contact in the prior 28 days varied from 5.2% to 62.4%. There were 77 regions in which, on average, at least 10% of residents had recent contact in the prior 28 days with VHA acute care. The analysis results were almost identical to the main analysis (not shown). In this model, the impact of importation of acute care cases was identical (IRR per doubling, 1.23, 95% CI: 1.13, 1.34).

Tables

Table 1. Individual-Level Risk Factors for *C. difficile* Infection

	Cases (N, %)	Controls (N, %)	Incidence Rate Ratio* (95%CI)	Incidence Rate* (per 10,000 resident-days)
Gender				
Female	130 (2.2)	5287 (3.2)	Reference	2.3 (1.8, 3.0)
Male	5882 (97.8)	158154 (96.8)	1.52 (1.23, 1.87)	3.5 (3.0, 4.0)
Age				
Less than 60	902 (15.0)	27716 (17.0)	Reference	3.0 (2.6, 3.5)
60 to 69	1664 (27.7)	42366 (25.9)	1.23 (1.14, 1.34)	3.7 (3.1, 4.3)
70 to 79	1398 (23.3)	36105 (22.1)	1.23 (1.13, 1.34)	3.7 (3.1, 4.2)
80 and over	2048 (34.1)	57254 (35.0)	1.17 (1.08, 1.27)	3.5 (3.0, 4.0)
Hospitalization history in prior 28 days				
None	2921 (48.6)	133844 (81.9)	Reference	2.2 (1.9, 2.5)
Any	3091 (51.4)	29597 (18.1)	4.49 (4.25, 4.74)	9.9 (8.8, 11.0)
1 to 7 days in hospital	1343 (22.3)	16037 (9.8)	3.65 (3.41, 3.91)	8.0 (7.0, 9.2)
8 to 14 days in hospital	1102 (18.3)	9454 (5.8)	4.95 (4.59, 5.34)	10.9 (9.5, 12.3)
15 to 28 days in hospital	646 (10.7)	4106 (2.5)	6.92 (6.33, 7.56)	15.2 (13.3, 17.4)
Charlson Comorbidities				
None	1246 (20.7)	67874 (41.5)	Reference	1.8 (1.5, 2.1)
1 to 2	2613 (43.5)	58708 (35.9)	2.28 (2.13, 2.44)	4.1 (3.6, 4.7)
3 or more	2153 (35.8)	36859 (22.6)	3.04 (2.83, 3.26)	5.5 (4.8, 6.2)
Pharmaceutical exposures in previous 28 days				
Proton pump inhibitor				
None	2214 (36.8)	83443 (51.1)	Reference	2.5 (2.2, 2.9)
Any	3798 (63.2)	79998 (48.9)	1.76 (1.67, 1.86)	4.5 (3.9, 5.1)
Antibiotic Risk Class				
None	1165 (19.4)	105234 (64.4)	Reference	1.1 (1.0, 1.3)
Any	4847 (80.6)	58207 (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)	19368 (11.9)	4.40 (4.04, 4.79)	4.9 (4.3, 5.5)
High risk agents §	3846 (64.0)	36890 (22.6)	8.79 (8.23, 9.39)	9.7 (8.6, 11.0)

*Adjusted for days of follow-up in prior 28 days, † Residents with only tetracycline exposure in previous 28 days, ‡ Residents with penicillin, macrolide, or sulfanomide exposures, but no high-risk agent exposures, § Residents with carbapenem, monobactam, cephalosporin, fluoroquinolone, or clindamycin exposures, irrespective of other antibiotic exposures

Table 2. Predictors of Region-Level Long-Term Care *C. difficile* Infection Incidence

	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 1,000 resident-days, per increase of 100	1.26 (1.05, 1.51)	1.02 (0.91, 1.14)
Antibiotic use per 1,000 residents-days, per doubling	2.86 (2.34, 3.49)	2.08 (1.63, 2.64)
Importation of acute care C. difficile cases, per 10,000 patient-days, per doubling	1.59 (1.43, 1.78)	1.29 (1.18, 1.41)

IRR, incidence rate ration
* the adjusted model included all 5 region-level covariates

Table 3. Summary of Individual- and Region-Level Risk Factors for *C. difficile* Infection.

