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National prevalence estimates for resistant Enterobacteriaceae and *Acinetobacter* species in hospitalized patients in the United States

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ABSTRACT

Objectives: To determine antimicrobial nonsusceptibility rates for Enterobacteriaceae and *Acinetobacter* spp. in US hospitals.
Methods: We analyzed antimicrobial susceptibilities of non-duplicate Enterobacteriaceae and *Acinetobacter* spp. isolates reported in 2017 from 375 US hospitals in the BD Insights Research Database. Logistic and Poisson regression modeling methods were used to estimate proportions of resistant isolates and rates per 1000 hospital admissions. National projections were generated based on raking (weighting) methods.
Results: The nationwide proportions of resistant isolates in inpatients were an estimated 12.6%, 6.6%, and 1.2% for Enterobacteriaceae with extended-spectrum beta-lactamase (ESBL), multidrug resistant (MDR), and carbapenem-nonsusceptible (Carb-NS) phenotypes, respectively, and 42.4% and 34.5% for *Acinetobacter* spp. with MDR and Carb-NS phenotypes. Resistance varied by geographic region and hospital size/type. Estimated nationwide rates per 1000 hospital admissions ranged from a high of 7.1 for ESBL Enterobacteriaceae to a low of 0.3 for Carb-NS *Acinetobacter* spp. The estimated number of isolates occurring in US inpatients each year was 290,220 ESBL, 173,984 MDR, and 30,194 Carb-NS for Enterobacteriaceae and 12,274 MDR and 9,991 Carb-NS for *Acinetobacter* spp.
Conclusions: National prevalence estimates suggest high levels of antimicrobial resistance and a substantial number of patients with resistant Enterobacteriaceae and *Acinetobacter* spp. in US hospitals.

Introduction

In recognition of the importance of antibiotic-resistant pathogens to global health, the Centers for Disease Control and Prevention (CDC) (Anon, 2013) and the World Health Organization (WHO) (Anon, 2017; Tacconelli et al., 2018) have identified several pathogens that warrant national and international attention, including carbapenem-resistant Enterobacteriaceae (CRE), extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae, and multidrug-resistant (MDR) *Acinetobacter*. Because these pathogens are associated with high economic costs and poor outcomes, including increased mortality (Nelson et al., 2017; Bartsch et al., 2017; Tamma et al., 2017), their prevalence is an important concern.

Antimicrobial resistance rates in the hospital and community are driven by a number of factors, encompassing antibiotic use in humans, poultry, and livestock and the spread of pathogens in agriculture and by travel (Holmes et al., 2016; Hu et al., 2016). Although most resources are appropriately directed at infection control for hospital-acquired infections (HAIs), from a population standpoint these infections are only one part of the overall antimicrobial resistance milieu. Community infections caused by antimicrobial-resistant pathogens are a public health concern and may be more numerous and difficult to control compared with an inpatient outbreak (Enne, 2010). Recent studies have documented the treatment challenges posed by community antibiotic-resistant Enterobacteriaceae infections (Frazee et al., 2018; Thaden et al., 2016). Global estimates indicate that by 2030, more than half of *Escherichia coli* and

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Klebsiella pneumoniae pathogens will be resistant to third-generation cephalosporins (Alvarez-Uria et al., 2018).

Recent publications have noted the dearth of reliable information on the prevalence of antimicrobial-resistant pathogens at national and global levels (Anon, 2017; O'Neill, 2016; Temkin et al., 2018). Prevalence estimates are complicated by a lack of data on levels of resistance in different geographic regions as well as by inadequate reporting and surveillance data (Hay et al., 2018; Matsunaga and Hayakawa, 2018). Reliable data concerning the prevalence of resistant pathogens are critical for the accurate targeting and allocating of prevention and treatment resources at the community level, within hospitals, nationwide, and globally (O'Neill, 2016). These data also affect decisions on resources devoted to the development and utilization of new therapeutic and diagnostic advances. Incomplete knowledge of the prevalence of antimicrobial-resistant pathogens can hamper antimicrobial stewardship efforts and impact patient health.

In this study, we used microbiological laboratory data from a large US hospital database to determine the 2017 prevalence of antibiotic-resistant Enterobacteriaceae and *Acinetobacter* spp. in hospital inpatients. We evaluated resistance prevalence based on observed data and projected these figures to estimate the US national prevalence of resistant Enterobacteriaceae and *Acinetobacter* spp.

Table 1
Distribution of hospitals: Observed data vs CMS data.[a]

Hospital characteristic	Observed data		CMS data	
	n	%	n	%
Overall	375	100	4597	100
Bed size				
<100	95	25.3	2348	51.1
100–300	164	43.7	1375	29.9
>300	116	30.9	874	19.0
Urban/Rural				
Urban	290	77.3	2637	57.4
Rural	85	22.7	1960	42.6
Medical school affiliation				
No affiliation	241	64.3	3427	74.5
Limited	75	20.0	608	13.2
Major/Graduate	59	15.7	562	12.3
Geographic region (HHS regions)[b]				
Northeast (Regions 1–3)	55	14.7	762	16.6
Southeast (Region 4)	98	26.1	858	18.7
North central (Region 5)	93	24.8	847	18.4
South central (Region 6)	66	17.6	721	15.7
Midwest (Regions 7–8)	17	4.5	740	16.1
West (Regions 9–10)	46	12.3	669	14.6

CMS, Centers for Medicare & Medicaid Services; HHS, Health & Human Services.
[a] Data represent the year 2017 acute care and critical access hospitals, excluding children's and veteran's hospitals.
[b] Northeast: CT, ME, MA, NH, RI, VT, NJ, NY, DE, DC, MD, PA, VA, WV; Southeast: AL, FL, GA, KY, MS, NC, SC, TN; North central: IL, IN, MI, MN, OH, WI; South central: AK, LA, NM, OK, TX; Midwest: IA, KS, MO, NE, CO, MT, ND, SD, UT, WY; West: AZ, CA, HI, NV, AK, ID, OR, WA. US Territories were not included.

