

Recent Trends in Bacterial Infection–Related Hospitalizations in the United States

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BACKGROUND

- Antibiotic resistance in common bacteria is a growing public health issue. In the United States (US), antibiotic-resistant (ABR) bacteria infect more than 2 million people and cause approximately 23,000 deaths annually.¹
- In 2013, the Centers for Disease Control and Prevention (CDC) identified *Clostridium difficile*, carbapenem-resistant Enterobacteriaceae (CRE), and drug-resistant *Nisseria gonorrhoeae* as the top three ABR pathogens posing urgent public health threats due to their potential for substantial clinical and economic impacts.¹
 - C. difficile* is linked with approximately 250,000 infections and 14,000 deaths annually.¹ Although *C. difficile* largely is not resistant to the antibiotics used to treat it, it is resistant to antibiotics used to treat other infections.
 - Enterobacteriaceae, such as *Klebsiella pneumoniae* and *Escherichia coli*, are bacteria naturally occurring in intestinal flora. CRE are a subgroup of Enterobacteriaceae that are highly resistant to most antibiotics and typically infect patients in the health care setting. CRE account for approximately 9,000 drug-resistant infections and 600 deaths annually.¹
 - N. gonorrhoeae* causes gonorrhea, a sexually transmitted infection occurring in approximately 820,000 persons each year. Of those, approximately 30% are ABR infections.¹ Left untreated, gonorrhea can lead to serious complications such as ectopic pregnancies and infertility.

OBJECTIVE

- This study sought to describe annual rates and death discharges associated with *C. difficile*–, CRE–, and *N. gonorrhoeae*–related hospitalizations in the US between 2001 and 2012.

METHODS

Study Design and Data Source

- This study was a retrospective database analysis using discharge data from the 2001 through 2012 Healthcare Cost and Utilization Project (HCUP) National Inpatient Sample (NIS; formerly known as the Nationwide Inpatient Sample).
- The NIS is the largest all-payer inpatient care database in the US. It includes characteristics of inpatient stays, such as patient demographics, diagnosis codes, and discharge status.
- Sampling weights allowed for generating nationally representative estimates.
- This study was deemed exempt by the RTI Institutional Review Board.

C. difficile, CRE, and *N. gonorrhoeae* Identification

- Hospitalizations with a primary or secondary *International Classification of Disease, 9th Revision, Clinical Modification* diagnosis code indicating the pathogens of interest were selected for analysis. Codes were not restricted as being mutually exclusive.
 - C. difficile*: 008.45x
 - CRE: *K. pneumoniae* (482.0x) or *E. coli* (041.3x or 041.4x). Although both species contain resistant strains, these codes do not indicate carbapenem-resistant strains exclusively.
 - N. gonorrhoeae*: 098.0x

Study Measures and Analytical Methods

- Annual rates of *C. difficile*–, CRE–, and *N. gonorrhoeae*–related hospitalizations per 10,000 US population were estimated using NIS sampling weights and year-specific population denominators from US census data.
- Annual rates of *C. difficile*–, CRE–, and *N. gonorrhoeae*–related hospitalizations resulting in a death discharge per 10,000 *C. difficile*–, CRE–, and *N. gonorrhoeae*–related hospitalizations also were calculated.
- Incidence was analyzed descriptively and stratified by age and sex.

RESULTS

C. difficile

- The rate of *C. difficile*–related hospitalizations increased gradually from 5.2 per 10,000 persons in 2001 to 11.9 in 2012 (see Table 1; Figure 1).
- Among persons aged 85 years or older, *C. difficile*–related hospitalizations increased substantially from 55.7 in 2001 to a high of 113.3 in 2008. In comparison, persons aged 65 to 84 years had a hospitalization rate approximately half that observed among those aged 85 years or older, with a low of 23.5 in 2001 and a high of 47.4 in 2008 (Table 1; Figure 2).
- Females had substantially higher rates of *C. difficile*–related hospitalizations than males during each study year (Table 1; Figure 3).
- Death discharges associated with *C. difficile* increased slightly each year, from 1,336.9 per 10,000 *C. difficile*–related hospitalizations in 2001 to 1,660.1 in 2012 (Table 1; Figure 4).

