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Trends in admissions and outcomes of hospitalizations related to *Clostridioides difficile* infection: a nationwide analysis from 2005-2020

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Abstract

Background *Clostridioides difficile* infection (CDI) is one of the major causes of healthcare-associated infectious colitis. This study analyzed trends in CDI-related hospitalizations in the United States (US) from 2005-2020, focusing on changes in patient demographics, disease severity and outcomes.

Methods Our study was a retrospective observational analysis using the National Inpatient Sample (NIS) from 2005-2020, focusing on US adults with primary and secondary CDI diagnoses. We performed statistical analysis using SAS 9.4 and joinpoint regression models to identify trends and changes in CDI prevalence and severity, as well as patient outcomes, over the 15-year period.

Results The study analyzed 939,282 patients, 30.2% of whom had primary and 69.8% secondary CDI diagnoses. Over the study period, there was a decline in CDI prevalence from 94.8 to 78.1 per 10,000 hospitalizations. This trend showed an increase in prevalence among younger adults (18-34 years) but a notable decrease in older adults (≥85 years). Sex-related and racial/ethnic disparities were also evident. The incidence of megacolon surged from 12.9 per 10,000 hospitalizations in 2005 to 69.8 per 10,000 in 2020, a more than fivefold increase. In contrast, in-hospital mortality from CDI significantly decreased, from 1028 deaths per 10,000 CDI diagnoses in 2005 to 687 per 10,000 in 2020, a 33.1% reduction.

Conclusions Our study indicated improved management and prevention of CDI, as evidenced by the overall decrease in prevalence and mortality. However, the increase in severity markers and the variable trends across different demographic groups highlight the need for ongoing vigilance and targeted interventions.

Keywords *Clostridioides difficile*, epidemiology, hospitalization, mortality, severity

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Introduction

Clostridioides difficile infection (CDI) is a significant healthcare-associated infection characterized by a wide range of gastrointestinal symptoms, from mild diarrhea to severe, life-threatening colitis [1]. It has significant implications for patient morbidity and mortality, with over 70% of CDI cases linked to healthcare facility exposure [2].

The incidence and burden of CDI have varied substantially over time. In the United States (US), CDI affects approximately half a million patients annually, leading to significant healthcare costs and nearly 30,000 deaths [2]. Data from the Centers for Disease Control and Prevention (CDC) in 2019 report a crude overall incidence rate of 121.2 cases per 100,000 persons [3]. The burden of hospital-associated CDI has been estimated to have decreased by 21% from 2011-2017, probably as a result of improved infection control practices and antimicrobial stewardship programs [4]. More recently, several studies have looked at the impact of the

COVID-19 pandemic on CDI prevalence: while some found an increase [5,6] or a stable prevalence/incidence [7,8], most showed a decrease [9-11], associated with a reduction in inappropriate testing and an extraordinary expansion of infection prevention measures [8,12]. In contrast, community-associated CDI has nearly doubled in the past decade, with an incidence of 63.3 cases per 100,000 persons [13]. The incidence of community-associated CDI increased to 53% in 2019 compared to 47% in 2012 [14].

Given the changing epidemiology of CDI, a comprehensive analysis of CDI-related hospitalizations is required to inform clinical management and public health strategies. Our study utilized extensive data from the National Inpatient Sample (NIS) to analyze trends in CDI-related hospitalizations from 2005-2020. We aimed to provide a detailed overview of changes in patient demographics, disease severity and outcomes, offering valuable insights that may guide future interventions and healthcare policies.

Materials and methods

Data source

We conducted a retrospective observational study using the NIS, coordinated by the Healthcare Cost Utilization Project (HCUP), for the period 2005-2020. This timeframe includes important changes in healthcare policies, infection control practices, and coding systems, offering a robust dataset for evaluating evolving patterns in patient outcomes. HCUP is an administrative dataset of healthcare databases developed through a federal, state and industry partnership sponsored by the US Agency for Healthcare Research and Quality (AHRQ). The NIS is the largest hospital database in the US, containing discharge records from about 7-8 million hospital stays annually. The NIS is a stratified, clustered database that samples discharge records from 20% of non-federal community hospitals across the US. The database contains diagnoses and procedures coded using the International Classification of Disease, Ninth and Tenth Revision (ICD-9 and ICD-10) codes. Before 2012, the NIS included data on all discharges from a 20% sample of US hospitals, stratified by census region, ownership, location, teaching status and size (no. of beds). Since 2012, the NIS includes data on a 20% sample of discharges from all participating hospitals in the HCUP. Subsequently, the data elements and data structure for the NIS were changed in 2015. The Diagnosis and Procedure codes were changed from ICD-9-CM codes to ICD-10 codes, thereby splitting the NIS 2015 data structure into the first 9 months, containing ICD-9-CM codes, and the last 3 months, containing ICD-10-CM/PCS. This study was exempt from institutional review board approval because a deidentified administrative database was used. We adhered strictly to the NIS survey methodology regarding data interpretation, research design and data analysis, as described by the HCUP and recently highlighted by Khera *et al* [15].

