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Regional and seasonal variation in *Clostridium difficile* infections among hospitalized patients in the United States, 2001–2010

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Abstract

Background: This study identified national regional and seasonal variations in *Clostridium difficile* infection (CDI) incidence and mortality among hospitalized patients in the United States over a 10-year period.

Methods: This was a retrospective cohort study of the U.S. National Hospital Discharge Survey from 2001–2010. Eligible cases had an ICD-9-CM discharge diagnosis code for CDI (008.45). Data weights were used to derive national estimates. CDI incidence and mortality were presented descriptively. Regions were as defined by the U.S. Census Bureau. Seasons included the following: winter (December-February), spring (March-May), summer (June-August), and fall (September-November).

Results: These data represent 2.3 million CDI discharges. Overall, CDI incidence was highest in the Northeast (8.0 CDIs/1,000 discharges) and spring (6.2 CDIs/1,000 discharges). CDI incidence was lowest in the West (4.8 CDIs/1,000 discharges) and fall (5.6 CDIs/1,000 discharges). Peak CDI incidence among children occurred in the West (1.7 CDI/1,000 discharges) and winter (1.5 CDI/1,000 discharges). Mortality among all CDI patients was highest in the Midwest (7.3%) and during the winter (7.9%).

Conclusion: The region and season with the highest CDI incidence rates among patients hospitalized in U.S. hospitals were the Northeast and spring, respectively. The highest CDI mortality rates were seen in the Midwest and winter. Children exhibited different regional and seasonal CDI variations compared with adults and older adults.

Keywords

Clostridium difficile ; Epidemiology; Mortality

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Clostridium difficile infection (CDI), an increasingly common health careeassociated infection, continues to be a major public health concern as rates rise globally.[1,2] A prior study demonstrated that CDI incidence nearly doubled in the United States between 2001 and 2010.[3] CDI can result in mild diarrhea or, in certain cases, more severe clinical manifestations, such as prolonged ileus, toxic megacolon, intestinal perforation, sepsis, or death.[4] Additionally, patients who develop CDI during hospitalization experience significantly longer hospital stays with substantially increased costs.[5,6] Finally, death occurs in 7%−9% of hospitalized patients with CDI compared with 2% for all other inpatients.[2]

Antibiotic exposure is the primary risk factor for CDI because of disruption of gastrointestinal microbiota diversity, which may persist for weeks to months after cessation of therapy.[7,8] CDI may develop after exposure to any antibiotic class; however, clindamycin, cephalosporins, and fluoroquinolones have been found to have the highest CDI risk.[9] Prior studies have identified regional and seasonal variation in antibiotic use in the United States. Antibiotic use tends to be highest in the South, whereas the West traditionally has the lowest antibiotic use.[10] Antibiotic use also tends to be highest in the winter months because of increased incidence of respiratory infections and subsequent antibiotic use.[11–13]

Because of these variations in antibiotic use, we hypothesized that regional and seasonal variations in CDI also exist. Few studies have examined CDI incidence and mortality by region or season.[14,15] The primary objective of the study was to describe regional and seasonal variation in CDI incidence in the United States over a 10-year period. The secondary objectives were to describe regional and seasonal variations in mortality among patients with CDI and also to describe CDI incidence and mortality variations by age group.

METHODS

Data source

This study used data from the Centers for Disease Control and Prevention's National Hospital Discharge Survey (NHDS) from 2001–2010. These surveys provide a national probability sample of all nonfederal, short-stay hospital discharges annually in the United States. Hospital discharges are randomly sampled following a 3-stage sample design, including counties, hospitals, and discharges. This complex sampling methodology allows the user to apply data weights to derive national estimates representative of the U.S. population.[16]

