Clinical Infectious Diseases

MAJOR ARTICLE

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

Richard E. Nelson,[1,2] David Hyun,[3] Amanda Jezek,[4] and Matthew H. Samore[1,2]

[1]IDEAS Center, Veterans Affairs Salt Lake City Health Care System, Salt Lake City, Utah, USA; [2]Department of Internal Medicine, University of Utah School of Medicine, Salt Lake City, Utah, USA; [3]The Pew Charitable Trusts, Washington, DC, USA; and [4]Infectious Diseases Society of America, Arlington, Virginia, USA

(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 (8719–14 985) 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.

While antibiotic-resistant infections can have a substantial negative effect on individuals across the age spectrum, both physiological changes and comorbidities place elderly individuals at particularly elevated risks for these infections [1]. With more time spent in hospital and long-term care settings than younger individuals, this population has a higher risk of exposure to antibiotic-resistant bacteria [2–6]. As the US population continues to shift toward a higher proportion of elderly individuals, concerns regarding antibiotic-resistant infections will only continue to grow [7].

A number of national and international organizations have recognized the importance of developing action plans to prevent the spread of antibiotic-resistant pathogens [8–15]. Comprehensive measures of the healthcare costs and deaths associated with antibiotic-resistant infections, and the economic benefits stemming from prevention, are necessary to better understand the magnitude of investments needed by hospitals to fund activities to prevent antibiotic resistance.

Using data from the US Department of Veterans Affairs (VA), we designed this study to generate estimates of the attributable cost, inpatient days, and mortality due to antibiotic-resistant infections for the US Medicare population.

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

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Correspondence: R. E. Nelson, 500 Foothill Blvd, Salt Lake City, UT, USA 84148 (richard.nelson@utah.edu).

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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

Park test [29, 30]. Similarly, for our mortality outcome, we used a Poisson family and a log link in our GEE models to calculate a per-infection attributable mortality as the adjusted risk difference of death between patients with infection and their uninfected controls. GEE models were used because patients could enter into the analysis more than once. Standard errors in our regression models accounted for repeated measures at the individual and facility level.

Similarly, we used a multivariable GEE model with a Poisson family and a log link to estimate the attributable LOS due to CO infections. For the attributable LOS due to HO infections, however, we estimated the difference in LOS between patients with hospital-onset infections and uninfected patients using multistate survival models with the following 4 states: uninfected, infected, discharged alive, and died in hospital. We ran separate models for invasive and noninvasive infections for each of the 6 pathogens of interest. We used bootstrapping techniques to generate robust 95% confidence intervals (CIs) from 1000 resampling runs.

Finally, we generated estimates of the aggregate cost, inpatient days, and mortality of resistant infections by multiplying our pathogen-specific estimates of the attributable cost, inpatient days, and mortality of resistant infections by the annual number of cases of these infections published previously [25]. We combined uncertainty from the estimated number of cases and the estimated attributable costs or mortality when calculating CIs for the total attributable costs and mortality by pathogen. Details on this approach can be found in Supplementary Appendix A.

RESULTS

Characteristics for both patients with a positive culture and matched controls are provided in Tables 1 and 2 for each pathogen for CO and HO infections. The number of patients with CO cultures ranged from 436 for the CR *Acinetobacter* to 37 0350 for MRSA. For the HO analysis, there were 408 patients with CR *Acinetobacter* cultures and 9887 patients with MRSA cultures. The average age in these groups ranged from 75.2 to 78.3 years. Most of the patients in each group were male (>90% for all pathogens) and the most common race was White (ranging from 37.8% to 75.8%).

Figure 1 shows the mean unadjusted costs in patients with and without positive CO and HO cultures by pathogen. Patients with CR *Acinetobacter* cultures both for CO ($47 866) and HO ($125 840) cultures had the highest mean costs. Carbapenem-resistant *Acinetobacter* also had the highest unadjusted mortality rates both for CO (24.3%) and HO (44.6%) cultures as seen in Figure 2.

