American Journal of Infection Control 47 (2019) 521–526

Contents lists available at ScienceDirect

American Journal of Infection Control

journal homepage: www.ajicjournal.org

Major Article

# Societal willingness to pay to avoid mortality and morbidity from *Clostridioides difficile* and carbapenem-resistant Enterobacteriaceae infections in the United States

Aylin Sertkaya PhD [a,*], Hui-Hsing Wong MD, JD [b], Daniel H. Ertis AB [c], Amber Jessup PhD [b]

[a] *Eastern Research Group, Inc, Lexington, MA*
[b] *United States Department of Health and Human Services, Office of the Assistant Secretary for Planning and Evaluation, Office of Science and Data Policy, Washington, DC*
[c] *Eastern Research Group, Inc, Arlington, VA*

*Key Words:*
Avoided morbidity value
Avoided mortality value
Quality-adjusted life years
Value of a statistical life
Value of a statistical life year

***Background:*** *Clostridioides difficile* infection (CDI) is among the most common health care–associated infections in the United States and is increasingly affecting the elderly. Although carbapenem-resistant Enterobacteriaceae (CRE) infections are still relatively uncommon, there are reported increases in the rate of infection for certain strains, such as *Klebsiella pneumoniae*. This study examines the burden of mortality and morbidity for CDI and CRE infections in the United States and estimates the societal willingness to pay to avoid them.
***Methods:*** We use an analytic model to estimate the number of incident cases and associated health outcomes for CDI and CRE infections.
***Results:*** The number of CDI and CRE infection incident cases in the United States in 2016, is estimated at 468,567 and 9,620, respectively. These infections result in a total of 17,630 estimated deaths and 8,624 lost quality-adjusted life years among patients who survive per year.
***Conclusions:*** Given the significant mortality and morbidity from these infections, the estimated societal willingness to pay to avoid them is high at $176.7 billion per year, of which 93.9% ($166.0 billion) is for CDI. Our estimates far exceed the medical care costs for CDIs and CRE infections reported in the literature despite not capturing the additional costs borne by third-party payers. As incident cases increase or resistant strains develop, the societal willingness to pay is also expected to increase.


Growing antibiotic resistance is a significant public health concern. According to a 2013 report from the Centers for Disease Control and Prevention (CDC),[1] more than 2 million people get antibiotic-resistant infections each year in the United States, resulting in at least 23,000 deaths. The same report also prioritizes bacteria by level of concern into 1 of 3 categories: urgent, serious, and concerning.[1] Among those microorganisms with a threat level of urgent are *Clostridioides* (*Clostridium*) *difficile* and carbapenem-resistant Enterobacteriaceae (CRE).

*C difficile* is a gram-positive, spore-forming bacterium typically spread through the fecal–oral route.[2] Researchers are increasingly concerned with "the emergence of epidemic strains with novel virulence factors and antibiotic resistance, such as BI/NAP1/027".[3] According to a prevalence survey of 183 acute care US hospitals, *C difficile* (12.1%) is the most common single organism causing health care–associated infections, followed by *Staphylococcus aureus* (10.7%).[4] *C difficile* infections (CDIs) disproportionately affect people of advanced age owing to their increased health care utilization (especially antimicrobial exposure) and higher comorbidity. Incidence among individuals 65 years of age and older is 5 times that of younger people.[5,6]

Enterobacteriaceae, gram-negative bacteria, commonly cause community- and hospital-associated infections.[7] CRE refers to a subset of Enterobacteriaceae that are either not susceptible to imipenem, meropenem, doripenem, or ertapenem or possess a carbapenemase.[8] In the United States, the majority of CRE isolates belong to a single species of Enterobacteriaceae, *Klebsiella pneumoniae*.[7] According to the CDC's National Healthcare Safety Network, which tracks health

* Address correspondence to Aylin Sertkaya, PhD, Eastern Research Group, Inc, 110 Hartwell Ave, Lexington, MA 02421.
*E-mail address:* aylin.sertkaya@erg.com (A. Sertkaya).
Funding/support: Supported by the United States (US) Department of Health and Human Services, Office of the Assistant Secretary for Planning and Evaluation (contract no. HHSP233201500055I, task order no. HHSP23337001T).
The contents expressed in this article do not represent the views of the US Department of Health and Human Services, the Office of the Assistant Secretary for Planning and Evaluation, or Eastern Research Group, Inc.
Conflicts of interest: None to report.

https://doi.org/10.1016/j.ajic.2018.11.008
0196-6553/

care–associated infections in the United States, carbapenem resistance was detected in 0.9% cases of *Escherichia coli* and in 10.8% cases of *K pneumoniae* infections among patients with central line–associated bloodstream infections in 2006-2007.[9] During 2009-2010, these rates rose to 1.9% and 12.8%, respectively.[10] A similar trend was also observed for catheter-associated urinary tract infections (UTIs) with *K pneumoniae* (10.1% in 2006-2007 to 12.5% in 2009-2010) and ventilator-associated pneumonia (3.6% in 2006-2007 to 11.2% in 2009-2010).[9,10] Like CDIs, CRE infections are more prevalent among the elderly with comorbid conditions. Based on data from the CDC's Emerging Infections Program, during 2012-2013, 52.8% of the CRE infection cases reported to the program involved people aged 65 years or older, with >90% having a serious underlying comorbidity.[11]