Methods

Data source and study design

This was a retrospective study of antimicrobial susceptibility of all specified non-duplicate (first isolate of a species in 30 days from the same source) Enterobacteriaceae and *Acinetobacter* spp. isolates collected from hospitalized patients in the US between January 1 and December 31, 2017. For the purposes of this study, isolates that were nonsusceptible to an antibiotic (susceptibility result of resistant or intermediate) were considered "resistant." Isolates from respiratory, blood, urine, skin/wound, intra-abdominal, and other culture sources were included. Microbiology results likely associated with surveillance cultures (eg, nasal or rectal swabs) and environmental cultures were excluded from this analysis using a previously described algorithmic methodology that includes type of organism, culture source, time of collection, and duplicate samples (Brossette et al., 2006).

Analyses of antimicrobial resistance were confined to hospital inpatients. Hospital inpatient status was determined by hospital admission records using available census, admission, discharge, and transfer files provided by each institution on a more than daily basis.

Reporting institutions consisted of US hospitals included in the BD Insights Research Database (Becton, Dickinson and Company, Franklin Lakes, NJ). The electronic surveillance system and clinical research database (formerly the CareFusion Clinical Research Database) have been previously described (Brossette et al., 2006; Ridgway et al., 2016; Tabak et al., 2013; McCann et al., 2018). This database provides good geographical representation across the US and includes both small and large hospitals in urban and rural areas (Table 1). Hospital demographic information was sourced from the Centers for Medicare & Medicaid Services (CMS) Provider of Services files (Anon, 2018). Only US acute care and critical access hospitals were included. Geographical distribution was based on US Department of Health & Human Services (HHS) regions.

This study evaluated antimicrobial susceptibility in five groups of Gram-negative bacteria using the following definitions:

1. ESBL Enterobacteriaceae: *E. coli*,*K. pneumoniae*, *Klebsiella oxytoca*, and *Proteus mirabilis* isolates confirmed as ESBL positive by commercial laboratory panels OR with intermediate susceptibility or resistance to ceftriaxone, cefotaxime, ceftazidime, or cefepime (Woodworth et al., 2018).
2. MDR Enterobacteriaceae: *E. coli, K. pneumoniae, K. oxytoca, P. mirabilis, Enterobacter aerogenes, Enterobacter cloacae, Serratia marcescens, Citrobacter freundi,* and *Morganella morganii* isolates with intermediate susceptibility or resistance to at least one drug in three of the five following classes: extended-spectrum cephalosporins, fluoroquinolones, aminoglycosides, carbapenems, and piperacillin or piperacillin/tazobactam (see Supplemental Table S1 for specific drugs) (Magiorakos et al., 2012; Weiner et al., 2016).
3. Carbapenem-nonsusceptible (Carb-NS) Enterobacteriaceae: *E. coli, K. pneumoniae, K. oxytoca, P. mirabilis, E. aerogenes, E. cloacae, S. marcescens, C. freundi,* and *M. morganii* isolates with intermediate susceptibility or resistance to imipenem (excluded for *P. mirabilis* and *M. morganii*), meropenem, doripenem, or ertapenem.
4. MDR *Acinetobacter* spp.: *Acinetobacter baumannii/Acinetobacter haemolyticus* (henceforth referred to as *Acinetobacter* spp.) isolates with intermediate susceptibility or resistance to at least one drug in three of the six following classes: extended-spectrum cephalosporins, fluoroquinolones, aminoglycosides, carbapenems, piperacillin or piperacillin/tazobactam, and ampicillin/sulbactam (Supplemental Table S1).
5. Carb-NS *Acinetobacter* spp.: *A. baumanii/A. haemolyticus* isolates with intermediate susceptibility or resistance to imipenem, doripenem, or meropenem.

Outcomes

The primary outcomes were the proportion of antimicrobial-resistant pathogens in our hospital database (number of resistant isolates divided by number of isolates tested) and the rate of resistance per 1000 hospital admissions.

Statistical analysis

Using the observed data, we estimated the percent of resistant pathogens for inpatients using logistic regression models and estimated the resistance rate per 1000 admissions using Poisson regression models (or negative binomial regression models for those data with over-dispersion).

Our large-scale database from 375 US hospitals with widespread distribution across geographic regions of the United States (Table 1) provided a good representative sample of the national hospital population. To better generalize our results to a national level, we raked (weighted) our observed facility-level data to a US national hospital level data based on data in the CMS Provider of Service database (Anon, 2018). The raking variable included hospital bed size (grouped in three categories: <100, 100–300, and >300), urban/rural status, medical school affiliation status (a three-category variable: no affiliation, limited, and major/graduate), and geographic region (a six-category variable: Northeast, Southeast, North Central, South Central, Midwest, and West). Geographic region categories were based on HHS regions (Table 1) and defined so that each category accounted for at least 5% of the total to facilitate raking procedures (see Table 1 legend for specific states included in each region).

