Mortality, Length of Stay, and Healthcare Costs Associated With Multidrug-Resistant Bacterial Infections Among Elderly Hospitalized Patients in the United States

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(See the Viewpoints by Fowler et al on pages 1107–11.)

Background. This study reports estimates of the healthcare costs, length of stay, and mortality associated with infections due to multidrug-resistant bacteria among elderly individuals in the United States.

Methods. We conducted a retrospective cohort analysis of patients aged ≥65 admitted for inpatient stays in the Department of Veterans Affairs healthcare system between 1/2007–12/2018. We identified those with positive cultures for multidrug-resistant bacteria and matched each infected patient to ≤10 control patients. We then performed multivariable regression models to estimate the attributable cost and mortality due to the infection. We also constructed multistate models to estimate the attributable length of stay due to the infection. Finally, we multiplied these pathogen-specific attributable cost, length of stay, and mortality estimates by national case counts from hospitalized patients in 2017.

Results. Our cohort consisted of 87,509 patients with infections and 835,048 matched controls. Costs were higher for hospital-onset invasive infections, with attributable costs ranging from $22,293 (95% confidence interval: $19,101–$24,485) for methicillin-resistant Staphylococcus aureus (MRSA) to $57,390 ($34,070–$80,710) for carbapenem-resistant (CR) Acinetobacter. Similarly, for hospital-onset invasive infections, attributable mortality estimates ranged from 14.2% (12.2–16.2%) for MRSA to 24.1% (12.1–36.0%) for CR Acinetobacter. The aggregate cost of these infections was an estimated $1.9 billion ($1.3 billion–$2.5 billion) with 11,852 (8,719–14,985) deaths and 448,224 (354,513–541,934) inpatient days in 2017.

Conclusions. Efforts to prevent these infections due to multidrug-resistant bacteria could save a significant number of lives and healthcare resources.

Keywords. antimicrobial resistance; healthcare-associated infections; mortality; veterans.

METHODS
Study Design and Population
This study used a retrospective cohort design. We included patients with VA inpatient admissions between January 2007 and December 2018 who were aged 65 years or older on the date of
their admission. Patients with positive cultures during the 365-day period prior to the day before admission were excluded so as to isolate incident infections. We also excluded patients who had no evidence of receiving care in the VA system for at least 365 days prior to their hospital admission.

Data
The results from microbiology tests are contained in the VA electronic medical records as free text. A natural language-processing tool was created previously that extracts information regarding organism, antibiotic susceptibility, and specimen location [16]. This process converts this unstructured information into a structured format that allows it to be used in statistical analyses.

We assessed healthcare costs using data from the VA Health Economics Resource Center (HERC) Average Cost data [17], which has been used in a number of published studies [18, 19]. The cost of an encounter in this dataset is assigned to each patient encounter with the same characteristics and is computed by regressing cost-adjusted charges on length of stay (LOS), diagnosis-related group weight, whether the patient died in the hospital, age, gender, intensive care unit (ICU) stay, and number of diagnoses using Medicare data for veterans [20]. The estimated coefficients from this cost model are then applied to VA data to generate a predicted cost for each encounter.

Veterans’ Health Administration (VHA) Directive 1906 dictates that the VA collects death information for veterans from official sources, which include VHA facilities, death certificates, and the VA National Cemetery Administration. Because of this, the mortality data available in the VA Corporate Data Warehouse (CDW) provide a unique dataset to capture both in-hospital but also postdischarge deaths. These data have previously been used to estimate attributable mortality due to antimicrobial-resistant infections [21, 22].

Finally, patient demographic data were obtained from the VA CDW and diagnosis codes were obtained from VA Medical SAS datasets.

Outcome
Our healthcare cost outcomes captured the value of resources used to provide clinical care from the perspective of the healthcare provider during the index hospitalization. Cost values were converted to 2017 US dollars using the Personal Consumption Expenditures–Health price index [23]. Our LOS outcome was measured in terms of inpatient days. And finally, our mortality outcome was measured over the period of 30 and 90 days following the index date and was not limited to just in-hospital deaths.