Numerous studies examine the economic impact of CDIs and CRE infections on the health care system. CDI-attributable acute care hospital costs reported in the literature range from $3,427-$16,307 per episode in 2012.[12] This translates into $1.2- $5.9 billion per year in acute care hospital costs in the United States, based on the total number of discharges in the 2012 Healthcare Cost and Utilization Project data.[12] According to a recent study by Bartsch et al,[13] the median cost of a CRE infection ranges from $22,484-$66,031 for hospitals, $10,440-$31,621 for third-party payers, and $37,778-$83,512 for society. The hospital costs capture the opportunity cost of lost bed days because of additional length of stay attributable to CRE infections. The costs for third-party payers include direct costs such as hospitalization, drug treatments, and associated tests. The costs for society include direct and indirect costs, where indirect costs represent productivity losses owing to absenteeism and mortality is calculated as the net present value of missed lifetime earnings based on an estimate of yearly annual wage and years of life lost (assuming that patients with CRE infection are aged 60 years or older and a discount rate of 3%). Based on an infection incidence of 2.93 per 100,000 population (9,418 infections), the total cost of CRE infections ranges from $217-$334 million for hospitals, $129-$172 million for third-party payers, and $303 million to $1.6 billion for society as a whole.

These cost estimates, however, represent only a portion of the true economic impact of CDIs and CRE infections, as they fail to consider the willingness to pay for avoiding these illnesses. The CDC, for example, recently found that the social value of requiring antibiotic stewardship programs in hospitals ranged from $31-$438 billion when including the value of mortality risk reductions in health care–associated CDIs.[14] Here, we estimate the economic burden of mortality and morbidity associated with CDIs and CRE infections in the United States using the value of a statistical life (VSL). We then use quality-adjusted life years (QALYs) to estimate the willingness to pay to avoid these infections, an approach commonly employed in the evaluation of policies that impact human health.

## METHODS

We used an analytic model to evaluate the value of mortality and morbidity from CDIs and CRE infections in the United States. Our model parameters are primarily based on published studies and supplemented with expert opinion. Further, we relied on economic analysis guidelines published by the US Department of Health and Human Services[15] in monetizing our estimates of mortality and morbidity. The sections below discuss our key model parameters in further detail.

### *Expected number of incident cases in 2016*

According to statistics from the CDC's Emerging Infections Program, there were 453,000 incident cases of CDI and 9,300 incident cases of CRE infection in the United States in 2011.[1,6] Assuming a constant incidence rate over time and adjusting these figures for 3.4% population growth from 2011-2016,[16] the numbers of expected CDI and CRE infection incident cases in 2016 are 468,567 and 9,620, respectively.

### *Mortality*

Most cases of CDIs are mild to moderate, resulting in diarrhea and abdominal cramping that resolves in 7-11 days. Patients with CDI typically respond well to standard antibiotic treatments (metronidazole, vancomycin, or a combination of the 2), although 16% of patients go on to develop severe (fulminant) CDI colitis, which is the average range (5%-26%) for progressing to fulminant disease, reported in published studies.[17] In the most severe, complicated cases, patients may experience ileus, hypotension, shock or sepsis, toxic megacolon, and abdominal perforation. In such cases, patients often require intensive care transfer or hospital admission.[2,3,12] Of the severe cases of CDI, the majority of patients (80%) do not require surgery, but approximately 20%[18] of patients require colectomies.

Mortality rates for CDI vary with severity of infection and chosen intervention (Table 1). The CDI-attributable mortality rate is approximately 5.2% for patients who do not require surgery, which is estimated

**Table 1**
Mortality rates by type of infection

| Infection | Clinical state | Type | Duration | Probability of death (%) | Source |
|---|---|---|---|---|---|
| *Clostridioides difficile* | Severe | Surgically managed | First y | 30.7 | Halabi et al[19] |
| | | | 1-y postsurgery | 64.5 | Dallas et al[18] |
| | | | 2-y postsurgery | 71.1 | Dallas et al[18] |
| | | | 5-y postsurgery | 66.9 | Dallas et al[18] |
| | | | 7-y postsurgery | 59.7 | Dallas et al[18] |
| | | | 11-y postsurgery | 51.0 | Cho et al[20] |
| | | Nonsurgically managed | | 5.2 | Tabak et al,[21] Dubberke et al[22] |
| | Mild to moderate | | | 0.0 | Assumption |
| | Recurrent | | | 0.0 | Assumption |
| CRE | Primary–unidentified site | | | 22.7 | Neuner et al,[23] Hauck et al[24] |
| | UTI | No secondary bacteremia | | 0.0 | Hauck et al[24] |
| | | With secondary bacteremia | | 16.7 | Neuner et al,[23] Capone et al[25], Hauck et al[24] |
| | Pulmonary | No secondary bacteremia | | 25.3 | Hauck et al[24] |
| | | With secondary bacteremia | | 40.6 | Neuner et al,[23] Hauck et al[24] |
| | Intra-abdominal | No secondary bacteremia | | 28.5 | Falagas et al,[26] Hauck et al[24] |
| | | With secondary bacteremia | | 23.9 | Neuner et al,[23] Hauck et al[24] |
| | Other | No secondary bacteremia | | 28.5 | Falagas et al,[26] Hauck et al[24] |
| | | With secondary bacteremia | | 40.6 | Neuner et al,[23] Hauck et al[24] |