CRE

- The rate of CRE-related hospitalizations more than doubled between 2010 (5.6) and 2012 (11.9) (Table 1; Figure 1). This trend was observed in all groups when stratified by age and sex.
- The rate of CRE-related hospitalizations was highest for persons aged 85 years and older, followed by persons aged 65 to 84 years, in each study year (Table 1; Figure 2). The increase in hospitalizations between 2010 and 2012 was greatest among those aged 85 and older (56.2 in 2010 and 225.2 in 2012; a 300% increase).
- Females had substantially higher rates of CRE-related hospitalizations than males during each study year (Table 1; Figure 3). The increase in hospitalizations between 2010 and 2012 was greater among females (7.2 in 2010 and 31.1 in 2012; a 330% increase) than males (4.0 in 2010 and 11.4 in 2012; a 185% increase).
- Death discharges associated with CRE increased slightly from 1,407.9 per 10,000 CRE-related hospitalizations in 2001 to 1,793.8 in 2012 (Table 1; Figure 4).

N. gonorrhoeae

- The rate of *N. gonorrhoeae*–related hospitalizations remained fairly constant during the study period, ranging from 0.2 per 10,000 persons in 2001 to 0.1 in 2012 (see Table 1; Figure 1).
- Persons aged 18 to 64 years had the highest rate of *N. gonorrhoeae*–related hospitalizations in each year, followed by persons aged 5 to 17 years (Table 1).
- The rates of *N. gonorrhoeae*–related hospitalizations were approximately seven times higher among females than males during each study year (Table 1; Figure 3).
- Death discharges associated with *N. gonorrhoeae* increased slightly from 148.9 per 10,000 *N. gonorrhoeae*–related hospitalizations in 2001 to 339.0 in 2012 (Table 1; Figure 4).

Table 1. Incidence of *C. difficile*–, CRE–, and *N. gonorrhoeae*–Related Hospitalizations in the United States, 2001–2012

