Research Paper

Association of Community Factors with Hospital-onset Clostridioides (Clostridium) difficile Infection: A Population Based U.S.-wide Study

Ioannis M. Zacharioudakis,a,b,* Fainareti N. Zervou,a,c Fadi Shehadeh,a Evangelia K. Mylona,b Eleftherios Mylonakis,a***

a Infectious Diseases Division, Warren Alpert Medical School of Brown University, Providence, RI, USA
b Division of Infectious Diseases and Immunology, Department of Medicine, NYU School of Medicine, New York, NY, USA
c Department of Medicine, Warren Alpert Medical School of Brown University, Providence, RI, USA

**Abbreviations:** CA-CDI, Community-acquired Clostridioides difficile infection; CDC, Centers for Disease Control and Prevention; CDI, Clostridioides difficile infection; CSA, Combined Statistical Area; HO-CDI, Hospital-onset Clostridioides difficile infection; HSA, Hospital Service Area; PPIs, Proton-Pump Inhibitors.

* Correspondence to: I.M. Zacharioudakis, NYU School of Medicine, 550 1st Avenue, New York, NY 10016, USA.
** Correspondence to: E. Mylonakis, Infectious Diseases Division, Warren Alpert Medical School of Brown University, Rhode Island Hospital, 593 Eddy Street, POB, 3rd Floor, Suite 328/330, Providence, RI 02903, USA.
E-mail addresses: ioannis.zacharioudakis@nyulangone.org (I.M. Zacharioudakis), emylonakis@lifespan.org (E. Mylonakis).

Abstract

Background: Clostridioides (Clostridium) difficile ranks first among the pathogens of hospital-acquired infections [1]. The prevalence of Clostridioides difficile infection (CDI) has plateaued at historic highs, with recent estimates suggesting about 500,000 infections annually in the U.S. [2,3] The Centers for Disease Control and Prevention (CDC) reported that in 2015 approximately 29,000 patients died within 30 days of the initial CDI diagnosis, with 15,000 of deaths directly attributed to CDI. The above evidence have made the CDI prevention a national public health priority [4].

Healthcare facility-onset CDI (HO-CDI), defined as CDI diagnosis after day 3 of hospitalization in an acute care hospital [5], is considered mainly a hospital problem [6]. Hospital preventive strategies, including antimicrobial stewardship programs [7], contact precautions for infected patients, decontamination of infected areas, hand hygiene [8], and isolation of asymptomatic carriers [9,10] can decrease the rate of HO-CDI. However, the application of the above measures has been shown to be inadequate to contain the infection which prevalence has

1. Introduction

Clostridioides (Clostridium) difficile ranks first among the pathogens of hospital-acquired infections [1]. The prevalence of Clostridioides difficile infection (CDI) has plateaued at historic highs, with recent estimates suggesting about 500,000 infections annually in the U.S. [2,3] The Centers for Disease Control and Prevention (CDC) reported that in 2015 approximately 29,000 patients died within 30 days of the initial CDI diagnosis, with 15,000 of deaths directly attributed to CDI. The above evidence have made the CDI prevention a national public health priority [4].

Healthcare facility-onset CDI (HO-CDI), defined as CDI diagnosis after day 3 of hospitalization in an acute care hospital [5], is considered mainly a hospital problem [6]. Hospital preventive strategies, including antimicrobial stewardship programs [7], contact precautions for infected patients, decontamination of infected areas, hand hygiene [8], and isolation of asymptomatic carriers [9,10] can decrease the rate of HO-CDI. However, the application of the above measures has been shown to be inadequate to contain the infection which prevalence has

https://doi.org/10.1016/j.eclinm.2019.02.001
2589-5370/© 2019 Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
Research in context

Evidence Before This Study

*Clostridioides (Clostridium) difficile* ranks first among the pathogens of hospital-acquired infections and the prevalence of *Clostridioides (Clostridium) difficile* infection (CDI) has plateaued at historic highs. Hospital-based preventive strategies are only partially successful in containing the spread of hospital-onset CDI (HO-CDI). In this study we examined the impact of community population characteristics and parameters of community healthcare practice and delivery on the incidence of HO-CDI throughout the U.S. Data from the Medicare Hospital Compare, Medicare Provider Utilization Part D, and other publically available databases were used.