CRE, carbapenem-resistant Enterobacteriaceae; *UTI*, urinary tract infection.

as the average of nonsurgical CDI-attributable mortality rates, as reported in Tabak et al[21] (4.5% of 282 patients with CDI) and Dubberke et al[22] (5.7% of 390 patients with CDI), weighted by the number of patients with CDI included in each study. For patients who require colectomies, the CDI-attributable mortality rate is 30.7%.[19] Further, having a colectomy affects the likelihood of survival postsurgery even if the surgery is successful.

Another consideration for CDI is the relatively high probability of recurrence. Approximately 1 in 5 patients (20%) have at least 1 recurrence of CDI within 1 year of their initial infection.[27] However, recurrent CDI is typically not associated with a worsening clinical outcome.[28]

Based on these probabilities derived from the literature, we estimate that the total number of CDI-attributable deaths in 2016 is 16,532 (Table 2), more than twice that of the 7,739 CDI-attributable deaths in 2012 reported in the National Vital Statistics System, which is based on death certificates coded with ICD-10 code A04.7 (enterocolitis).[29]

A study by Vardakas et al[30] is the only 1 we identified that provides bacteremia rates by primary infection site among intensive care unit patients with carbapenem-resistant *K pneumoniae* (CRKp) infections in a general hospital in Thessaloniki, Greece. We used the rates provided in Vardakas et al[30] as a starting point for generating estimates of CRE infection cases by primary infection site for the United States. We acknowledge that the infection site-specific estimates of Vardakas et al[30] are not likely to be directly applicable to CRE infections in the United States given potential differences in hospital infection control practices, patient characteristics, and geographic variation in carbapenemase genes. Thus, based on CDC expert consultation,[31] we estimate that approximately 9% of patients with CRE infections develop catheter-related primary bacteremia (ie, bacteremia without an identified site of infection in the United States, as opposed to the 45.2% rate reported in Vardakas et al).[30] Of the remaining 91% of patients, we further estimate that 81% of patients develop a primary site infection without secondary bacteremia (UTI [55%], pneumonia [18%], intra-abdominal infection [5%], or infection at another site [3%] personal communication, 2016), and 10%[30] of patients develop 1 with secondary bacteremia.

Because multiple comorbidities and the severity of underlying diseases in patients with CRE infections, distinguishing between CRE infection-attributable mortality and CRE infection-associated (ie, crude or all-cause) mortality is difficult.[24] Using information reported in the Hauck et al[24] study, as described in the following, we adjusted the crude CRE infection mortality rates by infection site, as reported in Neuner et al,[23] Falagas et al,[26] and Capone et al.[25] The Hauck et al[24] study constructs a control group of 223 patients with CRKp urinary tract colonization without CRKp infection. The study reports a mortality rate of 9.4% (21 of 223 patients) for the control group. Hauck et al[24] selected patients with CRKp urinary tract colonization for their control group because comorbidity and risk factors for these patients are very similar to those with CRE infections. Because these deaths are attributable to causes other than CRE infection, we subtracted 9.4% from the reported crude CRE infection mortality rates by infection site in the literature to estimate CRE infection-attributable mortality rates by infection site (Table 1).

Based on the CRE infection mortality rates reported in Table 1, we estimated the total number of CRE infection-attributable deaths in 2016 to be 1,097, approximately 80% higher than CDC's estimate of 600 deaths[1] in 2013 (Table 2).

### *Morbidity*

QALYs measure the duration and severity of illness and are widely considered to provide a measure of a patient's lost "utility" owing to illness. The QALY loss associated with an illness is the health-related quality of life (HRQoL) loss times the duration of the illness. The HRQoL is bounded by 0 and 1, where a value of 1 is equivalent to perfect health and a value of 0 is equivalent to death. We estimate QALYs lost as a result of illness i for a given patient in perfect health as follows:

$$\text{QALYs Lost} = (1 - \text{HRQoL}_i) \times (\text{ID}_i \div 365) \qquad \text{(Equation 1)}$$

where $\text{HRQoL}_i$ is the HRQoL weight associated for illness i, as available from the Tufts University Cost-Effectiveness Analysis Registry, and $\text{ID}_i$ is duration of illness i in days. Since an HRQoL of 1 represents 1 full year in perfect health, Equation 1 adjusts the effect of the illness on the individual's well-being by accounting for the duration of that illness.