Characteristic	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Total <i>C. difficile</i>–related hospitalizations	5.21	6.68	7.15	8.34	10.01	10.39	10.64	11.12	10.55	10.78	11.90	11.88
Sex^a												
Male	4.32	5.70	6.02	7.02	8.48	8.85	9.21	9.58	9.16	9.39	9.73	9.39
Female	6.04	7.62	8.22	9.60	11.47	11.86	12.01	12.59	11.87	12.11	13.22	12.81
Age,^a years												
< 5	1.55	1.62	1.73	2.05	2.84	1.83	2.50	2.54	2.33	2.47	1.83	2.27
5 to 17	0.39	0.40	0.40	0.51	0.79	0.51	0.60	0.61	0.65	0.92	0.65	0.88
18 to 64	2.52	3.24	3.46	3.99	4.70	5.02	5.29	5.59	5.46	5.85	6.35	6.68
65 to 84	23.49	30.84	32.84	38.03	44.69	46.65	46.56	47.37	43.76	42.55	41.36	34.15
85+	55.73	68.23	73.51	87.62	109.11	110.67	108.23	113.27	103.86	103.88	106.82	95.14
Death discharge^b	1,336.90	1,355.92	1,369.31	1,598.69	1,576.18	1,584.71	1,582.97	1,601.98	1,610.79	1,638.21	1,640.33	1,669.05
Total CRE-related hospitalizations	3.95	3.89	3.99	4.09	4.40	4.67	4.93	5.20	5.58	5.64	10.10	22.89
Sex^a												
Male	2.69	2.71	2.76	2.92	3.13	3.32	3.52	3.66	3.88	3.98	5.86	11.44
Female	5.14	5.01	5.17	5.21	5.62	5.95	6.27	6.67	7.21	7.23	13.53	31.08
Age,^a years												
< 5	1.88	1.88	1.81	2.31	2.88	2.24	2.25	2.16	2.26	2.31	3.73	10.48
5 to 17	0.25	0.27	0.30	0.35	0.42	0.28	0.32	0.32	0.33	0.36	0.67	2.19
18 to 64	1.86	1.89	1.98	2.10	2.24	2.44	2.60	2.70	2.97	3.06	5.26	12.14
65 to 84	16.75	16.56	16.91	16.74	17.56	19.14	19.78	20.92	21.99	21.54	32.76	59.65
85+	49.10	44.79	44.55	44.02	47.76	48.76	51.31	53.33	56.04	56.21	101.35	225.24
Death discharge^b	1,407.91	1,415.72	1,501.54	1,779.06	1,798.74	1,826.09	1,851.77	1,937.14	1,905.30	1,982.38	1,907.24	1,793.76
Total <i>N. gonorrhoeae</i>–related hospitalizations	0.20	0.19	0.17	0.19	0.18	0.19	0.19	0.17	0.15	0.15	0.14	0.14
Sex^a												
Male	0.05	0.05	0.05	0.06	0.05	0.05	0.05	0.04	0.04	0.05	0.04	0.03
Female	0.33	0.32	0.29	0.31	0.31	0.32	0.32	0.29	0.25	0.26	0.23	0.22
Age,^a years												
< 5	0.03	0.04	0.06	0.06	0.04	0.02	0.02	0.03	0.02	0.02	0.02	0.02
5 to 17	0.21	0.18	0.15	0.15	0.18	0.14	0.14	0.12	0.10	0.10	0.08	0.08
18 to 64	0.24	0.24	0.22	0.25	0.23	0.26	0.26	0.23	0.20	0.21	0.20	0.19
65 to 84	0.03	0.03	0.02	0.01	0.03	0.01	0.03	0.02	0.03	0.02	0.01	0.01
85+	0.04	0.06	0.02	0.01	0.03	0.03	0.04	0.04	0.04	0.02	0.01	0.03
Death discharge^b	148.90	201.94	155.67	250.84	185.29	235.44	241.35	222.13	242.71	345.50	304.10	338.98

^a Incidence rate per 10,000 US population.

^b Incidence rate per 10,000 *C. difficile*–, CRE–, or *N. gonorrhoeae*–related hospitalizations.

Figure 1. Overall Incidence of *C. difficile*–, CRE–, and *N. gonorrhoeae*–Related Hospitalizations in the United States, 2001–2012