Independent Variables
The exposure of interest in our analyses was a positive clinical culture for one of the following pathogens: methicillin-resistant Staphylococcus aureus (MRSA), extended-spectrum cephalosporin resistance in Enterobacteriaceae suggestive of extended-spectrum β-lactamase (ESBL) production, vancomycin-resistant Enterococcus (VRE), carbapenem-resistant (CR) Acinetobacter species, carbapenem-resistant Enterobacteriaceae (CRE), or multidrug-resistant (MDR) Pseudomonas aeruginosa. We used the same definitions for cases the Centers for Disease Control and Prevention (CDC) used to estimate national burden of antibiotic-resistant healthcare pathogens (see Supplementary Appendix B) [24, 25]. During the time period of our study, most, although not all, VA laboratories were Clinical Laboratory Improvement Amendment (CLIA) certified. Costs, LOS, and mortality were estimated for each pathogen individually, stratified by whether the onset of the infection was in the hospital or the community, as well as whether the infection was invasive or noninvasive. We excluded cultures that were likely collected for surveillance purposes (ie, cultures labeled as rectal, perirectal, or nasal). Positive cultures were defined as community-onset (CO) if they were obtained on the day before admission or during the first 3 days of an inpatient stay. Hospital-onset (HO) positive cultures were those obtained between day 4 and the the discharge date. We categorized positive cultures that were obtained from a body site that is typically sterile (blood, bone, bone marrow, cerebrospinal fluid, pleural fluid, synovial fluid, and lymph node) as invasive infections, while noninvasive infections were all other cultures (eg, urine, sputum, wounds).

Other independent variables included the following: demographic characteristics (age, race, marital status, insurance status, gender); body mass index (BMI); outpatient costs in the 365 days prior to admission; indicators for the following events during the first 48 hours of an inpatient stay—surgery, mechanical ventilation, and hemodialysis; direct admission to a medical or surgical ICU; and comorbidities as measured using a risk index that combines the Charlson and Elixhauser indices [26].

Statistical Analyses
Each patient with a positive culture was matched using an exposure density sampling approach [27] with up to 10 control patients who had not had a positive culture up until that point in their hospitalization but were admitted to the same inpatient facility and had the same admitting diagnosis. Potential control patients could either have had a negative culture or no culture obtained. We performed this matching exercise separately for positive cultures occurring on the day prior to admission up to 40 days after admission for inpatient hospitalization. The patients with a positive culture and their matched controls were then pooled. This pooled dataset was then used to run multivariable generalized estimating equation (GEE) models with a gamma family and log link [28] to estimate the per-infection attributable cost as measured by an adjusted risk difference between infection patients and their uninfected controls. The gamma distribution for our GEE regressions was chosen for the cost outcome based on results from the modified
Acinetobacter infection attributable costs were highest for CR seen in Figure 2.

tality rates both for CO (24.3%) and HO (44.6%) cultures as resistant ($125,840) cultures had the highest mean costs. Carbapenem-$77,145) and CO invasive infections ($16,952; 95% CI: $31,844–$35,838) for MDR Acinetobacter for HO infections. In addition, attributable LOS estimates were highest for CRE (4.43; 95% CI: 3.15–5.67 days) for HO invasive infections and for CR Acinetobacter (4.11; 95% CI: 3.32–4.89 days) for HO noninvasive infections (Table 4).

As seen in Table 5, attributable 30-day mortality for CR Acinetobacter was highest in multivariable models for both HO invasive infections (.269; 95% CI:.099–.439) and CO invasive infections (.180; 95% CI:.110–.250). For noninvasive infections, attributable 30-day mortality was highest for CR Acinetobacter for both HO (.180; 95% CI:.110–.250) and CO (.067; 95% CI:.028–.107) infections. Results were similar for 90-day mortality (data not shown).

Table 6 shows aggregate cost estimates overall and by pathogen, location of onset, and body site for CO infections for 2017. Overall, we estimate that infections due to the pathogens of interest resulted in $1.1 billion (95% CI: $0.8 billion–$1.4 billion) during this 1-year period. Despite substantially fewer invasive infections relative to noninvasive infections (39,535 vs 263,412), the aggregate burden of these infections with onset in the community was approximately equal ($535.8 million; 95% CI: $411.8 million–$659.8 million) for invasive and $568.0 (95% CI: $368.8 million–$767.1 million) for noninvasive infections. The total number of bed-days lost for CO infections was 328,325 (95% CI: 254,380–402,270). Aggregate deaths for CO-positive cultures for 2017 were 9564 (95% CI: 7106–12,022) overall, with 3882 (95% CI: 3068–4696) for invasive infections and 5682 (95% CI: 4038–7326) for noninvasive infections.

The aggregate economic burden of HO infections was $781.2 million (95% CI: $528.4 million–$1034.0 million) overall. Of this, invasive infections accounted for $227.5 million (95% CI: $144.5 million–$310.5 million) and noninvasive infections accounted for $553.7 million (95% CI: $383.9 million–$767.1 million) (see Table 7). The total number of bed-days lost was 119,898 (95% CI: 100,133–139,664) for HO infections. And finally, the attributable deaths in 2017 for these HO infections were 808 (95% CI: 592–1025) for invasive infections, 1480 (95% CI: 1022–1938) for noninvasive infections, and 2288 (95% CI: 1613–2963) overall.

