# Recent Trends in Urgent Antibacterial Threat–Related Hospitalization in the US

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## BACKGROUND

- Antibiotic resistance (ABR) poses a threat to public health in the United States (US). The US Centers for Disease Control and Prevention (CDC) provides the following estimates:
  - Approximately 23,000 people die each year as a result of antibiotic-resistant infections.[1]
  - Annual direct health care costs associated with ABR have been estimated to be as high as $20 billion, with lost productivity estimated to be another $35 billion annually.[1]
  - Annually, there are nearly 8 million inpatient days associated with ABR.[2]
- The CDC recently released a report that describes ABR and its potential consequences if action is not taken to control this threat.[1]
- ABR threats were determined by their potential for clinical and economic impact, incidence and 10-year projected incidence, transmissibility, availability of effective antibiotics, and barriers to prevention.
- Among all antibiotic-resistant pathogens identified, three were classified as urgent or "high consequence antibiotic-resistance threats because of significant risks identified across several criteria. These threats may not be currently widespread but have the potential to become so" [1]:
  - *Clostridium difficile* – A type of intestinal flora often associated with watery diarrhea. *C. difficile* is a hardy series of bacteria, able to tolerate high heat and exposure to alcohol and hand washing, which flourishes in an abnormal intestinal climate.[3] Thus, use of antibiotics could increase a patient's risk of *C. difficile* infection.
  - Carbapenem-resistant Enterobacteriaceae (CRE) – A subgroup of Enterobacteriaceae that are highly resistant to most antibiotics and typically infect patients in the health care setting who are being treated for other conditions.
  - *Neisseria gonorrhoeae* – A type of sexually transmitted disease in which approximately 30% of infections are antibiotic resistant. Latent infections can lead to sterility and joint and cardiovascular damage.
- Despite the risk of increased ABR, it is considered economically unattractive to invest in the development of new antibiotics because these therapies are used for an acute period of time, the societal value of antibiotics is not reflected in their price, and, ironically, antibiotic stewardship has a negative influence on a company's return on their investment.[4]
- Data exist that estimate the overall scope of ABR, but these data are often older or limited to a smaller inpatient setting, thus making it difficult to ascertain the national burden of ABR in an inpatient care setting.

## OBJECTIVE

- To document the number of, and associated length of stay (LOS) and costs for, CDC-defined urgent ABR threat–related hospitalizations in the US.

## METHODS

### Study Design

- A retrospective database analysis was conducted using the Healthcare Cost and Utilization Project's National Inpatient Sample (NIS) (formerly known as the Nationwide Inpatient Sample) database.
- The NIS database is based on discharge data and is not linked to individual patient information; therefore, this study was deemed exempt by the RTI Institutional Review Board.

### Data Source

- Hospital discharge data were taken from the 2001 through 2012 NIS database.
- The NIS, the largest inpatient care database in the US, is the only national inpatient database with charge information on all patients, regardless of payer.
- The NIS includes many clinical and nonclinical variables for each inpatient stay, including patient demographics, diagnosis codes, LOS, total charges and costs, admission source and discharge disposition, payer, and hospital-specific characteristics (e.g., bed size).
- Sampling weights allow for generating nationally representative estimates.

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

- Hospitalizations with a primary or secondary *International Classification of Disease, 9th Revision, Clinical Modification* (ICD-9-CM) diagnosis code indicating any of the three pathogens of interest were selected. Codes were not restricted to being mutually exclusive.
  - *C. difficile*: 008.45x
  - The Enterobacteriaceae is a large family of Gram-negative bacteria. For purposes of this research, CRE was defined as *Klebsiella pneumonia* (482.0x) and *Escherichia coli* (041.3x or 041.49x). Although both species contain resistant strains, these codes do not indicate carbapenem-resistant strains exclusively.
  - *N. gonorrhoeae:* 098.0x

### Study Measures and Analytical Methods

- All analyses conducted were descriptive in nature.
- For each of the 12 years assessed, we generated weighted estimates of the number of hospitalizations for each urgent ABR threat.
- For these hospitalizations, mean LOS and total costs (in 2014 US dollars) were calculated.
- Costs were first estimated as discharge-associated charges, converted to costs using methods by Friedman et al.,[5] and inflated to 2014 US dollars using US Bureau of Labor and Statistics inflation factors.[6]
- All data management and analyses were carried out using SAS statistical software, version 9.3.