Study population

The study included all hospitalizations of US adults aged 18 years and older, with primary (principal) or secondary diagnoses of CDI, between January 1, 2005, and December 31, 2020. CDI was defined using ICM-9-CM codes (008.45) from January 1, 2005, to September 30, 2015, and the corresponding ICD-10-CM codes (A047, A0471, A0472) starting October 1, 2015. Only those patients whose records had complete data on key variables, including age, sex, race/ethnicity, mortality status and length of hospital stay, were included.

After patients who lacked data on age, mortality and sex had been excluded, the study population was further stratified into patients with a principal or a secondary diagnosis of CDI. We also excluded patients with elective hospitalizations unrelated to CDI, as defined by specific admission codes.

Principal or primary diagnosis includes patients whose primary reason for hospitalization was CDI, denoted by ICD-9-CM or ICD-10-CM codes in the first position. Secondary CDI diagnosis included patients hospitalized for conditions other than CDI, denoted by ICD-9-CM or ICD-10-CM codes in any position other than the first. We further extracted demographics such as age, sex (male and female), race/ethnicity (Whites, Blacks, Hispanics, Asian or Pacific islanders, Native Americans and others), and patient-level characteristics. The expected primary payment sources were Medicare, Medicaid, private and self-pay. Comorbidity at discharge was estimated using Elixhauser Comorbidity Software, and an index score was derived. The Elixhauser Comorbidity Software is a widely used tool designed to identify and quantify comorbid conditions based on administrative healthcare data. It includes a comprehensive set of 31 comorbidity indicators derived from diagnostic codes in hospital discharge records. These indicators account for a wide range of chronic conditions, including cardiovascular diseases, diabetes, renal failure and chronic pulmonary diseases. In the context of our study, adverse events related to CDI include clinical complications such as sepsis, septic shock, perforated intestine, megacolon, acute renal failure, prolonged ileus, and the need for surgical interventions such as colectomy. These events were identified using specific ICD-9 and ICD-10 diagnostic and procedure codes from hospital discharge records. Additionally, inflammatory bowel disease was identified independently with diagnostic codes and included in the analysis. Comparative analyses were conducted between the 2 cohorts, primary or secondary CDI diagnosis.

We defined CDI severity using indicators that included shock, sepsis/septicemia, perforated intestine, prolonged ileus, megacolon, acute renal failure and colectomy, as described by prior studies. These indicators were identified using ICD-9/ICD-10 diagnostic and procedure codes.

Statistical analysis

Weighted values were generated, to obtain a nationally representative estimate of the hospitalized patients, and were then used to produce mean values and percentages for the variables.

Continuous variables were expressed as weighted mean values with standard deviation and compared between the groups using independent *t*-tests, whereas categorical variables were expressed as percentages and compared using the chi-square test. Survey methodology was used for all analyses to account for the clustering and stratification of hospitalizations in the NIS, as recommended by the AHRQ. Hospitalizations with missing data on age, sex or in-hospital mortality represented less than 10 percent and were excluded from the analyses. To compare the primary and secondary CDI in terms of demographic and clinical characteristics, we performed bivariate analyses using the chi-square test for categorical variables and the *t*-test for continuous variables. For trend analyses, we determined the annual prevalence rates for CDI by dividing the total CDI hospitalizations for each year by the total hospitalizations. The prevalence of CDI primary and secondary diagnoses was derived similarly. Data weights were applied to derive national estimates, and rates were presented as CDI hospitalizations per 10,000. Trends were also derived for CDI prevalence rates per age groups (18-34, 35-44, 45-54, 55-64, 65-74, 75-84, and ≥85), sex (male and female), and race/ethnicity (Whites, Blacks, Hispanics, Asian or Pacific islanders, Native Americans and others). In addition, trends of in-hospital mortality were calculated as the total number of death events divided by CDI diagnoses per 10,000, and CDI severity as counts of adverse events divided by the CDI diagnoses for each year per 10,000. In the context of our study, adverse events related to CDI included clinical complications, such as sepsis, septic shock, perforated intestine, megacolon, acute renal failure, prolonged ileus, and the need for surgical interventions, including colectomy. These events were identified using specific ICD-9 and ICD-10 diagnostic and procedure codes from hospital discharge records. Temporal trends in CDI prevalence, baseline characteristics, CDI severity and in-hospital mortality were measured by the annual percentage change (APC) and average annual percentage change (AAPC), with 95% confidence intervals (CIs), using joinpoint regression models. A 2-tailed alpha of <0.05 was required for statistical significance. We accounted for the complex survey design of the NIS in the analyses. Data manipulation and statistical analyses were performed using SAS 9.4 software (SAS Institute Inc., Cary, NC, US). Joinpoint regression was conducted using Joinpoint software version 4.5.0.1 (Bethesda, Maryland).

Results

Baseline characteristic of the study population

We identified 1,055,257 patients with CDI hospitalizations between January 1, 2005, and December 31, 2020. Following the application of our inclusion and exclusion criteria, 939,282 patients were included in the final study population. Of the 939,282 patients with CDI hospitalizations, 283,808 (30.2%) were primary diagnoses and 655,474 (69.8%) were secondary CDI diagnoses (Fig. 1).

