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SUPPLEMENT ARTICLE

National Estimates of Healthcare Costs Associated With Multidrug-Resistant Bacterial Infections Among Hospitalized Patients in the United States

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Background. Treating patients with infections due to multidrug-resistant pathogens often requires substantial healthcare resources. The purpose of this study was to report estimates of the healthcare costs associated with infections due to multidrug-resistant bacteria in the United States (US).

Methods. We performed retrospective cohort studies of patients admitted for inpatient stays in the Department of Veterans Affairs healthcare system between January 2007 and October 2015. We performed multivariable generalized linear models to estimate the attributable cost by comparing outcomes in patients with and without positive cultures for multidrug-resistant bacteria. Finally, we multiplied these pathogen-specific, per-infection attributable cost estimates by national counts of infections due to each pathogen from patients hospitalized in a cohort of 722 US hospitals from 2017 to generate estimates of the population-level healthcare costs in the US attributable to these infections.

Results. Our analysis cohort consisted of 16 676 patients with community-onset infections and 172 712 matched controls and 8246 patients with hospital-onset infections and 66 939 matched controls. The highest cost was seen in hospital-onset invasive infections, with attributable costs (95% confidence intervals) ranging from $30 998 ($25 272–$36 724) for methicillin-resistant *Staphylococcus aureus* to $74 306 ($20 377–$128 235) for carbapenem-resistant (CR) *Acinetobacter*. The highest attributable costs for community-onset invasive infections were seen in CR *Acinetobacter* ($62 396; $20 370–$104 422). Treatment of these infections cost an estimated $4.6 billion ($4.1 billion–$5.1 billion) in 2017 in the US for community- and hospital-onset infections combined.

Conclusions. We found that antimicrobial-resistant infections led to substantial healthcare costs.

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

Antibiotic-resistant infections are a major public health concern in the United States and around the world. Recent data show substantial increases in the use of vancomycin and broad-spectrum antibiotics such as carbapenems, third- and fourth-generation cephalosporins, and β-lactam/β-lactamase inhibitor combination antibiotics [1]. These data, combined with evidence that 30% of antibiotic prescriptions may be inappropriate [2], suggest that antibiotic-resistant bacteria will continue to be a substantial threat in the near future. The US Centers for Disease Control and Prevention (CDC) recently released a report highlighting the burden and trends of important antibiotic-resistant pathogens, including several that are commonly associated with healthcare [3, 4].

The importance of these antibiotic-resistant pathogens, both domestically and internationally, has been illustrated by the establishment of the Presidential Advisory Council on Combating Antibiotic-Resistant Bacteria in the US Department of Health and Human Services [5] as well as in recent actions plans including the US National Action Plan for Combating Antibiotic-Resistant Bacteria [6] and others published by the UK Ministry of Health [7, 8], the Organization for Economic Co-operation and Development [9, 10], the World Bank [11], and the World Health Organization (WHO) [12]. The WHO report emphasized that countries should assess "investment needs for implementation of their national action plans on antimicrobial resistance, and should develop plans to secure and apply the required financing." To better understand the magnitude of the investments needed by hospitals to fund activities to prevent antibiotic resistance, comprehensive measures of the healthcare costs associated with antibiotic-resistant infections, and the economic benefits stemming from prevention, are necessary. These healthcare costs—which are monetary measures of the personnel, equipment, and space necessary to care for

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these patients—represent valuable resources that could be used for a number of other meaningful purposes if these infections could be prevented.

There are a number of data- and analysis-related obstacles to estimating the healthcare costs that are attributable to antibiotic-resistant infections. Robust estimates of the costs of these infections require detailed datasets that include microbiology and susceptibility information, in addition to clinical, demographic, and cost data. Because these events are still relatively rare these studies also require large databases of information. This combination of data elements is not easily accessible in administrative datasets that are commonly used to estimate healthcare costs. In addition, it can be challenging to accurately estimate costs attributable to specific events, such as an antibiotic-resistant infection, because the care of hospitalized patients, many of whom have multiple comorbid conditions, is complex and multifaceted. Finally, many attempts to identify the cost of drug-resistant infections have been subject to confounding and time-dependent bias, leading to inaccurate estimates.