NHDS data are collected manually or automatically by trained hospital staff, U.S. Census Bureau staff, or National Center for Health Statistics staff. The data collected include patient demographics (age, race, sex, and marital status), year of discharge, expected sources of payment, geographic region in the United States, hospital length of stay (LOS), and hospital discharge status. Diagnoses and procedures are also reported as ICD-9-CM codes. NHDS data have previously been used in several infectious diseases epidemiologic studies, including those for health careeassociated infections.[3,14]

Study design and definitions

This was a retrospective cohort study of all patients discharged from U.S. hospitals from 2001–2010 with a principal or secondary ICD-9-CM discharge diagnosis code for CDI (008.45). The patient cohort was stratified by age into the following 3 groups: adults (18–64 years), older adults (≥65 years), and pediatrics (<18 years).

A more detailed explanation of the study design and definitions has been described previously.[3] In brief, patient baseline characteristics were classified based on the categories provided in the NHDS for patient sex, hospital size (number of beds), hospital ownership (proprietary, government, or nonprofit), and admission type (emergency, urgent, elective, or newborn). Other patient characteristics were classified by limited definitions designed to encompass the following NHDS categories: race (white, black, and other), expected primary source of payment (private, Medicare, Medicaid, self-pay, and other), and admission source (emergency department, transfer, referral, and other).

Patient mortality was identified by the discharge status item of the NHDS. This represents all-cause, in-hospital mortality for patients with CDI. Hospital LOS was extracted from the days of care item of the NHDS and was presented as medians (interquartile ranges). Regions were those defined by the U.S. Census Bureau and consisted of Northeast, Midwest, South, and West. Seasons were defined as winter (December-February), spring (March-May), summer (June-August), and fall (September-November).

Data and statistical analyses

First, baseline patient demographics were summarized using medians (interquartile ranges) for continuous variables and counts (percentages) for categorical variables. We compared baseline characteristics between age groups using the χ^2 test for categorical variables and Wilcoxon rank-sum test for continuous variables.

Next, we identified cases of CDI and applied data weights to derive national estimates. Incidence rates were calculated as CDI discharges per 1,000 total discharges. Regional and seasonal incidence rates were calculated using CDI discharges for each region or season as the numerator and total discharges per region or season as the denominator. CDI incidence and mortality were presented descriptively overall and for each age group. Importantly, there were too few pediatric CDI deaths to accurately describe national mortality estimates in this population; therefore, mortality descriptions and comparisons were limited to adults and older adults. CDI incidence was compared between age groups, regions, and seasons using the z test. Mortality was compared between age groups, regions, and seasons using the χ^2 test. Because of the large sample size provided by this data source, statistical significance was defined as $P < .0001$. JMP 10.0 (SAS Corp, Cary, NC) was used for all statistical comparisons.

RESULTS

Overall, these data represent approximately 2.3 million CDI discharges from U.S. hospitals over the study period. Of these patients, 28.9% were adults, 67.5% were older adults, and 3.6% were pediatric patients. The overall patient population had a median (interquartile

range) age of 74 (59–83) years. Patients were pre-dominately women (59%) and white (86%). Overall, the principal payment source for 67% of discharges was Medicare, reflecting the high proportion of older adult discharges in the sample. Adult, older adult, and pediatric patients with CDI significantly differed with respect to patient sex, race, hospital size and ownership, principal payment source, and admission type and source ($P < .0001$ for all) (Table 1).

The overall CDI incidence was 5.9 CDI discharges per 1,000 total discharges. The median (interquartile range) hospital LOS for hospitalized patients with CDI was 8 (4–14) days, and the all-cause, in-hospital mortality was 6.9%. CDI incidence was significantly higher for older adults (11.6 CDI discharges/1,000 total discharges) than adult (3.5 CDI discharges/1,000 total discharges) and pediatric populations (1.2 CDI discharges/1,000 total discharges) ($P < .0001$ for all comparisons). Similarly, mortality was significantly higher for older adults (8.8%) than adult (6.9%) and pediatric populations (3.1%) ($P < .0001$ for each age group comparison).