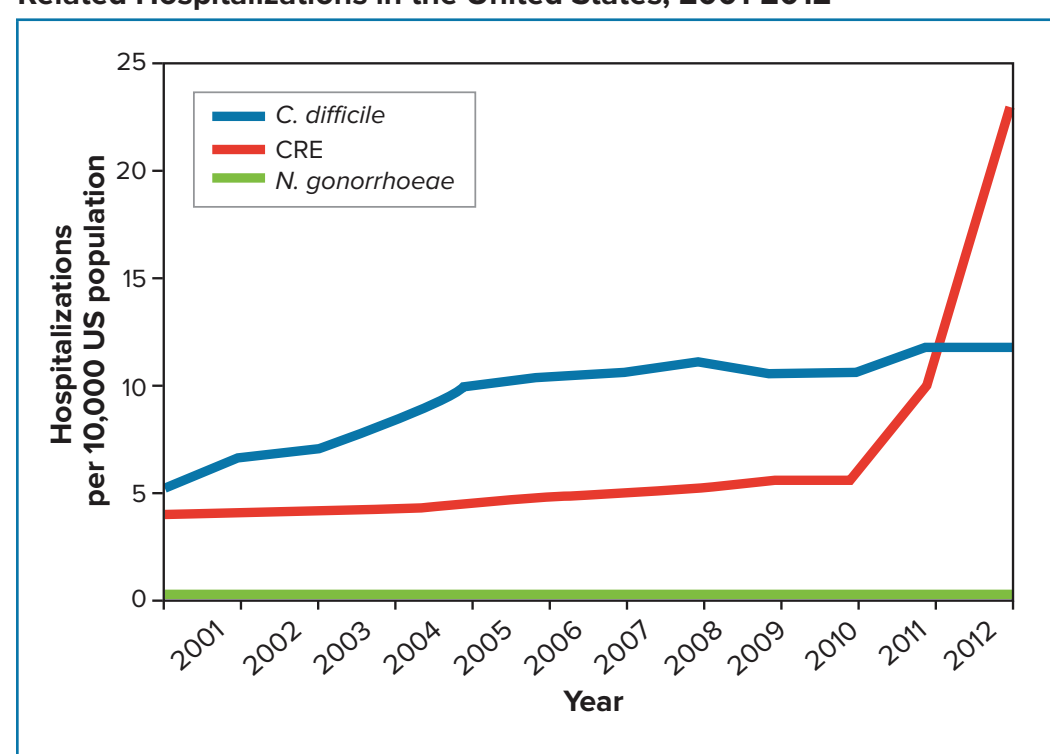


Figure 3. Incidence of *C. difficile*–, CRE–, and *N. gonorrhoeae*–Related Hospitalizations in the United States by Sex, 2001–2012

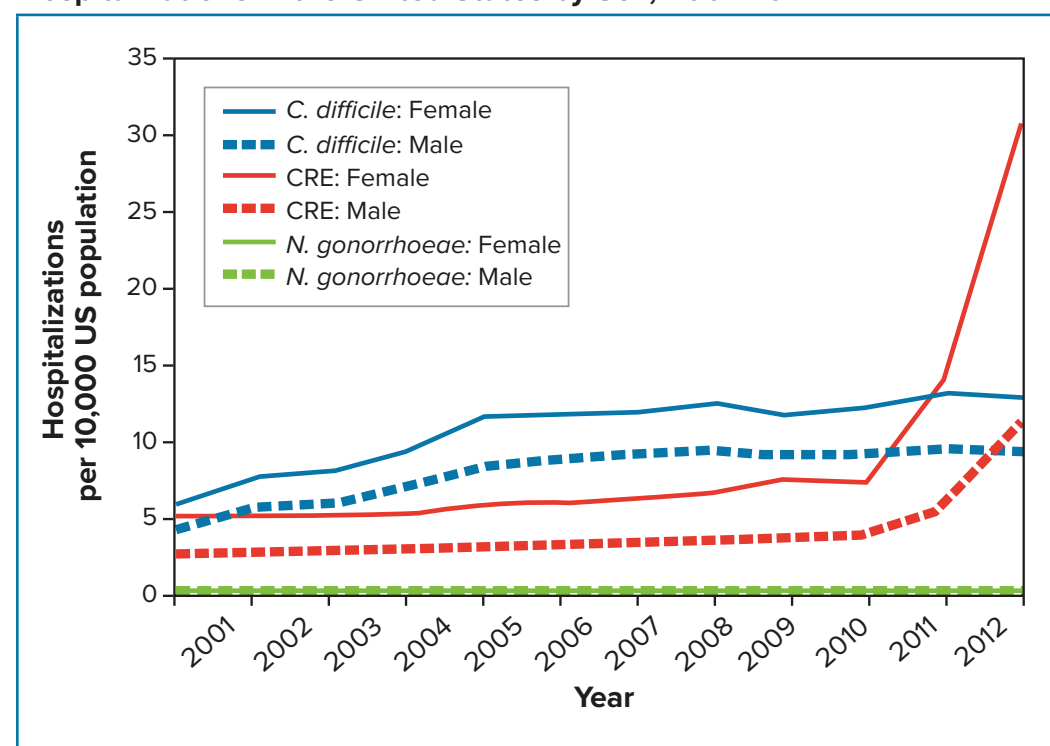


Figure 2. Incidence of *C. difficile*– and CRE-Related Hospitalizations Among Persons Aged 65 Years and Older, 2001–2012