Added Value of This Study

The study showed a significant association between community population characteristics (i.e. percentage of population > 85 years old), community practices (i.e. prescription of antimicrobials in the community), and characteristics of the healthcare delivery system (i.e. density of hospitals in each hospital service area) with the incidence of HO-CDI. In high-incidence areas our study indicates, that a 10% reduction in the prescription of antimicrobial agents in the community, could lead up to an almost 25% decrease in the rate of HO-CDI.

Implications of All the Available Evidence

The results of this study indicate that the prevention of HO-CDI is not only a matter of hospital policies, but requires a multifaceted effort across all aspects of healthcare and community. Community antimicrobial stewardship should become a priority. Prescription of acid suppressants, and infection control policies in the out of hospital healthcare settings, such as nursing homes, may also be modifiable factors that can reduce the rate of HO-CDI. The above efforts should focus on specific geographic hot spots where the association is higher and, in some cases, cross state lines.

remained unchanged between 2011 and 2015 [11,12]. Current evidence supports that the role of patients with symptomatic infection in transmission of HO-CDI is not as important as previously thought [13,14]. Also, recent work supports the hypothesis that HO-CDI and community-acquired CDI (CA-CDI) are closely linked. For example, the increased risk for CDI after exposure to antimicrobial agents persists for 3 months or more [15], with evidence from Europe indicating the important association of antimicrobial consumption both in the community and in hospitals with the CDI rate [16]. Also, patients who are colonized with toxinogenic *C. difficile* on admission to the hospital have a higher risk of developing CDI during hospitalization [17].

In this study, we examined the impact of community population characteristics and parameters of community healthcare practice and delivery on the incidence of HO-CDI throughout the U.S.

2. Methods

2.1. Data Extraction

Cases of HO-CDI reported between 01/01/2015 and 12/31/2015 were extracted from the Medicare Hospital Compare 12/2016 dataset [18]. In 2015, the Medicare Hospital Compare had information about the *C. difficile* laboratory-identified events at 4807 Medicare-certified hospitals (86.4% of all U.S. hospitals). For reporting purposes, HO-CDI diagnosis requires a positive test for toxin-producing *C. difficile* on an unformed stool specimen collected > 3 days after hospital admission [5].

The risk factors that were examined in our analysis were extracted from the study by Ofri et al. who systematically reviewed factors associated with CA-CDI (symptom onset within the community and ≤ 48 h after hospital admission) [19]. Factors associated with CA-CDI included proximity to nursing homes [20] and use of acid suppressants and oral antimicrobial agents [21,22]. The percentage of population > 65 and > 85 years old were also examined based on current evidence that CDI disproportionately affects elderly patients [23,24]. Finally, the number of hospitals in each Hospital Service area (HSA) (as defined below)
was studied as a characteristic of the healthcare delivery system that contributes to the rate of HO-CDI, given the known higher risk of *C. difficile* colonization among patients who have been exposed to the hospital environment [25,26].

Claims for antimicrobial agents and gastric acid suppressants were collected from Centers for Medicare & Medicaid Services. We used the Medicare Provider Utilization and Payment Data: 2015 Part D Prescriber Public Use File that includes data on approximately 70% of all Medicare beneficiaries [27]. Specifically, all claims for oral antimicrobial agents, including 1st and 2nd generation cephalosporins, penicillins, penicillin-beta-lactamase inhibitors, clindamycin, macrolides, fluoroquinolones, trimethoprim-sulfamethoxazole [21,22], as well as claims for proton-pump inhibitors and H2-receptor antagonists were collected.

Demographic data were extracted from the U.S. Census Bureau. We used American Community Survey 5-Year Estimates to extract the percentage of population aged > 65 and > 85 years old in 2015 [28]. Data on nursing homes and number of certified beds were extracted from Medicare Nursing Home Compare 12/2015 dataset [29].

### 2.2. Study Design

In an effort to match the parameters of interest with the HO-CDI incidence, we used the HSAs, as recorded in The Dartmouth Atlas (Supplementary Appendix) [30]. The HSA geographic boundary files were derived from Medicare data based on the residence zip codes of the hospitalized patients. Specifically, a zip code was assigned to the service area of a specific hospital, if the plurality of Medicare beneficiaries of this zip code was admitted to this specific hospital.