Regional variations

Overall, CDI incidence significantly differed among U.S. geographic regions ($P < .0001$). CDI incidence was highest in the Northeast (8.0 CDI discharges/1,000 total discharges) followed by the Midwest (6.4 CDI discharges/1,000 total discharges), South (5.0 CDI discharges/1,000 total discharges), and West (4.8 CDI discharges/1,000 total discharges). Adult and older adult CDI incidence followed overall trends; in contrast, CDI incidence among children was highest in the West (1.7 CDI discharges/1,000 total pediatric discharges) (Fig 1). CDI incidence increased for all regions over the study period (Fig 2). CDI incidence was consistently higher in the Northeast than in the other regions. There was a distinct divergence in 2005, when CDI incidence in the Northeast hit its peak (10.3 CDI discharges/1,000 total discharges) and the West reached one of its lowest rates (3.5 CDI discharges/1,000 total discharges).

Regional mortality is depicted in Figure 3. Overall, CDI mortality by region was highest in the Midwest (7.3%), followed by the Northeast (6.9%), South (6.9%), and West (6.2%). Adult rates were also highest in the Midwest (3.6%), but older adult mortality was highest in the Midwest (9.0%) and South (9.0%). Notably, adult and older adult CDI mortality rates were lowest in the Northeast (2.2% and 8.6%, respectively). Mortality significantly differed between regions overall ($P < .0001$) and for each age group ($P < .0001$ between regions for each age group).

Seasonal variations

CDI incidence significantly differed between seasons ($P < .0001$). CDI incidence was highest in the spring (6.2 CDI discharges/1,000 total discharges), followed by the winter (5.9 CDI discharges/1,000 total discharges), summer (5.9 CDI discharges/1,000 total discharges), and fall (5.6 CDI discharges/1,000 total discharges) (Fig 4). Specifically, peak CDI incidence occurred in the month of March (7.6 CDI discharges/1,000 total discharges). Adult and older adult CDI incidence followed overall trends; however, peak CDI incidence among children occurred in the winter (1.5 CDI discharges/1,000 pediatric discharges).

Seasonal mortality is depicted in Figure 5. Overall, CDI mortality was highest in the winter (7.9%), followed by the summer (6.8%), fall (6.6%), and spring (6.2%). Older adult CDI mortality followed overall trends; however, peak CDI mortality among adults occurred in the fall (3.7%). Lowest CDI mortality rates occurred in the spring for both the adult (2.7%) and older adult (7.8%) populations. Mortality significantly differed between seasons overall and for each age group ($P < .0001$ between seasons for each age group).

DISCUSSION

This study described the burden of CDI in the United States by region and season. Overall, CDI incidence in U.S. hospitals was highest in the Northeast and spring. Mortality occurred most frequently in the Midwest and winter. Remarkably, older adult CDI incidence rates were approximately 3 times that of the adult rates and were almost 10-fold greater than that of the pediatric rates.

Overall, the incidence of CDI in U.S. hospitals was greatest in the Northeast and lowest in the West, consistent with the results of prior studies using the Healthcare Cost and Utilization Project database.[2,17] Similarly, Archibald et al[18] evaluated regional trends in hospital-acquired CDI in the United States from 1987–2001 using the National Nosocomial Infections Surveillance System and found the highest CDI incidence occurred in the mid-Atlantic region of the United States, which approximates the Northeast region in our study. Additionally, a prior study using NHDS data between 1996 and 2003 found that the rate of CDI discharge diagnosis was highest in the Northeast and lowest in the West.[19] These consistent trends using disparate data sources support a regional variation in CDI incidence.

