Current Trends of Clostridioides difficile infections (CDI) in the United States: Results from the National Inpatient Sample Database

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Abstract

Background

Clostridioides difficile infection (CDI) is a cause of significant hospital morbidity and mortality in the United States.

Objective

Our aim was to analyze the current trends of CDI burden using the National Inpatient Sample (NIS) database, which tracks all hospital discharges in the United States.

Methods

Using the NIS, all adult discharges (age ≥ 18 years) between 2012 and 2017 were evaluated. Discharges with CDI were identified based on the appropriate ICD9 (00845) and ICD10 (A047, A0471, A0472) codes. All data was analyzed after applying recommended weights using Stata Statistical Software: Release 16. (College Station, TX) and pandas statistical package in Python.

Main Measures

The overall CDI trends, including incidence, mortality, age, and length of stay were analyzed. The incidence and mortality rates were also analyzed with respect to race, sex, comorbidity (diabetes, hypertension, hyperlipidemia), and hospital location, size, and ownership.

Key Results

Records representing 181,132,460 adult discharges in the United States over 6 years (2012 – 2017) were included in the analysis; of these, 2,088,825 (1.15%) discharges had CDI. Overall incidence increased until peaking in 2015 at 1.21%, before declining to 1.06% in 2017. Despite the fluctuation in incidence rate, the mortality rate exhibited a steady decrease from 7.32% in 2012 to 6.25% in 2017. Also, the average length of stay decreased from 10.6 days to 9.9 days, along with average age of CDI patients dropping from 67.9 years to 66.2 years. Incidence and mortality rates were consistently higher in males compared to females. Incidence was typically higher in White Americans; however, Asians/Pacific Islanders regularly demonstrated the highest mortality rates during the study period. Finally, incidence and mortality rates were highest in large-bedded, urban teaching hospitals.

Conclusion

Improvement in overall mortality rate (Δ -1.07%) outpaced improvement in the incidence rate (Δ -0.09%), which may be indicative of improved diagnosis and management of CDI. Specifically, the adoption of oral vancomycin and fidaxomicin as standard treatments may be a key reason for our findings. However, primary prevention efforts are still struggling to effectively control the spread of CDI, especially in large-bedded, urban teaching hospitals – this may be due in part to a higher acuity patient population. Despite limitations, these findings suggest a lessening of overall burden of CDI in the United States.

Introduction

Clostridioides difficile (C. diff), formerly known as *Clostridium difficile*, is an anaerobic, spore-forming, toxin-producing, gram-positive bacillus that is transferred among humans via the fecal-oral route.[1] The main risk factors for primary infection are age ≥ 65 years, antibiotic use (odds increase with extra antibiotics), and recent hospital admission.[2] Clostridioides difficile infection (CDI) clinical practice guidelines recommend oral vancomycin or fidaxomicin for initial and recurrent episodes; however, primary prevention of CDI remains a national healthcare priority due to its overall burden.[3,4]

CDI results in more healthcare-associated infections in the United States than any other pathogen.[5,6] CDI was first identified as a source of antibiotic-associated diarrhea and pseudomembranous colitis in 1978, but it wasn't until the early 2000's that CDI incidence, and thus burden, increased considerably.[3,5] Studies suggest that the shift in CDI incidence trends is mostly owed to the emergence of the epidemic strain ribotype 027 and the advent of nucleic acid amplification testing for diagnosis.[3] Overall, the burden of CDI in the United States is significant and well-established; however, its scope and magnitude continue to evolve.

According to the Center for Disease Control and Prevention (CDC), CDI accounts for 15-25% of all episodes of antibiotic-associated diarrhea.[6] The CDC estimates that the national burden was 462,100 incident cases in 2017, down from 476,400 in 2011.[3] A separate study estimates that the national burden was approximately 453,000 cases and 29,000 deaths in 2011, with 24% (107,600) of infections occurring in hospital settings.[7] In 2015, Leffler et al. reported a CDI infection-related mortality of 5% and all-cause mortality of 15-20%.[1] As previously mentioned, CDI is the most frequently reported nosocomial infection – it adds significant costs to each hospitalization and can ultimately more than quadruple total costs.[1] According to Zimlichman et al., nosocomial CDIs increase annual healthcare expenditures by nearly $1.5 billion in the United States.[8] Other estimates of costs attributed to CDIs in acute-care facilities range from $1 billion to a staggering $4.9 billion.[9]

Current CDI trends reported by the CDC rely on data from the Emerging Infections Program (EIP) which identifies CDI cases at 10 U.S. sites to estimate the national burden, first recurrences, hospitalizations, and in-hospital deaths.[3] We believe that additional data analysis is necessary to quantify CDI trends with respect to race, sex, comorbidity, and hospital size, location, and ownership – this may allow us to draw further conclusions as to the sources of variation in CDI trends may also contribute to improvement of CDI prevention and management strategies.

Methods

Data Sources

We drew our study population from the National Inpatient Sample (NIS) database, which is now a sample of discharge records from all HCUP-participating hospitals. The NIS contains information on all hospital stays, including data on demographics, diagnoses, procedures, and length of hospital stay, hospital characteristics, such as location, teaching status and bed size, are also available. We pooled all adult hospitalizations (age ≥ 18 years) between 2012 and 2017.

Primary Outcome

Our primary outcome is CDI and it was identified based on the ICD-9-CM diagnosis codes (00845) and ICD-10-CM diagnosis codes (A047, A0471, A0472) codes. We summarized baseline characteristics of the study using descriptive statistics, including incidence, mortality, age, race and length of stay were analyzed.