We designed this study to overcome those barriers and to generate estimates of the attributable cost due to antibiotic-resistant infections for CDC's updated national estimates for antibiotic-resistant pathogens associated with healthcare use. Using combined datasets from the Department of Veterans Affairs (VA) that include both detailed microbiology data and healthcare costs, we were able to classify infections by pathogen and resistance profile, by body site, and by timing during an inpatient admission. These methods allowed for the most detailed estimates to date of the cost consequences of antibiotic-resistant infections. We then multiplied these pathogen-specific attributable cost estimates by previously published national case counts to generate estimates of the total healthcare costs attributable to these infections. The findings in this report serve as the basis for updated cost estimates found in the CDC's *Antibiotic Resistance Threats in the United States, 2019* [3].

METHODS

Settings

As the largest integrated healthcare system in the United States, the VA provides care for a unique patient population: individuals who served in active duty in one of the armed forces. Of the roughly 22 million veterans in the United States, nearly 9 million are enrolled in the VA [13] and approximately 6 million veterans per year [14] receive care in 1 of 170 VA medical centers or more than 1000 outpatient clinics in the United States [15]. The VA electronic medical record (EMR) was one of the first such systems in the United States [16].

Study Design and Population

We used a retrospective cohort design for our attributable cost analysis. We included patients with VA inpatient admissions between January 2007 and October 2015. Patients could have been hospitalized multiple times during the time frame of our study, but we included only patients' first hospitalization for any reason in this analysis. To isolate incident infections, we excluded patients with positive cultures during the 365-day period prior to the day before admission. In addition, we excluded patients without evidence of receiving care in the VA system for at least 365 days prior to their hospital admission.

Data

The VA EMR contains the results from microbiology tests as free text. To convert this unstructured information into a structured format that would allow it to be used in a statistical analysis, our team developed a natural language processing (NLP) tool to extract information regarding organism, antibiotic susceptibility, and specimen location [17]. Healthcare costs were assessed using data from the VA Health Economics Resource Center (HERC) Average Cost data [18]. In this dataset, which has been used in a number of published studies [19, 20], an average cost is assigned to each patient encounter with the same characteristics. This average cost is computed by performing a cost regression using Medicare data for veterans [21]. The dependent variable in this regression is cost-adjusted charges and the independent variables are length of stay, diagnosis-related group weight, whether the patient died in the hospital, age, gender, intensive care unit (ICU) stay, and number of diagnoses. The estimated coefficients from this cost model are then applied to VA data to generate a predicted cost for each encounter. The VA Corporate Data Warehouse was the source for patient demographic data. Finally, International Classification of Diseases, 9th revision (ICD-9), codes were obtained from VA Medical SAS datasets.

Outcome

Our study outcome was healthcare cost for the index inpatient admission. Our attributable cost estimates represent the excess direct medical costs of a positive clinical culture from the perspective of the healthcare provider but do not include any other downstream healthcare costs that may take place after the index hospitalization. In addition, these estimates do not include any economic impacts to the patient from lost work time, patient co-pays, diminished productivity, pain or suffering, mortality, or any long-term morbidities resulting from the infection. Cost values were converted to 2017 US dollars using the Personal Consumption Expenditures–Health price index [22].

Independent Variables

The key independent variable in our analyses was a positive clinical culture for 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 *Acinetobacter* species (CRAsp), carbapenem-resistant *Enterobacteriaceae* (CRE), or multidrug-resistant (MDR) *Pseudomonas aeruginosa*. We used the same definitions for cases used by the CDC to estimate national burden of antibiotic-resistant healthcare pathogens [3, 4]. Costs were estimated for each pathogen individually, stratified by onset (hospital vs community) and body site (invasive vs noninvasive). We classified positive cultures obtained on the day before admission or during the first 3 days of an inpatient stay as community onset. Positive cultures obtained between day 4 and the discharge date were considered hospital onset. Positive cultures obtained from a body site that is typically sterile (blood, bone, bone marrow, cerebrospinal fluid, pleural fluid, synovial fluid, and lymph node) were categorized as invasive infections while all other cultures (eg, urine, sputum, wounds) were considered noninvasive. Cultures likely collected for surveillance purposes (ie, cultures labeled as rectal, perirectal, or nasal) were excluded.

Other independent variables in our analyses included demographic characteristics (age, race, marital status, insurance status, gender); body mass index; outpatient costs in the 365 days prior to admission; indicators for surgery, mechanical ventilation, and hemodialysis during the first 48 hours of the inpatient stay; direct admission to a medical or surgical ICU; and comorbidities as measured using a risk index that combines the Charlson and Elixhauser indices [23].