The regional differences in CDI incidence could be caused by several factors. First, there might be variations in inpatient and outpatient antibiotic prescribing patterns between regions. Prior studies have found that outpatient antibiotic use tends to be lowest in the West,[10] which supports our finding of lowest CDI incidence in this region. However, regional trends in inpatient antibiotic prescribing are unknown. Second, regional differences could be caused by the age distributions in each region because advanced age is a risk factor for CDI development.[20,21] In fact, the Northeast had the largest proportion of older adults (73%) compared with the West, with 60% aged 65 years or older. Next, hospital characteristics in each region could account for regional CDI differences. In 2010, the Northeast had the longest overall hospital LOS at 5.5 days on average compared with 4.4 days in the West.[22] Because hospitalization is a major risk factor for CDI, this longer hospital exposure could predispose patients to CDI in the Northeast to a greater extent than those in other regions.[23] Other hospital characteristics, such as patient overcrowding, understaffing, and differences in infection control procedures, could account for regional CDI incidence differences.

Regional variations may also be attributed to the molecular epidemiology of *C difficile*. Of the 2 most common strains of CDI found in the United States, isolates of ribotype 014/020 are more common in the West than ribotype 027, whereas the reverse is true in the Northeast.[24] Ribotype 014/020 isolates are susceptible to most antimicrobial agents and may be less virulent than ribotype 027,[24,25] whereas ribotype 027 isolates have been

associated with increased transmissibility and severity of CDI.[26,27] The regional incidence rates in our study correspond to the regional prevalence of these CDI strain types, in support of our study results. Furthermore, variations in incidence by year could reflect changing distributions of *C difficile* strains throughout the study period.

Overall, the incidence of CDI peaked in the spring and was lowest in the fall. The peak incidence in the spring could be attributed to increased utilization of antibiotics in winter months for respiratory infections. Prior studies have found a 1–2 month lag time between antibiotic exposure and the development of CDI[12,28]; therefore, it is expected that peak CDI incidence would occur in the months after peaks in other infections. Prior studies have also demonstrated increased CDI incidence after seasonal peaks for influenza,[12,14,29] pneumonia,[14] and respiratory syncytial virus.[12] Prior studies have demonstrated that peak influenza and pneumonia seasons occur in January and February, with a subsequent peak in CDI incidence in March.[14,18] This is consistent with our findings. The increased incidence of CDI in relation to the increased use of antimicrobial agents emphasizes the importance of antimicrobials use as a risk factor for CDI. A model constructed for hospitalized patients demonstrated that a 30% reduction in the use of broad-spectrum antibiotics would result in a 26% reduction in CDI,[30] highlighting the need for antimicrobial stewardship programs to reduce CDI during high-risk seasons. There are a number of other factors that might occur in the winter months that could contribute to a higher rate of CDI in the spring, including reduced hospital staffing, hospital overcrowding, interhospital transfer, changes in infection control practices, or greater severity of illness during the winter months.

Prior studies examining secular trends in mortality in CDI patients are limited; however, the overall mortality rate in our study is consistent with prior literature.[2,19] In our study, mortality (7%) among all CDI patients was highest in the Midwest and during the winter months, whereas it was lowest in the West and during the spring. Previous studies have shown that infection-specific and overall mortality are highest in the United States during the winter months, in support of our findings for seasonal trends in CDI mortality.[31,32] Regional variation in mortality is likely multifactorial, but may be related to the lower overall age in the West compared with all other regions[33] and the lower prevalence of *C difficile* ribotype 027 in this region.[25,27]

The overall rates for CDI incidence and mortality were heavily influenced by the high proportion of older adult patients diagnosed with CDI, who had significantly higher CDI incidence rates and mortality than adult and pediatric populations. These findings correlate with the current literature that indicates older adults, who traditionally have more comorbidities and broad-spectrum antimicrobial use, are at the highest risk for CDI.[2,19,30] Notably, children exhibited different regional and seasonal CDI variations than adults and older adults. This is likely because of differences in the prevalence and timing of acquisition of comorbid illnesses. For example, respiratory illnesses tend to peak earlier among younger patients.[34,35]

Our findings indicate the need for additional resources when and where health care burdens are highest. Importantly, prior literature suggests hospitalized patients with CDI have greater mortality and are more severely ill than hospitalized patients in general.[2,17] These results

underscore the need for improved infection control and antimicrobial stewardship measures to prevent CDI and its transmission, particularly in high-risk regions and seasons. Further studies are needed to identify factors that contribute to regional and seasonal variations in CDI.