Statistical Modeling

We used logistic regression with backward variable selection (p-value criterion <0.01 – stricter than usual criteria to account for the very large sample size) also combined with ROC curve to determine correlates associated with CDI incidence rates and mortality rates. We ran separate models for CDI incidence rates and mortality rates. We calculated odds ratios (OR) and 95% confidence intervals (95% CI) of the associated correlates to determine their relative contribution to the risk of developing our primary outcome and the risk of mortality. CDI incidence and mortality rates modeling with odds ratio estimates were computed with respect to race, sex, comorbidity (diabetes, hypertension, hyperlipidemia), and hospital location, size, and ownership.

All data was analyzed after applying weighting and stratification using Stata IC: Release 16. (College Station, TX) and pandas statistical package in Python.

Results

In this study, records representing 181,132,460 adult discharges were analyzed from 2012 – 2017 and a total of 2,088,825 (1.15%) discharges had CDI (Table 1). The overall incidence rate increased from 1.15% to 1.21% between 2012 and 2015 before declining to 1.16% in 2016 and 1.06% in 2017 (Δ -0.09%) (Figure 1). Mortality rate also exhibited a steady decrease from 7.32% to 6.25% (Δ -1.07%) over the 6-year period (Figure 2); however, incidence and mortality rates varied depending on sex, race, comorbidity, and hospital facility. The odds ratio for CDI incidence with respect to age is 1.0264; The odds ratio for CDI mortality and age is 1.0304. Overall, the average length of stay decreased from 10.6 days to 9.9 days, along with average age of CDI dropping from 67.9 years to 66.2 years (Table).

Table 1: CDI incidence, mortality, age, and length of stay (Overall)						
Duration: 2012 – 2017 (6 years)						
Total Adult Hospitalizations: 181,132,460						
Total Adult Hospitalizations with CDI: 2,088,825 (1.15%)						
	2012	**2013**	**2014**	**2015**	**2016**	**2017**

Total number hospitalized	30,704,144		29,957,241		29,738,494		30,150,582		30,161,092		30,420,907	
Hospitalizations with CDI, N (%)	352,485 (1.15)		347,835 (1.16)		351,655 (1.18)		363,350 (1.21)		350,960 (1.16)		322,540 (1.06)	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Mortality	25,810	7.32%	25,305	7.28%	23,970	6.82%	24,245	6.68%	22,010	6.28%	20,130	6.25%
Age	67.9		67.3		66.6		66.3		66.0		66.2	
95% CI	67.75 – 67.997		67.18 – 67.44		66.45 – 66.70		66.17 – 66.42		65.86 – 66.11		66.08 – 66.34	
LOS (days)	10.6		10.4		10.5		10.2		10.1		9.9	
95% CI	10.51 – 10.71		10.34 – 10.53		10.37 – 10.57		10.07 – 10.26		10.03 – 10.22		9.79 – 9.98	

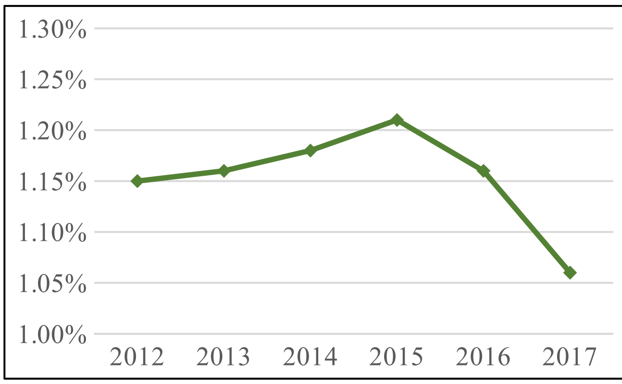

Figure 1: Overall CDI Incidence

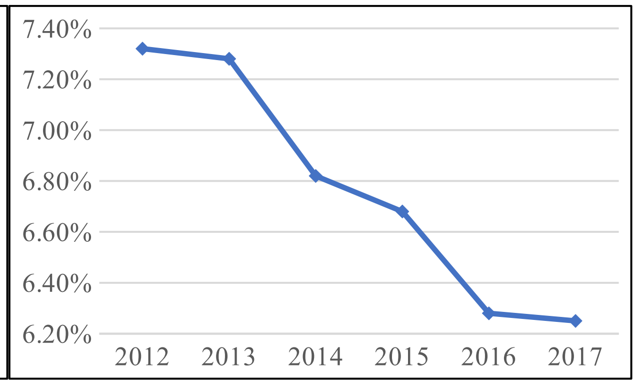

Figure 2: Overall CDI Mortality

Of the 2,088,825 admissions with CDI, 873,195 (41.8%) were males and 1,215,185 (58.2%) were females (Appendix Table I). The incidence of CDI continued to remain marginally high in males compared to females as the years progressed (from 1.16% to 1.07% (Δ -0.09%) in males vs 1.14% to 1.05% (Δ -0.09%) in females) (Figure 3); however, this was not statistically significant. The mortality rates in males with CDI was 8.26% in 2012 and decreased to 7.13% by 2017 (Δ -1.13%); In the same period, the mortality rates in females decreased from 6.67% to 5.58% (Δ -1.09%). Overall, males with CDI had a higher mortality rate than females (Figure 4) – the odds ratio for CDI mortality in females is 0.777.