Statistical Analyses

We matched each patient with a positive culture with up to 10 control patients, admitted to the same inpatient facility and with the same admitting diagnosis, who had not had a positive culture up until that point in their hospitalization using an exposure density sampling approach [24]. We performed this matching exercise separately for positive cultures occurring on the day prior to admission up to 40 days after admission of an inpatient hospitalization, and therefore excluded any cases with a culture after 40 days. For example, we matched up to 10 controls who did not have a positive culture on or before day 3 to each of the patients who had a positive culture on day 3. The patients with a positive culture and their matched controls were then pooled for the multivariable generalized linear models (GLMs) with a γ distribution and log link [25] to estimate the attributable cost of an infection. We use the term "attributable" to indicate that efforts have been taken to reduce the effects of confounding so that these costs are those that are, in fact, incurred because of the infection. This attributable cost estimate is defined as the marginal effect [26–28] or mean difference in inpatient costs between patients with a positive culture and their matched controls, adjusting for the measured confounders listed above [29]. The γ distribution for our GLM regressions was chosen based on results from the modified Park test [30, 31]. Standard errors in our regression models accounted for repeated measures at the individual and facility level using commonly employed extension [32–34] of the Huber and White sandwich estimate of variance [35, 36].

Finally, we generated pathogen-specific estimates of the aggregate cost-resistant infections at the US population level by multiplying our pathogen-specific, per-infection estimates of the attributable cost of resistant infections by the annual number of cases of these infections in a cohort of 722 US hospitals from 2017 published previously [4]. These pathogen-specific, population-level estimates were then summed to produce an estimate of the total, population-level estimate of healthcare costs in the United States attributable to these infections. CRE and ESBL organisms and phenotypes were not mutually exclusive, such that the same isolate could be potentially considered a case for both phenotypes. If a specimen was determined to be a case for both CRE and ESBL, we only counted that specimen once as CRE. Because of this nuance, the total estimated attributable costs reported do not exactly match the simple sum of attributable costs by pathogen. To calculate confidence intervals (CIs) for the total attributable costs by pathogen, we combined uncertainty from the estimated number of cases and the estimated attributable costs as detailed in Supplementary Appendix A. Confidence intervals for total costs were calculated using the de-duplicated numbers and a combined standard error estimate.

RESULTS

Characteristics for both patients with a positive culture and matched controls are provided in Tables 1 and 2 for each pathogen for community-onset and hospital-onset infections. The number of patients with community-onset cultures ranged from 101 for the CRAsp to 13 523 for MRSA. For the hospital-onset analysis, there were 1025 patients with ESBL cultures and 3889 patients with MRSA cultures. The average age in these groups ranged from 61.4 to 71.8 years. Most of the patients in each group were male (ranging from 91.3% to 99.4%), and the most frequent races were white (58.4% to 72.6%) and Black (16.8% to 29.7%).

Figure 1 shows the mean unadjusted costs in patients with and without positive cultures stratified by location of onset, timing of culture, and pathogen. The highest costs were seen in patients with CRAsp cultures for community onset ($104 264) and MDR *Pseudomonas* cultures for hospital onset ($208 836).

After controlling for observable characteristics in multivariable regressions, attributable costs were highest for invasive CRAsp after controlling for observable characteristics in multivariable regressions, with estimates of $74 306 (95% CI, $20 377–$128 235) for hospital-onset cultures and $62 396