Limitations

This study has potential limitations. First, this study relied on administrative data using ICD-9-CM coding to identify CDI and other diagnoses; therefore, it may not fully capture all CDI cases otherwise ascertained with clinical or microbiologic data. A prior study evaluating the use of the ICD-9-CM code to identify CDI found high sensitivity (78%) and specificity (99.7%)[36]; however, using this method alone precludes our ability to confirm CDI diagnosis using laboratory methods. Importantly, our CDI case definition did not change over the study period; therefore, any coding error would persist throughout the study years and would have limited effects on CDI trends. Additionally, an initial CDI episode could not be discriminated from a recurrent CDI episode or readmission, each of which is associated with a slightly different set of risk factors.[37–39] This lack of distinction could have led to an overestimation of incident CDI cases in our study. Next, there are several factors that could have contributed to differences in CDI incidence or mortality between regions and seasons that we were not able to account for in our analyses, including antibiotic exposure, differences in CDI testing procedures, severity of illness, and *C difficile* strain. Finally, the NHDS includes a large sample size, resulting in a high study power. This limits the utility of *P* values to establish differences among groups because small variations are likely to be statistically significant. This database also excludes federal hospitals and long-term care hospitals, potentially limiting the generalizability of our results and underestimating the true burden of CDI in the United States.

CONCLUSIONS

CDI incidence in U.S. hospitals was highest in the Northeast and spring; however, mortality occurred most frequently in the Midwest and winter months. Children exhibited different regional and seasonal CDI variations than adults and older adults. Results of this study may be used to direct resources and implement targeted control measures where and when they are needed most.

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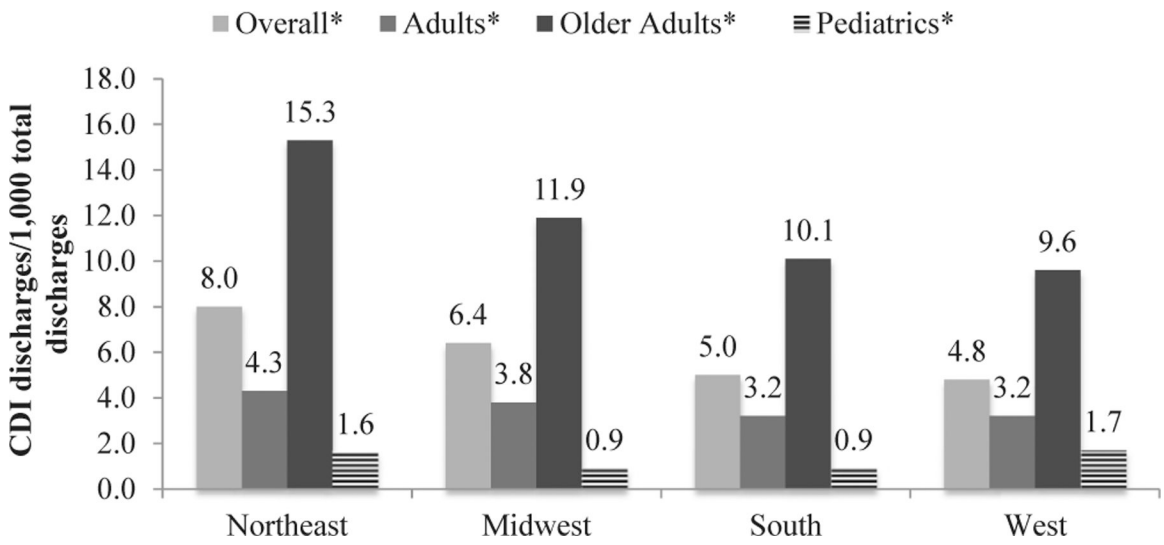

Fig 1.