**DISCUSSION**

We generated both per-case and aggregate attributable cost, inpatient days, and mortality estimates by pathogen, location of onset (community or hospital), and body site (invasive or
| Characteristics | No Infection | Infection | No Infection | Infection | No Infection | Infection |
|-----------------|-------------|-----------|-------------|-----------|-------------|-----------|
| Community-onset analysis | | | | | | |
| Total | 379,211 | ... | 37,030 | ... | 85,400 | ... |
| Invasive | ... | ... | 7211 | 19.47% | ... | ... |
| Age (mean), years | 75.8 | 8.1 | 76.2 | 8.1 | 76.4 | 8.2 |
| Insurance | 53,034 | 14.0% | 3373 | 9.1% | 10,875 | 12.7% |
| Male | 371,492 | 98.0% | 36,505 | 98.6% | 83,653 | 98.0% |
| Race/ethnicity | | | | | | |
| White | 233,654 | 74.8% | 28,077 | 75.8% | 63,981 | 74.9% |
| Black | 56,910 | 15.0% | 5280 | 14.3% | 13,276 | 15.5% |
| Other | 24,752 | 6.5% | 2239 | 6.0% | 4876 | 5.7% |
| Unknown/missing | 13,895 | 3.7% | 1434 | 3.9% | 3267 | 3.8% |
| Married | 176,475 | 46.5% | 16,543 | 44.7% | 39,698 | 46.5% |
| Surgery | 83,684 | 22.1% | 9616 | 26.5% | 17,720 | 20.7% |
| ICU direct admission | 9049 | 2.4% | 663 | 1.8% | 2207 | 2.6% |
| Mechanical ventilation | 12,720 | 3.4% | 2186 | 5.9% | 3329 | 3.9% |
| Hemodialysis | 9491 | 2.5% | 1261 | 3.4% | 2286 | 2.7% |
| Comorbidity index (mean) | 2.4 | 2.4 | 2.5 | 2.5 | 2.4 | 2.6 |
| Outpatient cost (mean) | $18,700 | $21,321 | $19,432 | $25,101 |
| Hospital-onset analysis | | | | | | |
| Total | 93,078 | ... | 9887 | ... | 60,247 | ... |
| Invasive | NA | ... | 1761 | 178.1% | NA | ... |
| Age (mean), years | 76.0 | 7.9 | 76.4 | 7.7 | 75.9 | 7.9 |
| Insurance | 8509 | 9.1% | 519 | 5.2% | 5140 | 8.5% |
| Male | 91,456 | 98.3% | 9745 | 98.6% | 59,249 | 98.3% |
| Race/ethnicity | | | | | | |
| White | 64,932 | 69.8% | 7205 | 72.9% | 41,477 | 68.8% |
| Black | 17,067 | 18.4% | 1562 | 15.8% | 11,941 | 19.8% |
| Other | 7561 | 8.1% | 727 | 7.4% | 4403 | 7.3% |
| Unknown/missing | 34,98 | 3.8% | 393 | 4.0% | 2426 | 4.0% |
| Married | 41,363 | 44.4% | 4348 | 44.0% | 26,514 | 44.0% |
| Surgery | 28,640 | 30.8% | 3165 | 32.0% | 19,379 | 32.0% |
| ICU direct admission | 3605 | 3.9% | 322 | 3.3% | 2382 | 4.0% |
| Mechanical ventilation | 7751 | 8.3% | 1,076 | 10.9% | 5529 | 9.2% |
| Hemodialysis | 2678 | 2.9% | 251 | 2.5% | 1992 | 3.3% |
| Comorbidity index (mean) | 2.4 | 2.5 | 2.5 | 2.5 | 2.4 | 2.4 |
| Outpatient cost (mean) | $18,457 | $26,817 | $19,179 | $22,761 |

Abbreviations: ESBL, extended-spectrum β-lactamase; ICU, intensive care unit; MRSA, methicillin-resistant Staphylococcus aureus; VRE, vancomycin-resistant Enterococci; SD, standard deviation.

*Within first 2 days of admission.