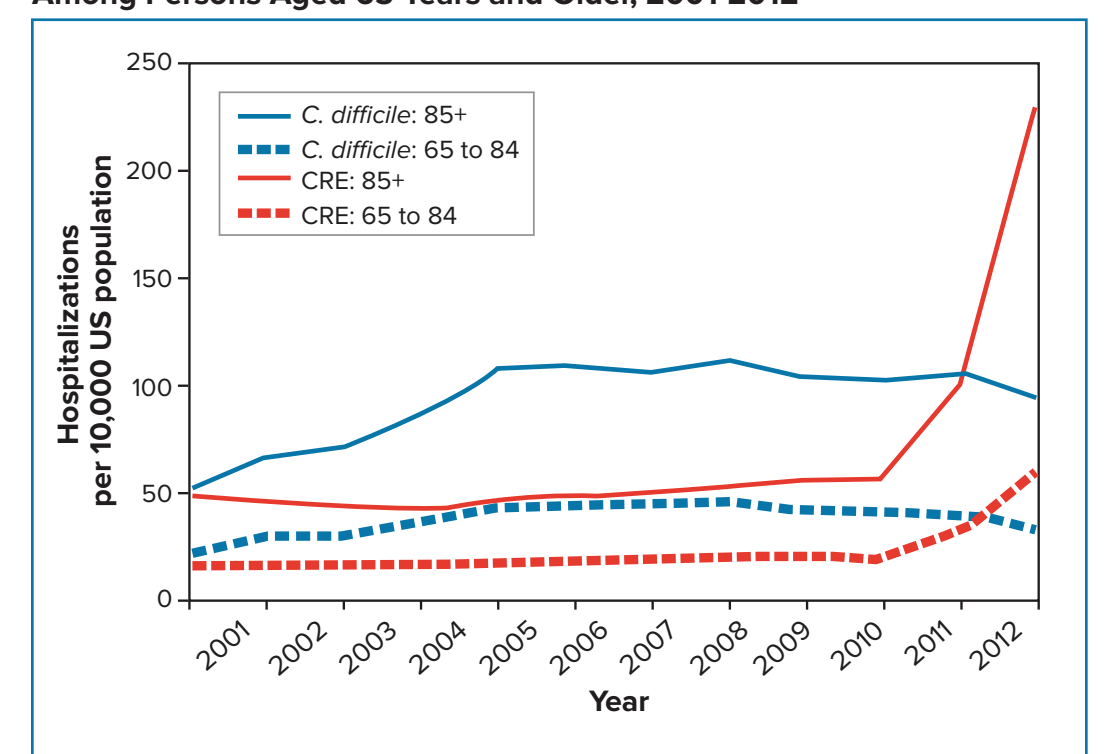
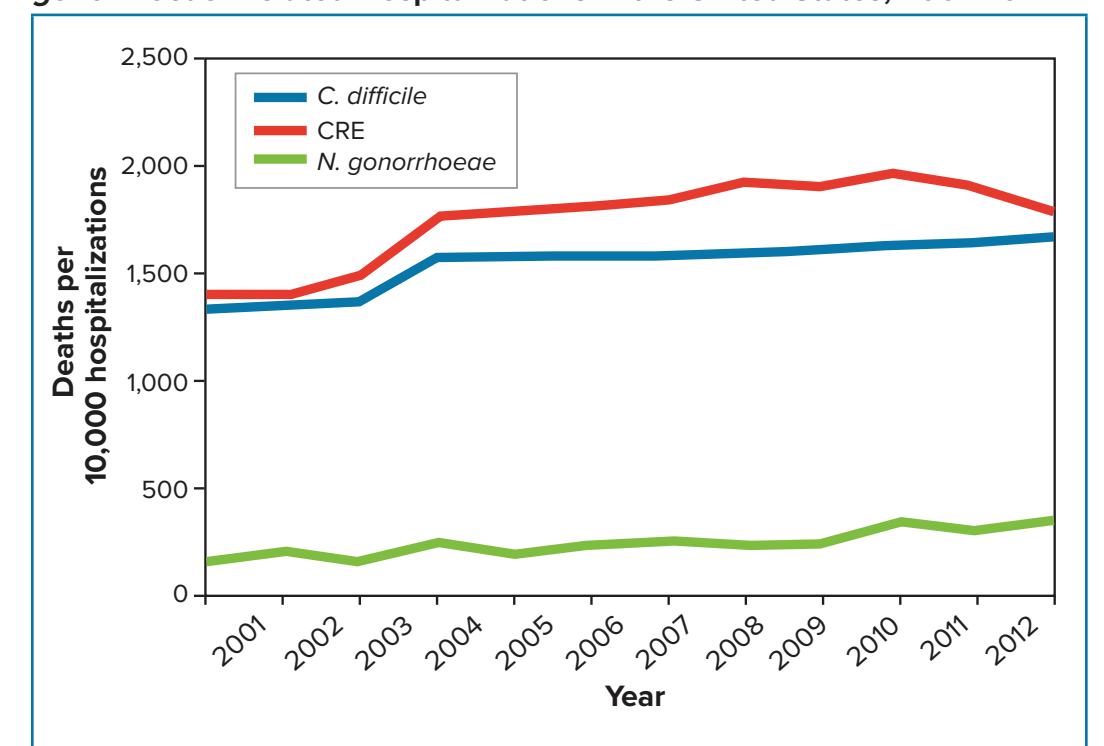