After controlling for observable characteristics, the per-infection attributable costs were highest for CR *Acinetobacter* both for HO invasive infections ($54 494; 95% CI: $31 844–$77 145) and CO invasive infections ($16 952; 95% CI: $3209–$30 695) (see Table 3). For pathogen, attributable costs for noninvasive infections were lower than those for invasive infections. These estimates ranged from $1378 (95% CI: $1010–$1746) for MRSA to $13 676 (95% CI: $7773–$19 579) for CR *Acinetobacter* for CO infections and from $4892 (95% CI: $3334–$6449) for VRE to $25 651 (95% CI: $15 465–$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–$723.5 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

Table 1. Descriptive Statistics for Patient Characteristics by Pathogen (MRSA, VRE, and ESBL) and Onset

	MRSA				VRE				ESBL			
	No Infection		Infection		No Infection		Infection		No Infection		Infection	
Characteristics	Mean or No.	SD or %	Mean or No.	SD or %	Mean or No.	SD or %	Mean or No.	SD or %	Mean or No.	SD or %	Mean or No.	SD or %
Community-onset analysis												
Total	379 211	…	37 030	…	85 400	…	9557	…	112 200	…	12 810	…
Invasive	…	…	7211	19.47%	…	…	1020	10.67%	…	…	1792	13.99%
Age (mean), years	75.8	8.1	76.2	8.1	76.4	8.2	77.2	8.2	77.1	8.3	77.8	8.3
Insurance	53 034	14.0%	3373	9.1%	10 875	12.7%	504	5.3%	15 004	13.4%	1111	8.7%
Male	371 492	98.0%	36 505	98.6%	83 653	98.0%	9332	97.6%	109 954	98.0%	12 425	97.0%
Race/ethnicity												
White	283 654	74.8%	28 077	75.8%	63 981	74.9%	7006	73.3%	67 650	60.3%	7395	57.7%
Black	56 910	15.0%	5280	14.3%	13 276	15.5%	1587	16.6%	20 704	18.5%	2536	19.8%
Other	24 752	6.5%	2239	6.0%	4876	5.7%	542	5.7%	20 295	18.1%	2415	18.9%
Unknown/missing	13 895	3.7%	1434	3.9%	3267	3.8%	422	4.4%	3551	3.2%	464	3.6%
Married	176 475	46.5%	16 543	44.7%	39 698	46.5%	4 308	45.1%	53 444	47.6%	5848	45.7%