The raking procedure created weights for each hospital in the observed dataset based on the specified characteristics. Post-raking analyses were conducted to estimate national prevalence using logistic regression analysis for proportion of resistant isolates and Poisson models for resistance rate per 1000 admissions. The estimated nationwide resistance counts were generated using a weighted means procedures with Jackknife method used for variance estimation. The raking procedures utilized here were the Statistical Analysis System (SAS) macros created by Izrael and colleagues (Izrael et al., 2004, 2009). All statistical analyses were conducted using SAS V9.4 (SAS Institute, Cary, NC).

Results

The tested non-duplicate isolates in the study data included 314,904 Enterobacteriaceae isolates and 3,966 *Acinetobacter* spp. isolates from 375 US hospitals with 4,885,097 admissions. The majority (77.3%) of the hospitals were in urban areas and most (64.3%) had no medical school affiliation. Geographically, the greatest numbers of hospitals were in southeast and north central states (Table 1). The distribution of Enterobacteriaceae and *Acinetobacter* spp. isolates generally followed the same pattern as the distribution of hospitals.

Proportion of resistant isolates in observed data

Of 274,515 nonduplicate Enterobacteriaceae isolates tested, 35,509 (12.9%; 95% confidence interval [CI], 12.8%–13.1%) had an ESBL phenotype in observed data (Supplemental Table S2, Table 2). The proportion of Enterobacteriaceae with an MDR phenotype was

Table 2
Proportion of resistant *Enterobacteriaceae* isolates in US inpatients in 2017: Observed data estimate and projected national prevalence.

Hospital characteristic	% ESBL				% MDR				% Carb-NS			
	Observed		National projection		Observed		National projection		Observed		National projection	
	Estimate (95% CI)	*p*	Estimate (95% CI)	*p*	Estimate (95% CI)	*p*	Estimate (95% CI)	*p*	Estimate (95% CI)	*p*	Estimate (95% CI)	*p*
All	12.9 (12.8–13.1)		12.6 (12.6– 12.7)		6.9 (6.8–7.0)		6.6 (6.6–6.7)		1.2 (1.2–1.2)		1.2 (1.1–1.2)	
Bed size		<0.001		<0.001		0.189		<0.001		0.205		0.013
<100	12.0 (11.5– 12.6)		11.6 (11.5– 11.7)		5.9 (5.5–6.2)		5.9 (5.8–6.0)		0.8 (0.7–1.0)		0.9 (0.9– 1.0)	
100–300	12.0 (11.7– 12.3)		11.9 (11.8– 12.0)		6.1 (5.9–6.4)		6.3 (6.2–6.3)		0.8 (0.8–0.9)		0.9 (0.8–0.9)	
>300	12.6 (12.2– 12.9)		12.2 (12.1– 12.3)		6.0 (5.8–6.2)		5.9 (5.9–6.0)		0.9 (0.8–1.0)		0.9 (0.9–0.9)	
Urban/Rural		0.003		<0.001		<0.001		<0.001		0.004		<0.001
Urban	12.6 (12.3– 12.9)		12.4 (12.3– 12.5)		6.3 (6.1–6.5)		6.3 (6.3–6.4)		1.0 (0.9–1.0)		1.0 (1.0–1.0)	
Rural	11.8 (11.4– 12.3)		11.4 (11.3– 11.5)		5.7 (5.4–6.0)		5.8 (5.7–5.8)		0.8 (0.7–0.9)		0.8 (0.8–0.8)	
Medical school affiliation		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001
No affiliation	10.7 (10.5– 11.0)		10.6 (10.6– 10.7)		5.5 (5.3–5.7)		5.6 (5.6–5.7)		0.7 (0.6–0.8)		0.7 (0.7–0.8)	
Limited	12.2 (11.9–12.6)		11.5 (11.3–11.6)		6.2 (5.9–6.5)		6.0 (5.9–6.1)		0.9 (0.8–1.0)		0.9 (0.9–0.9)	
Major/ Graduate	13.7 (13.3–14.2)		13.7 (13.6–13.8)		6.3 (6.0–6.5)		6.5 (6.5–6.6)		1.0 (0.9–1.1)		1.1 (1.1–1.1)	
Region		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001
Northeast	12.3 (11.9–12.7)		11.8 (11.7– 11.9)		5.9 (5.7–6.2)		5.7 (5.6–5.7)		1.6 (1.5–1.8)		1.6 (1.5–1.6)	
Southeast	12.9 (12.6–13.2)		12.8 (12.7–12.9)		6.6 (6.3–6.8)		6.8 (6.7–6.8)		1.2 (1.1–1.3)		1.3 (1.3–1.4)	
North central	9.8 (9.5–10.1)		9.5 (9.4–9.6)		5.9 (5.7–6.1)		5.8 (5.7–5.8)		1.1 (1.0–1.2)		1.0 (1.0–1.0)	
South central	13.5 (13.1–13.9)		13.3 (13.2–13.4)		7.5 (7.2–7.8)		7. 5 (7.4–7.6)		0.8 (0.8–0.9)		1.0 (1.0–1.0)	
Midwest	8.3 (7.5–9.1)		8.2 (8.1–8.4)		3.0 (2.6–3.4)		3.3 (3.2–3.3)		0.3 (0.2–0.5)		0.3 (0.3–0.4)	
West	18.5 (18.0–19.1)		17.4 (17.2–17.5)		8.9 (8.5–9.2)		8.9 (8.8–9.0)		0.7 (0.6–0.8)		0.7 (0.7–0.8)	

ESBL, extended-spectrum beta-lactamase-producing phenotype; MDR, multidrug resistant; Carb, carbapenem; CI, confidence interval; NS, nonsusceptible.