	Incidence Rate Ratio* (95%CI)
Individual-level	
Male	1.41 (1.14, 1.76)
Age	
Less than 60	Reference
60 to 69	1.23 (1.12, 1.34)
70 to 79	1.31 (1.19, 1.45)
80 and over	1.49 (1.34, 1.65)
Acute care hospitalization in previous 28 days	1.85 (1.71, 2.01)
Charlson Comorbidities	
None	Reference
1 to 2	1.28 (1.17, 1.39)
3 or more	1.50 (1.37, 1.63)
Pharmaceutical exposures in previous 28 days	
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 acute care *C. difficile* cases, per doubling	1.23 (1.14, 1.33)

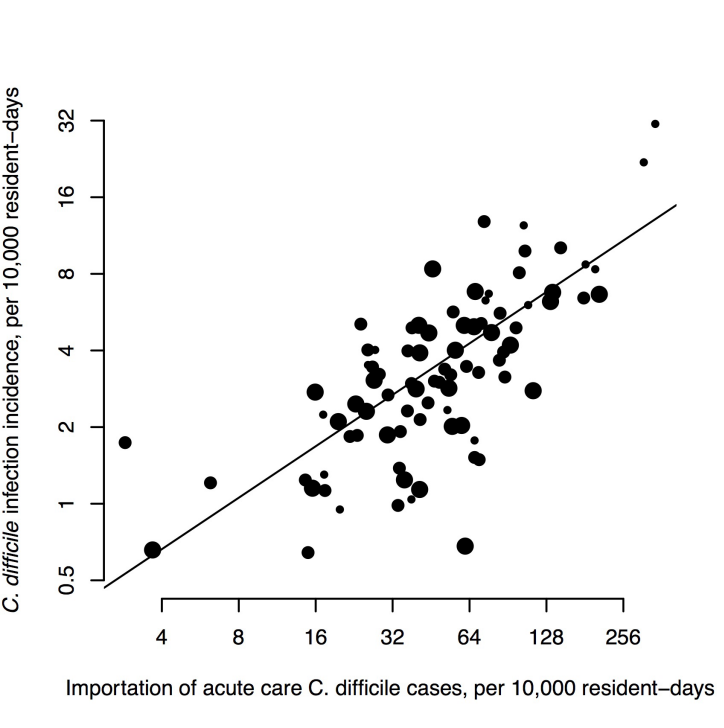
* This model included adjustment for days of follow-up in prior 28 days

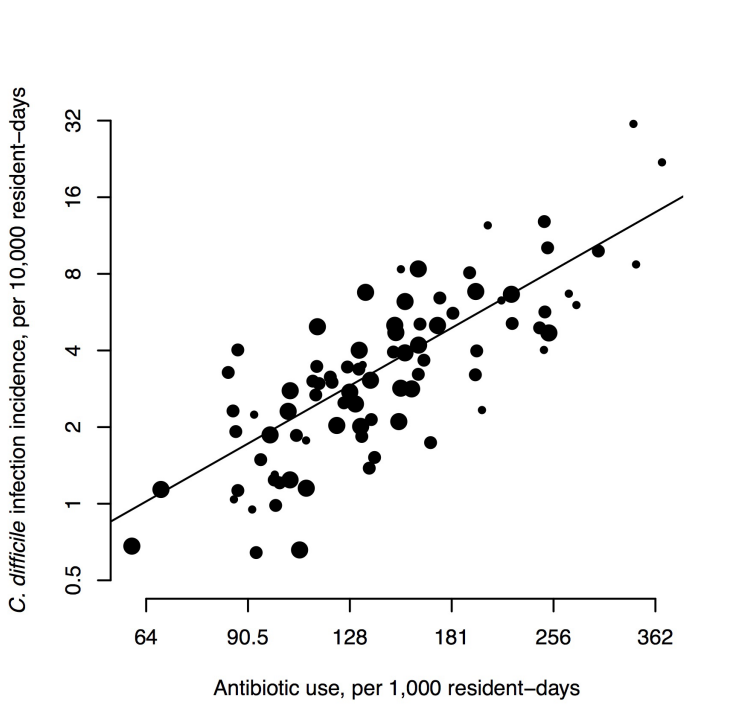
Appendix Table. Summary of Sensitivity Analyses for Adjusted Predictors of *C. difficile* Incidence. All numbers represent incidence rate ratios and 95% confidence intervals from multilevel Poisson GEE models that included adjustment for days of follow-up.