Surgery[a]	83 684	22.1%	9816	26.5%	17 720	20.7%	1 963	20.5%	19 362	17.3%	2206	17.2%
ICU direct admission	9049	2.4%	663	1.8%	2207	2.6%	110	1.2%	2569	2.3%	145	1.1%
Mechanical ventilation[a]	12 720	3.4%	2186	5.9%	3329	3.9%	533	5.6%	4452	4.0%	704	5.5%
Hemodialysis[a]	9491	2.5%	1261	3.4%	2286	2.7%	539	5.6%	2525	2.3%	270	2.1%
Comorbidity index (mean)	2.4	2.4	2.6	2.5	2.6	2.5	3.1	2.6	2.3	2.4	2.5	2.4
Outpatient cost (mean)[b]	$18 700	$21 321	$21 432	$25 062	$19 338	$20 921	$24 625	$29 670	$18 766	$21,349	$22 274	$25 101
Hospital-onset analysis												
Total	93 078	…	9887	…	60 247	…	6666	…	33 659	…	3742	…
Invasive	NA	…	1761	17.81%	NA	…	1383	20.75%	…	…	521	13.92%
Age (mean), years	76.0	7.9	76.4	7.7	75.9	7.9	75.9	7.6	76.7	8.0	77.0	7.8
Insurance	8509	9.1%	519	5.2%	5140	8.5%	330	5.0%	3069	9.1%	216	5.8%
Male	91 456	98.3%	9745	98.6%	59 249	98.3%	6520	97.8%	33 193	98.6%	3677	98.3%
Race/ethnicity												
White	64 932	69.8%	7205	72.9%	41 477	68.8%	4492	67.4%	18 149	53.9%	1997	53.4%
Black	17 087	18.4%	1562	15.8%	11 941	19.8%	1461	21.9%	6638	19.7%	767	20.5%
Other	7561	8.1%	727	7.4%	4403	7.3%	461	6.9%	7903	23.5%	860	23.0%
Unknown/missing	3498	3.8%	393	4.0%	2426	4.0%	252	3.8%	969	2.9%	118	3.2%
Married	41 363	44.4%	4348	44.0%	26 514	44.0%	3010	45.2%	15 039	44.7%	1763	47.1%
Surgery[a]	28 640	30.8%	3165	32.0%	19 379	32.2%	2193	32.9%	9750	29.0%	1193	31.9%
ICU direct admission	3605	3.9%	322	3.3%	2382	4.0%	175	2.6%	1462	4.3%	118	3.2%
Mechanical ventilation[a]	7751	8.3%	1,076	10.9%	5529	9.2%	664	10.0%	3467	10.3%	516	13.8%
Hemodialysis[a]	2678	2.9%	251	2.5%	1992	3.3%	316	4.7%	1001	3.0%	137	3.7%
Comorbidity index (mean)	2.6	2.4	2.7	2.5	2.6	2.5	2.8	2.5	2.4	2.4	2.6	2.5
Outpatient cost (mean)[b]	$18 457	$26 817	$19 179	$22 761	$19 008	$23 042	$20 723	$27 287	$18 236	$33,553	$19 919	$23 515