The overall CDI population were elderly, with a mean age of 68±16.8 years, predominantly female (58%), White (74.9%), and insured by Medicare (68.3%). Table 1 shows the baseline characteristics of the overall CDI, primary and secondary populations. Comparing primary and secondary CDI patients, patients with a primary CDI diagnosis were elderly, had a higher proportion of females and Whites, and a higher prevalence of inflammatory bowel disease. On the other hand, patients with a secondary CDI diagnosis had higher Elixhauser comorbidity index values and higher severity indicators, including shock, sepsis, perforated intestine, ileus, acute renal failure, colectomy and mortality, as well as longer hospital stays.

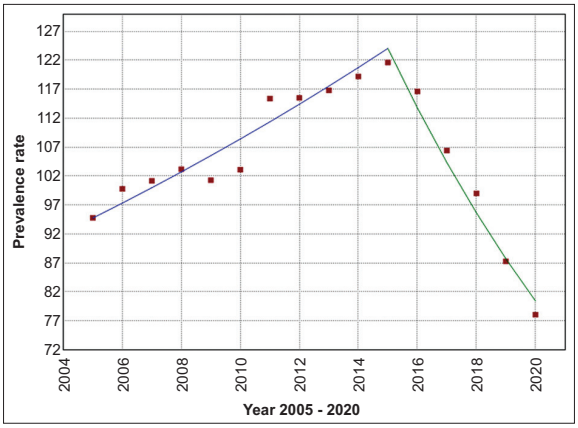

Figure 1 Patient selection flow diagram

Temporal trends in CDI hospitalization by age, sex and race/ethnicity

Supplementary Tables 1 and 2 show the prevalence estimates per year and joinpoint regression analysis of the temporal trend of CDI hospitalization by age, sex and race/ethnicity. The total CDI prevalence showed a significant decrease from 94.8 per 10,000 in 2005 to 78.1 per 10,000 in 2020 (AAPC -1.1%; 95%CI -1.6 to -0.6) (Fig. 2). It initially showed a slight increase from 2005-2015 (APC 2.7%; 95%CI 2.0-3.6) followed by a moderate decrease from 2015-2020 (APC -8.3%; 95%CI -10.3 to -6.2). Primary CDI and secondary CDI showed similar patterns to the overall CDI, with an initial increase and then a decrease (Fig. 3). Primary CDI showed a stable decrease across the study period, from 24.0 per 10,000 in 2005 to 20.3 per 10,000 in 2020 (AAPC -0.96%; 95%CI -2.12 to 0.31), with an initial rapid increase from 2005-2008 (APC 12.06%; 95%CI 6.39-27.20), a stable increase from 2008-2016 and a rapid decrease from 2016-2020 (APC -12.55%; 95%CI -19.13 to -8.97). Secondary CDI exhibited a decrease from 70.8/10,000 to 57.9/10,000 (AAPC -1.35%; 95%CI -1.72 to -1.00). It started with a stable decrease from 2005-2009, then a slight increase from 2009-2015 (APC 4.19%; 95%CI 3.23-6.44), and finally a decrease from 2015-2020 (APC -7.90%; 95%CI -9.10 to -6.72).

Regarding the patients' age, the CDI prevalence showed a slight increase in the younger age groups (18-34, 35-44, 45-54), a stable increase for 55-64, and a decrease in the older age groups (65-74, 75-84 and ≥85). Overall, the highest increase in CDI prevalence was observed among

Table 1 Baseline characteristics of patients

Characteristics	Overall CDI	Principal CDI	Secondary CDI	P-value
	(n=939,282)	(n=283,808)	(n=655,474)	
Age, mean (SD)	68.0 (16.8)	68.1 (17.5)	67.9 (16.6)	0.0054
Age, %				<0.001
18-44	10.4	11.4	9.9	
45-64	26.3	24.9	27.0	
65-74	21.6	20.1	22.3	
75-84	24.9	25.4	24.7	
≥85	16.8	18.3	16.1	
Female, %	58.0	64.8	55.0	<0.001
Race, %				<0.001
White	74.9	78.9	73.1	
Black	12.5	10.0	13.6	
Hispanic	7.8	7.3	8.0	
Asian or Pacific Islanders	1.9	1.3	2.1	
Native Americans and Others	3.0	2.5	3.2	
Payer, %				<0.001
Medicare	68.3	68.2	68.4	
Medicaid	9.8	8.3	10.5	
Private	17.6	19.2	16.9	
Self	2.1	2.3	2.0	
Others	2.1	2.0	2.2	
Elixhauser Comorbidity Index, %				<0.001
0	5.2	8.1	4.0	
1	12.4	16.5	10.6	
2	18.3	21.0	17.1	
≥ 3	64.1	54.5	68.3	
Inflammatory bowel disease	3.7	5.2	3.1	<0.001
Severity				
Shock	9.6	1.4	13.2	<0.001
Sepsis	26.8	3.2	37.0	<0.001
Perforated Intestine	0.4	0.1	0.5	<0.001
Ileus	4.1	2.6	4.8	<0.001
Megacolon	0.3	0.3	0.3	0.0025
Acute renal failure	29.7	20.4	33.8	<0.001
Colectomy	0.7	0.3	0.9	<0.001
Mortality	7.7	2.5	10.0	<0.001