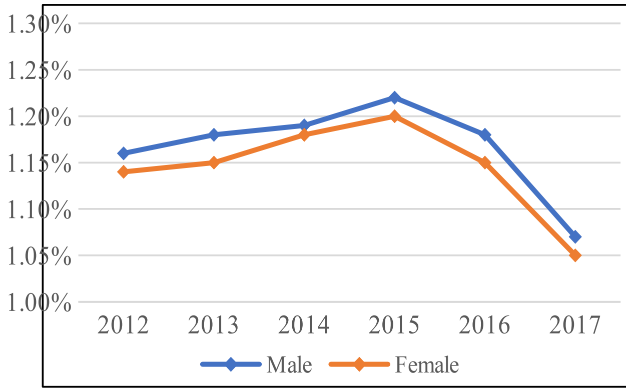

Figure 3: CDI incidence with respect to sex

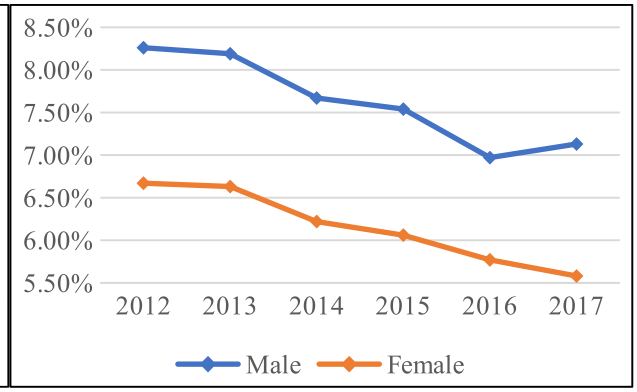

Figure 4: CDI mortality with respect to sex

When CDI was analyzed according to race, several disparities were noted. The overall incidence of CDI was higher in White Americans in most years compared to other groups (Appendix Table II). The incidence in Black Americans fluctuated, initially increasing from 0.99% in 2012 to 1.04% in 2015, before declining to 0.91% in 2017 (Figure 5). Hispanics and Asians/Pacific Islanders also experienced similar trends; however, Asian/Pacific Islanders had the lowest incidence rate by the end of the study period (0.72%) (Appendix Table II). Though there is a minimal decrease in the overall incidence of CDI from 2012 – 2017 (1.15% to 1.06%; Δ -0.09%), the incidence of CDI in Native Americans dramatically increased from 0.89% to 1.18% (Δ +0.29%) during this time (Figure 5). Additionally, there is an overall decrease in mortality rates in CDI with a statistically significant difference in mortality rates with respect to race. Amongst various races, the mortality rate was highest in Asians/Pacific Islanders, ranging from 10.6% to 9.26% from 2012-2017, and lowest in White Americans (7.14% to 6.03%) (Figure 6). Further, in 2015 & 2016 the mortality rates in Native Americans were the lowest of all racial groups (5.28% & 5.15% respectively) (Figure 6). Odds ratios for CDI incidence with respect to race are 1.00, 0.907, 0.809, 0.736, 1.137, and 0.802 for White, Black, Hispanic, Asian/Pacific Islander, Native American, and Other, respectively. Odds ratios for CDI mortality with respect to race are 1.00, 1.305, 1.184, 1.522, 1.215, and 1.308 for White, Black, Hispanic, Asian/Pacific Islander, Native American, and Other, respectively.