Risk of hospitalization because of severe CDI increases with age. In 2009, the average age of patients hospitalized because of CDI was 67.9 years.[31] Thus, we estimated the baseline QALY weight for

**Table 2**
Estimated number of deaths in the United States in 2016 by type of infection

| Infection | Clinical state | Type | Duration | No. of deaths* |
|---|---|---|---|---|
| *Clostridioides difficile* | Severe | Surgically managed | First y | 4,603 |
| | | | 1-y postsurgery† | 1,917 |
| | | | 2-y postsurgery† | 1,514 |
| | | | 5-y postsurgery† | 1,589 |
| | | | 7-y postsurgery† | 1,822 |
| | | | 11-y postsurgery† | 1,970 |
| | | Nonsurgically managed | | 3,117 |
| | Mild to moderate | | | 0 |
| | Recurrent | | | 0 |
| | Total | | | 16,532 |
| CRE | Primary—unidentified site | | | 197 |
| | UTI | No secondary bacteremia | | 0 |
| | | With secondary bacteremia | | 80 |
| | Pulmonary | No secondary bacteremia | | 438 |
| | | With secondary bacteremia | | 78 |
| | Intra-abdominal | No secondary bacteremia | | 137 |
| | | With secondary bacteremia | | 46 |
| | Other | No secondary bacteremia | | 82 |
| | | With secondary bacteremia | | 39 |
| | Total | | | 1,097 |

CRE, carbapenem-resistant Enterobacteriaceae; UTI, urinary tract infection.
*Numbers may not add up due to rounding.
†Deaths in future years are discounted at 3%. For example, if the number of patients expected to survive 5 y postsurgery is 1,843, then the number of discounted *C difficile* infection-attributable deaths is 1,589, which is equal to $1{,}843 \times (1 \div [1 + 0.03]^5)$.

patients with CDI at 0.826 (instead of 1), which is the average of mean EQ-5D scores (where the EQ-5D is a descriptive system that measures 5 dimensions of health status [mobility, self-care, usual activities, pain and discomfort, and anxiety and depression] with 3 levels per dimension [no problem, some problem, and extreme problems[35]]) for men and women aged 60-69 years[32] (Table 3).

A colectomy reduces the HRQoL of a patient by 0.507 from a baseline level of 0.826-0.319[33] for an average of 27 days,[19] during which the patient is hospitalized. Further, due to changes in urinary and sexual habits postdischarge, a patient experiences a permanent 0.096 reduction in his or her HRQoL to 0.730. However, not all hospitalized patients require surgery. For those patients whose CDI can be managed via medication, the loss in HRQoL is 0.256[17] for an average of 10 days[22] spent in the hospital or at home.

Mild to moderate as well as recurrent cases of CDI often do not need hospitalization and are treated with oral antibiotics (eg, metronidazole, vancomycin, or a combination of both). There are no HRQoL weights specifically for CDI. Following precedent in the literature, we used surrogate HRQoL weights for noninfectious diarrhea and estimate the average reduction in HRQoL for such cases at 0.120.[17,34] A patient with a mild to moderate case of CDI often has complete resolution of symptoms within 7-11 days (average 8.5 days).[12] Further, a recurrent CDI episode typically lasts for 13 days.[28] We estimate that a patient experiences an average of 2 recurrent episodes (26 days total) within 1 year of the initial episode in the analytical model.

CRE infections typically occur in elderly patients with significant comorbidities. The most common comorbidities associated with these patients include diabetes, renal failure, heart disease, chronic obstructive pulmonary disease, and various malignancies.[24] Thus, we estimate the baseline HRQoL for patients with CRE infections at 0.748, which is the average of the median EQ-5D scores reported in Sullivan et al[35] associated with the CRE infection comorbidities identified in Hauck et al.[24]

Depending on the site of infection and whether the infection results in secondary bacteremia (ie, the infection progresses into the bloodstream), the HRQoL losses for patients with CRE infections range from 0.218 (CRE infection with secondary bacteremia), 0.168 (pulmonary CRE infection), 0.106 (primary bacteremia, intra-abdominal CRE infection, and other type of CRE infection), to 0.018 (UTI CRE)[36] (Table 3).

The median length of stay for patients with CRKp urinary tract colonization without CRKp infection (ie, the control group of Hauck et al[24]) is 9 days. To estimate CRE infection-attributable illness duration, we subtract 9 days from the site-specific durations reported in Hauck et al[24] for those cases not involving secondary bacteremia.

The median length of hospital stay for patients with CRKp who develop a secondary bacteremia is 37 days.[37] We estimate the average illness duration for these patients at 28 days, which is the difference between the median length of stay in Ben-David et al[37] (37 days) and the median length of stay for the control group of Hauck et al[24] (9 days).

### *VSL*

VSL is an analytical construct used to value mortality risk reductions in policy analysis. It reflects the marginal rate of substitution between income and mortality risk and is estimated by dividing the value of a small risk reduction by the size of the risk change.[15,38] For example, if one is willing to pay $500 for a 1 in 10,000 reduction in risk of death in a given year, then the VSL is $5 million (= $500 ÷ 1/10,000) for that year.