Table 3
Proportion of resistant *Acinetobacter* spp. isolates in US inpatients in 2017: Observed data estimate and projected national prevalence.

Hospital characteristic	% MDR				% Carb-NS			
	Observed		National projection		Observed		National projection	
	Estimate (95% CI)	*p*	Estimate (95% CI)	*p*	Estimate (95% CI)	*p*	Estimate (95% CI)	*p*
All	42.4 (40.9–44.0)		42.4 (41.8–42.9)		34.9 (33.4–36.4)		34.5 (33.9–35.0)	
Bed size		0.018		<0.001		0.032		<0.001
<100	28.5 (21.0–37.4)		27.6 (25.7–29.5)		20.5 (13.9–29.0)		18.8 (17.1–20.6)	
100–300	39.7 (34.5–45.0)		39.2 (37.7–40.7)		30.3 (25.4–35.7)		28.5 (27.0–30.0)	
>300	41.5 (36.0–47.2)		37.4 (35.8–38.9)		31.9 (26.6–37.7)		27.6 (26.2–29.1)	
Urban/Rural		0.109		<0.001		0.021		<0.001
Urban	39.8 (35.4–44.4)		40.4 (39.3–41.5)		32.3 (27.9–37.0)		32.9 (31.8–34.0)	
Rural	33.0 (25.5–41.4)		29.1 (27.1–31.1)		22.7 (16.3–30.7)		18.0 (16.3–19.7)	
Medical school affiliation		0.001		<0.001		<0.001		<0.001
No affiliation	32.6 (27.8–37.7)		29.9 (28.7–31.1)		22.2 (18.0–27.0)		19.3 (18.3–20.3)	
Limited	39.8 (33.9–46.0)		36.4 (34.6–38.2)		30.6 (24.9–36.9)		26.5 (24.9–28.3)	
Major/Graduate	36.8 (31.1–42.9)		37.5 (35.9–39.1)		29.4 (23.9–35.6)		28.9 (27.4–30.6)	
Region		<0.001		<0.001		<0.001		<0.001
Northeast	43.0 (37.0–49.1)		42.5 (40.8–44.0)		30.6 (25.1–36.7)		29.3 (27.7–30.9)	
Southeast	21.5 (18.1–25.3)		22.2 (21.0–23.3)		15.3 (12.4–18.7)		14.8 (13.9–15.8)	
North central	49.7 (44.0–55.4)		45.8 (44.0–47.7)		38.7 (32.9–44.9)		33.7 (31.9–35.5)	
South central	38.4 (32.8–44.3)		37.6 (35.9–39.4)		31.4 (25.9–37.4)		28.9 (27.2–30.6)	
Midwest	23.6 (12.5–40.2)		20.4 (18.1–22.9)		18.4 (8.8–34.5)		15.4 (13.3–17.7)	
West	46.7 (39.6–54.0)		43.8 (41.6–45.9)		34.6 (27.9–42.0)		31.4 (29.3–33.5)	

MDR, multidrug resistant; Carb, carbapenem; CI, confidence interval; NS, nonsusceptible.

21,668/314,904 (6.9%; 95% CI, 6.8%–7.0%) and the proportion of Carb-NS Enterobacteriaceae was 3,758/314,904 (1.2%; 95% CI, 1.2%–1.2%). For the 3,966 *Acinetobacter* spp. isolates tested, 1,682 (42.4%; 95% CI, 40.9%–44.0%) were MDR and 1,383 (34.9%; 95% CI, 33.4%–36.4%) were Carb-NS (Supplemental Table S3, Table 3).

The proportions of resistant isolates in observed data were significantly correlated with urban/rural status, medical school affiliation status, and geographic region. For all reported phenotypes of antibiotic-resistant Enterobacteriaceae, urban hospitals had a higher proportion of resistant isolates than rural hospitals, and hospitals with a major/graduate affiliation had a higher proportion of resistant isolates than those without a medical school affiliation (Table 2). For ESBL, hospital bed size was also significantly associated with resistance (hospitals with >300 beds had the highest resistance). For *Acinetobacter* spp., >300 beds and medical school affiliation were associated with greater proportions of resistance in observed data (Table 3). The geographic patterns of resistant Enterobacteriaceae and *Acinetobacter* spp. isolates varied. Hospitals in the midwest had the lowest proportions of resistant Enterobacteriaceae; hospitals in the west had the highest proportions of ESBL and MDR isolates, while those in the northeast had the highest proportions of Carb-NS Enterobacteriaceae (Table 2). For *Acinetobacter* spp., hospitals in the southeast had the lowest proportions of resistant isolates in observed data and hospitals in the north central had the highest (Table 3).