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	138 329		13 523		10 406		986		16 133		1550	
Invasive	NA		1822	13.5%	NA		121	12.3%	NA		258	16.6%
Age, years	62.63	14.19	61.35	15.33	65.21	14.56	70.65	13.43	64.18	15.04	70.77	14.06
Insurance	36 374	26.3%	2828	20.9%	2495	24.0%	123	12.5%	4107	25.5%	289	18.6%
Male	130 829	94.6%	12 965	95.9%	9803	94.2%	949	96.2%	14 734	91.3%	1456	93.9%
Race/ethnicity												
White	99 707	72.1%	9594	70.9%	7474	71.8%	692	70.2%	11 046	68.5%	1059	68.3%
Black	26 674	19.3%	2583	19.1%	2025	19.5%	181	18.4%	3629	22.5%	326	21.0%
Other	2775	2.0%	305	2.3%	199	1.9%	10	1.0%	409	2.5%	32	2.1%
Unknown/missing	9173	6.6%	1041	7.7%	708	6.8%	103	10.4%	1049	6.5%	133	8.6%
Married	59 123	42.7%	5049	37.3%	4318	41.5%	439	44.5%	7070	43.8%	743	47.9%
Surgery[a]	31 409	22.7%	3837	28.4%	2249	21.6%	220	22.3%	3060	19.0%	283	18.3%
ICU direct admission	10 955	7.9%	1130	8.4%	1110	10.7%	150	15.2%	1515	9.4%	206	13.3%
Mechanical ventilation[a]	3355	2.4%	603	4.5%	401	3.9%	67	6.8%	476	3.0%	96	6.2%
Hemodialysis[a]	982	.7%	134	1.0%	125	1.2%	36	3.7%	189	1.2%	27	1.7%
Comorbidity index	.88	1.64	.91	1.66	1.17	1.77	1.50	1.95	1.05	1.75	1.27	1.83
Outpatient cost[b]	$8518	$10 779	$8299	$11 ,487	$9548	$13 045	$8605	$11 440	$9735	$12 663	$12 185	$97 388
Hospital-onset analysis												
Total	33 571		3889		16 615		2281		8422		1025	
Invasive	NA		695	17.9%	NA		564	24.7%	NA		174	17.0%
Age, years	67.50	13.54	67.96	13.36	67.88	13.29	68.63	12.62	68.99	13.96	70.36	13.25
Insurance	6098	18.2%	503	12.9%	2681	16.1%	250	11.0%	1452	17.2%	137	13.4%
Male	32 475	96.7%	3782	97.2%	16 051	96.6%	2200	96.4%	8200	97.4%	996	97.2%
Race/ethnicity												
White	23 445	69.8%	2749	70.7%	11 469	69.0%	1510	66.2%	5826	69.2%	706	68.9%
Black	6788	20.2%	711	18.3%	3422	20.6%	514	22.5%	1861	22.1%	223	21.8%
Other	638	1.9%	68	1.7%	313	1.9%	47	2.1%	148	1.8%	21	2.0%
Unknown/missing	2700	8.0%	361	9.3%	1411	8.5%	210	9.2%	587	7.0%	75	7.3%
Married	13 421	40.0%	1543	39.7%	6648	40.0%	913	40.0%	3544	42.1%	478	46.6%
Surgery[a]	10 222	30.4%	1343	34.5%	5290	31.8%	713	31.3%	2475	29.4%	361	35.2%
ICU direct admission	4892	14.6%	605	15.6%	2452	14.8%	340	14.9%	1320	15.7%	170	16.6%
Mechanical ventilation[a]	2846	8.5%	514	13.2%	1541	9.3%	242	10.6%	899	10.7%	179	17.5%
Hemodialysis[a]	424	1.3%	64	1.6%	277	1.7%	59	2.6%	129	1.5%	28	2.7%
Comorbidity index	1.30	1.81	1.36	1.80	1.38	1.86	1.43	1.90	1.30	1.87	1.41	1.84
Outpatient cost[b]	$9146	$11 824	$8936	$12 189	$9590	$13 050	$9656	$14 313	$8834	$11 113	$9250	$13 071

Abbreviations: CR, carbapenem-resistant; CRE, carbapenem-resistant *Enterobacteriaceae*; ESBL, extended-spectrum β-lactamase; ICU, intensive care unit; MDR, multidrug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; NA, not applicable; VRE, vancomycin-resistant *Enterococci*.

[a]Within first 2 days of admission.
[b]During 365 days prior to admission.

(95% CI, $20 370–$104 422) for community-onset cultures (see Table 3). Adjusted attributable costs were lowest for noninvasive infections: community-onset costs were lowest for MRSA, a nonsignificant $596 (95% CI, –$162 to $1355), and among hospital-onset cultures, costs were lowest for VRE at $6835 ($3630–$10 039).

Table 4 shows aggregate cost estimates for the United States overall and by pathogen, location of onset, and body site for 2017. We estimate that infections due to these pathogens resulted in $4.6 billion (95% CI, $4.1–$5.1 billion) during this 1-year period. Aggregate community-onset positive cultures ($2.7 billion; 95% CI, $2.3–$3.2 billion) accounted for higher total cost than those with onset in the hospital ($1.9 billion; 95% CI, $1.7–$2.1 billion). Similarly, noninvasive infections ($2.8 billion; 95% CI, $2.4–$3.3 billion) accounted for higher total cost than invasive infections ($1.8 billion; 95% CI, $1.6–$2.0 billion). The pathogens with the highest aggregate costs were MRSA with $1.2 billion (95% CI, $0.9–$1.4 billion) for community-onset infections and $580.2 million (95% CI, $459.8–$700.5 million) for hospital-onset infections and ESBL with $752.4 million (95% CI, $431.9–$1073.0 million) for community-onset