For analyses conducted in 2014 dollars, the US Department of Health and Human Services guidance[15] recommends the use of a central VSL estimate of $9.30 million. Adjusting this value to account for inflation (0.08% from 2014-2016), the 2014 VSL in 2016 dollars, $VSL_{2014}$, is $9.31 million.[39] Because VSL increases as real income increases, it is also necessary to account for changes in real income growth, ΔRI, from 2014-2016. Thus, assuming a constant income elasticity, we calculate the 2016 VSL in 2016 dollars, $VSL_{2016}$, at $9.78 million as follows:

$$VSL_{2016} = VSL_{2014} \times (1 + \Delta RI_{2015}) \times (1 + \Delta RI_{2016}) \quad \text{(Equation 2)}$$

where $\Delta RI_{2015}$ and $\Delta RI_{2016}$ are 3.42% and 1.60%, respectively, based on data from the Bureau of Economic Analysis[40] and the Congressional Budget Office.[41]

### *VSLY*

VSLY is the VSL divided by the discounted expected number of years remaining. It represents the rate at which an individual

**Table 3**
HRQoL weights, illness duration, and lost QALYs for patients who survive by type of infection

| Infection | Health outcome | | | No. of survivors (2016) | Baseline HRQoL weight | HRQoL weight | Illness duration (days) | QALYs lost* | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | Per patient | Total |
| *Clostridioides difficile* | Severe | Surgically managed | First y | 10,391 | 0.826 | 0.319 | 27.0 | 0.1273 | 1,308 |
| | | | 1-y postsurgery | 1,975 | — | 0.730 | 365.0 | 0.0927† | 183 |
| | | | 2-y postsurgery | 1,607 | — | — | 730.0 | 0.1827† | 294 |
| | | | 5-y postsurgery | 1,843 | — | — | 1,825.0 | 0.4374† | 806 |
| | | | 7-y postsurgery | 2,240 | — | — | 2,555.0 | 0.5950† | 1,333 |
| | | | 11-y postsurgery | 2,727 | — | — | 4,015.0 | 0.8836† | 2,409 |
| | | Nonsurgically managed | | 56,860 | — | 0.570 | 10.0 | 0.0070 | 400 |
| | Mild | | | 393,596 | 1.000 | 0.880 | 8.5 | 0.0028 | 1,100 |
| | Recurrent | | | 90,091 | — | — | 26.0 | 0.0085 | 770 |
| CRE | Primary—unidentified site | | | 669 | 0.748 | 0.642 | 5.0 | 0.0015 | 0.9714 |
| | UTI | No secondary bacteremia | | 5,291 | — | 0.730 | 1.0 | 0.0000 | 0.2609 |
| | | With secondary bacteremia | | 401 | — | 0.530 | 28.0 | 0.0167 | 6.7027 |
| | Pulmonary | No secondary bacteremia | | 1,294 | — | 0.580 | 10.0 | 0.0046 | 5.9553 |
| | | With secondary bacteremia | | 114 | — | 0.530 | 28.0 | 0.0167 | 1.9117 |
| | Intra-abdominal | No secondary bacteremia | | 344 | — | 0.642 | 4.0 | 0.0012 | 0.3993 |
| | | With secondary bacteremia | | 146 | — | 0.530 | 28.0 | 0.0167 | 2.4479 |
| | Other‡ | No secondary bacteremia | | 206 | — | 0.642 | 4.0 | 0.0012 | 0.2396 |
| | | With secondary bacteremia | | 57 | — | 0.530 | 28.0 | 0.0167 | 0.9558 |

CRE, carbapenem-resistant Enterobacteriaceae; HRQoL, health-related quality of life; QALYs, quality-adjusted life years; UTI, urinary tract infection.
*Computed using Eq 1. Figures may not add up due to rounding.
†Calculated as the present value of the QALYs lost over the remaining life years, where the discount rate is 3%. For example, if the patient survives for 1 y postsurgery, the QALYs lost for the given patient is computed as $(0.826 - 0.730) \div (1 + 0.03)^1 = 0.0927$.
‡The QALY weights and illness durations for the category are assumed to be equivalent to that for intra-abdominal CRE infections.

**Table 4**
Societal willingness to pay to avoid mortality and morbidity in the United States from CDI and CRE infection in 2016

| Parameter | | | Value* | | |
|---|---|---|---|---|---|
| | | | CDI | CRE infection | Total |
| Total no. (per y, in 2016) | Initial | | 468,567 | 9,620 | 478,187 |
| | Recurrent | | 90,091 | NA | 90,091 |
| No. of deaths | Initial | First y | 7,720 | 1,097 | 8,817 |
| | | 1-y postsurgery† | 1,917 | NA | 1,917 |
| | | 2-y postsurgery† | 1,514 | — | 1,514 |
| | | 5-y postsurgery† | 1,589 | — | 1,589 |
| | | 7-y postsurgery† | 1,822 | — | 1,822 |
| | | 11-y postsurgery† | 1,970 | — | 1,970 |
| | Recurrent | | 0 | — | 0 |
| VSL per patient (in 2016, $million) | | | — | $9,779,000 | — |
| Burden of mortality (in 2016, $billion) | | | $161.7 | $10.7 | $172.4 |
| No. of patients who survive | Initial | First y | 460,847 | 8,522 | 469,369 |
| | | 1-y postsurgery | 1,975 | NA | 1,975 |
| | | 2-y postsurgery | 1,607 | — | 1,607 |
| | | 5-y postsurgery | 1,843 | — | 1,843 |
| | | 7-y postsurgery | 2,240 | — | 2,240 |
| | | 11-y postsurgery | 2,727 | — | 2,727 |
| | Recurrent | | 90,091 | — | 90,091 |
| Lost QALYs | | | 8,604 | 20 | 8,624 |
| VSLY (in 2016) | | | — | $497,800 | — |
| Burden of morbidity (in 2016, $billion) | | | $4.3 | $0.01 | $4.31 |
| Total burden (in 2016, $billion) | | | $166.0 | $10.7 | $176.7 |