Resistance rate per 1000 hospital admissions in observed data

The rate of resistant Enterobacteriaceae isolates per 1000 hospital admissions was 7.3 for ESBL, 4.4 for MDR, and 0.8 for Carb-NS (Table 4). The rate of resistant *Acinetobacter* spp. isolates per 1000 hospital admissions was 0.4 for MDR and 0.3 for Carb-NS (Table 5). Geographic region was significantly associated with the rate of resistance for all phenotypes of resistant Enterobacteriaceae; hospitals in the west had the highest rates of resistant Enterobacteriaceae per 1000 hospital admissions and hospitals in the midwest had the lowest rates (Table 4). Medical school affiliation was associated with ESBL and Carb-NS, but not MDR Enterobacteriaceae. Medical school affiliation was the only hospital characteristic significantly associated with resistance rates per 1000 hospital admissions in *Acinetobacter* spp. (Table 5).

Projected national resistance

The estimated national proportion of resistant Enterobacteriaceae isolates in hospitalized patients was 12.6% for ESBL, 6.6% for MDR, and 1.2% for Carb-NS Enterobacteriaceae (Table 2). For *Acinetobacter* spp., the projected national proportion of resistant isolates was 42.4% for MDR and 34.5% for Carb-NS (Table 3). All hospital characteristics significantly associated with observed proportions of resistant isolates retained their significance in national projections. In addition, bed size became correlated with MDR and Carb-NS Enterobacteriaceae, and urban status became correlated with MDR *Acinetobacter* spp. in national projections.

Table 4
Rate of resistant *Enterobacteriaceae* isolates per 1000 admissions in US inpatients in 2017: Observed data estimate and projected national rates.

Hospital characteristic	ESBL per 1000 admissions				MDR per 1000 admissions				Carb-NS per 1000 admissions			
	Observed		National projection		Observed		National projection		Observed		National projection	
	Estimate (95% CI)	*p*	Estimate (95% CI)	*p*	Estimate (95% CI)	*p*	Estimate (95% CI)	*p*	Estimate (95% CI)	*p*	Estimate (95% CI)	*p*
All	7.3 (6.8–7.7)		7.1 (6.7–7.6)		4.4 (4.2–4.7)		4.3 (4.0–4.6)		0.8 (0.7–0.9)		0.7 (0.7–0.8)	
Bed size		0.760		0.373		0.366		0.138		0.919		0.700
<100	6.5 (4.9–8.5)		6.2 (5.2–7.4)		3.6 (2.7–4.7)		3.6 (3.0–4.4)		0.5 (0.3–0.9)		0.6 (0.4–0.8)	
100–300	7.1 (6.0–8.4)		7.1 (6.2–8.1)		4.1 (3.5–4.9)		4.3 (3.7–5.0)		0.6 (0.4–0.8)		0.6 (0.5–0.8)	
>300	6.9 (5.9–8.1)		6.7 (5.8–7.6)		3.8 (3.2–4.6)		3.8 (3.3–4.4)		0.6 (0.4–0.8)		0.5 (0.4–0.7)	
Urban/Rural		0.668		0.741		0.921		0.880		0.552		0.372
Urban	6.6 (5.8–7.6)		6.5 (5.9–7.2)		3.8 (3.3–4.4)		3.8 (3.4–4.3)		0.6 (0.4–0.8)		0.6 (0.5–0.7)	
Rural	7.0 (5.5–8.9)		6.8 (5.7–8.0)		3.9 (3.0–5.0)		3.9 (3.2–4.7)		0. 5 (0.3–0.8)		0. 5 (0.4–0.7)	
Medical school affiliation		0.032		0.010		0.313		0.195		0.033		0.009
No affiliation	6.2 (5.3–7.3)		6.2 (5.6–6.8)		3.6 (3.0–4.3)		3.7 (3.3–4.1)		0.5 (0.3–0.6)		0.5 (0.4–0.6)	
Limited	6.6 (5.5–8.0)		6.2 (5.2–7.4)		3.9 (3.2–4.7)		3.7 (3.0–4.5)		0.6 (0.4–0.8)		0.6 (0.4–0.8)	
Major/ Graduate	7.7 (6.4–9.3)		7.7 (6.7–9.0)		4.1 (3.3–5.0)		4.3 (3.6–5.1)		0.6 (0.4–0.9)		0.7 (0.5–0.9)	
Region		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001
Northeast	7.4 (6.2–9.0)		7.0 (6.0–8.1)		4.1 (3.4–5.0)		3.8 (3.2–4.5)		1.1 (0.8–1.5)		1.0 (0.8–1.3)	
Southeast	7.7 (6.6–9.0)		7.9 (6.8–9.3)		4.6 (3.9–5.4)		4.9 (4.1–5.8)		0.8 (0.6–1.1)		1.0 (0.7–1.2)	
North central	5.3 (4.4–6.4)		5.1 (4.3–6.2)		3.7 (3.1–4.4)		3.6 (2.9–4.3)		0.7 (0.5–0.9)		0.6 (0.5–0.8)	
South central	8.1 (6.8–9.7)		7.8 (6.6–9.2)		5.1 (4.2–6.1)		5.0 (4.2–5.9)		0.6 (0.4–0.8)		0.7 (0.5–0.9)	
Midwest	3.8 (2.2–6.6)		3.8 (2.9–5.1)		1.6 (0.8–3.1)		1.8 (1.2–2.5)		0.2 (0.0–0.6)		0.2 (0.1–0.4)	
West	10.7 (9.0–12.9)		10.2 (8.7–11.8)		5.8 (4.8–7.0)		5.9 (5.0–6.9)		0.5 (0.3–0.7)		0.5 (0.3–0.7)	

ESBL, extended-spectrum beta-lactamase-producing phenotype; MDR, multidrug resistant; Carb, carbapenem; CI, confidence interval; NS, nonsusceptible.