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	2762		266		1075		101		4179		270	
Invasive	NA		25	9.4%	NA		10	9.9%	NA		14	5.2%
Age, years	65.18	14.90	71.32	13.49	64.72	14.82	67.59	15.47	65.45	14.62	69.97	14.06
Insurance	711	25.7%	33	12.4%	197	18.3%	11	10.9%	902	21.6%	20	7.4%
Male	2568	93.0%	255	95.9%	1017	94.6%	97	96.0%	3925	93.9%	264	97.8%
Race/ethnicity												
White	1956	70.8%	190	71.4%	706	65.7%	59	58.4%	2982	71.4%	186	68.9%
Black	573	20.7%	48	18.0%	279	26.0%	30	29.7%	825	19.7%	49	18.1%
Other	68	2.5%	5	1.9%	23	2.1%	3	3.0%	74	1.8%	2	.7%
Unknown/missing	165	6.0%	23	8.6%	67	6.2%	9	8.9%	298	7.1%	33	12.2%
Married	1184	42.9%	120	45.1%	435	40.5%	42	41.6%	1834	43.9%	116	43.0%
Surgery[a]	495	17.9%	54	20.3%	155	14.4%	16	15.8%	853	20.4%	41	15.2%
ICU direct admission	328	11.9%	50	18.8%	170	15.8%	30	29.7%	568	13.6%	59	21.9%
Mechanical ventilation[a]	129	4.7%	28	10.5%	87	8.1%	17	16.8%	296	7.1%	44	16.3%
Hemodialysis[a]	37	1.3%	4	1.5%	12	1.1%	4	4.0%	45	1.1%	5	1.9%
Comorbidity index	1.07	1.76	1.29	1.93	1.21	1.78	.97	1.38	1.22	1.81	1.33	1.69
Outpatient cost[b]	$9804	$12 608	$9005	$11 927	$9914	$12 844	$6763	$9907	$10 034	$11 961	$9201	$14 307
Hospital-onset analysis												
Total	2801		368		1371		157		4686		590	
Invasive	NA		66	17.9%	NA		10	21.0%	NA		60	10.1%
Age, years	71.81	13.03	71.66	13.13	67.80	14.18	67.84	11.88	68.81	14.05	68.81	14.05
Insurance	432	15.4%	45	12.2%	188	13.7%	12	7.6%	638	13.6%	43	7.3%
Male	2736	97.7%	361	98.1%	1330	97.0%	156	99.4%	4541	96.9%	580	98.3%
Race/ethnicity												
White	2038	72.8%	267	72.6%	876	63.9%	109	69.4%	3199	68.3%	402	68.1%
Black	510	18.2%	62	16.8%	368	26.8%	34	21.7%	1037	22.1%	131	22.2%
Other	30	1.1%	4	1.1%	27	2.0%	4	2.5%	77	1.6%	10	1.7%
Unknown/missing	223	8.0%	35	9.5%	100	7.3%	10	6.4%	373	8.0%	47	8.0%
Married	1268	45.3%	190	51.6%	563	41.1%	68	43.3%	2010	42.9%	283	48.0%
Surgery[a]	792	28.3%	142	38.6%	374	27.3%	49	31.2%	1410	30.1%	221	37.5%
ICU direct admission	497	17.7%	83	22.6%	282	20.6%	51	32.5%	896	19.1%	166	28.1%
Mechanical ventilation[a]	393	14.0%	93	25.3%	217	15.8%	43	27.4%	684	14.6%	175	29.7%
Hemodialysis[a]	37	1.3%	10	2.7%	30	2.2%	6	3.8%	107	2.3%	13	2.2%
Comorbidity index	1.33	1.90	1.49	1.82	1.35	1.87	1.32	1.75	1.33	1.82	1.38	1.81
Outpatient cost[b]	$8505	$11 177	$9009	$11 469	$9142	$13 011	$7744	$9492	$9272	$13 563	$9691	$17 362

Abbreviations: CR, carbapenem-resistant; CRE, carbapenem-resistant *Enterobacteriaceae*; ICU, intensive care unit; MDR, multidrug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; NA, not applicable.

[a]Within first 2 days of admission.

[b]During 365 days prior to admission.