*CDI, Clostridioides difficile* infection*; CRE*, carbapenem-resistant Enterobacteriaceae; *NA*, not applicable, *QALYs*, quality-adjusted life years; *VSL*, value of a statistical life; *VSLY*, value of a statistical life year.
*Figures may not add up due to rounding.
†Deaths in future years are discounted at 3%.

substitutes money for gains in life expectancy.[15] Essentially, this method amortizes the VSL over the expected years of life, much in the same way that a 30-year home mortgage is divided into 30 years of equal monthly payments. For example, if the VSL is $5 million for an expected 30 years of life remaining, this is financially equivalent to an annuity of around $255,000 per year over 30 years, where $255,000 is the value of a statistical life year (VSLY). We compute the VSLY by dividing the $VSL_{2016}$ by the discounted expected number of life years remaining as follows:

$$VSLY_{2016} = VSL_{2016} \div \Sigma p_{j,t} \times (1+d)^{j-t} \quad \text{(Equation 3)}$$

where $p_{j,t}$ is the probability that an individual at age j survives to age t, and d is the social discount rate (set equal to 3% in our model). Assuming that the average individual is 40 years old, we used the EQ-5D results reported in Hanmer et al[32] to estimate the HRQoL in each subsequent year along with the conditional likelihood of survival for each year of age based on the population-averages reported by the CDC. This results in a $VSLY_{2016}$ estimate of $498,000.

## RESULTS

The estimated societal value of avoiding mortality and morbidity from CDI and CRE infection in the United States is significant at $176.7 billion in 2016 (Table 4). A large portion of this (93.9%) is attributable to CDIs, which affect almost 50 times more people than CRE infections. However, the mortality rate for CRE infections overall (11.4%) is more than 3 times that for CDIs (3.5%). Although CRE infections are still relatively uncommon in the United States, there is some evidence that the rate of carbapenem resistance among Enterobacteriaceae is increasing. For example, from 2004-2008, there has been an increase from 0.6%-5.4% in resistant *K pneumoniae* strains.[42] This, coupled with a high mortality rate, is alarming.

Of the $176.7 billion, the estimated societal willingness to pay is primarily attributable to avoiding mortality owing to CDIs and CRE infections, which account for $172.4 billion (97.6%). Given the high number of deaths associated with CDIs (7,720 deaths in the first year and 8,812 discounted deaths in future years) compared to CRE infections (1,097 deaths), the estimated social value of avoiding CDI mortality ($161.7 billion) is more than 15 times higher than that for deaths owing to CRE infections ($10.7 billion) (Table 2 and Table 4). Should CRE infection incidence significantly increase in the future, the estimated societal willingness to pay to avoid CRE infections could potentially exceed that for CDIs owing to the higher mortality rate associated with CRE infections (11.4% for CRE infection vs 3.5% for CDI).

## DISCUSSION

The societal willingness to pay to avoid morbidity from CDIs and CRE infections in the United States is estimated at $4.31 billion in 2016, with most ($4.30 billion) from CDIs. Total lost QALYs among patients who survive are 8,604 and 20 for CDI and CRE infection, respectively, with the average QALY loss per case of 0.0190 for CDI and 0.0023 for CRE infection. The high morbidity cost for CDIs ($4.30 billion) in comparison to that for CRE infections ($9.9 million) is related to (1) a significantly higher number of CDI cases than CRE infection and (2) an average QALY loss per case for CDI that is more than 8 times that for CRE infection.

The costs attributable to mortality and morbidity presented in this study far exceed the medical care costs reported by Kwon et al[12] for CDI and Bartsch et al[13] for CRE infection by orders of magnitude, although they do not include those costs that would be incurred by third-party payers (eg, private health insurance and Medicare). Given the significant estimated willingness to pay to avoid these illnesses, coupled with growing antibiotic resistance, policies designed to mitigate disease transmission in health care settings, improve rapid diagnosis, and encourage antibiotic stewardship are expected to have high societal benefit-cost ratios.

## CONCLUSIONS

The burden of CDIs and CRE infections in the United States is significant, with an estimated 468,567 and 9,620 incident cases occurring in 2016 for CDIs and CRE infections, respectively. We estimate that the

societal willingness to pay to avoid mortality and morbidity associated with CDIs and CRE infections is $176.7 billion ($166 billion for CDI and $10.7 billion for CRE infection), not including the costs to third-party payers, which are not quantified in this study. Given the high estimated societal willingness to pay to avoid these infections, policies designed to stimulate rapid diagnosis and thereby reduce transmission rates are desirable.

