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## Major Article

# Effect of varying federal definitions on prevalence and characteristics associated with carbapenem-resistant Enterobacteriaceae in veterans with spinal cord injury

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Surveillance

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**Background:** Patients with spinal cord injury (SCI) have a high risk for multidrug-resistant organisms, including carbapenem-resistant Enterobacteriaceae (CRE). Accurate and easily applied definitions are critical to identify CRE. This study describes CRE and associated characteristics in veterans with SCI per Centers for Disease Control and Prevention (CDC) and Department of Veterans Affairs (VA) definitions.

**Methods:** A retrospective cohort of veterans with SCI and more than 1 culture with *Escherichia coli*, *Klebsiella* spp and/or *Enterobacter* spp between 2012 and 2013 was examined. Antibiotic susceptibility criteria of pre-2015 (CDC1) and post-2015 (CDC2) CDC definitions and pre-2017 (VA1) and post-2017 (VA2) VA definitions were used to identify CRE. CRE prevalence and characteristics are described for isolates meeting each definition, and agreement was assessed with the Cohen kappa.

**Results:** We reviewed 21,514 isolates cultured from 6,974 veterans; 423 isolates met any CRE definition. Although agreement among definitions was high (kappa = 0.82–0.93), definitions including ertapenem resistance led to higher CRE prevalence (VA1 = 1.7% and CDC2 = 1.9% vs VA2 = 1.4% and CDC1 = 1.5%). Forty-four of 142 VA facilities had more than 1 CRE case defined by VA2; 10 facilities accounted for 60% of CRE cases. Almost all CRE was isolated from high-complexity, urban facilities, and the South had the highest proportion of CRE.

**Conclusions:** Varying federal definitions give different CRE frequencies in a high-risk population. Definitions including ertapenem resistance resulted in higher CRE prevalence but may overemphasize noncarbapenemase isolates. Thus, both federal definitions now highlight the importance of carbapenemase testing.

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The prevalence of infections caused by multidrug-resistant organisms (MDROs) has been steadily increasing in both health care and community settings.<sup>1</sup> Carbapenem-resistant Enterobacteriaceae (CRE) are among the most difficult to treat MDROs and have been designated by the Centers for Disease Control and Prevention (CDC) at the highest-level antibiotic resistance threat owing to steadily increasing rates of colonization and infections in health care settings every year.<sup>2</sup> In 2012, 3.9% of short-stay hospitals and 17.8% of long-term acute care hospitals reported at least 1 CRE health care–associated infection, which was significantly higher than in previous years.<sup>3</sup> In addition, CRE infections are associated with high morbidity and mortality, longer hospital length of stay, and increased health care costs.<sup>4,5</sup>

Both the Department of Veterans Affairs (VA) and the CDC have established guidelines for CRE surveillance and infection prevention practices within health care facilities.<sup>6,7</sup> Different CRE definitions have been proposed by the CDC and the VA, with both organizations having updated their CRE definitions with the publication of their most recent guidelines. Accurate and easily applied definitions are critical to identify MDROs, to conduct local facility and national surveillance, to allocate infection prevention resources, and to implement infection prevention strategies most effectively in the highest-risk patient populations.

Patients with spinal cord injury (SCI) represent one such high-risk population and have an increased prevalence of many MDROs, including CRE.<sup>8–10</sup> This increased prevalence is attributed to the use of indwelling medical devices, high rates of antibiotic use, and frequent hospitalizations, all of which are associated with MDRO colonization and infection.<sup>9,11–15</sup> Within the VA, patients with SCI are often cared for in specialty care settings, such as specialized SCI units and long-term care facilities. Care in such settings has also been associated with an increased risk for CRE infection.<sup>16</sup> In a high-risk population such as patients with SCI, understanding the effect of varying definitions for MDROs can contribute valuable information for targeted surveillance and infection prevention. In this study, we applied the 4 different federal definitions of CRE to a large population of veterans with SCI from inpatient, outpatient, and long-term care settings to determine CRE prevalence. We also assessed whether differences in

federal definitions affect CRE estimates and identified patient characteristics associated with the various CRE definitions.