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

[a]Within first 2 days of admission.

[b]During 365 days prior to admission.

Table 2. Descriptive Statistics for Patient Characteristics by Pathogen (CRE, CR *Acinetobacter*, and MDR *Pseudomonas*) and Onset

	CRE				CR Acinetobacter				MDR Pseudomonas			
	No Infection		Infection		No Infection		Infection		No Infection		Infection	
Characteristics	Mean or No.	SD or %	Mean or No.	SD or %	Mean or No.	SD or %	Mean or No.	SD or %	Mean or No.	SD or %	Mean or No.	SD or %
Community-onset analysis												
Total	21 635	…	2536	…	4150	…	436	…	15 706	…	1656	…
Invasive	NA	…	292	11.51%	NA	…	54	12.39%	NA	…	111	6.70%
Age (mean), y	77.6	8.2	78.3	8.1	76.4	8.2	76.1	8.0	77.0	8.2	77.0	7.8
Insurance	2932	13.6%	192	7.6%	439	10.6%	19	4.4%	1812	11.5%	60	3.6%
Male	21 311	98.5%	2477	97.7%	4079	98.3%	431	98.9%	15 396	98.0%	1635	98.7%
Race/ethnicity												
White	10 146	46.9%	1160	45.7%	2649	63.8%	265	60.8%	10 531	67.1%	1093	66.0%
Black	2829	13.1%	394	15.5%	895	21.6%	113	25.9%	2497	15.9%	265	16.0%
Other	8054	37.2%	906	35.7%	479	11.5%	37	8.5%	2150	13.7%	218	13.2%
Unknown/missing	606	2.8%	76	3.0%	127	3.1%	21	4.8%	528	3.4%	80	4.8%
Married	10 619	49.1%	1240	48.9%	1889	45.5%	191	43.8%	7566	48.2%	773	46.7%
Surgery[a]	3704	17.1%	457	18.0%	769	18.5%	83	19.0%	2792	17.8%	301	18.2%
ICU direct admission	511	2.4%	34	1.3%	124	3.0%	17	3.9%	422	2.7%	41	2.5%
Mechanical ventilation[a]	1017	4.7%	202	8.0%	281	6.8%	75	17.2%	834	5.3%	191	11.5%
Hemodialysis[a]	556	2.6%	58	2.3%	121	2.9%	21	4.8%	375	2.4%	45	2.7%
Comorbidity index (mean)	2.3	2.4	2.4	2.4	2.5	2.4	2.4	2.3	2.4	2.4	2.6	2.4
Outpatient cost (mean)[b]	$17 832	$19 616	$19 550	$20 630	$19 072	$21 487	$19 706	$21 987	$18 186	$20 571	$20 110	$29 260
Hospital-onset analysis												
Total	11 844	…	1318	…	4288	…	408	…	13 630	…	1463	…
Invasive	NA	…	196	14.87%	NA	…	75	18.38%	NA	…	135	9.23%
Age (mean), y	77.5	7.9	77.4	7.7	76.4	7.9	75.2	7.3	76.7	7.9	76.5	7.7
Insurance	1034	8.7%	72	5.5%	357	8.3%	15	3.7%	979	7.2%	45	3.1%
Male	11 718	98.9%	1304	98.9%	4223	98.5%	404	99.0%	13 439	98.6%	1448	99.0%
Race/ethnicity												
White	4438	37.5%	485	36.8%	2269	52.9%	211	51.7%	7751	56.9%	810	55.4%
Black	1773	15.0%	205	15.6%	923	21.5%	100	24.5%	2556	18.8%	316	21.6%
Other	5373	45.4%	588	44.6%	941	21.9%	86	21.1%	2,921	21.4%	295	20.2%
Unknown/missing	260	2.2%	40	3.0%	155	3.6%	11	2.7%	402	2.9%	42	2.9%
Married	5585	47.2%	651	49.4%	1875	43.7%	189	46.3%	6126	44.9%	717	49.0%
Surgery[a]	3031	25.6%	395	30.0%	1276	29.8%	116	28.4%	4068	29.8%	462	31.6%
ICU direct admission	579	4.9%	54	4.1%	239	5.6%	26	6.4%	700	5.1%	93	6.4%
Mechanical ventilation[a]	1428	12.1%	224	17.0%	621	14.5%	104	25.5%	1860	13.6%	321	21.9%
Hemodialysis[a]	349	2.9%	41	3.1%	146	3.4%	25	6.1%	454	3.3%	55	3.8%
Comorbidity index (mean)	2.3	2.3	2.5	2.4	2.5	2.4	2.3	2.2	2.5	2.4	2.6	2.5
Outpatient cost (mean)[b]	$17 352	$22 131	$18 917	$23 176	$18 612	$23 297	$19 053	$26 651	$18 082	$20 677	$19 026	$23 200

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.