CDI, Clostridioides difficile infection; SD, standard deviation

patients aged 18-34 years, and the lowest decrease among those ≥85. In the age group 18-34, CDI prevalence increased from 18.4/10,000 to 23.4/10,000 across the study period (AAPC 1.91%; 95%CI 1.36-2.43). It started with an initial increase from 2005-2009 (APC 4.71%; 95%CI -0.22 to 7.37), followed by a rapid increase from 2009-2015 (APC 10.96%; 95%CI 9.5-13.74), and finally a rapid decrease from 2015-2020 (APC -9.95%; 95%CI -11.52 to -8.53). On the other hand, age ≥85 showed a different pattern across the study period, with a decrease from 200/10,000 in 2005 to 107.9/10,000 in 2020 (AAPC -4.14%; 95%CI -4.55 to -3.76). It began with a stable increase from 2005-2012, followed by a minor decrease from 2012-2016 (APC -3.66%; 95%CI -6.63 to -1.57) and then a rapid decrease from 2016-2020 (APC -12.28%; 95%CI -14.40 to -10.69).

As regards sex, CDI prevalence showed a significant decrease among males and females across the study period (Fig. 4). In males, there was a slight but significant increase from 2005-2016 (APC 1.56%; 95%CI 1.12 to 2.04) and then a rapid decrease from 2016-2020 (APC -10.8%; 95%CI -12.16 to -8.68). CDI prevalence in females also started with a minor increase from 2005-2015 (APC 3.19%; 95%CI 2.43 to 3.97), followed by a decrease from 2015-2020 (APC -8.11%; 95%CI -10.12 to -6.07).

Overall, from 2005-2020, the CDI prevalence declined in all race/ethnic groups, with the fastest decline among Native Americans and others (AAPC -1.90%; 95%CI -1.80 to -0.13) and the slowest decline among Blacks. Whites exhibited a decrease from 105.4/10,000 to 87.1/10,000 (AAPC -1.06%; 95%CI -1.62 to -0.60), with an initial minor rise from 2005-

2015 (APC 2.58%; 95%CI 1.80-3.42) and then a decrease from 2015-2020 (APC -7.94%; 95%CI -10.24 to -5.90). Blacks also had an initial increase from 2005-2015 (APC 3.52%; 95%CI 2.61-4.51), followed by a decrease from 2015-2020 (APC -8.72%; 95%CI -11.26 to -6.42).

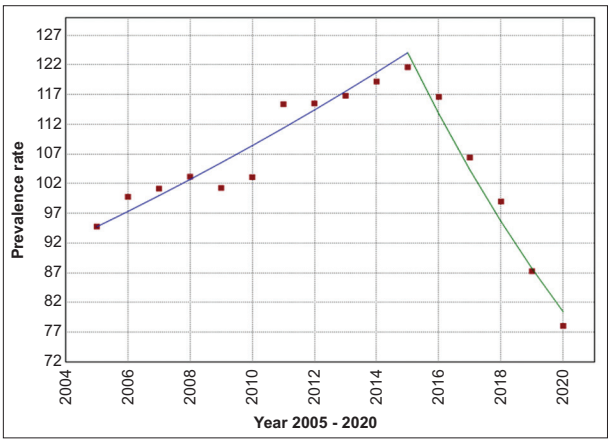

Figure 2 Prevalence of total *Clostridioides difficile* infection from 2005-2020

Temporal trends in CDI severity

Supplementary Table 3 shows the temporal trends of the prevalence of CDI severity indicators. From 2005-2020, the severity indicators exhibited an increase, except for prolonged ileus. The largest increase was found for megacolon, from 12.9/10,000 in 2005 to 69.8/10,000 in 2020 (AAPC 12.22%; 95%CI 10.56-14.31). The prevalence of megacolon exhibited an initial rapid increase from 2005-2010 (APC 13.95%; 95%CI 8.11-29.70), followed by a rapid decrease from 2010-2013 (APC -14.66%; 95%CI -20.79 to -2.07) and a rapid rise from 2013-2020 (APC 24.82%; 95%CI 20.25-31.81). The prevalence of shock and acute renal failure followed a similar pattern in trend Joinpoints, with an initial rapid increase from 2005-2009 (APC 16.89%; 95%CI 13.58-21.28, and APC 12.84%; 95%CI 11.63-13.91, respectively) and an additional minor increase from 2009-2020 (APC 3.33%; 95%CI 2.62-3.96, and APC 2.91%; 95%CI 2.58-3.20, respectively). Prolonged ileus showed an overall slight stable decrease, with a minor significant increase from 2005-2011 (APC 2.38%; 95%CI 0.10-7.58), a minor decrease from 2011-2016 (APC -5.43%; 95%CI -11.04 to -2.23)