## Acknowledgments

The authors gratefully acknowledge R. Douglas Scott (Centers for Disease Control and Prevention [CDC]), L. Clifford McDonald (CDC), and Alexander J. Kallen (CDC) for their insightful comments, advice, and guidance. The authors also would like to thank Nyssa Ackerley (Eastern Research Group, Inc) and Calvin Franz (Eastern Research Group, Inc), who provided invaluable research support.

## References

1. Centers for Disease Control and Prevention. Antibiotic resistance threats in the United States 2013. Available from: https://www.cdc.gov/drugresistance/threat-report-2013/index.html. Accessed July 23, 2018.
2. Surawicz CM, Brandt LJ, Binion DG, Ananthakrishnan AN, Curry SR, Gilligan PH, et al. Guidelines for diagnosis, treatment, and prevention of *Clostridium difficile* infections. Am J Gastroenerol 2013;108:478-98.
3. Kociolek LK. Gerding DN. Breakthroughs in the treatment and prevention of *Clostridium difficile* infection. Nat Rev Gastroenterol Hepatol 2016;13:150-60.
4. Magill SS, Edwards JR, Bamberg W, Beldavs ZG, Dumyati G, Kainer MA, et al. Multistate point-prevalence survey of health care–associated infections. N Engl J Med 2014;370:1198-208.
5. Hunter JC, Mu Y, Dumyati GK, Farley MM, Winston LG, Johnston HL, et al. Burden of nursing home-onset *Clostridium difficile* infection in the United States: estimates of incidence and patient outcomes. Open Forum Infectious Dis 2016;3:ofv196.
6. Lessa F, Mu Y, Bamberg WM, Beldavs ZG, Dumyati GK, Dunn JR, et al. Burden of *Clostridium difficile* infection in the United States. N Engl J Med 2015;372:825-34.
7. Lutgring JD, Limbago BM. The problem of carbapenemase-producing-carbapenem-resistant Enterobacteriaceae detection. J Clin Microbiol 2016;54:529-34.
8. Centers for Disease Control and Prevention. Healthcare-associated infections. Available from: https://www.cdc.gov/hai/organisms/cre/definition.html. Accessed January 30, 2018.
9. Hidron AI, Edwards JR, Patel J, Horan TC, Sievert DM, Pollock DA, et al. NHSN annual update: antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006-2007. Infect Control Hosp Epidemiol 2008;29:996-1011.
10. Sievert DM, Ricks P, Edwards JR, Schneider A, Patel J, Srinivasan A, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009–2010. Infect Control Hosp Epidemiol 2013;34:1-14.
11. Guh AY, Bulens SN, Mu Y, Jacob JT, Reno J, Scott J, et al. Epidemiology of carbapenem-resistant Enterobacteriaceae in 7 US communities, 2012-2013. JAMA 2015;314:1479-87.
12. Kwon JH, Olsen MA, Dubberke ER. The morbidity, mortality, and costs associated with *Clostridium difficile* infection. Infect Dis Clin North Am 2015;29:123-34.
13. Bartsch S, McKinnell JA, Mueller LE, Miller LG, Gohil SK, Huang SS, et al. Potential economic burden of carbapenem-resistant Enterobacteriaceae (CRE) in the United States. Clin Microbiol Infect 2017;23:48.e9-48.e16.
14. Scott RII, Slayton R, Baggs J, Jernigan J. Including the economic value of mortality risk reductions in cost-benefit analysis (CBA) of healthcare-associated infections. Open Forum Infect Dis 2015;2(Suppl 1):311.
15. US Department of Health and Human Services, Office of the Assistant Secretary for Planning and Evaluation. Guidelines for regulatory impact analyses. Available from: https://aspe.hhs.gov/pdf-report/guidelines-regulatory-impact-analysis. Accessed July 23, 2018.
16. US Census Bureau. National population projections datasets. Available from: https: // www.census.gov/data/datasets/2014/demo/popproj/2014-popproj.html. Accessed January 23, 2017.
17. Varier RU, Biltaji E, Smith KJ, Roberts MS, Jensen MK, LaFleur J, et al. Cost-effectiveness analysis of treatment strategies for initial *Clostridium difficile* infection. Clin Microbiol Infect 2014;20:1343-51.
18. Dallas KB, Condren A, Divino CM. Life after colectomy for fulminant *Clostridium difficile* colitis: a 7-year follow up study. Am J Surg 2014;207:533-9.
19. Halabi WJ, Nguyen VQ, Carmichael JC, Pigazzi A, Stamos MJ, Mills S. *Clostridium difficile* colitis in the United States: a decade of trends, outcomes, risk factors for colectomy, and mortality after colectomy. J Am Coll Surg 2013;217:802-12.
20. Cho H, Klabunde CN, Yabroff KR, Wang Z, Meekins A, Lansdorp-Vogelaar I, et al. Comorbidity-adjusted life expectancy: a new tool to inform recommendations for optimal screening strategies. Ann Intern Med 2013;159:660-6.