## METHODS

### Study setting and design

This was a retrospective cohort study of all adult patients with existing SCI who were treated at any Veterans Affairs medical center (VAMC) between January 1, 2012, and December 31, 2013. VAMCs are classified into 3 major complexity levels determined, in part, by volume, patient characteristics, and research and teaching activities (Levels 1a–c, 2, and 3, with Level 1a being the highest). We defined high-complexity facilities as Levels 1a–c and low-complexity facilities as Levels 2 and 3. VA also uses the Rural-Urban Commuting Areas system to classify VAMCs into urban versus rural.<sup>17</sup> Urban VAMCs are located in census tracts with at least 30% of the population residing in an urbanized area as defined by the US Census Bureau. Rural VAMCs are located in areas not defined as urban. Veterans with multiple sclerosis, amyotrophic lateral sclerosis, and Guillain-Barre syndrome were excluded because the VA SCI system of care focuses on individuals with stable, nonprogressive spinal cord neurologic deficits. The institutional review board at the Edward Hines Jr VA Hospital approved this study.

### Clinical and microbiology data collection

All bacterial cultures performed for patients with SCI during the study period that grew *Escherichia coli*, *Klebsiella* spp, or *Enterobacter* spp were included. Although other species of Enterobacteriaceae can be carbapenem resistant, we chose to focus on these species because they are most commonly associated with carbapenem resistance and are the focus of the current VA definition. Cultures could be obtained from any site and performed in any health care setting (inpatient, outpatient, rehabilitation, or long-term care). Multiple cultures from the same patient within 30 days were removed. National VA clinical and microbiology datasets were used to collect data on patient demographics, modified Charlson comorbidity index, level and extent of SCI, health care use, microbiologic data, and medication exposures. US Census Bureau categories were used to define geographic regions.

**Table 1**  
Summary of CRE definitions

	Definition			
	VA1	VA2	CDC1	CDC2
Organisms	<i>Escherichia coli</i> <i>Klebsiella</i> spp <i>Enterobacter</i> spp	<i>E coli</i> <i>K pneumoniae/oxytoca</i> <i>Enterobacter</i> spp (especially <i>E cloacae</i> )	All Enterobacteriaceae	All Enterobacteriaceae
Carbapenem criteria	Intermediate (“I”) or resistant (“R”) to imipenem, meropenem, and/or doripenem OR Resistant (“R”) to ertapenem AND (see next row)	Resistant (“R”) to imipenem, meropenem, and/or doripenem	Intermediate (“I”) or resistant (“R”) to imipenem, meropenem, and/or doripenem AND (see next row)	Resistant (“R”) to any carbapenem
Cephalosporin criteria	Resistant (“R”) to any tested third-generation cephalosporin	None	Resistant (“R”) to all of the following third-generation cephalosporins that were tested: ceftriaxone, cefotaxime, ceftazidime	None
Additional criteria*	Positive modified Hodge test	Positive molecular diagnostic test (PCR)		Documented that organism produces a carbapenemase

CDC1, Centers for Disease Control and Prevention pre-2015; CDC2, Centers for Disease Control and Prevention post-2015; CRE, carbapenem-resistant Enterobacteriaceae; PCR, polymerase chain reaction; VA1, Veterans Affairs pre-2017; VA2, Veterans Affairs post-2017.

\*These criteria were not assessed as part of this study.