CDI incidence by region among hospitalized patients in the United States (n = 2,279,004 CDI discharges). *CDI, Clostridium difficile* infection. **P* < .0001 between regions.

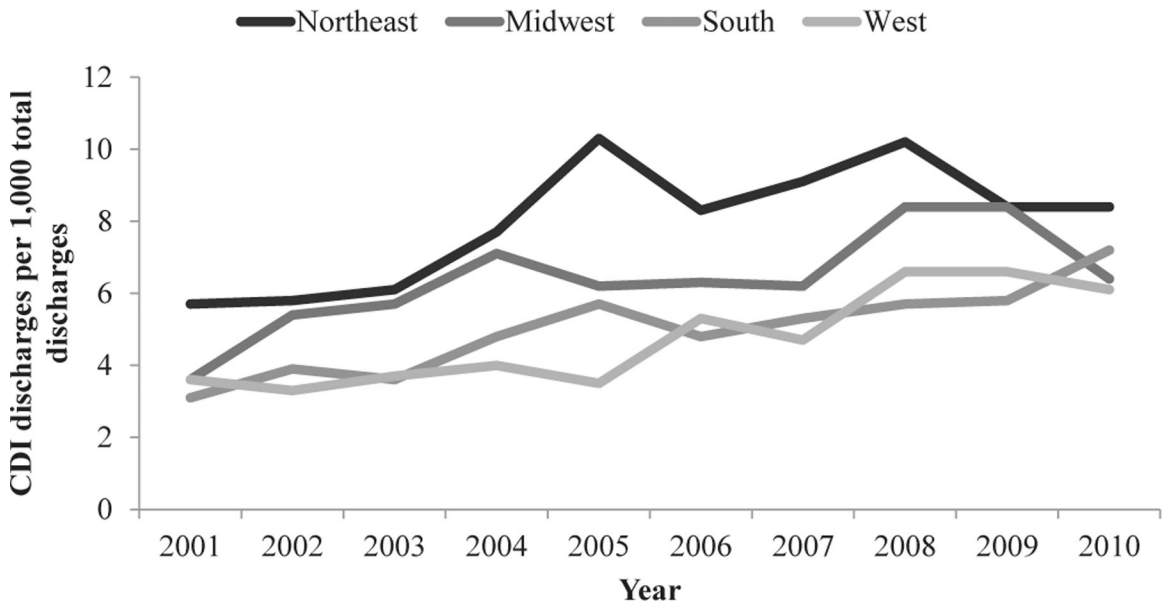

Fig 2.

CDI incidence by region and year among hospitalized patients in the United States (n = 2,279,004 CDI discharges). *CDI, Clostridium difficile* infection.