Drug claims were available per provider. In order to georeference the drug claims, the zip codes of the providers were converted to zip code tabulation areas and then converted to points by calculating their centroid coordinates [31,32]. The same transformation was applied to nursing home locations (Supplementary Appendix).

### Table 2

Results of the simple Ordinary Least Squares (OLS) linear regressions for all the risk factors of interest.

| Risk factor                  | Adjusted coefficient of determination |
|------------------------------|--------------------------------------|
| Antimicrobial category       | **0.041** (p < 0.001)                |
| Fluoroquinolones             | **0.057** (p < 0.001)                |
| Macrolides                   | **0.046** (p < 0.001)                |
| Clindamycin                  | **0.029** (p < 0.001)                |
| Penicillins                  | **0.024** (p < 0.001)                |
| Penicillin combinations      | **0.019** (p < 0.001)                |
| Sulfonamides                 | **0.013** (p < 0.001)                |
| 1st and 2nd generation       | **0.012** (p < 0.001)                |
| Acid suppressants/10,000 population | **0.020** (p < 0.001)                |
| Proton-Pump Inhibitors (PPIs) | **0.023** (p < 0.001)                |
| H2 blockers                  | **0.005** (p < 0.001)                |
| Hospitals/HSA km²            | **0.063** (p < 0.001)                |
| Nursing homes/HSA km²        | **0.020** (p < 0.001)                |
| Nursing home beds            | **0.017** (p < 0.001)                |
| Percentage of population > 65 years old | **0.000** (p = 0.39)                |
| Percentage of population > 85 years old | **0.016** (p < 0.001)                |

HSA: hospital service area, km²: square kilometer.
Fig. 3. Results of the Geographically Weighted Regression (GWR) model in A. the Boston-Worcester-Providence B. New York-Newark, C. Philadelphia-Reading-Camden, D. Central-South Florida, E. Los Angeles-Long Beach, F. Detroit-Warren-Ann Arbor Combined Statistical Areas (CSAs). The size of the dots represents the regression coefficient for the rate of antimicrobial claims. The color represents the Coefficient of Determination ($R^2$).
Fig. 3 (continued).
of antimicrobial claims.

Table 3

| CSA                | Mean regression coefficient for the rate of antimicrobial claims (SD) | Decrease in the rate of HO-CDI for every 10% decrease in the rate of antimicrobial claims |
|--------------------|---------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| New England        | 0.009 (0.003)                                                       | 23.1%                                                                                |
| New York-Newark     | 0.005 (0.005)                                                       | 13.7%                                                                                |
| Detroit-Warren-Anna Arbor | 0.003 (0.0001)                                                  | 10%                                                                                 |
| Central-South Florida | 0.002 (0.0007)                                                  | 8.8%                                                                                 |
| Los Angeles-Long Beach | 0.002 (0.002)                                                   | 8.3%                                                                                 |
| Philadelphia-Reading-Camden | 0.001 (0.0004)                                              | 5.4%                                                                                 |

CSA = Core Statistical Area, SD = Standard Deviation.

2.3. Study Analysis

HO-CDI cases and drug claims were expressed per 10,000 population, by dividing the number of cases and claims with the population of each HSA. The effect of nursing homes, number of nursing home beds and hospitals on the HO-CDI incidence was expressed as the number of them per HSA km². Demographic data were expressed as the percentage of the HSA population that had the studied characteristic.

A geographic approach was chosen for this analysis and a spatial statistical analysis was performed using the ESRI ArcGIS 10.4.1. Geographic Information Systems are used to model the spatial distribution of known or potential risk factors, and identify associations with infectious diseases [32]. Multiple simple Ordinary Least Squares linear regressions [34] were initially performed regarding the risk factors of interest described above, using the HO-CDI incidence as the dependent variable. An Ordinary Least Squares exploratory linear regression was then conducted using only the statistically significant independent variables and a Global Moran’s I test was run to identify the most fitted global model and check for global multicollinearity (Supplementary Appendix).

A Hot Spot analysis using the Getis-Ord Gi* statistic [35] was performed to identify clusters of HO-CDI hot spots, and define the areas of interest for our study. Hot spots were defined as HSAs with high HO-CDI rate and high HO-CDI rate in the surrounding HSAs. This was determined by the local sum of HO-CDI rates within the HSA and its neighboring area that was then compared proportionally to the sum of all HSAs. The HSAs in which the local sum was very different from the expected local sum, and the difference was too large to be the result of random chance, were considered hot spots (z-score > 1.96).