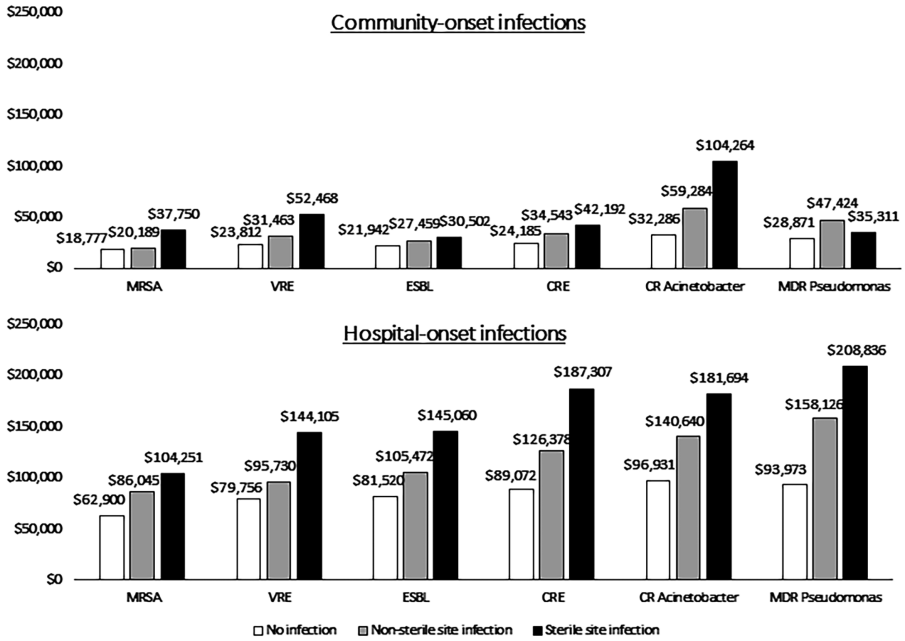

Figure 1. Unadjusted hospital costs by pathogen type and onset. Abbreviations: CR, carbapenem-resistant; CRE, carbapenem-resistant *Enterobacteriaceae*; ESBL, extended-spectrum β-lactamase; MDR, multidrug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus*.

infections and $470.5 million (95% CI, $339.8–$601.2 million) for hospital-onset infections.

DISCUSSION

In this study, we found that the national costs associated with these 6 MDR infections can be substantial at more than $4.6 billion annually. Our results provide important pathogen-specific estimates as well as national projections of total attributable cost. We demonstrate that, despite having lower costs per case, MRSA and ESBL contribute the most towards total aggregate costs nationally due to their high burden. Similarly, despite being less costly per infection than those with onset in the hospital, community-onset infections contribute a larger aggregate cost. 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.

The attributable cost of resistant infections can be used for economic evaluations of infection-control interventions. Comprehensive assessments of such interventions, which could include methods to improve hand hygiene adherence, improved

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

	Invasive			Noninvasive		
Pathogen	Estimate	95% CI		Estimate	95% CI	
Community onset						
MRSA	$19 749	$17 414	$22 084	$596	-$162	$1355
VRE	$17 490	$8475	$26 505	$7590	$4796	$10 384
ESBL	$7352	$3903	$10 802	$3914	$1880	$5948
CRE	$8354	–$1191	$17 899	$5154	$908	$9400
CR *Acinetobacter*	$62 396	$20 370	$104 422	$29 265	$11 412	$47 119
MDR *Pseudomonas*	$13 442	–$5257	$32 140	$11 882	$5987	$17 776
Hospital onset						
MRSA	$30 998	$25 272	$36 724	$9588	$7088	$12 087
VRE	$37 893	$31 598	$44 188	$6835	$3630	$10 039
ESBL	$33 637	$20 074	$47 200	$16 240	$11 316	$21 163
CRE	$54 614	$26 992	$82 236	$16 606	$8684	$24 529
CR *Acinetobacter*	$74 306	$20 377	$128 235	$30 590	$12 784	$48 396
MDR *Pseudomonas*	$66 934	$32 943	$100 925	$50 810	$41 062	$60 558

Abbreviations: CI, confidence interval; CR, carbapenem-resistant; CRE, carbapenem-resistant *Enterobacteriaceae*; ESBL, extended-spectrum β-lactamase; ICU, intensive care unit; MDR, multidrug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococci*.

Table 4. National Cost Estimates for Each Pathogen and Total by Onset and Body Site, 2017