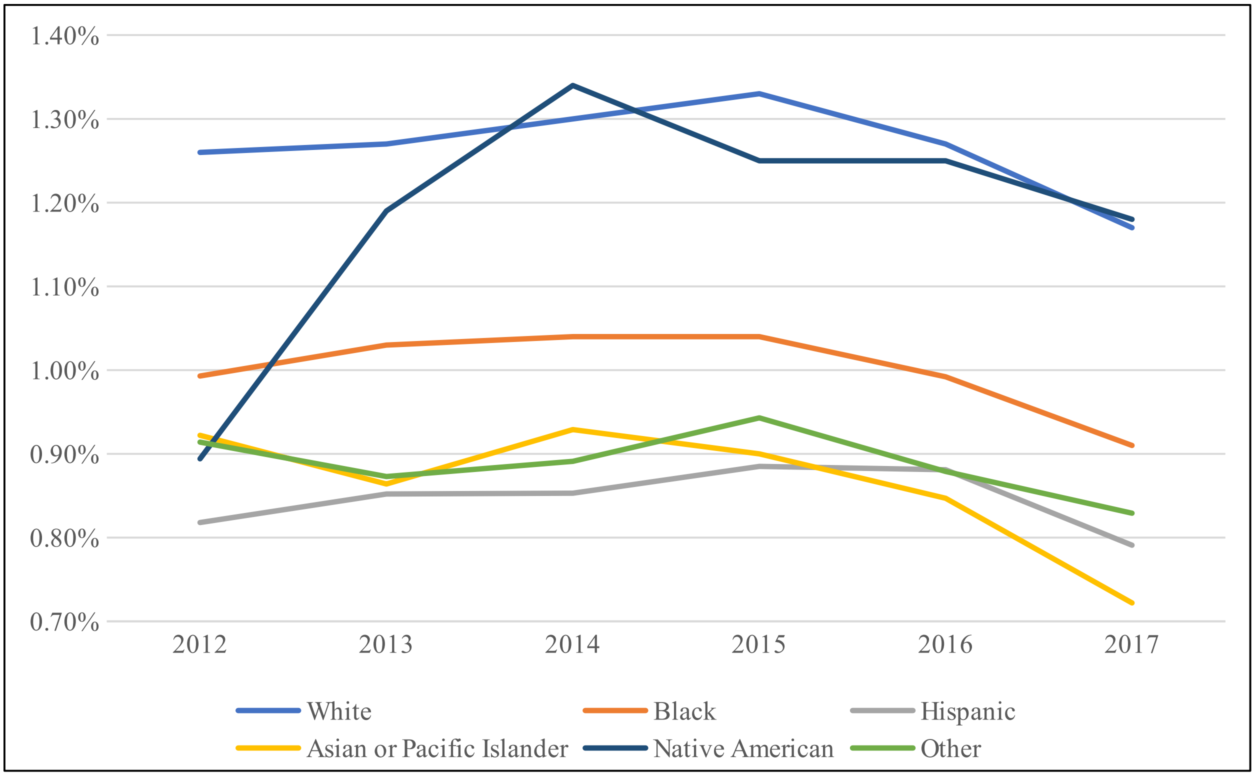

Figure 5: CDI incidence with respect to race

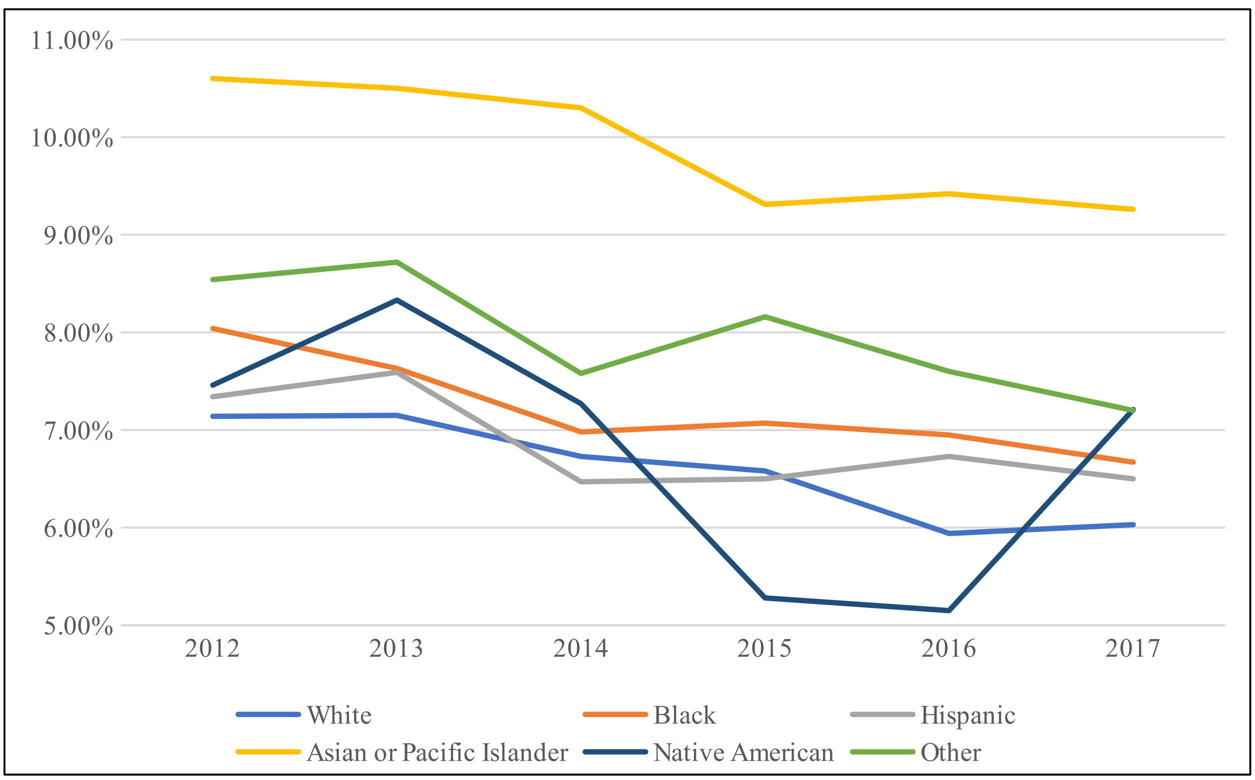

Figure 6: CDI mortality with respect to race

During the study period, urban hospitals had 1,905,860 (91.24%) and rural hospitals had 182,965 (8.76%) CDI admissions (Appendix Table III). Further, urban teaching hospitals had 1,282,145 (67.27%) and urban non-teaching hospitals had 623,715 (32.73%) CDI admissions (Appendix Table III). CDI incidence was higher in large-bedded hospitals, trending from 1.19% to 1.10% (Δ -0.09%) and lowest in small-bedded hospitals, 1.07% to 1.00% (Δ -0.07%) (Appendix Table IV). At the end of the study, private non-profit hospitals had a higher CDI incidence (1.10%) than government non-federal (1.04 %) and private investor owned hospitals (0.87%) (Appendix Table V, Figure 7).

Though mortality rates in both rural and urban hospitals showed an overall decline from 2012-2017, urban teaching hospitals had a higher mortality rate than urban non-teaching [90,885 (68.91%) vs 40,995 (31.09%) deaths] (Appendix Table III). Mortality rates were also higher in large bedded hospitals with a significant improvement seen in medium-bedded hospitals after 2013 (Appendix Table IV). Mortality rates in government non-federal hospitals peaked in 2013 (7.74%) but there appears to be an increasing trend in 2016, although not statistically significant (Appendix Table V, Figure 8).