Our main analysis examined the association of the modifiable risk factors of interest in each hot spot cluster with HO-CDI incidence using a Geographically Weighted Regression [36,37]. A Geographically Weighted Regression assumes that the relationships between the dependent and independent variables, and thus the regression coefficients, do not remain fixed over space (Supplementary Appendix) [36].

3. Results

Based on the Dartmouth atlas, the U.S. is divided into 3436 HSAs. Among the available HSAs, 71.1% included at least 1 hospital and were considered for further analysis. Of those, 470 HSAs (19.2%) did not report any HO-CDI cases and another 7 had incomplete data on antimicrobial prescriptions and were excluded, leaving 2966 HSAs with a population of 287,488,746 people (89.8% of the 2015 population of the U.S.) in the final analysis (Fig. 1).

The included HSAs had 1–23 hospitals each, with a mean number of 1.5 hospitals, for a total number of 2953 hospitals (Fig. 1). Of these HSAs, 1535 (78%) included exactly 1 hospital each. The percentage of people across the HSAs who were > 65 years old was 16.0% (range 5.3%–49.5%), whereas 2.1% were > 85 years old (range 0.4%–11.5%). Based on the Medicare Nursing Home Compare dataset, there were 62,608 nursing homes throughout the U.S. The 52,497 (83.9%) nursing homes that were located in the HSAs of interest were included in the final analysis. Each HSA had a mean of 27 nursing homes and 2948 nursing home beds.

In 2015, there were 99,552 cases of HO-CDI reported in the Medicare Hospital Compare among the 2953 hospitals included in this analysis [18]. The mean number of HO-CDI cases reported per hospital was 33, ranging from 1 to 407 (mean CDI rate 2.67 cases per 10,000 population). Throughout the 1966 HSAs, there were in total 29,639,416 antimicrobial claims reported in the Medicare Payment Data Part D for the categories of interest and 53,166,513 acid suppressant claims. The mean rate of antimicrobial claims throughout the U.S. was 1350 per 10,000 population. The most commonly prescribed antimicrobial category was fluoroquinolones with a total number of 9,380,303 claims, followed by macrolides with 6,150,460 claims (Table 1). Among the acid suppressants, 45,434,116 claims were for PPIs and 8,732,397 for H2-blockers (Table 1).

Multiple, simple linear regression analyses were performed for the risk factors of interest (Table 2). The number of antimicrobial claims per 10,000 population was significantly associated with the incidence of HO-CDI (adjusted $R^2 = 0.045$, $p < 0.001$), as did the rate of claims for each of the antimicrobial classes studied ($p < 0.001$ in all sub-analyses). The acid suppressant claims per 10,000 population were also significantly associated with the HO-CDI rate (adjusted $R^2 = 0.020$, $p < 0.001$), as did separately the PPI claims (adjusted $R^2 = 0.023$, $p < 0.001$), and the H2-blockers claims (adjusted $R^2 = 0.005$, $p < 0.001$). The number of hospitals (adjusted $R^2 = 0.063$, $p < 0.001$), nursing homes (adjusted $R^2 = 0.020$, $p < 0.001$), and nursing home beds (adjusted $R^2 = 0.017$, $p = 0.001$) were all significantly associated with the HO-CDI incidence. In regard to the population demographics, only the percentage of the population aged > 85 years old (adjusted $R^2 = 0.016$, $p < 0.001$), and not that > 65 years old (adjusted $R^2 = 0.000$, $p = 0.39$), was correlated with the HO-CDI rate.

Based on the aforementioned results, an exploratory Ordinary Least Squares linear regression analysis was conducted to identify the best fitted global model to explain the variation of HO-CDI rate among the HSAs throughout the U.S. Specifically, the rate of antimicrobial and PPIs claims, the number of hospitals and nursing homes per HSA km², and the percentage of population aged > 85 years old were used in the exploratory regression analysis. Based on this analysis, the regression model that included the rate of antimicrobial claims and the number of hospitals per HSA km² was able to explain the highest degree of the observed variation of HO-CDI rate (adjusted $R^2 = 0.10$, $p < 0.001$) (Akaike Information Criterion $= 9571$) (Supplementary Table 1).