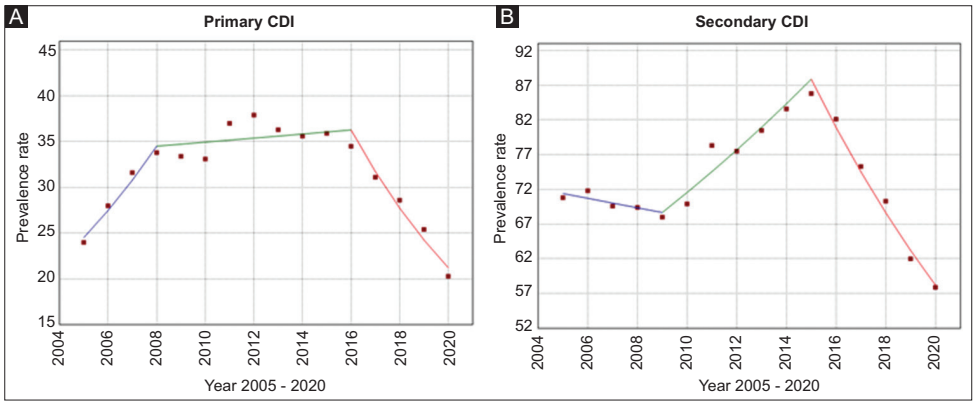

Figure 3 Prevalence of *Clostridioides difficile* infection (CDI) from 2005-2020: (A) prevalence of primary CDI from 2005-2020; (B) prevalence of secondary CDI from 2005-2020

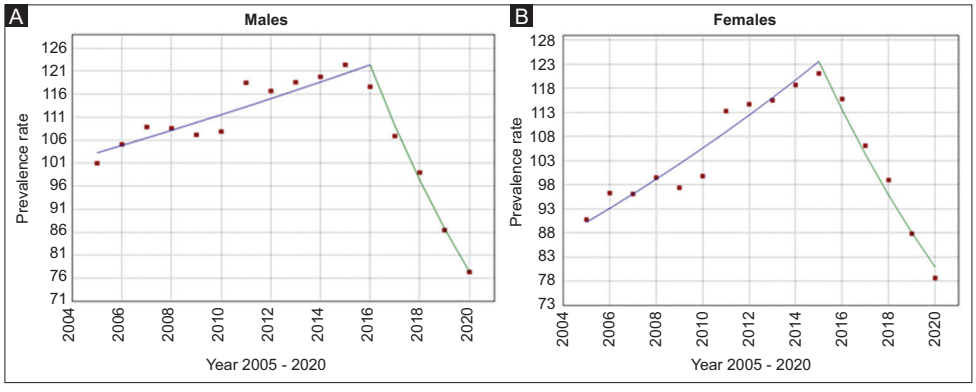

Figure 4 Prevalence of *Clostridioides difficile* infection (CDI) from 2005-2020: (A) Prevalence of CDI in males from 2005-2020; (B) prevalence of CDI in females from 2005-2020

and a final stable increase from 2016-2020 (APC 2.54%; 95%CI -2.03 to 11.68).

Temporal trends in CDI mortality

The prevalence of mortality among CDI patients demonstrated an overall significant decrease from 1028/10,000 in 2005 to 687/10,000 in 2020 (AAPC -3.13%; 95%CI -4.47 to -2.47). The mortality initially exhibited a minor decrease from 2005-2018 (APC -4.55%; 95%CI -8.52 to -2.90) and then a late stable non-significant increase from 2018-2020 (APC 6.61%; 95%CI -4.16 to 12.51) (Fig. 5).

Discussion

Our study analyzed data from the NIS covering the period 2005-2020 and found that the prevalence of CDI declined over that time. We also found disparities based on age, sex and race, with a higher prevalence in younger age groups, similar declining trends in both sexes, and a more rapid decline in Native Americans compared with Blacks. We also found a notable increase in severity markers such as megacolon, acute renal failure, and shock and a decrease in in-hospital mortality during the initial years.

In contrast to our findings, several studies have shown that the number of hospitalizations in the US with a principal diagnosis of CDI increased from 1998-2009 and from 2001-2011, respectively, with one study attributing this to the emergence of a new genotype [1, 2,]. Several studies conducted over the years show a declining trend, corroborating the findings of our study. For example, a study by Guh *et al* showed that the estimated national CDI burden and associated hospitalizations decreased from 2011-2017 as a result of declining healthcare-associated infections, while the rate of community-acquired infections remained unchanged [16]. Similarly, Sammons showed both

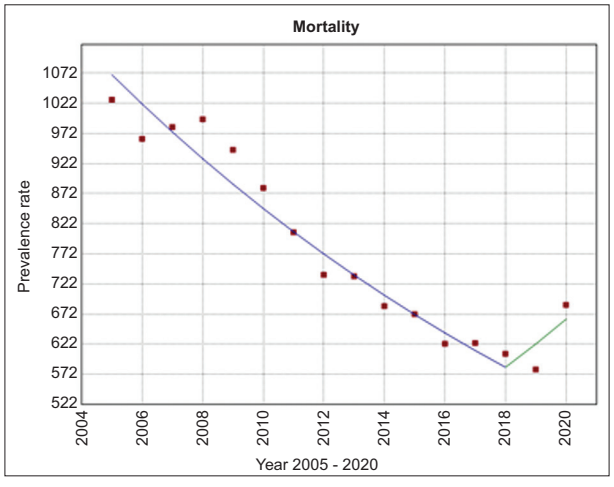

Figure 5 Temporal trend in mortality of *Clostridioides difficile* infection from 2005-2020

an upward trend in community-acquired infections and higher rates of infections in younger age groups [17]. Sumons *et al* also demonstrated a decline in the incidence of CDI and hospital-acquired infections. They attributed their findings primarily to the reduced use of antibiotics, such as fluoroquinolones, clindamycin and third generation cephalosporins [18].