Projected national rates of resistance per 1000 hospital admissions for Enterobacteriaceae were 7.1 for ESBL, 4.3 for MDR, and 0.7 for Carb-NS (Table 4). For *Acinetobacter* spp., projected national resistance rates per 1000 hospital admissions were 0.3 for both MDR and Carb-NS (Table 5). Significant correlations with hospital characteristics were the same as those found with observed data (geographic region for all Enterobacteriaceae resistance phenotypes and medical school affiliation for ESBL and Carb-NS Enterobacteriaceae and MDR and Carb-NS *Acinetobacter* spp.)

The projected national annual numbers of resistant, non-duplicate Enterobacteriaceae isolates from US hospital inpatients were 290,220 (95% CI, 252,352–328,088) for ESBL, 173,984 (95% CI, 153,438–194,529) for MDR, and 30,194 (95% CI, 24,661–35,728) for Carb-NS (Table 6). For *Acinetobacter* spp., the estimated national prevalence was 12,274 (95% CI, 9,168–15,380) non-duplicate isolates for MDR and 9,991 (95% CI, 7,216–12,766) for Carb-NS (Table 6).

Discussion

In this large database of US hospitals, high rates of antimicrobial resistance were observed in non-duplicate Enterobacteriaceae and *Acinetobacter* spp. isolates from inpatients. Our findings provide strong support for CDC and WHO targeting of these pathogens as national and global threats (Anon, 2013,2017; Tacconelli et al., 2018).

The inpatient proportions of resistant isolates are on the same order of magnitude as those reported in other large databases (Castanheira et al., 2019), but lower than those for HAIs, as might be expected from the predominance of pathogens from critical care units in HAI reports (Weiner et al., 2016). For instance, in the most recent National Healthcare Safety Network (NHSN) data, the 2015 ESBL rate in device-associated HAIs (central line-associated bloodstream infections and catheter-associated urinary tract infections) in short-stay acute care hospitals was 16.5% and the CRE rate was 3.1% (Woodworth et al., 2018), compared with an ESBL national inpatient rate of 12.6% and a Carb-NS Enterobacteriaceae rate of 1.2% estimated in this study. NHSN *Acinetobacter* resistance rates for HAIs were also higher: 49.5% of tested *Acinetobacter* isolates were Carb-NS in 2014 data (Anon, 2015a) compared with 34.4% estimated here for inpatients. Consistent with these data, McCann et al. observed a higher proportion of Carb-NS Gram-negative isolates in hospital-onset (6.8%) versus admission (2.4%) cultures in the BD Insights database (McCann et al., 2018).

Although it is not surprising that resistance rates are lower in the overall inpatient population compared with patients with HAIs, what is perhaps more unexpected is the overall high burden of resistant Gram-negative pathogens in US hospitals outside those involved in specific HAIs, as shown in calculations of resistant isolates per 1000 hospital admissions. Our study evaluated the rate per 1000 admissions to allow for relative comparison of incidences across different resistance phenotypes. Based on our data, isolates

Table 5
Rate of resistant *Acinetobacter* spp. isolates per 1000 admissions in US inpatients in 2017: Observed data estimate and projected national rates.

Hospital characteristic	MDR per 1000 admissions				Carb-NS per 1000 admissions			
	Observed		National projection		Observed		National projection	
	Estimate (95% CI)	*p*	Estimate (95% CI)	*p*	Estimate (95% CI)	*p*	Estimate (95% CI)	*p*
All	0.4 (0.3–0.4)		0.3 (0.3–0.4)		0.3 (0.3–0.4)		0.3 (0.2–0.3)	
Bed size		0.782		0.532		0.739		0.497
<100	0.2 (0.1–0.5)		0.2 (0.1–0.4)		0.1 (0.0–0.4)		0.1 (0.1–0.3)	
100–300	0.3 (0.2–0.4)		0.3 (0.2–0.4)		0.2 (0.1–0.4)		0.2 (0.1–0.3)	
>300	0.3 (0.2–0.5)		0.2 (0.2–0.3)		0.2 (0.1–0.4)		0.2 (0.1–0.3)	
Urban/Rural		0.302		0.051		0.233		0.021
Urban	0.3 (0.2–0.5)		0.3 (0.2–0.4)		0.2 (0.1–0.4)		0.3 (0.2–0.4)	
Rural	0.2 (0.1–0.5)		0.2 (0.1–0.3)		0.1 (0.0–0.4)		0.1 (0.0–0.2)	
Medical school affiliation		0.004		0.004		0.001		<0.001
No affiliation	0.2 (0.1–0.3)		0.2 (0.1–0.2)		0.1 (0.1–0.2)		0.1 (0.1–0.2)	
Limited	0.3 (0.2–0.5)		0.3 (0.2–0.4)		0.2 (0.1–0.5)		0.2 (0.1–0.3)	
Major/Graduate	0.3 (0.2–0.5)		0.3 (0.2–0.5)		0.2 (0.1–0.4)		0.2 (0.1–0.4)	
Region		0.244		0.109		0.241		0.187
Northeast	0.3 (0.2–0.6)		0.3 (0.2–0.5)		0.2 (0.1–0.4)		0.2 (0.1–0.4)	
Southeast	0.3 (0.2–0.4)		0.3 (0.2–0.4)		0.2 (0.1–0.3)		0.2 (0.1–0.3)	
North central	0.4 (0.2–0.6)		0.3 (0.2–0.5)		0.3 (0.1–0.5)		0.2 (0.1–0.4)	
South central	0.3 (0.2–0.5)		0.3 (0.2–0.5)		0.2 (0.1–0.4)		0.2 (0.1–0.4)	
Midwest	0.1 (0.0–0.7)		0.1 (0.0–0.3)		0.1 (0.0–0.7)		0.1 (0.0–0.2)	
West	0.2 (0.1–0.4)		0.2 (0.1–0.4)		0.2 (0.1–0.3)		0.1 (0.1–0.3)	