As shown in Fig. 2, the statistically significant HO-CDI hot spots ($z$-score $> 1.95$, $p < 0.05$) were located in the states of California, Connecticut, Delaware, Florida, Massachusetts, Michigan, New Hampshire, New Jersey, New York, Ohio, Pennsylvania, Rhode Island, Virginia, and West Virginia. The clusters of HO-CDI hot spot crossed the state borders and were found to be better contained by the borders of Combined Statistical Areas (CSAs) (Supplementary Fig. 1), areas containing a population nucleus with a high degree of economic and social integration as defined by the U.S. Census Bureau [28]. Specifically, the HO-CDI hot spots were organized in 5 Combined Statistical Areas, the CSAs of Boston-Worcester-Providence, New York-Newark, Philadelphia-Reading-Camden, Los Angeles-Long Beach, Detroit-Warren-Ann Arbor, and Central-South Florida.

The community prescription of antimicrobial agents had the highest impact on the observed variance of HO-CDI rate in the Boston-Worcester-Providence CSA (Fig. 3A). The mean of local $R^2$ was 0.71 (95% CI: 0.66–0.76), meaning that the rate of antimicrobial claims in the community was associated with, in average, 71% of the observed variation in HO-CDI rate between the HSAs of this CSA. The mean regression coefficient for the rate of antimicrobial claims was 0.009 (95% CI: 0.008–0.010).
CI: 0.0085–0.1004), meaning that on average every decrease of the claims by 100 per 10,000 population could lower the HO-CDI rate by 0.9 per 10,000 population. Given that the mean rate of antimicrobial claims in this CSA was 873 per 10,000 population, and the mean HO-CDI rate is 3.7 per 10,000 population, a 10% decrease in the rate of antimicrobial claims on average could correspond to a 23.1% lowering in the HO-CDI rate.

In the New York-Newark CSA (Fig. 3B), the rate of antimicrobial claims in the community was associated, on average, with 18% of the variation observed in the rate of the HO-CDI rate ($R^2 = 0.18$; 95% CI: 0.16–0.20) (Fig. 3B). Based on the mean rate of antimicrobial claims and the mean HO-CDI rate in this CSA, a 10% decrease in the rate of antimicrobial claims on average could correspond to a 13.7% lowering in the HO-CDI rate (Table 3). In the other 4 hot spots (Figs. 3C-3F), the antimicrobial claims on average could correspond to a 5.4% lowering in the mean HO-CDI rate in this CSA, a 10% decrease in the rate of antimicrobial claims on average could correspond to a 42% (R2 = 0.42; 95% CI: 0.37–0.46) of the variation in the HO-CDI rate (Table 3). A 10% decrease in the rate of antimicrobial claims in the above 4 CSAs could correspond to a 5.4%–10% lowering in HO-CDI rate as shown in Table 3, with the highest effect seen in the Detroit-Warren-Ann Arbor CSA.

4. Conclusions

Using nationwide data, we examined the association between population risk factors, community level healthcare practices (including rate of antimicrobial and acid suppressant prescription), and healthcare delivery system parameters (such as density of hospitals and nursing homes per HSA) with the incidence of HO-CDI. Antimicrobial agents prescribed in the community and the number of hospital centers per HSA km² were the risk factors that were associated with the highest percentage of the variation in the HO-CDI incidence. The geographically weighted regression model in the hot spots indicated that the rate of antimicrobial claims alone was associated with up to almost three-quarters of the observed variance in the rate of HO-CDI. Moreover, a 10% decrease in the rate of antimicrobial claims could decrease the HO-CDI incidence on average by 5.4%–23.1%, with the highest effect observed in the Boston-Worcester-Providence area.

Current inpatient bundle strategies, including isolation of infected and colonized patients, antimicrobial stewardship programs and novel methods of decontamination, although effective [5] have not been able to contain HO-CDI [2,3]. It is unclear if the difficulty to control the infection is exclusively secondary to inconsistent compliance with the suggested policies, or if there is also a need for identification of factors that remain unrecognized. In an effort to incentivize hospitals to increase compliance with preventive strategies, Medicare is implementing reimbursement penalties for hospitals with a higher than “predicted HO-CDI rate” [6]. The predicted HO-CDI rate for each hospital is estimated based on several factors, related to hospital practices [38], such as the method used for diagnosis, number of hospital and ICU beds etc. However, this Medicare policy of non-payment for preventable hospital-acquired infections does not account for outpatient patients and, so far, has had limited results [39].