*During 365 days prior to admission.
| Characteristics | Community-onset analysis | Hospital-onset analysis |
|-----------------|--------------------------|-------------------------|
|                 | CRE                      | Acinetobacter           | MDR Pseudomonas          |
|                 | No Infection             | Infection               | No Infection             | Infection               | No Infection             | Infection               |
| Mean or No.     | SD or %                  | Mean or No.             | SD or %                  | Mean or No.             | SD or %                  | Mean or No.             | SD or %                  |
| Total           | 21 635                   | 2536                    | 4150                     | 436                     | 15 706                   | 1656                    | 1656                     |
| Invasive        | NA                       | 292                     | 11.51%                   | NA                      | 54                      | 12.39%                  | NA                      | 111                     | 6.70%                   |
| Age (mean), y   | 77.6                     | 8.1                     | 76.4                     | 8.2                     | 76.1                     | 8.0                     | 77.0                     | 8.2                     | 77.0                     | 7.8                     |
| Insurance       | 29.32                    | 13.6%                   | 43.9                     | 10.6%                   | 19                      | 4.4%                    | 1812                     | 11.5%                   | 60                      | 3.6%                    |
| Male            | 21 311                   | 98.5%                   | 4079                     | 98.3%                   | 431                     | 98.9%                   | 15 396                   | 98.0%                   | 1635                    | 98.7%                   |
| Race/ethnicity  |                          |                         |                          |                         |                          |                         |                          |                         |                          |                         |
| White           | 10 146                   | 46.9%                   | 2649                     | 63.8%                   | 265                     | 60.8%                   | 10 531                   | 67.1%                   | 1093                    | 66.0%                   |
| Black           | 28.29                    | 13.1%                   | 895                      | 21.6%                   | 113                     | 25.9%                   | 2497                     | 15.9%                   | 265                     | 16.0%                   |
| Other           | 80.54                    | 37.2%                   | 479                      | 11.5%                   | 37                      | 8.5%                    | 2150                     | 13.7%                   | 218                     | 13.2%                   |
| Unknown/missing | 60.6                     | 2.8%                    | 127                      | 3.1%                    | 21                      | 4.8%                    | 528                      | 3.4%                    | 80                      | 4.8%                    |
| Married         | 10 619                   | 49.1%                   | 1889                     | 45.5%                   | 191                     | 43.8%                   | 7566                     | 48.2%                   | 773                     | 46.7%                   |
| Surgery*        | 37.04                    | 17.1%                   | 769                      | 18.5%                   | 83                      | 19.0%                   | 2792                     | 17.8%                   | 301                     | 18.2%                   |
| ICU direct admission | 51.1                    | 2.4%                    | 124                      | 3.0%                    | 17                      | 3.9%                    | 422                      | 2.7%                    | 41                      | 2.5%                    |
| Mechanical ventilation* | 1017              | 4.7%                    | 281                      | 6.8%                    | 75                      | 17.2%                   | 834                      | 5.3%                    | 191                     | 11.5%                   |
| Hemodialysis*   | 556                      | 2.6%                    | 121                      | 2.9%                    | 21                      | 4.8%                    | 375                      | 2.4%                    | 45                      | 2.7%                    |
| Comorbidity index (mean) | 2.3                  | 2.4                     | 2.4                      | 2.4                     | 2.4                     | 2.3                     | 2.4                      | 2.4                     | 2.4                     |                          |
| Outpatient cost (mean)* | $17 832                  | $19 616                  | $19 550                  | $20 630                 | $19 072                  | $21 487                  | $19 706                  | $21 987                 | $18 186                  | $20 571                 | $20 110                  | $29 260                 |
| Abbreviations: CR, carbapenem-resistant; CRE, carbapenem-resistant Enterobacteriaceae; ICU, intensive care unit; MDR, multidrug-resistant; SD, standard deviation. |
*a*Within first 2 days of admission.  
*b*During 365 days prior to admission.
noninvasive). In our analysis, we found that these 6 MDR infections led to costs of nearly $1.9 billion, more than 400,000 inpatient days, and more than 10,000 deaths among Medicare-aged patients in the United States in 2017. The per-case attributable cost, inpatient days, and mortality estimates were highest for CR Acinetobacter, but the aggregate burden was highest for

Figure 1. Unadjusted mean hospital costs per patient by pathogen type and onset. Abbreviations: CR, carbapenem-resistant; CRE, carbapenem-resistant Enterobacteriaceae; ESBL, extended-spectrum β-lactamase; MDR, multidrug-resistant; MRSA, methicillin-resistant Staphylococcus aureus; VRE, vancomycin-resistant Enterococcus.

Figure 2. Unadjusted 30-day probability of mortality by pathogen type and onset. Abbreviations: CR, carbapenem-resistant; CRE, carbapenem-resistant Enterobacteriaceae; ESBL, extended-spectrum β-lactamase; MDR, multidrug-resistant; MRSA, methicillin-resistant Staphylococcus aureus; VRE, vancomycin-resistant Enterococcus.
ESBL and MRSA due to high case counts. While estimates were generated using VA patients, they have enhanced generalizability due to the utilization of VA HERC costs that are based on Medicare costs.