## Definitions

CRE was defined using the antibiotic susceptibility criteria of both old and new VA and CDC definitions (Table 1). The first VA definition (VA1) was established in December 2014 with publication of the 2015 Guideline for Control of Carbapenem-Resistant Enterobacteriaceae (CRE).<sup>7</sup> The VA1 definition focused on *E coli*, *Klebsiella* spp, and *Enterobacter* spp and included recommendations for confirmation of carbapenemase production using the modified Hodge test. The second VA definition (VA2) was established in February 2017 when an updated guideline was published: VHA 2017 Guideline for Control of Carbapenemase Producing-Carbapenem Resistant Enterobacteriaceae (CP-CRE).<sup>18</sup> Antibiotic susceptibility criteria for VA2 were simplified (Table 1). The VA2 definition focused on *E coli*, *Klebsiella pneumoniae/oxytoca*, *Enterobacter cloacae*, and other *Enterobacter* spp and recommended polymerase chain reaction–based tests to identify carbapenemase production.

The first CDC definition (CDC1) was established in 2012 with publication of the Facility Guidance for Control of Carbapenem-Resistant Enterobacteriaceae (CRE): 2012 CRE Toolkit.<sup>19</sup> The second CDC definition (CDC2) was established in November 2015 with publication of the 2015 update to the CDC CRE Toolkit.<sup>6</sup> Similar to the VA definition, antibiotic susceptibility criteria for CDC2 were simplified (Table 1). CDC2 also emphasizes carbapenemase testing using the modified Hodge test, Carba NP, polymerase chain reaction, and/or metallo- $\beta$ -lactamase screens. Neither CDC definition focuses on specific genera or species; rather, they include all Enterobacteriaceae.

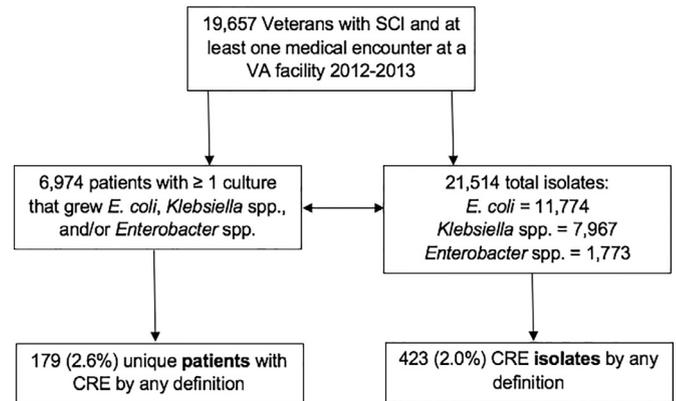
## Statistical analysis

Each CRE definition (VA1, VA2, CDC1, and CDC2) was applied to the cohort to determine how differences among the definitions contributed to differing CRE prevalence in patients with SCI. Agreement among the definitions was assessed using kappa coefficients. Descriptive statistics were used to summarize patient demographics, clinical and SCI characteristics, and prior health care and antibiotic exposures. Bivariate statistics with unadjusted logistic regression were used to compare geographic trends of isolates meeting only the less restrictive definition and isolates meeting both definitions combined. Bonferroni correction for multiple comparisons was applied, with  $P < .025$  considered significant. Statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC) and Stata version 12.1 (StataCorp LP, College Station, TX) software.

## RESULTS

Figure 1 displays the development of our CRE cohort, starting with data from 19,657 veterans with SCI and at least 1 medical encounter at a VAMC during the study period. Overall, 2.6% ( $n = 179$ ) of patients with cultures positive for target Enterobacteriaceae had CRE by any definition; these patients contributed 423 CRE isolates (Fig 1). Basic demographics and clinical characteristics of the patients with CRE are displayed in Table 2. Consistent with the VA population, most patients were older and of the male sex, and most had paraplegia with incomplete SCI. Most patients were receiving care in an acute inpatient setting at the time of positive CRE culture.