In this study, we examined factors that have already been shown to increase the likelihood of either acquiring the pathogen, or transitioning from acquisition/colonization to infection, assuming that these factors may add to the risk of patients who reside in the community to develop HO-CDI during a subsequent hospitalization. Antimicrobial consumption was associated with up to three quarters of the observed variation in the incidence of HO-CDI. The above is even more important given recent estimates that the antimicrobial consumption has increased by 65% in 2000–2015 [40]. Fluoroquinolones was the most frequently prescribed antimicrobial class and most likely was the class to drive the observed association between antimicrobial agents and HO-CDI incidence. Thus, it would be reasonable for future community antimicrobial stewardship programs to target this antimicrobial class first, by substituting, for example, fluoroquinolones with doxycycline in cases of community-acquired pneumonia [41,42]. The effectiveness of the above policy is supported by evidence from the U.K., where Dingle et al. demonstrated that the restriction of the prescription of fluoroquinolones both in the community and the hospitals drove a significant reduction in CDI in the U.K. after 2007 [16].

Community antimicrobial stewardship programs that will aim to contain HO-CDI should take into account the observation that the areas with high incidence of HO-CDI were characterized by a high degree of economic and social integration and were not confined by state borders (Supplementary Fig. 1). This finding highlights the need for cross-state collaborations in the effort to control HO-CDI. For example, a 10% reduction in the prescription of antimicrobial agents in the Boston-Worcester-Providence area, could achieve an almost 25% decrease in the rate of HO-CDI, comparable to the effect of some hospital environmental disinfecting techniques [43].

Advanced age, comorbid conditions, frequent antibiotic use and hospitalizations of nursing home residents render this population susceptible to acquire C. difficile [44] and develop CDI [24]. In this study, we found a significant association between the density of nursing homes in a HSA and the rate of HO-CDI. This association supports the recently mandated antimicrobial stewardship programs in this healthcare setting [45]. Similarly, the rate of the acid suppressant claims in the HSAs was significantly associated with the observed variation in the HO-CDI incidence. Taking into account the significant percentage of inappropriate prescription of acid suppressants in the community [46], nursing homes [47] and acute healthcare settings [48], the implementation of restrictions in both the prescribed and over-the-counter use of acid suppressants suggests an achievable goal in the effort to contain HO-CDI. The currently available guidelines regarding the appropriate prescription of PPIs in the elderly patients can guide future efforts for evidence-based use of acid suppressants [49]. It should be noted that both the density of nursing homes and the claims of acid suppressants were not included in the GWR analysis and therefore it is unclear to what degree these two factors influence the rates of HO-CDI at the local level.

Limitations of this study should be considered. First, the study was at a population level and provides no evidence about the causality of the observed associations [42]. However, our results indicate that the above factors add to our understanding of the observed variation in the rate of HO-CDI and should be taken into consideration during the evaluation of the individual hospital performance. Based on CDC reporting policies [50], a CDI case is defined when there is a positive laboratory test result for C. difficile toxin A and/or B or any detection of toxin-producing C. difficile organisms by culture or other laboratory means on an unformed stool specimen. The use of a variety of diagnostic methods with different specificity by the participating hospitals might contribute to the observed difference in HO-CDI rate [51]. Moreover, factors in the hospitals and nursing homes, such as policies for infection control, number of beds etc., that might also contribute to the observed variation of HO-CDI were not examined. Also, antimicrobial and acid suppressant claims were retrieved from the Medicare Provider Utilization Part D, which is an optional benefit to Medicare beneficiaries, and does not include information for non-Medicare beneficiaries. Even though it is not known what percentage of the total number of antimicrobial and acid suppressant claims refer to Medicare beneficiaries, Medicare is the largest payer of health care in the U.S. and the beneficiaries of Medicare Part D consist nearly two-thirds of the 10–15% U.S. population who receive Medicare [52]. Thus, the observed association between the community antimicrobial claims and the HO-CDI rate is generalizable to the U.S. population. The possibility of incomplete reporting of HO-CDI cases from individual hospitals to the Medicare Hospital Compare dataset should also be acknowledged, but there are no available data about its extent.