## RESULTS

### Number of ABR-Related Hospitalizations (Table 1)

- The total number of all hospitalizations in the NIS remained relatively stable throughout the 12 years of observation (2001: 36,093,550; 2012: 36,484,846)
- The number of *N. gonorrhoeae*–related hospitalizations decreased during the study period from 5,440 in 2001 to 4,130 in 2012.
- Conversely, the number of CRE- and *C. difficile*–related hospitalizations each increased during the study period:
  - CRE: 109,304 in 2001 to 692,680 in 2012. Interestingly, the number of CRE-related hospitalizations almost doubled from 2010 to 2011 (164,920 to 303,198 hospitalizations) and again from 2011 to 2012 (303,198 to 692,680 hospitalizations).
  - *C. difficile*: 144,312 in 2001 to 359,395 in 2012. The greatest year-to-year increases were seen earlier in the observation period, from 2003 to 2004 (201,158 to 236,649 hospitalizations) and from 2004 to 2005 (236,649 to 286,338 hospitalizations).

### Mean LOS for ABR-Related Hospitalizations (Figure 1)

- The mean LOS for all hospitalizations in the US from 2001 to 2012 was 4.58 days. Mean LOS remained consistent throughout the period of observation.
  - In 2001 the LOS was 4.63 days, and in 2012, the LOS was 4.53 days.
- LOS for *N. gonorrhoeae* decreased until 2005 (LOS: 3.92 days), when it began to fluctuate until 2010. In 2010, LOS began to decrease (2010 LOS: 4.32 days; 2011 LOS: 4.29 days; 2012 LOS: 3.93 days).
- LOS for CRE initially decreased in 2002 (LOS: 9.99 days) but increased in duration until 2010 when LOS began to decrease again (2010 LOS: 10.08 days; 2011 LOS: 8.10; 2012 LOS: 6.99).
- The LOS for *C. difficile* consistently decreased from 2001 (LOS: 13.53 days) until 2012 (LOS: 10.41 days).

### Mean Total Cost for ABR-Related Hospitalizations (Figure 2)

- Overall, the mean per-patient cost was $16,168 for ABR-related hospitalizations. Mean per-patient cost consistently increased from 2001 until 2012.
  - In 2001, the mean per-patient cost was $12,508, increasing to $19,423 in 2012.
- The greatest year-to-year increase was from 2002 to 2003 when mean per-patient costs increased by $1,268. Year-to-year cost increases for subsequent years were more modest, with a range of $450 from 2005 to 2006 to an increase of approximately $780 from 2011 to 2012. An exception from this trend was from 2003 to 2004, when costs decreased by $178.
- Mean total cost increased for *N. gonorrhoeae*, with two of the sharpest increases occurring from 2005 to 2006 ($10,620 to $12,811) and 2009 to 2010 ($12,566 to $15,517).
- Mean total cost for CRE steadily increased from 2001 to 2007 and began to decrease in 2008, with the greatest year-to-year decrease occurring from 2010 to 2011 ($39,022 to $31,815).
- Mean total cost for *C. difficile* was not consistent, especially during 2003 to 2010, when costs were as low as $39,590 in 2004 to as high as $45,698 in 2009; however, costs increased during the study period from $36,896 in 2001 to $43,632 in 2012.