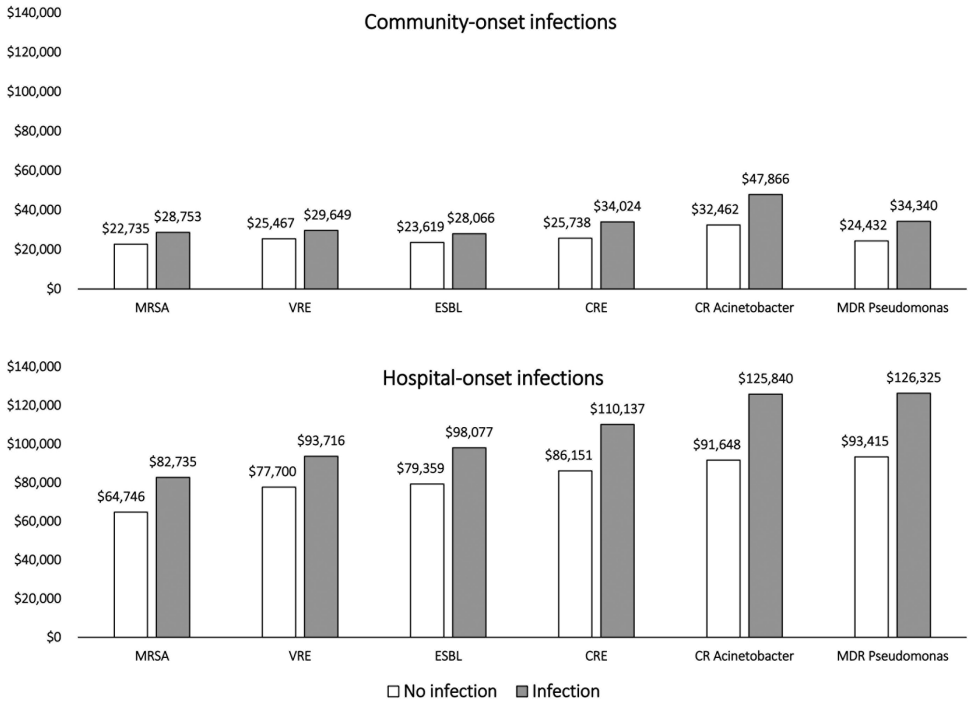

Figure 1. Unadjusted mean hospital costs per patient by pathogen type and onset. Abbreviations: CR, carbapenem-resistant; CRE, carbapenem-resistant *Enterobacteriaceae*; ESBL, extended-spectrum β-lactamase; MDR, multidrug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant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

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

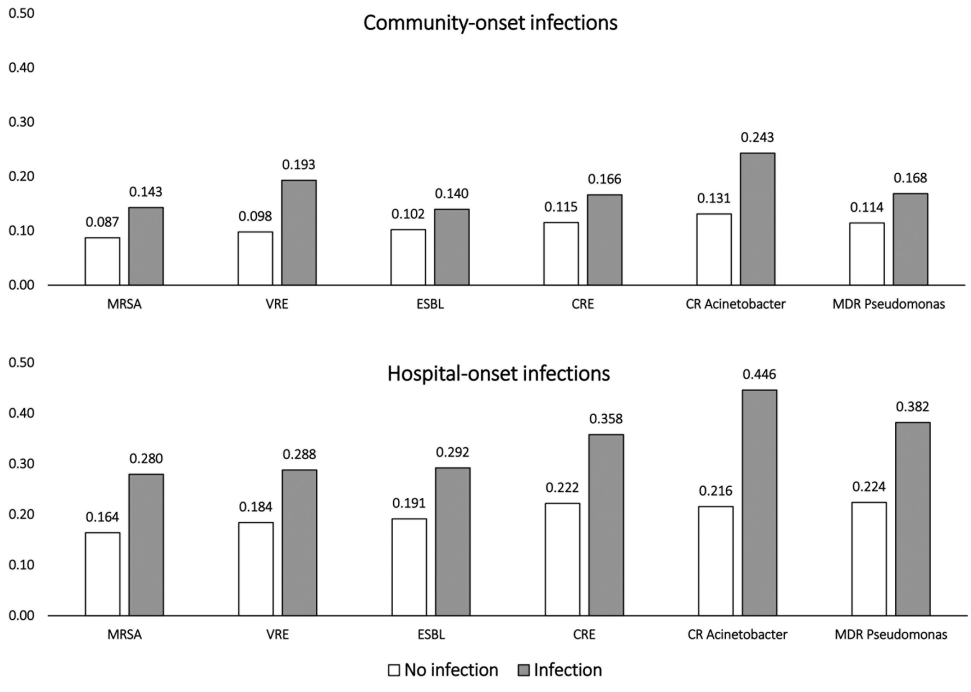

Figure 2. Unadjusted 30-day probability of mortality by pathogen type and onset. Abbreviations: CR, carbapenem-resistant; CRE, carbapenem-resistant *Enterobacteriaceae*; ESBL, extended-spectrum β-lactamase; MDR, multidrug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus*.