Our study showed that the prevalence of CDI initially increased in the first years of the study period and then steadily decreased. This can partly be attributed to the increased testing, followed by increased awareness of antibiotic stewardship programs. This is also evident from studies by Valiquette *et al* and Fowler *et al*, which show declining trends in CDI following the implementation of antibiotic stewardship programs [19,20]. Similarly, a study by the Blue Cross Blue Shield organization showed that the number of antibiotics administered in outpatient settings was declining among commercially insured Americans, with the greatest decline in the number of broad-spectrum antibiotics administered between 2010 and 2016, which correlates with the declining trend observed in our study [21]. Additionally, with COVID-19 and more strict hygiene regulations, some studies found a decrease in healthcare-associated CDI [22] Additionally, the increased antibiotic prescription for the disease post-COVID has led to an increased prevalence, reaffirming the link between antibiotic prescription and CDI [23].

Although better institutional vigilance and infection control measures have caused a decline in healthcare-associated infections, studies show that community-acquired infections continue to rise [24-26]. This could be partly due to the overuse of antibiotics and a lack of awareness of infection control measures. We also saw increasing severity markers across our study period. These could be due to concomitant chronic diseases as confounding factors, but the lack of this information in our study makes it difficult to reach any conclusion. Thus, further studies are needed that include the study population's baseline characteristics, together with chronic diseases and their disease severity.

Our study also showed a higher decline in the White population compared to Blacks. Although this result could be explained by socioeconomic and institutional inequalities affecting marginalized communities, and unequal access to quality healthcare and health insurance, further studies are needed for a better understanding and resolution of these disparities [27]. Furthermore, although our study used an extensive database, the retrospective nature of the analysis prevents us from establishing any causal relationships. Moreover, reliance on coded information may have introduced biases or caused underreporting. Additionally, it is important to note that this trend was only observed in inpatient data. Future research could focus on the specific factors contributing to the observed trends, which include but are not limited to infection control practices and antibiotic stewardship programs. One notable limitation of our study is the change in the NIS sampling methodology starting in 2012. The transition from sampling all discharges from a 20% subset of hospitals to a 20% sample of all discharges from participating hospitals may have introduced heterogeneity in the dataset. This change could affect trend analysis, particularly when comparing data across this time

point. To mitigate this limitation, we conducted sensitivity analyses and ensured that key findings were consistent when analyzed separately for the periods before and after 2012. We recommend that temporal trends should be interpreted with this context in mind.

In conclusion, we provide a comprehensive analysis of CDI trends, showing the evolution of infection throughout the years, necessitating the need for continued vigilance, targeted therapies, and further research to lower the healthcare burden of CDI.

Summary Box

What is already known:

- *Clostridioides difficile* infection (CDI) is a significant healthcare-associated infection, leading to considerable morbidity and mortality globally
- CDI prevalence had previously shown increasing trends, particularly in healthcare settings, due to factors such as antimicrobial use and infection control measures
- The implementation of antimicrobial stewardship and infection control programs has led to variable outcomes in CDI prevalence over the years

What the new findings are:

- This study demonstrates a significant decline in overall CDI prevalence in hospitalized patients from 2005-2020, particularly in older adults, though an increase in younger populations was noted
- Despite the overall decrease in CDI prevalence, severity indicators such as megacolon and acute renal failure showed a marked rise, suggesting worsening severity of cases
- In-hospital mortality due to CDI decreased significantly, reflecting improvements in clinical management and care for CDI patients over the 15-year study period
- Despite these overall improvements, the study emphasizes the need for targeted interventions to address increasing CDI severity and persistent demographic disparities. This is crucial to ensure equitable healthcare outcomes across age, sex, and racial/ethnic groups

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Supplementary Table 1 Trends in the clinical and demographic characteristics of the study cohort