Of course, it is important to keep in mind that the costs reported here include a combination of both fixed and variable costs. Therefore, not all of these costs could be prevented [31]. As an alternative, we also present estimates of the number of bed-days attributable to HO infections generated using methods that account for the time-varying nature of these events. These estimates can be combined with estimates of the value of bed-days, which have been reported for Australian [32] and European [33] hospital decision makers but, to the best of our knowledge, not for the US setting.

As the analyses were done in parallel, these results can be seen as complementary to those reported in the CDC's Antibiotic Resistance Threats in the United States, 2019 [24], and in subsequent published papers [34, 35], which reported the per-case attributable cost and mortality and aggregate cost and infection-related deaths for antibiotic-resistant bacterial infections in the US adult population. The aggregate cost of these infections in the Medicare population as identified in the

Table 3. Pathogen-Specific Estimates of Adjusted Attributable Cost by Onset and Body Site

| Pathogen                  | Community-onset infections | Hospital-onset infections |
|---------------------------|----------------------------|---------------------------|
|                           | Invasive                   |                          | Noninvasive               |                          |
|                           | Estimate | 95% CI       | Estimate | 95% CI       | Estimate | 95% CI       | Estimate | 95% CI       |
|                           | LL       | UL           | LL       | UL           | LL       | UL           | LL       | UL           |
| MRSA                      | $15,994  | $15,018      | $16,971  | $1378        | $1010    | $17,465      |
| VRE                       | $14,399  | $11,785      | $17,014  | $3,744       | $2984    | $4,505       |
| ESBL                      | $9,094   | $8,468       | $11,430  | $2,636       | $1,999   | $3,273       |
| CRE                       | $12,357  | $8,056       | $16,658  | $5,786       | $4,134   | $7,438       |
| CR Acinetobacter          | $16,952  | $12,209      | $30,695  | $13,676      | $7,773   | $19,579      |
| MDR Pseudomonas           | $12,657  | $8,013       | $19,300  | $5,826       | $3,969   | $7,883       |

Abbreviations: CI, confidence interval; CR, carbapenem-resistant; CRE, carbapenem-resistant Enterobacteriaceae; ESBL, extended-spectrum β-lactamase; LL, lower limit; MDR, multidrug-resistant; MRSA, methicillin-resistant Staphylococcus aureus; UL, upper limit; VRE, vancomycin-resistant Enterococcus.

Table 4. Pathogen-Specific Estimates of Adjusted Attributable Length of Stay by Onset and Body Site

| Pathogen                  | Community-onset infections | Hospital-onset infections |
|---------------------------|----------------------------|---------------------------|
|                           | Invasive                   |                          | Noninvasive               |                          |
|                           | Estimate | 95% CI       | Estimate | 95% CI       | Estimate | 95% CI       | Estimate | 95% CI       |
|                           | LL       | UL           | LL       | UL           | LL       | UL           | LL       | UL           |
| MRSA                      | 4.08     | 3.81         | 4.34     | 0.47         | 0.36     | 0.58         |
| VRE                       | 3.34     | 2.69         | 3.99     | 1.09         | 0.87     | 1.30         |
| ESBL                      | 2.85     | 2.38         | 3.33     | 0.95         | 0.74     | 1.15         |
| CRE                       | 3.32     | 1.98         | 4.66     | 1.55         | 1.07     | 2.03         |
| CR Acinetobacter          | 3.53     | -0.54        | 7.60     | 3.06         | 1.65     | 4.46         |
| MDR Pseudomonas           | 3.17     | 1.16         | 5.17     | 1.89         | 1.33     | 2.46         |

Abbreviations: CI, confidence interval; CR, carbapenem-resistant; CRE, carbapenem-resistant Enterobacteriaceae; ESBL, extended-spectrum β-lactamase; LL, lower limit; MDR, multidrug-resistant; MRSA, methicillin-resistant Staphylococcus aureus; UL, upper limit; VRE, vancomycin-resistant Enterococcus.
current study was approximately one-third of the overall cost burden identified in the CDC report ($4.6 billion). Similarly, the aggregate number of deaths found in the Medicare population accounted for 30% of the approximately 35,000 overall deaths documented in the CDC report. One important difference between the 2 analyses is that, to simplify our analysis in the previous study, we used only the first hospitalization for patients from 2007–2015, while our current study included all hospitalizations for patients between 2007 and 2018.