The odds ratios for CDI incidence with respect to hospital size, using small-bedded facilities as the control, are 1.085 and 1.211 for medium- and large-bedded hospitals, respectively. The odds ratios for CDI incidence with respect to hospital location, using rural facilities as the control, are 1.246 and 1.373 for urban non-teaching and urban teaching hospitals, respectively.

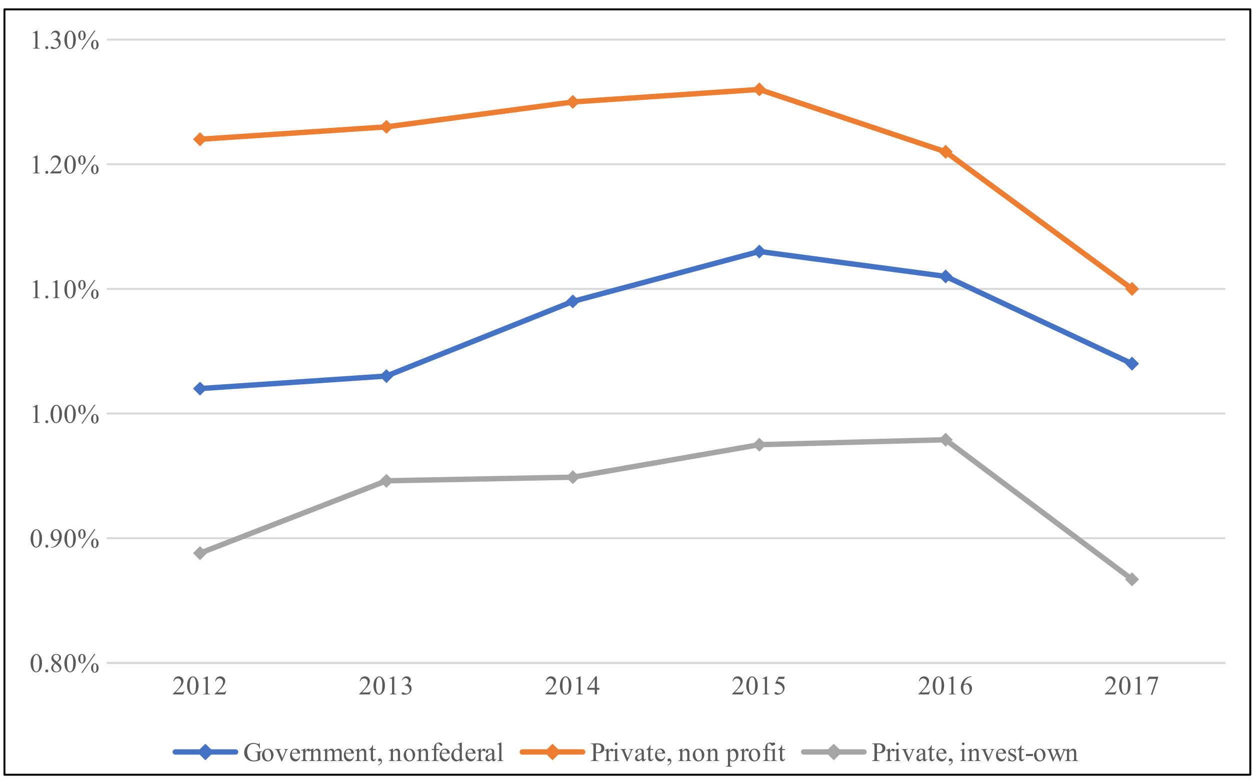

Figure 7: CDI incidence with respect to hospital ownership

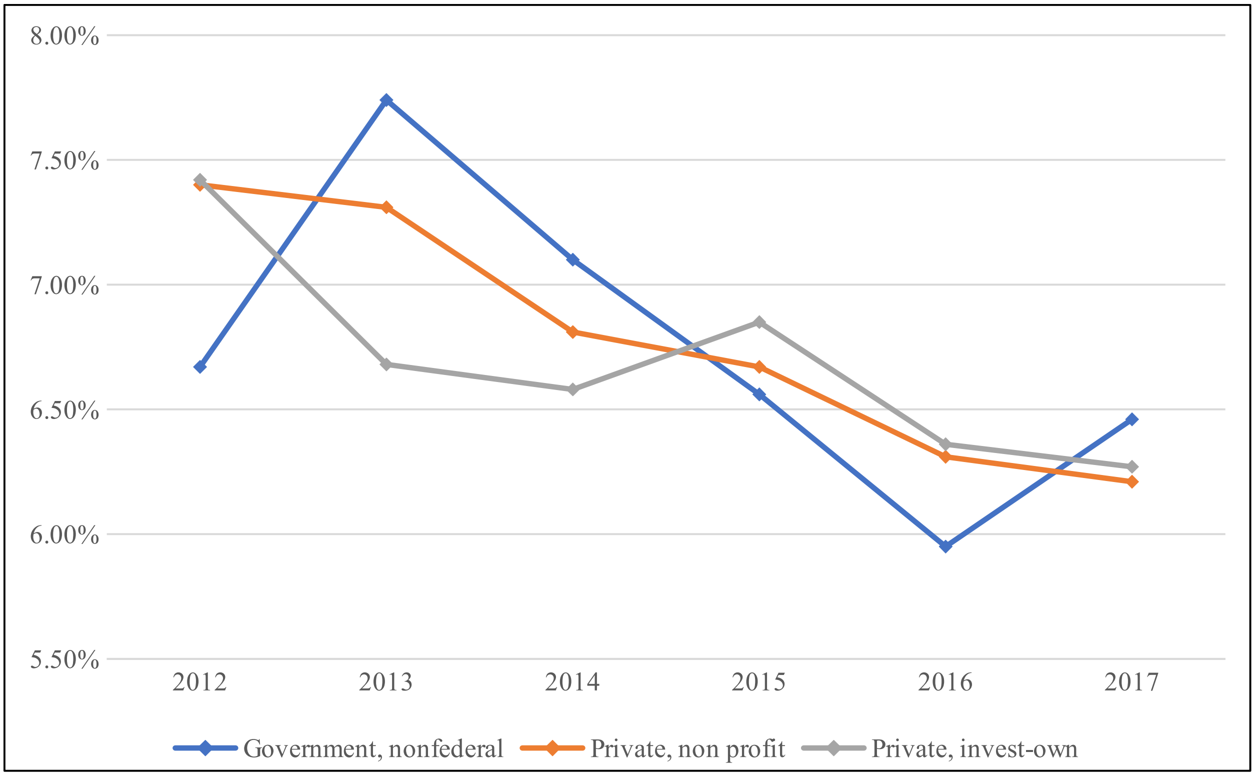

Figure 8: CDI mortality with respect to hospital ownership

The three most common comorbidities associated with CDI are hypertension (HTN), diabetes (DM), and hyperlipidemia (HLD). The odds ratios for CDI incidence with respect to comorbidities are as follows: 1.392 for DM alone, 0.854 for HTN alone, 0.826 for both DM and HTN, and 0.821 for HLD. Regarding CDI mortality, the odds ratios are 0.877 for DM alone, 0.553 for HTN alone, 0.579 for both DM and HTN, and 0.687 for HLD.

The logistic regression model of CDI incidence includes 34,494,995 observations with an area under ROC curve of 0.6505 (Appendix Figure I). Variables included to reach the highest goodness of fit (ROC curve) include age, race, hypertension, diabetes, hyperlipidemia, hospital bed size, and hospital location. The logistic regression model of CDI mortality includes 384,716 observations with an area under ROC curve of 0.6503 (Appendix Figure II). Variables included to reach the highest goodness of fit include age, race, sex, hypertension, and hyperlipidemia.

Discussion

In this study, we utilized the NIS database to analyze records representing 181,132,460 adult discharges and found 2,088,825 (1.15%) CDI cases in the United States from 2012 to 2017. The available data allowed us to determine the current overall CDI trends before analyzing trends with respect to potential confounding variables such as race, sex, hospital location, size, and ownership. We discovered that the while both incidence and mortality were lower in 2017 than 2012, improvement in mortality is outpacing that of incidence (Δ -1.07% vs Δ -0.09%, respectively). This may be indicative of improved management of CDI especially in the acute setting; whereas prevention efforts are either less effective or being implemented at a slower pace. Specifically, the adoption of vancomycin as standard treatment may be a key reason for our findings. Another significant finding of our study is the decreasing length of stay (10.6 to 9.9 days) for CDI hospitalization. Ultimately, our findings suggest a lessening of overall burden of CDI in the United States.