	Noninvasive infections			Invasive infections			Total		
		95% CI			95% CI			95% CI	
Pathogen	Estimate	LL	UL	Estimate	LL	UL	Estimate	LL	UL
Community-onset infections									
MRSA	$134 165 455	−$37 161 014	$305 491 924	$1 030 341 036	$862 052 205	$1 198 629 866	$1 164 506 491	$924 352 604	$1 404 660 378
VRE	$237 673 373	$144 514 287	$330 832 459	$84 894 134	$39 141 145	$130 647 123	$322 567 507	$218 779 496	$426 355 519
ESBL	$579 751 789	$270 482 731	$889 020 848	$172 693 411	$88 429 174	$256 957 648	$752 445 200	$431 902 204	$1 072 988 196
CRE	$44 956 382	$7 274 134	$82 638 630	$7 335 517	−$1 201 579	$15 872 612	$52 291 899	$13 654 691	$90 929 107
CR *Acinetobacter*	$156 202 986	$55 491 942	$256 914 031	$26 531 116	$6 954 724	$46 107 507	$182 734 102	$80 138 051	$285 330 153
MDR *Pseudomonas*	$262 368 585	$127 536 196	$397 200 973	$12 676 242	−$5 239 046	$30 591 531	$275 044 827	$139 027 437	$411 062 218
Total[a]	$1 394 970 932	$998 801 468	$1 791 140 396	$1 330 918 156	$1 135 954 399	$1 525 881 913	$2 725 889 088	$2 284 345 080	$3 167 433 096
Hospital-onset infections									
MRSA	$384 804 977	$274 159 212	$495 450 743	$195 361 939	$147 947 537	$242 776 341	$580 166 917	$459 789 963	$700 543 870
VRE	$104 963 155	$53 422 467	$156 503 843	$111 123 083	$83 751 172	$138 494 994	$216 086 238	$157 728 171	$274 444 306
ESBL	$369 839 969	$247 004 412	$492 675 527	$100 659 813	$56 053 606	$145 266 019	$470 499 782	$339 815 859	$601 183 705
CRE	$49 543 634	$23 951 805	$75 135 463	$28 478 410	$11 932 855	$45 023 964	$78 022 044	$47 547 512	$108 496 575
CR *Acinetobacter*	$75 114 131	$27 462 565	$122 765 696	$23 246 114	$3 407 678	$43 084 551	$98 360 245	$46 744 014	$149 976 475
MDR *Pseudomonas*	$463 520 602	$334 427 913	$592 613 291	$28 804 890	$12 158 298	$45 451 483	$492 325 492	$362 163 933	$622 487 051
Total[a]	$1 423 777 299	$1 205 404 257	$1 642 150 340	$478 675 262	$403 712 822	$553 637 702	$1 902 452 561	$1 671 571 308	$2 133 333 813
Overall									
Total	$2 818 748 231	$2 366 379 985	$3 271 116 476	$1 809 593 418	$1 600 714 903	$2 018 471 933	$4 628 341 649	$4 130 077 398	$5 126 605 899

The burden of each pathogen was based on estimates from the Centers for Disease Control and Prevention's *Antibiotic Resistance Threats in the United States, 2019*. Abbreviations: CI, confidence interval; CR, carbapenem-resistant; CRE, carbapenem-resistant *Enterobacteriaceae*; ESBL, extended-spectrum β-lactamase; ICU, intensive care unit; LL, lower limit; MDR, multidrug-resistant; MRSA, methicillin-resistant *Staphylococcus aureus*; UL, upper limit; VRE, vancomycin-resistant *Enterococci*.

[a]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.

surveillance and patient isolation techniques, or antimicrobial stewardship programs, should include both the costs of the resources required to undertake the interventions and the benefits of prevented mortality and morbidity through infection reduction [37].

These results build upon previously published studies. Most similar is an earlier study by our group that used VA data to estimate the attributable cost of hospital-acquired infections due to MRSA [38], MDR *Acinetobacter*, MDR *Pseudomonas*, and MDR *Enterobacteriaceae* [39]. The current study includes additional pathogens (VRE, ESBL, CRE) and patients with community-onset cultures. In addition, by utilizing similar methodology to facilitate the combination of the attributable cost per case estimates with published estimates of the number of cases per year, we generated estimates of the total costs associated with these pathogens. To remain consistent with the CDC's *Antibiotic Resistance Threats in the United States, 2019* [3], this study analyzes only patients who had been admitted to an acute-care facility and extrapolates our findings to estimate national costs among hospitalized patients. Previous VA estimates included patients in both long-term care facilities and acute-care facilities.