Our study had several limitations. First, because it was not possible to identify true infections definitively in our electronic VA microbiology data, we instead used positive clinical

### Table 5. Pathogen-Specific Estimates of Adjusted Attributable 30-Day Mortality by Onset and Body Site

| Pathogen                | Invasive          | Non-Invasive     |
|-------------------------|-------------------|------------------|
|                         | Estimate | 95% CI LL | UL     | Estimate | 95% CI LL | UL     |
| **Community-onset infections** |         |           |        |         |           |        |
| MRSA                    | 0.115    | 0.106 | 0.123 | 0.021    | 0.017 | 0.024 |
| VRE                     | 0.140    | 0.114 | 0.166 | 0.063    | 0.056 | 0.071 |
| ESBL                    | 0.067    | 0.050 | 0.083 | 0.021    | 0.014 | 0.027 |
| CRE                     | 0.106    | 0.053 | 0.160 | 0.025    | 0.009 | 0.041 |
| CR Acinetobacter        | 0.174    | 0.029 | 0.319 | 0.067    | 0.028 | 0.107 |
| MDR Pseudomonas         | 0.125    | 0.072 | 0.179 | 0.034    | 0.016 | 0.051 |
| **Hospital-onset infections** |         |           |        |         |           |        |
| MRSA                    | 0.148    | 0.128 | 0.168 | 0.072    | 0.063 | 0.080 |
| VRE                     | 0.200    | 0.175 | 0.225 | 0.047    | 0.036 | 0.059 |
| ESBL                    | 0.162    | 0.125 | 0.198 | 0.065    | 0.051 | 0.079 |
| CRE                     | 0.167    | 0.108 | 0.226 | 0.092    | 0.066 | 0.118 |
| CR Acinetobacter        | 0.269    | 0.099 | 0.439 | 0.180    | 0.110 | 0.250 |
| MDR Pseudomonas         | 0.206    | 0.139 | 0.272 | 0.105    | 0.080 | 0.130 |

### Table 6. National Estimates of Cases, Costs, Length of Stay, and Deaths for Each Pathogen and Total by Body Site: Community-Onset Infections, 2017

| Pathogen                | Invasive | Non-Invasive |
|-------------------------|----------|--------------|
|                         | Estimate | 95% CI | Costb (million $) | Length of stay (days) | Deaths |
|                         |          | LL | UL | Estimate | LL | UL | Estimate | LL | UL | Estimate | LL | UL |
| **Community-onset infections** |         |    |    |         |    |    |         |    |    |         |    |    |
| MRSA                    | 20,593   | 18,319 | 22,867 | $329.4 | 274.7 | 384.1 | 83,971 | 73,242 | 94,701 | 2358 | 2025 | 2691 |
| VRE                     | 3109     | 2703 | 3514 | $44.8 | 28.3 | 61.3 | 10,379 | 7963 | 12,795 | 435 | 329 | 541 |
| ESBL                    | 14,567   | 12,835 | 16,299 | $144.9 | 108.6 | 181.3 | 41,557 | 33,164 | 49,950 | 971 | 698 | 1244 |
| CRE                     | 578      | 491 | 665 | $7.1 | 12.0 | 13.0 | 1917 | 1,102 | 2733 | 61 | 26 | 97 |
| CR Acinetobacter        | 211      | 167 | 255 | $3.6 | −12.3 | 8.3 | 745 | −114 | 1603 | 37 | 3 | 70 |
| MDR Pseudomonas         | 477      | 411 | 544 | $6.0 | 0.2 | 11.9 | 1512 | 548 | 2476 | 20 | −12 | 53 |
| **Total**               | 39,535   | 34,926 | 44,144 | $535.8 | 411.8 | 659.8 | 140,082 | 115,905 | 164,258 | 3882 | 3068 | 4696 |

### Table 6. National Estimates of Cases, Costs, Length of Stay, and Deaths for Each Pathogen and Total by Body Site: Community-Onset Infections, 2017