In conclusion, we report the results of a US-wide analysis that documented a clear association between community practices and characteristics of the healthcare delivery system with the incidence of HO-CDI.
CDI. These results provide potential targets in the effort to decrease HO-CDI rate, such as community stewardship programs regarding the prescription of antimicrobial agents and acid suppressants, and infection control policies in the out of hospital healthcare settings, such as nursing homes. Prevention of HO-CDI seems that it may not only be a matter of hospital policies, but requires a multifaceted effort across all aspects of healthcare and community. These efforts should focus on specific hot spots that, in some cases, cross state lines and require wide policy coordination.

Conflicts of Interest

EM has received grant support from Boehringer Ingelheim, Germany; T2 Biosystems, United States and Sanofi Pasteur, United States. The other authors have no conflict of interest to declare.

Funding

No funding was received.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eclinm.2019.02.001.

References

[1] Magill SS, Edwards JR, Bamberg W, et al. Multistate point-prevalence survey of health care-associated infections. N Engl J Med 2014;370:1195–206.
[2] Lessa FC, Mu Y, Bamberg WM, et al. Burden of Clostridium difficile infection in the United States. The other authors have no conflict of interest to declare.
[3] Dubberke ER, Olsen MA. Burden of Clostridium difficile infection on the healthcare system. Clin Infect Dis 2013;55:238–92.
[4] Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States. The other authors have no conflict of interest to declare.
[5] Grigoras CA, Zervou FN, Zacharioudakis IM, Siettos CI, Mylonakis E. Isolation of toxinogenic Clostridium difficile in the United States. The other authors have no conflict of interest to declare.
[6] Anderson DJ, Rojas LF, Watson S, et al. Identification of novel risk factors for community-acquired Clostridium difficile infection using spatial statistics and geo-graphics. Antimicrobial information system analyses. PLoS One 2017;12:e0176285.
[7] Deshpande A, Pasupuleti V, Thota P, et al. Community-associated Clostridium difficile infection and antibiotics: a meta-analysis. J Antimicrob Chemother 2013;68:1951–61.
[8] Braley KA, Khanaler N, Daneman N, Fisman DN. Meta-analysis of antibiotics and the risk of community-associated Clostridium difficile infection. Antimicrob Agents Chemother 2013;57:2326–32.
[9] Laflan AM, Bellantoni MF, Greenough 3rd WB, Zenilman JM. Burden of Clostridium difficile-associated diarrhea in a long-term care facility. J Am Geriatr Soc 2006;54:1068–73.
[10] Ziakas PD, Joyce N, Zacharioudakis IM, et al. Prevalence and impact of Clostridium difficile infection in elderly residents of long-term care facilities, 2011: a nationwide study. Medicine (Baltimore) 2016;95:e4187.
[11] Samore MH, DeGirolami PC, Tucko A, Lichtenberg DA, Melvin ZA, Karchmer AW. Clostridium difficile colonization and diarrhea at a tertiary care hospital. Clin Infect Dis 1994;18:181–7.
[12] Leekha S, Aronhalt KC, Sloan LM, Patel R, Orenstein R. Asymptomatic Clostridium difficile colonization in a tertiary care hospital: admission prevalence and risk factors. Am J Infect Control 2013;41:390–3.
[13] Galdys AL, Curry SR, Harrison LH. Asymptomatic Clostridium difficile colonization as a reservoir for Clostridium difficile infection. Expert Rev Anti-Infect Ther 2014;1–14.
[14] Shim JK, Johnson S, Samore MH, Bliss DZ, Gerding DN. Primary symptomless colonisation by Clostridium difficile and decreased risk of subsequent diarrhoea. Lancet 1998;351:633–6.
[15] Nursing Home Compare Datalinks. https://data.medicare.gov/data/nursing-home-compare. [accessed January 5 2018].
[16] Kelly CP, LaMont JT. Clostridium difficile—in more difficult than ever. N Engl J Med 2005;353:1932–40.