MDR, multidrug resistant; Carb, carbapenem; CI, confidence interval; NS, nonsusceptible.

of the most common antibiotic-resistant phenotype in our study, ESBL Enterobacteriaceae, are present in 1 of every 141 inpatients. We have previously shown that a given isolate in our database may have multiple antibiotic-resistant phenotypes (for instance, Carb NS Enterobacteriaceae could potentially also be MDR) (McCann et al., 2018), so it is not appropriate to add inpatient rates from different resistance phenotypes to estimate an overall burden. Nevertheless, the ESBL figure alone indicates that the magnitude of resistant Enterobacteriaceae within US hospitals is substantial.

As a further test of the projected isolate counts reported here, we used our projected rates per 1000 hospital admissions and the number of 2017 hospital admissions reported by the American Hospital Association (AHA; 36,510,207) (Anon, 2019) to estimate isolate counts based on this independent hospital admissions data. For all resistance types included in our study, the numbers calculated by this approach were slightly lower than our projections but fell well within the 95% CIs. For instance, the estimate based on AHA admissions was 259,222 ESBL isolates nationwide compared with our projection of 290,220 (95% CI, 252,352–328,088). The concordance of these results implies that the methodology used in this study is as rigorous as others using large databases for resistance analyses, and helps corroborate our estimates as potential reference points for future assessments. Such data will be important to help estimate the public health implications of MDR organisms, which have been estimated to cost from $1718 to $4617 per US hospital inpatient case (depending on the specific pathogen involved) for an estimated national cost of up to $3.38 billion (Johnston et al., 2019).

Both observed and projected proportions of resistant Enterobacteriaceae and *Acinetobacter* spp. isolates were significantly influenced by hospital characteristics, including bed size, urban/rural status, medical school affiliation, and geographic regions. However, in analyses of resistance rates per 1000 admissions, medical school affiliation was the only characteristic correlated with resistance rates for both Enterobacteriaceae and *Acinetobacter* spp.; geographic region was correlated with resistance in Enterobacteriaceae only. Geographic regions with the highest burden of resistant Enterobacteriaceae varied depending on the specific resistance profile. For ESBL and MDR Enterobacteriaceae, hospitals in the west had the highest proportions of resistant isolates and the highest rates per 1000 hospital admissions, whereas for Carb-NS Enterobacteriaceae resistance was highest in hospitals in the northeast. This variation may reflect different antibiotic usage patterns in these geographic areas, although other explanations, such as travel patterns and differences in agriculture pathogen exposure or population densities, may also influence these findings. Other reports using our database have also noted extensive regional differences in rates of nonsusceptible pathogens (McCann et al., 2018). The wide variation in resistance among different geographic regions supports the need for expanded use of regional antibiograms to help guide antibiotic therapy and stewardship.

When considering these data, it is important to note that comparisons of national estimates across independent databases are problematic. In addition to variability introduced by the databases themselves, including data sources, patient populations,

Table 6
Projected national numbers of resistant isolates in US hospital inpatients in 2017.

Hospital characteristic	Estimated numbers (95% CI)				
	Enterobacteriaceae			*Acinetobacter* spp.	
	ESBL	MDR	Carb-NS	MDR	Carb-NS
All	290,220 (252,352–328,088)	173,984 (153,438–194,529)	30,194 (24,661–35,728)	12,274 (9,168–15,380)	9,991 (7,216–12,766)
Bed size					
< 100	39,426 (28,054–50,798)	24,000 (16,269–31,731)	3,515 (2,060–4,969)	699 (319–1,079)	462 (184–741)
100–300	99,846 (81,526–118,165)	62,658 (50,056–75,260)	9,230 (6,671–11,790)	3,700 (2,525–4,876)	2,877 (1,823–3,932)
>300	150,948 (112,411–189,486)	87,325 (67,549–107,102)	17,449 (12,232–22,667)	7,875 (4,859–10,891)	6,651 (3,981–9,321)
Urban/Rural					
Urban	248,326 (209,370–287,282)	148,091 (127,220–168,962)	26,606 (21,093–32,118)	11,637 (8,520–14,753)	9,625 (6,844–12,407)
Rural	41,894 (30,427–53,361)	25,893 (17,781–34,004)	3,589 (2,102–5,075)	637 (278–997)	366 (132–599)
Medical school affiliation					
No affiliation	156,523 (134,162–178,884)	97,362 (82,187–112,538)	14,439 (11,104–17,774)	4,884 (3,723–6,044)	3,592 (2,601–4,583)
Limited	39,896 (28,467–51,325)	23,700 (16,821–30,579)	4,284 (2,472–6,095)	1,999 (1,206–2,792)	1,654 (923–2,384)
Major/Graduate	93,801 (57,560–130,042)	52,921 (34,902–70,940)	11,472 (6,788–16,155)	5,391 (2,408–8,375)	4,745 (2,101–7,389)
Region					
Northeast	67,331 (43,031–91,631)	36,423 (23,384–49,462)	10,549 (5,838–15,260)	3,685 (963–6,407)	3,007 (628–5,386)
Southeast	56,232 (42,624–69,840)	34,574 (25,349–43,798)	6,778 (3,806–9,751)	2,133 (1,179–3,087)	1,631 (836–2,426)
North central	40,346 (29,520–51,171)	27,670 (19,668–35,672)	4,977 (3,325–6,629)	2,680 (1,606–3,754)	2,248 (1,249–3,248)
South central	47,807 (33,884–61,731)	30,677 (21,666–39,687)	4,097 (2,687–5,507)	1,966 (1,018–2,915)	1,695 (788–2,602)
Midwest	12,775 (5,339–20,210)	6,125 (2,478–9,771)	583 (97–1,070)	244 (-21–509)	187 (-66–440)
West	65,729 (34,164–97,295)	38,515 (22,329–54,701)	3,209 (1,831–4,587)	1,566 (692–2,440)	1,223 (477–1,968)