Characteristics	Hospitalizations for *Clostridioides difficile* infections (CDI), weighted estimates																
	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	P-value for trend
	222,802	241,616	240,659	276,182	285,209	300,063	344,707	336,170	330,270	336,105	347,620	336,170	312,325	291,890	257,715	210,640	
CDI per 10,000	94.8	99.8	101.2	103.2	101.3	103.1	115.4	115.5	116.8	119.2	121.6	116.6	106.4	99.0	87.3	78.1	0.68
Primary CDI	24.0	28.0	31.6	33.8	33.4	33.1	37.0	37.9	36.3	35.6	35.9	34.5	31.1	28.6	25.4	20.3	0.51
Secondary CDI	70.8	71.8	69.6	69.4	68.0	69.9	78.3	77.5	80.5	83.6	85.8	82.1	75.3	70.3	62.0	57.9	0.83
Age																	
18-34	18.4	19.9	19.3	21.5	21.0	25.0	28.0	31.9	34.4	36.4	38.8	37.5	34.2	31.1	27.9	23.4	0.01
35-44	39.3	42.3	43.2	46.3	45.2	49.8	56.6	60.4	64.2	70.1	74.0	71.1	65.4	59.0	53.5	44.0	0.02
45-54	63.1	64.4	68.1	71.3	68.3	74.1	82.3	88.6	96.9	103.7	108.0	105.2	98.9	90.5	81.7	72.6	0.01
55-64	85.0	92.4	97.0	95.3	97.8	98.2	110.9	115.0	116.2	122.9	127.3	124.5	112.2	108.9	96.2	88.7	0.13
65-74	121.2	126.1	129.0	130.3	131.7	132.9	145.5	146.9	146.7	149.7	151.4	147.9	132.9	123.9	108.6	101.6	0.56
75-84	169.9	181.0	186.1	180.7	177.0	176.8	193.2	188.4	183.3	183.4	182.0	170.4	153.2	142.0	122.4	111.6	<0.01
≥ 85	200.0	209.5	212.0	206.4	205.7	203.1	217.8	209.3	205.5	197.8	194.4	178.5	160.2	141.9	123.4	107.9	<0.01
Sex																	
Male	101.0	105.1	108.9	108.6	107.2	107.9	118.5	116.7	118.6	119.8	122.4	117.6	106.9	99.0	86.5	77.4	0.22
Female	90.8	96.3	96.1	99.5	97.4	99.8	113.3	114.7	115.5	118.7	121.1	115.8	106.1	99.0	87.9	78.7	0.91
Race																	
White	105.4	110.3	112.0	111.0	111.1	113.9	125.2	126.2	127.0	129.8	133.2	127.4	116.7	109.0	95.6	87.1	0.65
Black	72.7	82.1	83.7	90.3	84.6	86.2	97.9	99.3	102.7	104.2	104.1	99.2	91.0	85.2	76.2	66.5	0.88
Hispanic	60.6	68.8	66.8	75.3	74.0	69.8	86.4	81.8	85.1	85.4	88.5	88.1	79.1	72.4	64.7	53.7	0.75
Asian/Pacific Isl.	62.5	75.7	80.6	83.0	80.3	80.2	98.4	92.2	86.4	92.8	90.0	84.8	72.1	63.3	56.5	54.2	0.23
Native & Others	73.1	81.3	92.6	86.2	79.9	84.8	98.6	91.1	92.7	96.6	99.9	94.4	88.9	82.0	73.1	66.6	0.74
Severity																	
Shock	474.1	528.8	694.1	758.2	884.1	897.8	959.6	949.5	1019.9	1052.9	1088.1	1105.8	1118.4	1169.3	1188.7	1345.9	<0.01
Sepsis	1828.0	1918.9	2154.0	2326.4	2453.8	2471.5	2530.9	2549.3	2692.8	2817.0	3005.1	2995.2	3106.2	3174.0	3162.6	3400.6	<0.01
Perforated Intestine	30.1	28.6	33.1	39.8	37.6	40.7	35.3	36.4	37.2	45.2	37.5	38.5	49.8	49.3	45.2	59.8	<0.01
Ileus	425.0	404.8	408.0	450.7	449.6	473.8	459.6	420.2	421.3	429.3	411.7	323.9	352.4	383.9	384.1	391.4	0.02
Megacolon	12.9	14.0	15.3	24.2	21.0	24.1	20.1	17.3	16.8	21.4	19.6	26.1	41.9	52.6	57.2	69.8	<0.01
Acute renal failure	1709.8	1870.0	2187.2	2490.6	2733.2	2884.9	2923.1	2898.2	3069.2	3196.8	3284.9	3353.9	3432.0	3548.8	3610.2	3877.9	<0.01
Colectomy	49.5	51.1	54.2	62.7	105.3	102.0	101.0	84.5	83.9	74.7	75.4	66.4	61.5	63.0	65.0	67.2	0.95
Mortality	1028.0	962.7	982.4	995.3	944.7	881.2	807.7	737.3	735.0	685.4	672.1	622.9	624.2	606.1	580.3	687.2	<0.01

Supplementary Table 2 Relative changes in the yearly prevalence rates of CDI from 2005-2020 based on Joinpoint regression analysis