Table 3 shows CRE frequency by isolate and unique patient, bacterial species, and culture sources grouped by CRE definition. Most isolates were obtained from urine, and *Klebsiella* spp were isolated most frequently. CRE prevalence by unique patient and isolate was higher with the VA1 definition than with the VA2 definition; however, the reverse was true for the CDC definitions (Table 3). Agreement between the various definitions was high, with kappa coefficients all above 0.8. The less restrictive definitions (VA1 and CDC2;  $\kappa = 0.91$ ; 95% confidence interval [CI], 0.89–0.93) and more restrictive definitions (VA2 and CDC1;



**Fig 1.** Study cohort with numbers of patients with carbapenem-resistant Enterobacteriaceae (CRE) and carbapenem-resistant Enterobacteriaceae isolates included. SCI, spinal cord injury; VA, Department of Veterans Affairs.

$\kappa = 0.93$ ; 95% CI, 0.91–0.95) exhibited the highest level of agreement. Of 37 patients with isolates meeting the VA1 definition but not the VA2 definition, most met VA1 criteria owing to ertapenem resistance in the absence of resistance to other carbapenems ( $n = 32$ , 86.5%). Likewise, of 62 patients with isolates meeting the CDC2 definition but not the CDC1 definition, most met the CDC2 criteria owing to isolated ertapenem resistance ( $n = 45$ , 72.6%).

Interesting trends in this study were observed in the geographic distribution of patients with CRE. The 6,974 patients with cultures that grew target Enterobacteriaceae were cared for at 142 different VAMCs, with 44 (31%) of these medical centers having at least 1 patient with CRE. Most CRE isolates were identified in high-complexity, urban VAMCs (Table 1). Figure 2 shows the geographic distribution of patients with CRE meeting the old (VA1) and new (VA2) VA definitions. Overall, the South, which included Puerto Rico, had the most CRE patients (Fig 2). Although most patients with CRE were seen at VA facilities associated with SCI centers ( $n = 91$ , 81.3% by VA2 definition), 23 VA facilities without an SCI center had at least 1 patient with CRE. On bivariate analysis, increased odds of meeting only the less restrictive VA definition (VA1) were observed in patients with CRE from the West (odds ratio [OR], 34.0; 95% CI, 4.03–286.83;  $P < 0.01$ ) and South (OR, 9.29; 95% CI, 1.13–76.51;  $P = .016$ ). A similar geographic association was not observed with the CDC definition, although a trend toward significance for the West region (OR, 2.91; 95% CI, 1.05–8.1;  $P = .039$ ) was observed.

## DISCUSSION

Accurate identification of CRE using validated, standardized laboratory techniques and definitions is a critical first step in preventing its spread. Development of a standard definition has been influenced by multiple factors, including the epidemiologic and clinical importance of distinguishing CP-CRE from non-CP-CRE, the availability of laboratory testing, and the complexity of definition implementation. As CRE has increased in prevalence over the past decade, many definitions have been developed, which have included varying bacterial species, antibiotic susceptibility results, and carbapenemase testing. Multiple groups have now focused on simplifying these various definitions to identify CRE in a way that is both accurate and easily implemented for all health care facilities. For example, initial CRE definitions developed by both the CDC and VA included third-generation cephalosporin susceptibility testing but proved cumbersome to implement as surveillance definitions and missed some CP-CRE.<sup>7,19</sup> They were then simplified with updated definitions that focused solely on carbapenem susceptibility testing with adjunctive laboratory testing for carbapenemase production, if available. Variability in surveillance definitions for MDROs