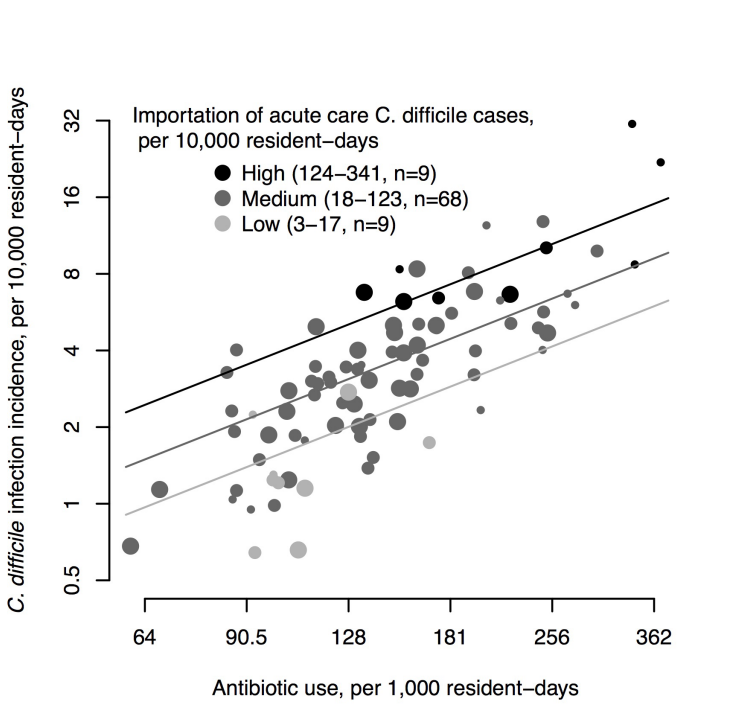
Sensitivity Analysis	Sensitivity Analysis 1: Time-varying region-level exposures	Sensitivity Analysis 2: Subset of residents with 28-days of follow-up	Sensitivity Analysis 3: 12-week antibiotic exposure window	Sensitivity Analysis 4: Larger 5% control sample size
Resident-level				
Male	1.41 (1.13, 1.75)	1.44 (1.11, 1.87)	1.42 (1.14, 1.77)	1.42 (1.14, 1.76)
Age				
Less than 60	Reference	Reference	Reference	Reference
60 to 69	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	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 and over	1.49 (1.34, 1.64)	1.35 (1.22, 1.50)	1.49 (1.35, 1.65)	1.50 (1.36, 1.66)
Acute care hospitalization in previous 28 days	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 or more	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 previous 4 weeks	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 previous 5-12 weeks	NA	NA	2.34 (2.08, 2.63)	NA
Proton pump inhibitor use in previous 4 weeks	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 acute care *C. difficile* cases, 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-day period				
Antibiotic use, per doubling	1.61 (1.39, 1.87)	NA	NA	NA
Importation of acute care *C. difficile* cases, per doubling	1.14 (1.10, 1.18)	NA	NA	NA