21. Tabak YP, Zilberberg MD, Johannes RS, Sun X, McDonald LC. Attributable burden of hospital-onset *Clostridium difficile* infection: a propensity score matching study. Infec Control Hosp Epidemiol 2013;34:588-96.
22. Dubberke ER, Butler AM, Reske KA, Agniel D, Olsen MA, D'Angelo G, et al. Attributable outcomes of endemic *Clostridium Difficile*–associated disease in nonsurgical patients. Emerg Infect Dis 2008;14:1031-8.
23. Neuner EA, Yeh JY, Hall GS, Sekeres J, Endimiani A, Bonomo RA, et al. Treatment and outcomes in carbapenem-resistant *Klebsiella pneumoniae* bloodstream infections. Diagn Microbiol Infect Dis 2011;69:357-62.
24. Hauck C, Cober E, Richter SS, Perez F, Salata RA, Kalayjian RC, et al. Spectrum of excess mortality due to carbapenem-resistant *Klebsiella pneumoniae* infections. Clin Microbiol Infect 2016;22:513-9.
25. Capone A, Giannella M, Fortini D, Giordano A, Meledandri M, Ballardini M, et al. High rate of colistin resistance among patients with carbapenem-resistant *Klebsiella pneumoniae* infection accounts for an excess of mortality. Clin Microbiol Infect 2013;19:e23-30.
26. Falagas ME, Tansarli GS, Karageorgopoulos DE, Vardakas KZ. Deaths attributable to carbapenem-resistant Enterobacteriaceae infections. Emerg Infect Dis 2014;20:1170-5.
27. Fekety R, McFarland LV, Surawicz CM, Greenberg RN, Elmer GW, Mulligan ME. Recurrent *Clostridium difficile* diarrhea: characteristics of and risk factors for patients enrolled in a prospective, randomized, double-blinded trial. Clin Infect Dis 1997;24:324-33.
28. McFarland LV, Surawicz CM, Rubin M, Fekety R, Elmer GW, Greenberg RN. Recurrent *Clostridium difficile* disease: epidemiology and clinical characteristics. Infect Control Hosp Epidemiol 1999;20:43-50.
29. Murphy SL, Kochanek KD, Xu J, Heron M. Deaths: final data for 2012. Natl Vital Stat Rep 2015: 63:1-117.
30. Vardakas KZ, Matthaiou DK, Falagas ME, Antypa E, Koteli A, Antoniadou E. Characteristics, risk factors and outcomes of carbapenem-resistant *Klebsiella pneumoniae* infections in the intensive care unit. J Infect 2015;70:592-9.
31. Jump RL. *Clostridium difficile* infection in older adults. Aging Health 2013;9:403-14.
32. Hanmer J, Lawrence WF, Anderson JP, Kaplan RM, Fryback DG. Report of nationally representative values for the noninstitutionalized US adult population for 7 health-related quality-of-life scores. Med Decis Making 2006;26:391-400.
33. Stranges PM, Hutton DW, Collins CD. Cost-effectiveness analysis evaluating fidaxomicin versus oral vancomycin for the treatment of *Clostridium difficile* infection in the United States. Value Health 2013;16:297-304.
34. Bartsch SM, Umscheid CA, Fishman N, Lee BY. Is fidaxomicin worth the cost? An economic analysis. Clin Infect Dis 2013;57:555-61.
35. Sullivan PW, Lawrence WF, Ghushchyan V. Preference-based EQ-5D index scores for chronic conditions in the United States. Med Decis Making 2006;26:410-20.
36. Lee BY, Bartsch SM, Wong KF, McKinnell JA, Slayton RB, Miller LG, et al. The potential trajectory of carbapenem-resistant Enterobacteriaceae, an emerging threat to health-care facilities, and the impact of the Centers for Disease Control and Prevention toolkit. Am J Epidemiol 2016;158:471-9.
37. Ben-David D, Kordevani R, Keller N, Tal I, Marzel A, Gal-Mor O, et al. Outcome of carbapenem resistant *Klebsiella pneumoniae* bloodstream infections. Clin Microbiol Infect 2012;18:54-60.
38. Hammitt JK. Valuing mortality risk: theory and practice. Environ Sci Technol 2000;34:1396-400.
39. Bureau of Labor Statistics. Consumer price index. Series ID: CUUR0000SA0, CUUS0000SA0, not seasonally adjusted. US city average, January 2016. Available from: https://data.bls.gov/timeseries/cuur0000sa0?series_id=cwur0000sa0. Accessed July 28, 2018.
40. Bureau of Economic Analysis. National income and product accounts. Table 2.1: personal income and its disposition. Available from: https://www.bea.gov/iTable/iTable.cfm?reqid=19&step=2#reqid=19&step=3&isuri=1&1921=survey&1903=58. Accessed July 23, 2018.
41. Congressional Budget Office. The 2015 long-term budget outlook. Available from: https: // www.cbo.gov/sites/default/files/114th-congress-2015-2016/reports/50250-longtermbudgetoutlook-4.pdf. Accessed May 25, 2018.
42. Thaden JT, Lewis SS, Hazen KC, Huslage K, Fowler VG Jr, Moehring RW, et al. Rising rates of carbapenem-resistant Enterobacteriaceae in community hospitals: a mixed-methods review of epidemiology and microbiology practices in a network of community hospitals in the southeastern United States. Infec Control Hosp Epidemiol 2014;35:978-83.