Evaluating CDI hospitalizations by sex, race, and hospital facility type may help us elucidate potential sources contributing to overall trends, and hopefully provide insight into areas requiring attention to further improve incidence and mortality. First, despite that fact that CDI incidence and mortality are greater in males compared to females, both sexes demonstrate similar trends (Figure 3, 4) – this suggests that a disparity between sexes is not the source of overall CDI trends.

Next, we identified several racial disparities with respect to CDI incidence and mortality. White Americans typically had a higher incidence of CDI, followed by Native Americans, in whom the incidence rate is seen to be dramatically increasing over the years. Solving the problem of increasing CDI incidence in Native Americans might be an area to focus to continue easing CDI burden. The mortality rates are lowest in Whites and highest in Asians or Pacific Islanders. Though previous studies show that the mortality rates were higher in Blacks, we found the mortality outcomes in Blacks to be better than the Asians or Pacific Islanders; however, these rates of all minority populations continue to be much higher than those of White populations. Though our study findings are statistically significant, the differences observed could be due to limitations of various racial groups access to healthcare.

Finally, CDI trends were broken down into hospital location, size, and ownership. What we found is that urban teaching hospitals had higher CDI incidence and mortality rates compared to urban non-teaching and rural hospitals. We suspect that this could be due in part to higher acuity patient populations in urban teaching hospitals. Large bedded hospitals had a higher CDI incidence and mortality rates. The incidence rate of CDI is higher in private, non-profit hospitals and lowest in private, invest own, but mortality rates do not show a statistically significant relationship.

Interestingly, the odds ratios for CDI incidence with respect to comorbidity suggest that patients with DM contract CDI more often when compared to those with HTN alone, HTN and DM, or HLD alone. These findings might give providers and hospitals the patient population to focus prevention efforts. Also, odds ratios for CDI mortality and comorbidities are all <1.

Despite limitations, our study contributes to the understanding of CDI burden in the United States. We believe that it highlights areas that will benefit from improved prevention and management strategies, further decreasing burden and racial disparities in healthcare.