[17] Loo VG, Poirier L, Miller MA, et al. A predominantly clonal multi-institutional out-break of Clostridium difficile-associated diarrhea with high morbidity and mortality. N Engl J Med 2005;353:2442–9.
[18] Longtin Y, Trottier S, Brosch G, et al. Impact of the type of diagnostic assay on Clostridium difficile infection and complication rates in a mandatory reporting clinic. Clin Infect Dis 2013;56:67–73.
[19] Haining R. GIS and public health, by E. K. Cromley and S. L. McAllister, New York, Guilford Press, 2012, 2nd edn., ISBN 10: 1609187504, ISBN 13 978-1609187507. Int J Geogr Inf Sci 2013;27: 1040–1.
[20] Watson GS. Linear least squares regression. Ann Math Statist 1967;38:1679–99.
[21] Getis A, Ord JK. The analysis of spatial association by use of distance statistics. Geogr Anal 1992;24:189–206.
[22] O’Sullivan D. Geographically weighted regression: the analysis of spatially varying relationships, by A. S. Fotheringham, C. Brunsdon, and M. Charlton. Geographical analysis 2003; vol. 35: 272–5.
[23] Kirby RS, Delmelle E, Eberth JM. Advances in spatial epidemiology and geographic information systems. Ann Epidemiol 2017;27:1–9.
[24] McDonald LC, Killicore GE, Thompson A, et al. An epidemic, toxin gene-variant strain of Clostridium difficile in elderly residents of long-term care facilities, 2011: a nationwide study. Medicine (Baltimore) 2016;95:e4187.
[25] Lee GM, Kleinman K, Soumerai SB, et al. Effect of nonpayment for preventable infections in U.S. hospitals. N Engl J Med 2012;367:1428–37.
[26] Klein EY, Yan Boeckel TP, Martinez EM, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2013. Proc Natl Acad Sci U S A 2014;111:E3463–4.
[27] Doernberg SB, Winston LG, Deck CH, Chambers HF. Does doxycycline protect against Clostridium difficile infection? Clin Infect Dis 2012;55:615–20.
[28] Tariq K, Che J, Kapoor S, et al. Low risk of primary Clostridium difficile infection with tetracyclines: a systematic review and meta-analysis. Clin Infect Dis 2018;66:514–22.
[29] Haas JP, Menz J, Dusza S, Montecalvo MA. Implementation and impact of ultraviolet environmental disinfection in an acute care setting. Am J Infect Control 2014;42:586–90.
[30] Ziakas PD, Zacharioudakis IM, Zervou FN, Grigoras C, Plakos EE, Mylonakis E. Asymptomatic carriers of toxigenic C. difficile in long-term care facilities: a meta-analysis of prevalence and risk factors. PLoS One 2015;10:e0117195.
[31] Lee GM, Kleinman K, Soumerai SB, et al. Effect of nonpayment for preventable infections in U.S. hospitals. N Engl J Med 2012;367:1428–37.
[32] Klein EY, Yan Boeckel TP, Martinez EM, et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2013. Proc Natl Acad Sci U S A 2014;111:E3463–4.
[33] Doernberg SB, Winston LG, Deck CH, Chambers HF. Does doxycycline protect against Clostridium difficile infection? Clin Infect Dis 2012;55:615–20.
[34] Tariq K, Che J, Kapoor S, et al. Low risk of primary Clostridium difficile infection with tetracyclines: a systematic review and meta-analysis. Clin Infect Dis 2018;66:514–22.
[35] Haas JP, Menz J, Dusza S, Montecalvo MA. Implementation and impact of ultraviolet environmental disinfection in an acute care setting. Am J Infect Control 2014;42:586–90.
[36] By the American Geriatrics Society Beers Criteria Update Expert. American Geriatrics Society 2015 updated beers criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc 2015;63:2227–46.
[37] Centers for Disease Control and Prevention. National Healthcare Safety Network (NHSN). https://www.cdc.gov/nhsn/faq/nhsn-mdro-cdiff.html - q1 (accessed January 5 2018).
[38] Gould CV, Edwards JR, Cohen J, et al. Effect of nucleic acid amplification testing on population-based incidence rates of Clostridium difficile infection. Clin Infect Dis 2013;57:1304–7.
[39] Medicare Part D at Ten Years: The 2015 Marketplace and Key Trends, 2006–2015, Accessed: date 28 April 2018.