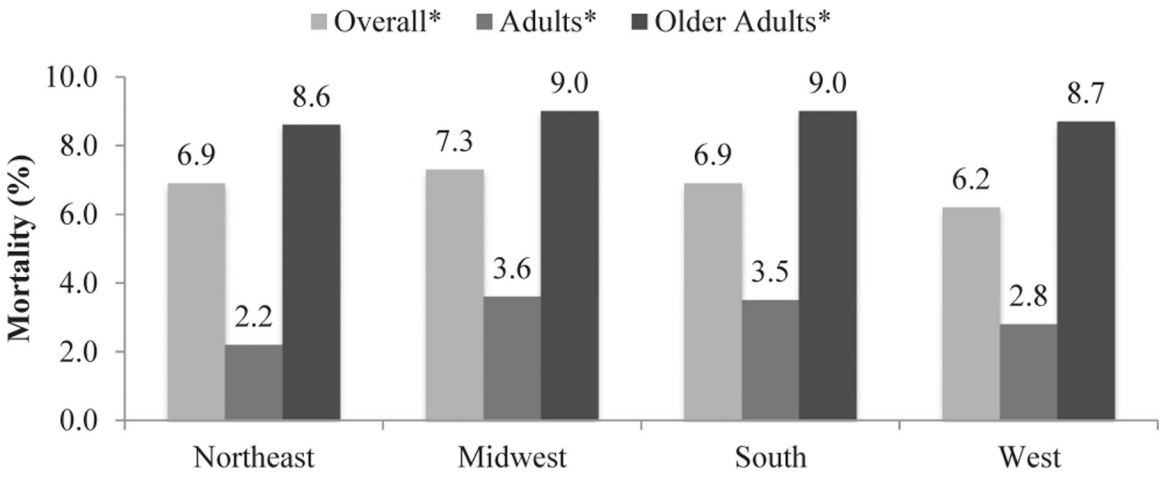

Fig 3.

CDI mortality by region among hospitalized patients in the United States (n = 2,279,004 CDI discharges). Pediatric patients were not included because of limited sample size. *CDI*, *Clostridium difficile* infection. **P* < .0001 between regions.

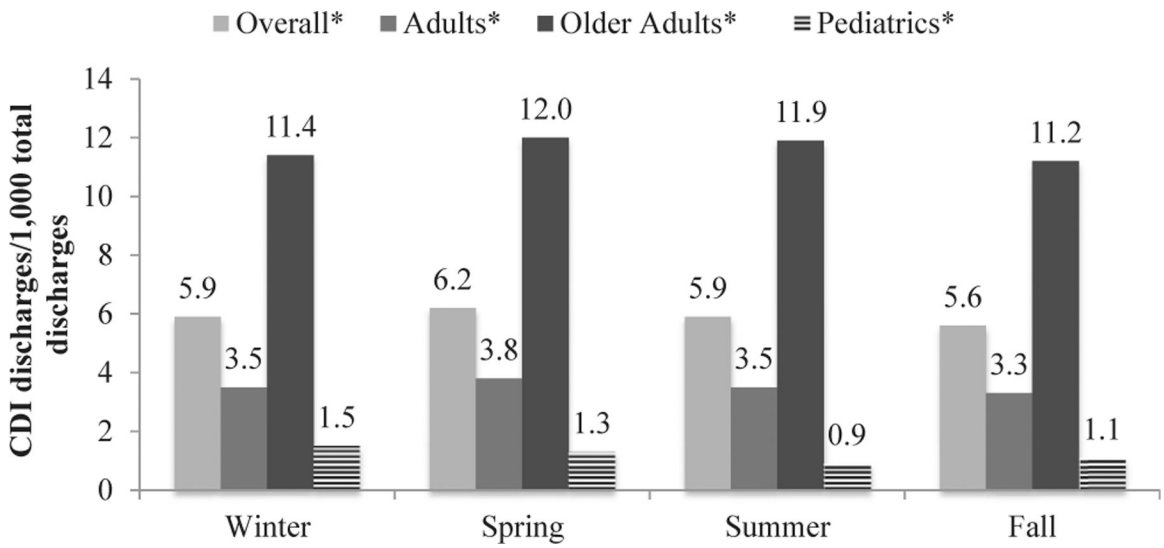

Fig 4.

CDI incidence by season among hospitalized patients in the United States (n = 2,279,004 CDI discharges). *CDI, Clostridium difficile* infection. **P* < .0001 between seasons.