**Table 1. Number of Hospitalizations in the US From 2001 to 2012, Overall and by Antibiotic-Resistant Pathogen**

| | 2001 | 2002 | 2003 | 2004 | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **All hospitalizations** | 36,093,550 | 36,523,831 | 37,074,605 | 37,496,978 | 37,843,039 | 38,076,556 | 38,155,908 | 38,210,889 | 37,734,584 | 37,352,013 | 36,962,415 | 36,484,846 |
| **Those with *C. difficile*** | 144,313 | 186,493 | 201,158 | 236,649 | 286,338 | 299,575 | 309,223 | 325,786 | 311,444 | 320,928 | 357,043 | 359,395 |
| **Those with CRE** | 109,304 | 108,615 | 112,351 | 116,130 | 125,927 | 134,583 | 143,170 | 152,245 | 164,920 | 167,924 | 303,198 | 692,680 |
| **Those with *N. gonorrhoeae*** | 5,440 | 5,349 | 4,882 | 5,341 | 5,236 | 5,478 | 5,552 | 4,951 | 4,284 | 4,601 | 4,242 | 4,130 |

**Figure 1. Mean LOS Among Hospitalizations in the US From 2001 to 2012, Overall and by Antibiotic-Resistant Pathogen**

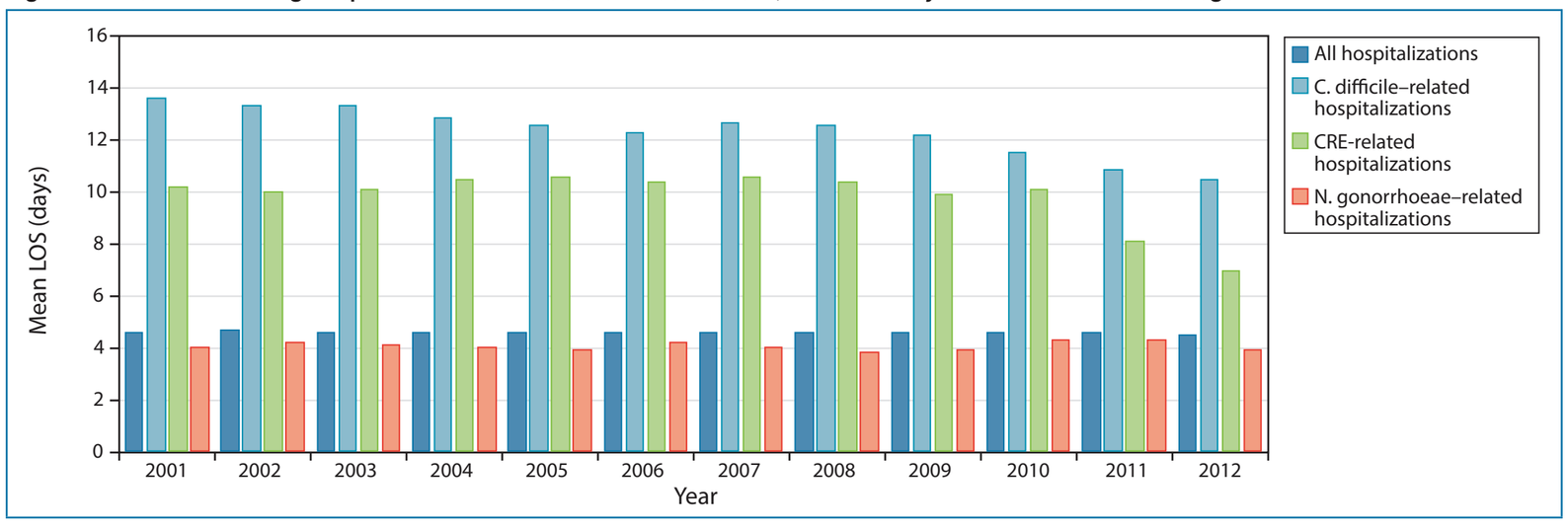
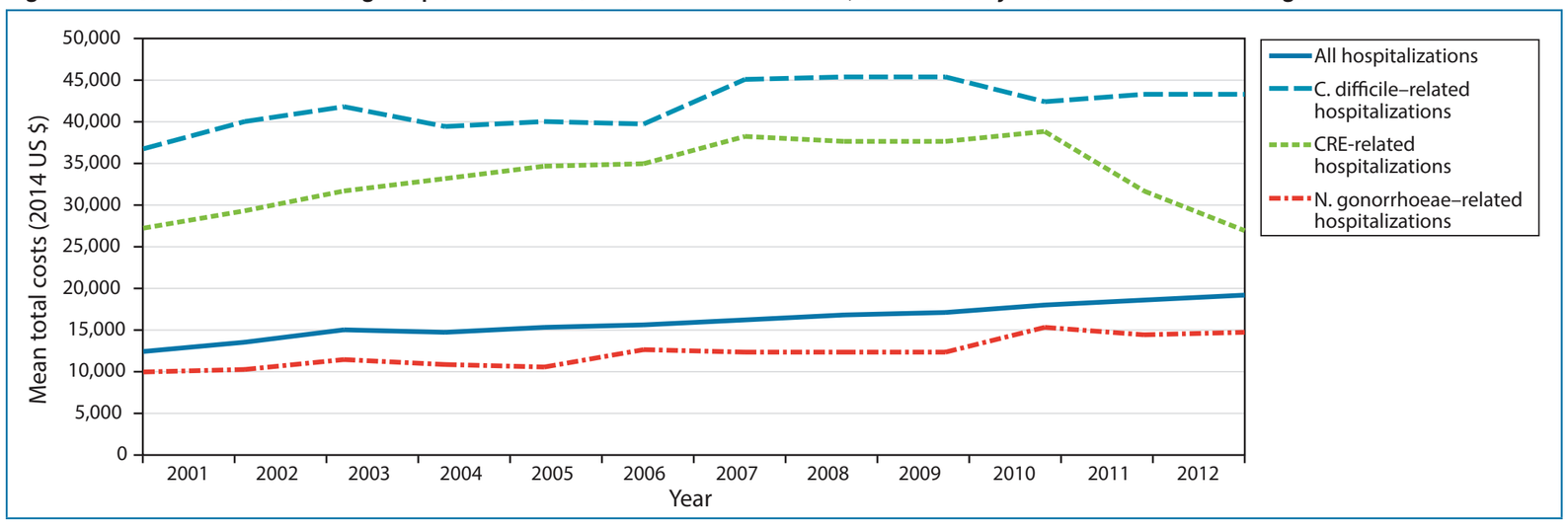