| Pathogen                | Invasive | Non-Invasive |
|-------------------------|----------|--------------|
|                         | Estimate | 95% CI | Costb (million $) | Length of stay (days) | Deaths |
|                         |          | LL | UL | Estimate | LL | UL | Estimate | LL | UL | Estimate | LL | UL |
| **Hospital-onset infections** |         |    |    |         |    |    |         |    |    |         |    |    |
| MRSA                    | 93,180   | 82,889 | 103,470 | $28.4 | 11.6 | 15.0 | 44,088 | 33,024 | 55,153 | 1921 | 1521 | 2320 |
| VRE                     | 18,630   | 16,201 | 21,060 | $69.8 | 46.3 | 93.2 | 20,290 | 15,544 | 25,035 | 1182 | 958 | 1406 |
| ESBL                    | 94,143   | 82,951 | 105,335 | $248.2 | 174.5 | 321.8 | 88,983 | 67,623 | 110,344 | 1941 | 1299 | 2583 |
| CRE                     | 4823     | 4098 | 5548 | $27.9 | 14.2 | 41.6 | 7488 | 4940 | 10,035 | 122 | 39 | 205 |
| CR Acinetobacter        | 2214     | 1751 | 2678 | $30.3 | 12.2 | 48.4 | 3000 | 1013 | 5242 | 149 | 54 | 245 |
| MDR Pseudomonas         | 10,887   | 9372 | 12,401 | $63.4 | 36.4 | 90.4 | 20,628 | 13,944 | 27,312 | 367 | 166 | 568 |
| **Total**               | 223,877  | 197,263 | 250,491 | $568.0 | 368.8 | 767.1 | 188,243 | 138,475 | 238,012 | 5682 | 4038 | 7326 |
| **Overall**             | 263,412  | 232,189 | 294,635 | $1103.8 | 780.6 | 1427.0 | 328,325 | 254,380 | 402,270 | 9564 | 7106 | 12,022 |

Abbreviations: CI, confidence interval; CR, carbapenem-resistant; CRE, carbapenem-resistant Enterobacteriaceae; ESBL, extended-spectrum β-lactamase; LL, lower limit; MDR, multidrug-resistant; MRSA, methicillin-resistant Staphylococcus aureus; UL, upper limit; VRE, vancomycin-resistant Enterococcus.

From Jernigan et al [25].

Total costs are de-duplicated for cases that met the definition of both ESBL and CRE so do not represent a direct summation of each individual pathogen.
Table 7. National Estimates of Cases, Costs, Length of Stay, and Deaths for Each Pathogen and Total by Body Site: Hospital-Onset Infections, 2017

| Pathogen               | Cases Estimate | 95% CI LL | 95% CI UL | Cost Estimate | 95% CI LL | 95% CI UL | Length of stay (inpatient days) Estimate | 95% CI LL | 95% CI UL | Deaths Estimate | 95% CI LL | 95% CI UL |
|------------------------|----------------|-----------|-----------|---------------|-----------|-----------|------------------------------------------|-----------|-----------|-----------------|-----------|-----------|
| **Invasive** MRSA      | 3436           | 3057      | 3816      | $80.1         | $57.5     | $102.6    | 10,412                                   | 8961      | 11,864    | 393            | 327       | 459       |
| VRE                    | 1573           | 1368      | 1778      | $46.8         | $30.6     | $63.1     | 5325                                    | 4448      | 6202      | 220            | 163       | 277       |
| ESBL                   | 2196           | 1935      | 2457      | $79.2         | $53.0     | $105.6    | 8511                                    | 6739      | 10,283    | 146            | 100       | 193       |
| CRE                    | 211            | 179       | 242       | $9.6          | $2.7      | $16.5     | 933                                     | 631       | 1234      | 22             | 7         | 37        |
| CR Acinetobacter       | 102            | 80        | 123       | $5.5          | $0.3      | $10.8     | 397                                     | 180       | 613       | 18             | 0         | 35        |
| MDR Pseudomonas        | 198            | 170       | 225       | $6.2          | $0.5      | $12.0     | 462                                     | 209       | 714       | 8              | 6         | 23        |
| Total                  | 7715           | 6789      | 8641      | $227.5        | $144.5    | $310.5    | 26,039                                  | 21,168    | 30,911    | 808            | 592       | 1025      |
| **Noninvasive** MRSA   | 15,548        | 13,831    | 17,265    | $178.9        | $140.1    | $217.6    | 25,928                                  | 22,619    | 29,237    | 320            | 246       | 394       |
| VRE                    | 9,427          | 8,198     | 10,657    | $46.1         | $25.4     | $66.8     | 12,896                                  | 10,792    | 14,997    | 598            | 480       | 716       |
| ESBL                   | 14,192         | 12,505    | 15,879    | $195.4        | $147.3    | $243.6    | 33,593                                  | 28,669    | 38,518    | 293            | 191       | 394       |
| CRE                    | 1,757          | 1,493     | 2,021     | $22.9         | $10.7     | $35.1     | 4,123                                   | 3,231     | 5,015     | 44             | 12        | 76        |
| CR Acinetobacter       | 1,066          | 843       | 1,289     | $27.3         | $11.4     | $43.3     | 4,386                                   | 3,151     | 5,622     | 72             | 25        | 119       |
| MDR Pseudomonas        | 4,512          | 3,884     | 5,139     | $83.0         | $49.1     | $117.0    | 12,934                                  | 10,504    | 15,365    | 152            | 67        | 238       |
| Total                  | 46,502         | 40,754    | 52,250    | $553.7        | $383.9    | $723.5    | 93,859                                  | 78,965    | 108,753   | 1,480          | 1,022     | 1,938      |
| **Overall** Total      | 54,217         | 47,543    | 60,892    | $781.2        | $528.4    | $1034.0   | 119,898                                 | 100,133   | 139,664   | 2,288          | 1,613     | 2,963      |