Characteristics	Duration	APC and 95%CI (%)	AAPC and 95%CI (%)
Total CDI	2005-2015	2.73 (1.97 to 3.55)*	-1.09 (-1.6 to -0.64)*
	2015-2020	-8.30 (-10.34 to -6.24)*	
Primary CDI	2005-2008	12.06 (6.39 to 27.20)*	-0.96 (-2.12 to 0.31)
	2008-2016	0.63 (-1.65 to 2.18)	
	2016-2020	-12.55 (-19.13 to -8.97)*	
Secondary CDI	2005-2009	-0.97 (-4.71 to 0.87)	-1.35 (-1.72 to -1.00)*
	2009-2015	4.19 (3.23 to 6.44)*	
	2015-2020	-7.90 (-9.10 to -6.72)*	
Age groups			
18-34	2005-2009	4.71 (-0.22 to 7.37)	1.91 (1.36 to 2.43)*
	2009-2015	10.96 (9.5 to 13.74)*	
	2015-2020	-9.95 (-11.52 to -8.53)*	
35-44	2005-2009	3.79 (-2.19 to 7.16)	1.03 (0.33 to 1.71)*
	2009-2015	8.81 (-2.94 to 13.07)	
	2015-2020	-9.52 (-12.01 to -6.79)*	
45-54	2005-2009	2.35 (-2.76 to 4.77)	1.10 (0.61 to 1.56)*
	2009-2015	8.25 (7.07 to 11.26)*	
	2015-2020	-7.78 (-9.29 to -6.23)*	
55-64	2005-2016	3.59 (2.85 to 4.43)*	0.09 (-0.57 to 0.61)
	2016-2020	-8.96 (-12.19 to -5.99)*	
65-74	2005-2015	2.50 (1.90 to 3.16)*	-1.14 (-1.57 to -0.78)*
	2015-2020	-8.05 (-9.62 to -6.19)*	
75-84	2005-2015	0.55 (-0.21 to 1.37)	-2.99 (-3.53 to -2.56)*
	2015-2020	-9.70 (-11.89 to -7.72)*	
≥85	2005-2012	0.55 (-0.18 to 2.19)	-4.14 (-4.55 to -3.76)*
	2012-2016	-3.66 (-6.63 to -1.57)*	
	2016-2020	-12.28 (-14.40 to -10.69)*	
Sex			
Male	2005-2016	1.56 (1.12 to 2.04)*	-1.90 (-2.25 to -1.58)*
	2016-2020	-10.81 (-12.16 to -8.68)*	
Female	2005-2015	3.19 (2.43 to 3.97)*	-0.72 (-1.22 to -0.28)*
	2015-2020	-8.11 (-10.12 to -6.07)*	
Race/ethnicity			
White	2005-2015	2.58 (1.80 to 3.42)*	-1.06 (-1.62 to -0.60)*
	2015-2020	-7.94 (-10.24 to -5.90)*	
Black	2005-2015	3.52 (2.61 to 4.51)*	-0.73 (-1.34 to -0.19)*
	2015-2020	-8.72 (-11.26 to -6.42)*	
Hispanic	2005-2016	3.28 (2.27 to 4.41)*	-1.04 (-1.90 to -0.35)*
	2016-2020	-11.99 (-16.66 to -8.26)*	
Asian/Pacific Isl.	2005-2007	13.06 (2.78 to 23.87)*	-1.39 (-2.62 to -0.31)*
	2007-2015	1.58 (-12.21 to 3.53)	
	2015-2020	-10.97 (-16.57 to -6.88)*	
Native Am. & Others	2005-2015	2.55 (1.34 to 4.10)*	-1.90 (-1.80 to -0.13)*
	2015-2020	-7.47 (-12.20 to -4.57)*	

*indicates that the APC and AAPC is significantly different from zero at the alpha=0.05 level

CDI, Clostridioides difficile infection; APC, annual percentage change; AAPC, average annual percentage change; CI, confidence interval

Supplementary Table 3 Relative changes in the yearly prevalence rates of CDI severity and mortality from 2005-2020 based on join point regression analysis

Characteristics	Duration	APC and 95%CI (%)	AAPC and 95%CI (%)
Shock	2005-2009	16.89 (13.58 to 21.28)*	6.78 (6.26 to 7.30)*
	2009-2020	3.33 (2.62 to 3.96)*	
Sepsis	2005-2008	8.89 (6.60 to 12.70)*	4.26 (3.97 to 4.56)*
	2008-2020	3.13 (2.77 to 3.45)*	
Perforated intestine	2005-2020	3.47 (1.66 to 5.26)*	3.47 (1.66 to 5.26)*
Ileus	2005-2011	2.38 (0.10 to 7.58)*	-0.25 (-1.18 to 0.76)
	2011-2016	-5.43 (-11.04 to -2.23)*	
	2016-2020	2.54 (-2.03 to 11.68)	
Megacolon	2005-2010	13.95 (8.11 to 29.70)*	12.22 (10.56 to 14.31)*
	2010-2013	-14.66 (-20.79 to -2.07)*	
	2013-2020	24.82 (20.25 to 31.81)*	
Acute renal failure	2005-2009	12.84 (11.63 to 13.91)*	5.46 (5.23 to 5.70)*
	2009-2020	2.91 (2.58 to 3.20)*	
Colectomy	2005-2010	17.09 (9.36 to 32.34)*	1.82 (-0.02 to 4.05)
	2010-2020	-5.05 (-8.57 to -2.56)*	
Mortality	2005-2018	-4.55 (-8.52 to -2.90)*	-3.13 (-4.47 to -2.47)*
	2018-2020	6.61 (-4.16 to 12.51)	

*indicates that the APC and AAPC are significantly different from zero at the alpha = 0.05 level

CDI, Clostridioides difficile infection; APC, annual percentage change; AAPC, average annual percentage change; CI, confidence interval