ESBL, extended-spectrum beta-lactamase-producing phenotype; MDR, multidrug resistant; Carb, carbapenem; CI, confidence interval; NS, nonsusceptible.

sampling methods (e.g. partial sampling of pathogens or sources vs. all reported results), and geographic regions, it is also important to consider differences in study design (surveillance vs. infection-associated, inclusion/exclusion criteria, definitions and categories of resistance) and in the statistical methodologies used to calculate the estimates. It is likely that many of the discrepancies among different reports can be explained by these variations. Given the large number of isolates and admissions typically involved in national prevalence studies, even subtle nuances can make important differences. For instance, as mentioned previously, the data reported here cannot be strictly compared with reports of HAIs (Woodworth et al., 2018; Anon, 2015a). Zilberberg et al. estimated a higher proportion of MDR *Acinetobacter* (35.2%) than in the current report, but their study included nursing home residents and was confined to blood and respiratory samples (Zilberberg et al., 2016). The CRE rate of an estimated 2.93 incidence cases per 100,000 population in a surveillance study of seven US communities cannot be compared with the Carb-NS rate of 0.7 per 1000 admissions reported here, as the methods for detecting carbapenem resistance, populations examined (surveillance versus inpatient), and denominator were very different (Guh et al., 2015). Surveillance methodology was also used to derive a Carb-NS *A. baumanni* rate of 1.2 cases/100,000 persons (Bulens et al., 2018) (compared with the rate of 0.3 per 1000 admissions for Carb-NS *Acinetobacter* spp. reported here).

Limitations of our study include the collection and analysis of data from the perspective of unique non-duplicated collected cultures and not from the perspective of unique patients, which prevents us from evaluating clinical outcomes associated with the antibiotic-resistant pathogens identified in this study. The results reported here represent culture-positive isolates and not confirmed invasive infections. In addition, susceptibility was based on local microbiology practices at each facility, which are known to vary (Shugart et al., 2018), and are not standardized across facilities. As in other epidemiological studies (Weiner et al., 2016), our analyses included nonsusceptible isolates (resistant or intermediate), which may have resulted in a slight overestimation of resistance. Expression of carbapenemases was not evaluated. Our study included only selected *Acinetobacter* species, and mechanisms of resistance were not investigated. Finally, as with all estimates (Hay et al., 2018; Matsunaga and Hayakawa, 2018), the accuracy of the projected numbers depends on assumptions made concerning mean numbers of infections and population weighting, as well as on the statistical models used to extrapolate data. Selection bias (higher likelihood of performing cultures in more severely ill patients) is a potential issue for all studies of antimicrobial resistance and may increase estimates of antimicrobial resistance. Hospital-specific culturing practices, infection control procedures, and antimicrobial stewardship programs could also bias results.

To the best of our knowledge, our antimicrobial resistance data are the most comprehensive available from the standpoint of admission and inpatient coverage, regional distribution across the US, and range of pathogens, including multiple Enterobacteriaceae species, from all available sources. The breadth and depth of our database provide us with an enhanced ability to identify regional areas of resistance and generalize data to estimate the nationwide prevalence of antimicrobial resistance. Our data show that

antibiotic resistance in Enterobacteriaceae and *Acinetobacter* spp. is a significant concern across the US. We hope the data reported here contribute to a broader view of the population affected by antibiotic resistance and help support measures that may be required to combat antimicrobial resistance, including coordinated infection control efforts, antimicrobial stewardship initiatives, and development of new antibiotics and diagnostics (Anon, 2015b; Barlam et al., 2016; Hill et al., 2018; Messacar et al., 2017; Morgan et al., 2017; Pogue et al., 2015; Spellberg et al., 2016; Yu et al., 2014; Hagiwara et al., 2018).

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Ethical approval

Outcome studies using this retrospective, deidentified dataset were approved and informed consent was waived by the New England Institutional Review Board (Wellesley, Massachusetts).

Conflict of interest

Dr Gupta, Dr Ye, Mr Murray, and Dr Yu are employees of Becton, Dickinson & Company. Dr Olesky and Dr Lawrence are employees of Tetraphase Pharmaceuticals.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ijid.2019.06.017.

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