Appendix

Table I: CDI incidence and mortality with respect to sex

	2012		2013		2014		2015		2016		2017	
Incidence	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Male	144,830	1.16%	144,740	1.18%	145,585	1.19%	151,880	1.22%	148,745	1.18%	137,415	1.07%
Female	207,630	1.14%	203,080	1.15%	206,045	1.18%	211,385	1.2%	201,925	1.15%	185,120	1.05%
	P = 0.0174		P = 0.0005		P = 0.1184		P = 0.0391		P = 0.0022		P = 0.0742	
Mortality	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Male	11,965	8.26%	11,850	8.19%	11,160	7.67%	11,445	7.54%	10,360	6.97%	9,795	7.13%
Female	13,845	6.67%	13,455	6.63%	12,810	6.22%	12,800	6.06%	11,635	5.77%	10,330	5.58%
	P < 0.0001		P < 0.0001		P < 0.0001		P < 0.0001		P < 0.0001		P < 0.0001	

Table II: CDI incidence and mortality with respect to race

	2012		2013		2014		2015		2016		2017	
Incidence	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
White	252,470	1.26%	246,690	1.27%	250,100	1.30%	257,975	1.33%	249,690	1.27%	230,550	1.17%
Black	42,350	0.99%	42,820	1.03%	43,340	1.04%	45,640	1.04%	43,400	0.99%	40,675	0.91%
Hispanic	24,405	0.82%	25,585	0.85%	25,650	0.85%	27,280	0.89%	27,580	0.88%	25,770	0.79%
Asian/ Pacific Islander	6,380	0.92%	6,095	0.86%	6,680	0.93%	6,945	0.90%	6,590	0.85%	5,835	0.72%
Native American	1,810	0.89%	1,980	1.19%	2,275	1.34%	2,180	1.25%	2,235	1.25%	2,150	1.18%
Other	8,840	0.91%	7,165	0.87%	7,590	0.89%	7,475	0.94%	7,435	0.88%	7,430	0.83%
	P = 0.0000		P = 0.0000		P = 0.0000		P = 0.0000		P = 0.0000		P = 0.0000	
Mortality	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
White	18,025	7.14%	17,640	7.15%	16,835	6.73%	16,960	6.58%	14,800	5.93%	13,885	6.03%
Black	3,405	8.04%	3,265	7.63%	3,025	6.98%	3,225	7.07%	3,015	6.95%	2,710	6.67%
Hispanic	1,790	7.34%	1,940	7.59%	1,660	6.47%	1,770	6.50%	1,855	6.73%	1,675	6.50%
Asian/ Pacific Islander	675	10.60%	640	10.50%	685	10.30%	645	9.31%	620	9.42%	540	9.26%
Native American	135	7.46%	165	8.33%	165	7.27%	115	5.28%	115	5.15%	155	7.21%
Other	755	8.54%	625	8.72%	575	7.58%	610	8.16%	565	7.60%	535	7.20%
	P = 0.0000		P = 0.0001		P = 0.0000		P = 0.0001		P = 0.0000		P = 0.0000	

Table III: CDI incidence and mortality with respect to hospital location

	2012	2013	2014	2015	2016	2017

Incidence	N	%	N	%	N	%	N	%	N	%	N	%
Rural	33,115	0.92%	34,395	1.00%	27,915	0.96%	30,525	1.06%	28,890	1.03%	28,125	1.00%
Urban, Non-teaching	135,175	1.14%	129,825	1.13%	92,660	1.15%	98,155	1.19%	93,110	1.17%	74,790	1.07%
Urban, Teaching	184,195	1.21%	183,615	1.22%	231,080	1.23%	234,670	1.23%	228,960	1.18%	219,625	1.07%
	P = 0.0000		P = 0.0000		P = 0.0000		P = 0.0000		P = 0.0000		P = 0.0000	
Mortality	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Rural	2,040	6.16%	1,900	5.53%	1,525	5.47%	1,600	5.24%	1,320	4.57%	1,205	4.29%
Urban, Non-teaching	9,955	7.37%	9,230	7.11%	6,055	6.54%	6,150	6.27%	5,450	5.86%	4,155	5.57%
Urban, Teaching	13,815	7.50%	14,175	7.72%	16,390	7.10%	16,495	7.03%	15,240	6.66%	14,770	6.73%
	P = 0.0006		P = 0.0000		P = 0.0000		P = 0.0000		P = 0.0000		P = 0.0000	

Table IV: CDI incidence and mortality with respect to hospital size

	2012		2013		2014		2015		2016		2017	
Incidence	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Small	46,425	1.07%	45,285	1.08%	61,505	1.10%	61,675	1.11%	61,255	1.07%	61,035	1.00%
Medium	88,595	1.09%	88,430	1.11%	100,945	1.16%	105,640	1.18%	99,215	1.13%	92,485	1.03%
Large	217,465	1.19%	214,120	1.20%	189,205	1.23%	196,035	1.25%	190,490	1.21%	169,020	1.10%
	P = 0.0000		P = 0.0000		P = 0.0000		P = 0.0000		P = 0.0000		P = 0.0000	
Mortality	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Small	2,950	6.36%	2,960	6.55%	3,785	6.16%	3,460	5.61%	3,265	5.33%	3,355	5.50%
Medium	6,605	7.46%	6,425	7.27%	6,580	6.52%	6,810	6.46%	6,240	6.29%	5,470	5.92%
Large	16,255	7.48%	15,920	7.44%	13,605	7.19%	13,975	7.13%	12,505	6.57%	11,305	6.69%
	P = 0.0006		P = 0.0129		P = 0.0001		P = 0.0000		P = 0.0000		P = 0.0000	