**Table 2**  
Demographics and clinical characteristics of CRE patients in the cohort

	Definitions					
	VA1 (n = 149)	VA2 (n = 127)	All VA (n = 164)	CDC1 (n = 116)	CDC2 (n = 174)	All CDC (n = 178)
Age, y, mean (SD)	66.1 (13.2)	65.5 (13.4)	65.5 (13.4)	66.9 (13.0)	65.5 (13.6)	65.3 (13.7)
Female	3 (2.0)	2 (1.6)	4 (2.2)	2 (1.7)	3 (1.7)	4 (2.2)
SCI characteristics*						
Level of injury						
Paraplegia	75 (50.3)	62 (48.8)	90 (50.3)	57 (49.1)	87 (50.0)	92 (50.0)
Tetraplegia	64 (43.0)	58 (45.7)	77 (43.0)	54 (46.6)	73 (42.0)	78 (42.4)
Extent of injury						
Incomplete	69 (46.3)	62 (48.8)	82 (45.8)	56 (48.3)	82 (47.1)	87 (47.3)
Complete	51 (34.2)	39 (30.7)	62 (34.6)	37 (31.9)	58 (33.3)	62 (33.7)
Onset of injury						
Nontraumatic	52 (34.9)	36 (28.3)	60 (33.5)	38 (32.8)	57 (32.8)	62 (33.7)
Traumatic	74 (49.7)	69 (54.3)	91 (50.8)	59 (50.9)	88 (50.6)	93 (50.5)
Duration of injury, y, median (range)	8 (0-62)	8 (0-62)	8 (0-62)	7 (0-62)	8 (0-62)	8 (0-62)
Charlson comorbidity index score, median (range)	2 (0-12)	2 (0-10)	2 (0-12)	2 (0-10)	2 (0-12)	2 (0-12)
Patient culture location						
Inpatient	83 (55.7)	67 (52.8)	98 (54.7)	63 (54.3)	93 (53.4)	96 (52.2)
LTCF	52 (34.9)	47 (37.0)	66 (36.9)	42 (36.2)	65 (37.4)	72 (39.1)
Outpatient	13 (8.7)	12 (9.4)	14 (7.8)	11 (9.5)	15 (8.6)	15 (8.2)
US Census region						
Northeast	25 (16.8)	27 (21.3)	30 (16.8)	24 (20.7)	34 (19.5)	37 (20.1)
Midwest	23 (15.4)	23 (18.1)	32 (17.9)	19 (16.4)	29 (16.7)	29 (15.8)
South	43 (28.9)	36 (28.3)	51 (28.5)	32 (27.6)	50 (28.7)	53 (28.8)
West	29 (19.5)	15 (11.8)	33 (18.4)	16 (13.8)	31 (17.8)	34 (18.5)
Other	29 (19.5)	26 (20.5)	33 (18.4)	25 (21.6)	30 (17.2)	31 (16.8)

NOTE. All data expressed as number (%) unless otherwise indicated.

CDC, Centers for Disease Control and Prevention; CDC1, Centers for Disease Control and Prevention pre-2015; CDC2, Centers for Disease Control and Prevention post-2015; CRE, carbapenem-resistant Enterobacteriaceae; LTCF, long-term care facility; SCI, spinal cord injury; SD, standard deviation; VA, Department of Veterans Affairs; VA1, Veterans Affairs pre-2017; VA2, Veterans Affairs post-2017.

\*Some data are missing for this variable.

may profoundly affect prevalence and associated risk factors, but this has not been well described for CRE.

In this study, we compared CRE prevalence associated with surveillance definitions from the VA and CDC among veterans with SCI—a cohort of patients at elevated risk for MDROs such as CRE.<sup>8–10,14,15</sup> We found that CRE prevalence was higher with the earlier VA definition (VA1), mostly owing to isolated ertapenem resistance in the absence of resistance to other carbapenems. The exclusion of

ertapenem from the updated 2017 VA definition (VA2) simplifies the definition and was intended to place greater emphasis on isolates producing carbapenemases. In contrast, the earlier CDC definition (CDC1) did not include resistance to ertapenem, but the later CDC definition (CDC2) does include this. As a result, we found greater CRE prevalence with CDC2 than with CDC1. Regardless of CRE definition, frequencies were high in this patient population, particularly when compared with general population-based CRE incidence rates recently described by the CDC.<sup>11</sup> Another important difference between VA and CDC definitions is the focus by the VA on specific species within the Enterobacteriaceae family. Focusing on *E coli*, *Klebsiella* spp, and *Enterobacter* spp allows a targeted approach to identifying organisms that are most often associated with carbapenem resistance mediated by carbapenemases. Furthermore, this focused approach minimizes confusion related to species with intrinsic imipenem resistance (ie, *Morganella*, *Proteus*, and *Providencia*). However, such a focused approach must be weighed against the risk of failing to identify CRE within these other species.