Abbreviations: CI, confidence interval; CR, carbapenem-resistant; CRE, carbapenem-resistant Enterobacteriaceae; ESBL, extended-spectrum β-lactamase; LL, lower limit; MDR, multidrug-resistant; MRSA, methicillin-resistant Staphylococcus aureus; UL, upper limit; VRE, vancomycin-resistant Enterococcus.

*From Jernigan et al [25].

**Total costs are de-duplicated for cases that met the definition of both ESBL and CRE so do not represent a direct summation of each individual pathogen.**

cultures. We then categorized these positive cultures as invasive if taken from sites that are typically sterile or noninvasive if taken from sites that are not typically sterile. It is highly likely that the invasive positive cultures in our study represent true infections, while the noninvasive positive cultures likely contain a mix of true infections and colonizations. Second, because HO infections are time-varying, estimates of the attributable cost and mortality of these infections are subject to time-dependent bias. We matched infected patients to uninfected patients based on the time in the hospital leading up to the infection in an attempt to reduce this bias, but this approach may not have entirely eliminated it. In addition to time-dependent bias, our attributable cost and mortality estimates may also be subject to residual confounding bias despite our best efforts to control for observable characteristics that might influence both infection and cost and mortality outcomes (comorbidities, surgery, ICU admission, mechanical ventilation, hemodialysis, and LOS in the hospital prior to infection or day of matching). In addition, in our analytical strategy for generating estimates of the attributable cost, inpatient days, and mortality due to resistant in-
fections, these outcomes were compared between patients with drug-resistant infections and those without infections. A recent commentary by de Kraker and Lipsitch recommends reporting results using both noninfected and uninfected control patients [36]. Third, while there are several benefits to using VA data for this analysis—for instance, the combination of microbiology data, cost data, and the ability to follow patients for death events postdischarge—one major limitation to this approach is that veterans differ from the US Medicare population overall. For example, our sample was almost entirely male. These results thus may not be generalizable to other populations and settings to the extent that differences exist between patients and healthcare delivery systems, respectively. Fourth, we matched patients with CO infections identified during a hospital stay to control patients who were also inpatients. If, in the absence of this infection, the patient would not have been admitted to the hospital, the ideal control patient would be one who was not admitted and, therefore, would have had lower costs. For this reason, our attributable cost estimate—which was calculated as the adjusted absolute difference in cost between patients with infection and noninfected controls—is likely an underestimate. In addition, our CO estimates do not distinguish between community-associated cases and those cases with onset in the community but with previous outpatient healthcare exposures. Finally, our estimates of the attributable cost and mortality of infections did not include postdischarge costs [37, 38] and mortality [22], nor did we include CO positive cultures that did not lead to a hospitalization. Thus, our aggregate estimates are likely an underestimate of the true burden associated with these infections.

Our study contributes to the literature in many important ways. First, our focus on the population aged 65 years and older...
allowed us to generate estimates of the burden of disease that are mainly felt by 1 payer, namely Medicare. Accordingly, these estimates can be useful for policy makers at the federal level to provide incentives for antibiotic stewardship, antibiotic development, and infection-control and -prevention initiatives. Second, we report aggregate estimates of several important metrics including cost, inpatient days, and mortality to convey a more complete picture of the overall burden of these infections. In addition, our estimation approach accounted for the timing of infection through matching on the day of infection for the cost and mortality estimates and using a multistate model for the LOS model. A recent systematic review of estimates of the burden of antimicrobial-resistant infections found that only 2 studies published between 2012 and 2016 used multistate modeling to minimize time-dependent bias [39]. Third, rather than just focusing on hospital-acquired infections, we estimated per-case cost and mortality attributable to both CO and HO infections, thereby providing a more comprehensive evaluation of the burden of these infections.

In conclusion, we estimate that antibiotic-resistant pathogens among hospitalized patients lead to a substantial number of deaths each year associated with substantial cost. Efforts to prevent these infections could save a significant number of lives and healthcare resources. 

Supplementary Data
Supplementary materials are available at Clinical Infectious Diseases online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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