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

	Invasive			Noninvasive		
		95% CI			95% CI	
Pathogen	Estimate	LL	UL	Estimate	LL	UL
Community-onset infections						
MRSA	$15 994	$15 018	$16 971	$1378	$1010	$1746
VRE	$14 399	$11 785	$17 014	$3744	$2984	$4505
ESBL	$9949	$8468	$11 430	$2636	$1999	$3273
CRE	$12 357	$8056	$16 658	$5786	$4134	$7438
CR *Acinetobacter*	$16 952	$3209	$30 695	$13 676	$7773	$19 579
MDR *Pseudomonas*	$12 657	$6013	$19 300	$5826	$3969	$7683
Hospital-onset infections						
MRSA	$23 301	$20 092	$26 511	$11 504	$10 177	$12 831
VRE	$29 775	$25 464	$34 085	$4892	$3334	$6449
ESBL	$36 077	$28 229	$43 924	$13 772	$11 511	$16 032
CRE	$45 668	$31 725	$59 610	$13 041	$9034	$17 048
CR *Acinetobacter*	$54 494	$31 844	$77 145	$25 651	$15 465	$35 838
MDR *Pseudomonas*	$31 468	$16 675	$46 261	$18 398	$14 032	$22 763

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*.

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

	Invasive			Noninvasive		
		95% CI			95% CI	
Pathogen	Estimate	LL	UL	Estimate	LL	UL
Community-onset infections						
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
Hospital-onset infections						
MRSA	3.03	2.76	3.28	1.67	1.56	1.77
VRE	3.39	3.06	3.73	1.37	1.24	1.50
ESBL	3.88	3.23	4.57	2.37	2.16	2.57
CRE	4.43	3.15	5.67	2.35	1.98	2.71
CR *Acinetobacter*	3.90	2.03	5.98	4.11	3.32	4.89
MDR *Pseudomonas*	2.33	1.05	3.53	2.87	2.53	3.26

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

	Invasive			Non-Invasive		
		95% CI			95% CI	
Pathogen	Estimate	LL	UL	Estimate	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

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

	Cases[a]			Cost[b] (million $)			Length of stay (days)			Deaths		
		95% CI			95% CI			95% CI			95% CI	
Pathogen	Estimate	LL	UL	Estimate	LL	UL	Estimate	LL	UL	Estimate	LL	UL
Invasive 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	$1.2	$13.0	1917	1,102	2733	61	26	97
CR *Acinetobacter*	211	167	255	$3.6	−$1.2	$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
Noninvasive infections												
MRSA	93 180	82 889	103 470	$128.4	$85.2	$171.6	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	6766	3400	10 132	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												
Total	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*.

[a]From Jernigan et al [25].

[b]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

	Cases[a]			Cost[b] (million $)			Length of stay (inpatient days)			Deaths		
		95% CI			95% CI			95% CI			95% CI	
Pathogen	Estimate	LL	UL	Estimate	LL	UL	Estimate	LL	UL	Estimate	LL	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	$105.5	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	13831	17 265	$178.9	$140.1	$217.6	25 928	22 619	29 237	320	246	394
VRE	9427	8198	10 657	$46.1	$25.4	$66.8	12 895	10 792	14 997	598	480	716
ESBL	14 192	12505	15 879	$195.4	$147.3	$243.6	33 593	28 669	38 518	293	191	394
CRE	1757	1493	2021	$22.9	$10.7	$35.1	4123	3231	5015	44	12	76
CR *Acinetobacter*	1066	843	1289	$27.3	$11.4	$43.3	4386	3151	5622	72	25	119
MDR *Pseudomonas*	4512	3884	5139	$83.0	$49.1	$117.0	12 934	10 504	15 365	152	67	238
Total	46 502	40754	52 250	$553.7	$383.9	$723.5	93 859	78 965	108 753	1480	1022	1938
Overall												
Total	54 217	47 543	60 892	$781.2	$528.4	$1034.0	119 898	100 133	139 664	2288	1613	2963

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*.

[a]From Jernigan et al [25].

[b]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 infections, 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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