Most patients with CRE (~60%) were seen at 10 of the 44 VA facilities that had at least 1 patient with CRE. Almost all of the VAMCs with CRE were Level 1 and located in urban areas. Such facilities care for more complex and more critically ill patients, who are at higher risk for CRE. These facilities are also more likely to have dedicated SCI centers and therefore more likely to care for patients in our cohort. Our prior work showed increased risk for other MDROs in patients seen at VA facilities with SCI centers, although this association is not maintained after adjustment for confounders such as age, comorbidity, and antibiotic and health care exposures.<sup>9,15</sup> However, 23 facilities without SCI centers also cared for at least 1 patient with CRE during our study period, suggesting that CRE may affect VA facilities of varying complexity level, geographic location, and size. Variability in CRE definitions has important implications for effective MDRO identification and surveillance at such facilities. Interestingly, patients with SCI who were seen at VA facilities in the West and South regions had greater odds of meeting only the less restrictive VA1 definition compared with both VA1 and VA2 definitions combined.

**Table 3**  
Characteristics of CRE isolates grouped by CRE definition

	Definition			
	VA1	VA2	CDC1	CDC2
No. of CRE isolates*	369 (1.7)	308 (1.4)	316 (1.5)	404 (1.9)
No. of unique patients <sup>†</sup>	149 (2.1)	127 (1.8)	116 (1.7)	174 (2.5)
Organism isolated				
<i>Escherichia coli</i>	17 (11.4)	16 (12.6)	8 (6.9)	23 (13.2)
<i>Klebsiella</i> spp	93 (62.4)	88 (69.3)	85 (73.3)	105 (60.3)
<i>Enterobacter</i> spp	39 (26.2)	23 (18.1)	23 (19.8)	46 (26.4)
Culture source				
Urine	99 (66.4)	87 (68.5)	81 (69.8)	119 (68.4)
Blood	11 (7.4)	8 (6.3)	9 (7.8)	12 (6.9)
Sputum	20 (13.4)	14 (11.0)	12 (10.3)	21 (12.1)
Other <sup>‡</sup>	19 (12.8)	18 (14.2)	14 (12.1)	22 (12.6)
No. of CRE isolates by facility complexity and location				
1a-1c (high)	363 (98.4)	297 (96.4)	309 (97.8)	392 (97.0)
2-3 (low)	6 (1.6)	11 (3.6)	7 (2.2)	12 (3.0)
Urban	368 (99.7)	305 (99.0)	314 (99.4)	401 (99.3)
Rural	1 (0.3)	3 (1.0)	2 (0.6)	3 (0.7)