Figure 4. Rate of Death Discharges Among *C. difficile*–, CRE–, and *N. gonorrhoeae*–Related Hospitalizations in the United States, 2001–2012



DISCUSSION

- C. difficile*– and CRE-related hospitalization rates have increased substantially over the past decade. Notably, CRE-related hospitalizations more than doubled between 2010 and 2012.
 - An increase in *C. difficile* incidence has been seen globally and is attributed to the emergence of a more virulent strain (BI/NAP1/027).² This may have contributed to the increase in hospitalization stays coded with a *C. difficile* diagnosis observed in this study.
 - The surge in CRE-related hospitalizations in recent years is consistent with findings that the rising rate of CRE infection may be attributed to the increased use of broad-spectrum carbapenems and increase of nosocomial infections.^{4,5}
- Both *C. difficile*– and CRE-related hospitalization rates were highest among persons aged 65 years or older. These findings are consistent with several other studies:
 - One study found that approximately 30% of patients in long-term care hospitals and whose mean age was 65 years had evidence of carbapenemase-producing *K. pneumoniae*.⁶
 - A review of US vital records found that more than 90% of deaths cause by *C. difficile* occurred in persons aged 65 years or older.⁷
- N. gonorrhoeae*–related hospitalization rates were consistently higher among females than males. As females are often asymptomatic, late detection and more severe health outcomes may have driven this trend.
- Gonorrhea increases risk of co-infection with HIV and syphilis, two diseases with high mortality rates. Therefore, prolonged gonorrhea infection due to antibiotic resistance may increase the rate of co-infection, thus potentially contributing to an increase in death discharges during the study period.
- In the past 8 years, treatment guidelines for *N. gonorrhoeae* were revised twice by the CDC in reaction to ABR strains. This may have mitigated the growth of antibacterial resistance, resulting in a relatively unchanged incidence of hospitalizations.⁷

- The lack of effective first-, second-, and even last-line treatments for ABR infections can lead to increased disease incidence, greater health care resource utilization, and more severe health outcomes (e.g., mortality, increased duration of hospital stays), particularly among vulnerable populations (e.g., patients receiving chemotherapy, organ transplantation).¹
- Therefore, continued research to identify and monitor emerging ABR strains, determine the impact of antibacterial resistance on patient health and the health care system, and develop new, effective therapies for treating these infections is paramount.

LIMITATIONS

- Patient discharges were identified based on diagnosis codes that, if recorded inaccurately, may cause misidentification of the diseases of interest.
- The diagnosis codes used to identify *C. difficile*, CRE, and *N. gonorrhoeae* were not specific to ABR strains. Therefore, the true incidence of ABR-related hospitalizations may be overestimated.
- As unique patient identifiers were not provided, we were unable to follow patients who moved from facility to facility; as such, hospitalization rates should not be used as a proxy for infection rates, particularly for *C. difficile*, which has a high recurrence rate.

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