Table V: CDI incidence and mortality with respect to hospital ownership

	2012		2013		2014		2015		2016		2017	
Incidence	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Government, Nonfederal	37,470	1.02%	37,365	1.03%	39,610	1.09%	40,940	1.13%	38,245	1.11%	36,390	1.04%
Private Non-	275,050	1.22%	268,42	1.23%	269,720	1.25%	277,165	1.26%	267,59	1.21%	247,035	1.10%

profit			5						0			
Private Invest-own	39,965	0.89%	42,045	0.95%	42,325	0.95%	45,245	0.98%	45,125	0.98%	39,115	0.87%
	P < 0.0001		P < 0.0001		P < 0.0001		P < 0.0001		P < 0.0001		P < 0.0001	
Mortality	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Government, Nonfederal	2,500	6.67%	2,890	7.74%	2,810	7.10%	2,685	6.56%	2,270	5.95%	2,345	6.46%
Private Non-profit	20,345	7.40%	19,610	7.31%	18,375	6.82%	18,465	6.67%	16,870	6.31%	15,335	6.21%
Private Invest-own	2,965	7.42%	2,805	6.68%	2,785	6.58%	3,095	6.85%	2,870	6.36%	2,450	6.27%
	P = 0.0722		P = 0.0308		P = 0.4195		P = 0.7401		P = 0.4560		P = 0.7032	

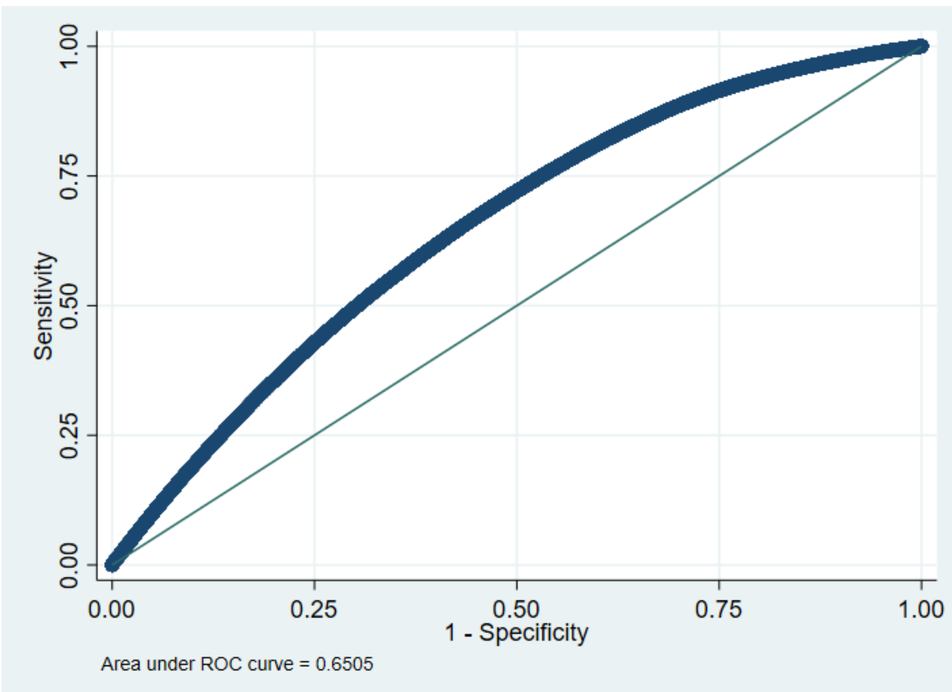

Figure I: Logistic regression model of CDI incidence

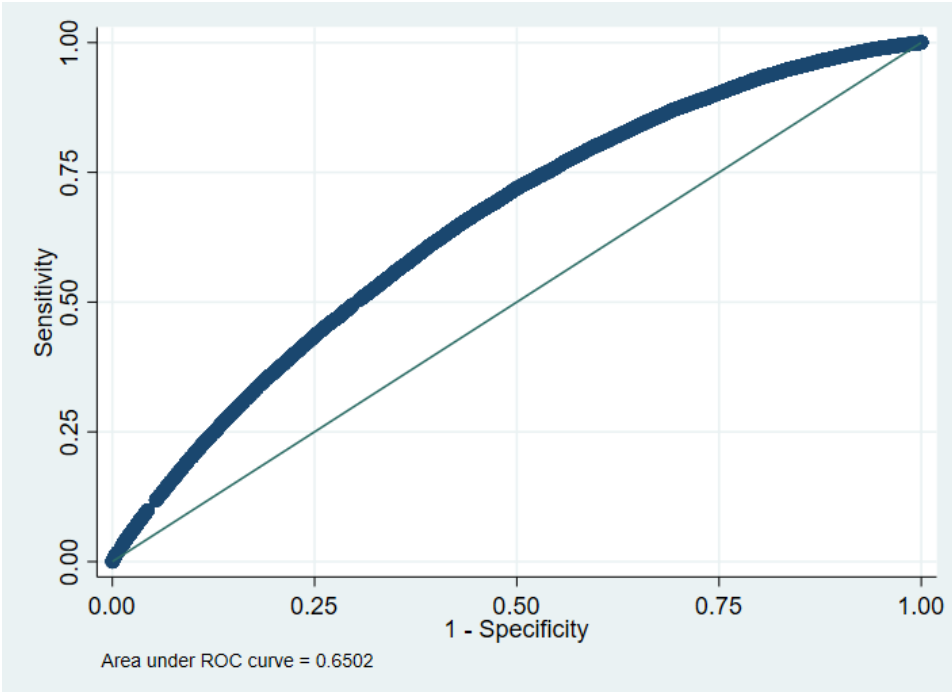

Figure II: Logistic regression model of CDI mortality

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