**Figure 2. Mean Total Costs Among Hospitalizations in the US From 2001 to 2012, Overall and by Antibiotic-Resistant Pathogen**




## CONCLUSIONS

- Although LOS among ABR-related hospitalizations in the US has decreased over time, costs have increased for both *N. gonorrhoeae* (+47%) and *C. difficile* (+18%). This could be due to more virulent strains of the bacteria causing infection and increased resistance to broad-spectrum antibiotics, thus necessitating the use for newer, more expensive treatments for antibiotic-resistant infections.[7, 8, 9]
- Efforts are under way to provide alternatives to traditional antibiotic use for the treatment of bacterial infections. These efforts could help to improve the public's health and decrease the associated economic burden.
  - Other therapies that may be helpful tools in combating ABR include fecal biotherapy, active and passive vaccines, and monoclonal antibodies; however, these therapies are not widely accepted for many reasons, including lack of public acceptance and cost.[3]
  - Development of dosing recommendations unique to the pharmacodynamic and pharmacokinetic characteristics of each class of antibiotics could be a simpler approach to combating ABR, but this would call for a change of clinical practice behavior.[10]
- This research had a few limitations that should be considered:
  - Patient discharges were identified based upon diagnosis codes that, if recorded inaccurately, may cause misidentification of ABR.
  - The study data lack details that would allow assessment of relevant clinical characteristics that might affect disease severity, in turn influencing LOS and costs.
  - The NIS does not include unique patient identifiers and, as such, following patients from facility to facility was not possible. As such, multiple hospitalizations cannot be attributed to a single person; therefore, patients hospitalized multiple times for a single infection or for recurrence of an infection cannot be distinguished from patients with a single infection.

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