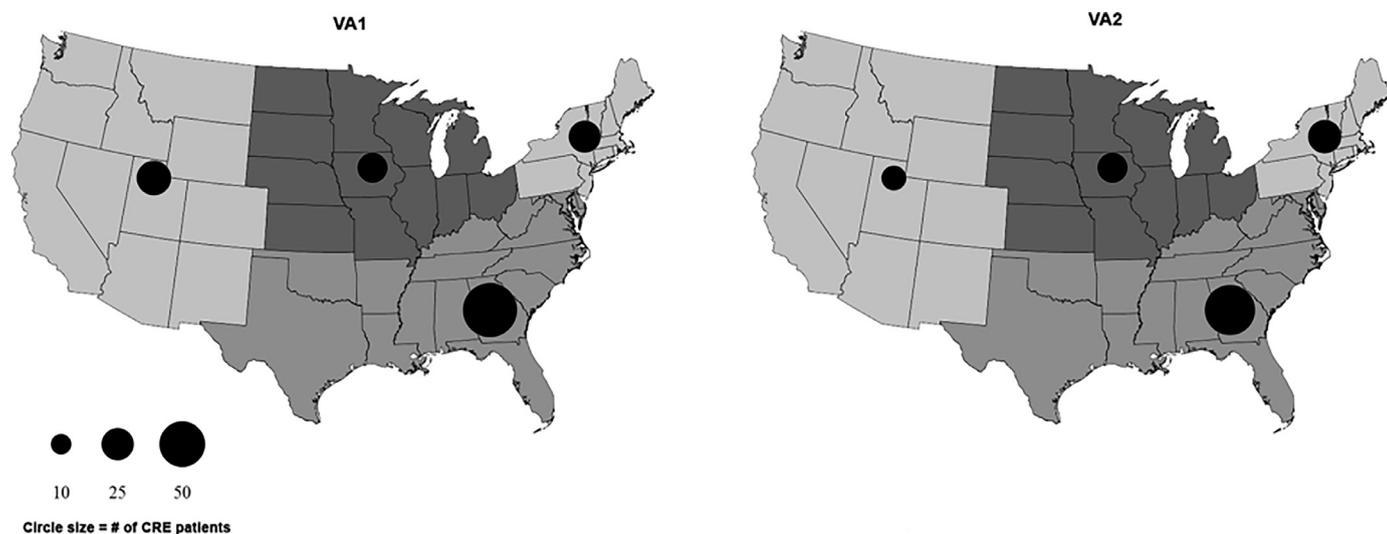
NOTE. All data expressed as number (%) unless otherwise indicated.

CDC1, Centers for Disease Control and Prevention pre-2015; CDC2, Centers for Disease Control and Prevention post-2015; CRE, carbapenem-resistant Enterobacteriaceae; VA1, Veterans Affairs pre-2017; VA2, Veterans Affairs post-2017.

\*Out of 21,514 total *E coli*, *Klebsiella* spp, and *Enterobacter* spp isolates.

<sup>†</sup>Out of 6,974 unique patients with at least 1 *E coli*, *Klebsiella* spp, and/or *Enterobacter* spp isolate.

<sup>‡</sup>Wound, tissue, and fluid.



**Fig 2.** Geographic distribution of carbapenem-resistant Enterobacteriaceae isolates based on Veterans Affairs pre-2017 (prior) and Veterans Affairs post-2017 (current) definitions. Circle size corresponds to number of patients with carbapenem-resistant Enterobacteriaceae, as indicated in the legend, with smaller circles indicating fewer patients and larger circles indicating more patients. The varying shades of gray represent states in each of the US Census Bureau regions (West, Midwest, Northeast, and South). Puerto Rico was analyzed with the South region.

The reasons behind this association may relate to local epidemiologic trends in these regions and/or greater presence of non-CP-CRE, which may be more likely to demonstrate isolated ertapenem resistance.

This study had several important limitations. First, we did not distinguish between patients who were infected versus colonized. Differentiation between CRE infection and colonization would be important for a study examining clinical outcomes but is less critical when assessing the effect of surveillance definitions on CRE prevalence and epidemiologic associations. Second, although we examined data during years that had no major modifications to the Clinical and Laboratory Standards Institute breakpoints for our organisms, the identification and reporting of bacterial susceptibilities in individual VA microbiology laboratories may have changed during our study period. We also did not include information on carbapenemase testing and relied only on antibiotic susceptibility criteria for the definitions. Given that many microbiology laboratories are not able to routinely identify carbapenemases, the results of our study may be more broadly applicable. Finally, we were not able to include microbiology cultures collected outside the VA.

In conclusion, accurate and timely identification, reporting, and surveillance for CRE are critical to controlling its spread. In our study, applying different federal CRE surveillance definitions led to variability in CRE prevalence in a cohort of veterans at elevated risk for MDRO infection and colonization, with isolated resistance to ertapenem contributing to much of the variability. Updated VA and CDC definitions now focus on more simplified antibiotic susceptibility criteria and emphasize the importance of testing for carbapenemase production to confirm CRE diagnosis.

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