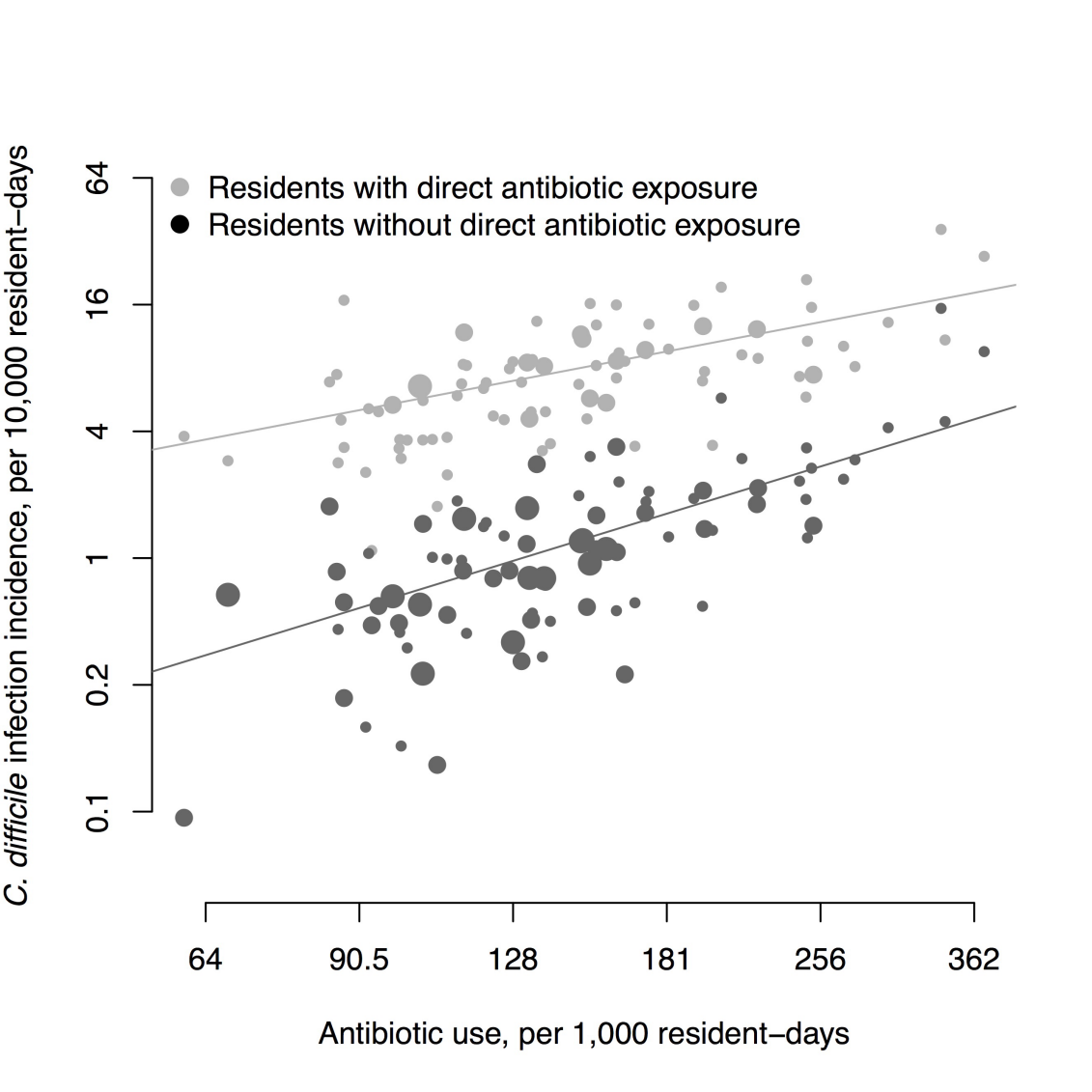
GEE, generalized estimating equation

* For sensitivity analysis 3, the referent group included residents with no antibiotic exposure in the previous 84 days. For all other sensitivity analyses, the referent category included residents with no antibiotic exposure in the previous 28 days only.


C. difficile infection incidence, per 10,000 resident−days
0.5
1
2
4
8
16
32
4
8
16
32
64
128
256
Importation of acute care C. difficile cases, per 10,000 resident−days


C. difficile infection incidence, per 10,000 resident−days
0.5
1
2
4
8
16
32
64
90.5
128
181
256
362
Antibiotic use, per 1,000 resident−days


Importation of acute care C. difficile cases,
per 10,000 resident−days
High (124−341, n=9)
Medium (18−123, n=68)
Low (3−17, n=9)
C. difficile infection incidence, per 10,000 resident−days
0.5
1
2
4
8
16
32
64
90.5
128
181
256
362
Antibiotic use, per 1,000 resident−days


Residents with direct antibiotic exposure
Residents without direct antibiotic exposure
C. difficile infection incidence, per 10,000 resident−days
0.1
0.2
1
4
16
64
64
90.5
128
181
256
362
Antibiotic use, per 1,000 resident−days