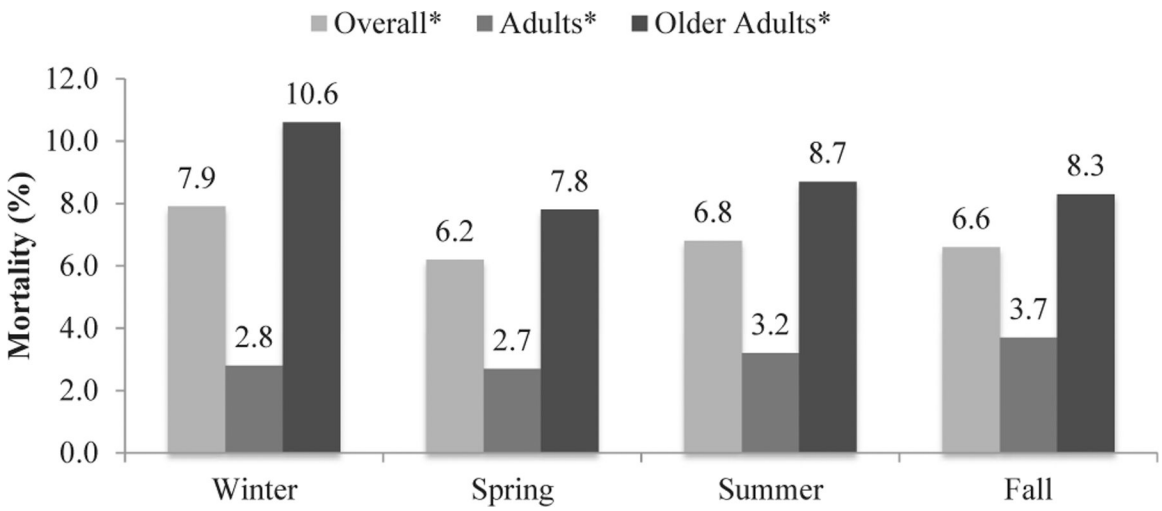

Fig 5.

CDI mortality by season among hospitalized patients in the United States (n = 2,279,004 CDI discharges). Pediatric patients were not included because of the limited sample size. *CDI*, *Clostridium difficile* infection. **P* < .0001 between all seasons.

Table 1

Baseline characteristics

Demographic	Overall (n = 2,279,004)	Adults (n = 657,513)	Older adults (n = 1,538,933)	Pediatrics (n = 82,558)	*P* value*
Age (y), median (IQR)	74 (59–83)	52 (43–59)	80 (74–85)	5 (2–11)	<.0001†
Female sex, %	58.7	54.4	61.5	39.4	<.0001†
Race, %					<.0001†
White	85.6	77.2	89.6	78.7	
Black	10.1	16.7	7.0	14.8	
Other	4.3	6.1	3.4	6.5	
Hospital size, %					<.0001†
6–99 beds	19.4	13.7	22.6	5.6	
100–199 beds	21.1	20.4	21.6	19.1	
200–299 beds	24.3	21.6	24.8	36.1	
300–499 beds	22.7	27.1	20.7	25.1	
≥500 beds	12.5	17.2	10.3	14.1	
Hospital ownership, %					<.0001†
Proprietary	11.7	8.2	13.5	5.7	
Government	8.6	12.9	6.8	8.0	
Nonprofit	79.7	78.9	79.7	86.3	
Principal payment, %					<.0001†
Medicare	67.0	25.9	88.3	0	
Medicaid	8.1	18.7	1.3	50.9	
Private	21.4	47.1	9.2	43.1	
Self-pay	1.6	4.6	0.4	0.1	
Other	1.9	3.7	0.8	5.9	
Admission type, %					<.0001†
Emergency	64.9	64.0	66.4	41.5	
Urgent	21.5	24.1	19.9	33.4	
Elective	13.4	11.9	13.7	20.6	
Newborn	0.2	0	0	4.5	
Admission source, %					<.0001†
Emergency room	59.3	60.3	59.8	37.6	
Transfer	15.1	8.8	18.0	8.6	
Referral	18.1	21.6	15.7	39.2	
Other	7.5	9.3	6.5	14.6	

IQR, interquartile range.

***P* values reflect comparisons between adult, older adult, and pediatric *Clostridium difficile* infection cohorts.

†Statistically significant at $\alpha < .0001$.