Our event-level cost results are similar to those published elsewhere. For example, using data from a single center, Roberts et al [40] estimated the attributable cost of community- and hospital-onset infections combined due to MRSA, VRE, and a combined cost measure for infections with amikacin- or imipenem-resistant *Enterobacter*, *Pseudomonas*, or *Acinetobacter* species to be $21 000, $39 000, and $56 500, respectively, in 2017 US dollars. A separate analysis using the VA Managerial Cost Accounting (MCA) system estimated the attributable cost of hospital-onset MRSA infections to be $28 038 (2017 US dollars), which is very comparable to our estimate of $30 998 [38]. Finally, another recent study from our group found the attributable cost of hospital-onset, invasive MDR *Acinetobacter*, *Pseudomonas*, and *Enterobacteriaceae* infections to be considerably lower than the estimate in our current study, likely because of a less-restrictive resistance phenotype (ie, *Acinetobacter*, *Pseudomonas*, and *Enterobacteriaceae* resistant to any 3 or more antibiotic drug classes) compared only with *Acinetobacter* and *Enterobacteriaceae* with carbapenem resistance, which are likely more serious and costly infections.

Our study results should be considered in light of the following limitations. First, the exposure variable in our statistical analyses was a positive clinical culture for one of several MDR organisms. From our administrative data, it was not possible to definitively say whether these cultures were true infections. In addition, while our NLP algorithm to identify these positive clinical cultures in electronic data has been shown to identify MRSA accurately 99.7% of the time [17], it may be less accurate for other organisms, leading to misclassification. Second, as has been demonstrated in previous studies, estimates of the attributable cost of hospital-onset infections are subject to time-dependent bias due to the time-varying nature of the infection-exposure variable. We have previously developed an approach to minimize time-dependent bias using the VA MCA data with which it is possible to separate the inpatient cost that the patient incurred prior to the infection from that incurred after the infection [38, 39]. While that approach was not possible in the VA HERC average cost data that we used for the current study, we did take steps to substantially reduce this bias. We did this by matching infected patients to uninfected patients based on the time in the hospital leading up to the infection. Third, our analyses used data from large administrative datasets that were not designed for research but for providing care to patients in these healthcare systems. In addition, the VA Health System is quite different than other health systems in the United States. For example, patients in the VA hospitals tend to be older and male compared with all hospitals in the United States. In addition, VA healthcare is financed through federal appropriations rather than third-party payers [41]. This means that these results may not be generalizable to other settings to the extent that differences exist between patients and healthcare delivery systems. Our community-onset estimates also do not distinguish between community-associated cases and those cases with onset in the community but with previous outpatient healthcare exposures. If the relative proportions of these types of cases vary by hospital, the attributable costs for community-onset estimates may not be generalizable to other hospitals. In addition, while we controlled for a number of observable characteristics that would increase the risk of both an antibiotic-resistant pathogen and increased healthcare costs—including comorbidity index, surgery, ICU admissions, and the cost of previous healthcare encounters—it is possible that residual confounding remains. Fourth, for community-onset infections, we matched cases to other hospitalized patients for controls. However, if the pathogen of interest was the only reason for the admission, one could assume the entire cost of the hospitalization was due to the pathogen of interest. In these instances, our strategy of matching all patients with positive cultures identified in an inpatient setting with control patients also admitted to an acute-care hospital without a positive culture may have led us to underestimating the attributable cost. Most of these limitations would lead to more conservative estimates of costs associated with the 6 MDR pathogens. Fifth, our decision to only examine healthcare costs during a patient's first hospitalization during the study time period may have biased our effect estimates in several important ways. For example, this decision likely resulted in a younger population of patients than if we had included subsequent admissions. In addition, as past healthcare costs are highly predictive of future healthcare costs [42–44], the healthcare costs included in these subsequent admissions are likely higher than in the initial admissions. Therefore, as with previous limitations, the effect of

this restriction is to bias the results down, leading to more conservative attributable cost estimates. Finally, our cost estimates likely underestimate total costs since studies have shown that hospital-onset infections can lead to increased costs even after discharge [45, 46]. Our cost estimates were taken only from the predischarge time period and ignore postdischarge and societal costs.

Despite the limitations outlined above, this study had a number of strengths. First, with nearly 25 000 infections, this is one of the largest studies to estimate the attributable cost associated with 6 high-priority antibiotic-resistant pathogens. Second, including a matched cohort allowed us to adjust for several covariates and reduce the influence of time-dependent bias. Third, we included a larger scope than most studies and assessed both community-onset and hospital-onset infections using comparable definitions to other efforts to estimate national burden, allowing for estimation of national costs.

In conclusion, we found a substantial cost attributable to infections caused by 6 antibiotic-resistant pathogens among hospitalized patients that were extrapolated to annual national costs exceeding $4.6 billion. These estimates underscore the importance of efforts to reduce transmission of antibiotic-resistant pathogens in hospitals. Future studies could seek to identify patient- and facility-level factors that contribute to increases or decreases in these per-infection costs, providing valuable information for clinicians and policymakers alike in tailoring infection-prevention efforts.

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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