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Detection and Characterization of Targeted Carbapenem-Resistant Health Care-Associated Threats: Findings from the Antibiotic Resistance Laboratory Network, 2017 to 2019

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ABSTRACT Carbapenemase gene-positive (CP) Gram-negative bacilli are of significant clinical and public health concern. Their rapid detection and containment are critical to preventing their spread and additional infections they can cause. To this end, CDC developed the Antibiotic Resistance Laboratory Network (AR Lab Network), in which public health laboratories across all 50 states, several cities, and Puerto Rico characterize clinical isolates of carbapenem-resistant *Enterobacterales* (CRE), *Pseudomonas aeruginosa* (CRPA), and *Acinetobacter baumannii* (CRAB) and conduct colonization screens to detect the presence of mobile carbapenemase genes. In its first 3 years, the AR Lab Network tested 76,887 isolates and 31,001 rectal swab colonization screens. Targeted carbapenemase genes (bla_{KPC}, bla_{NDM}, $bla_{OXA\text{-}48\text{-}like}$, bla_{VIM}, or bla_{IMP}) were detected by PCR in 35% of CRE, 2% of CRPA, and <1% of CRAB isolates and 8% of colonization screens tested, respectively. bla_{KPC} and bla_{VIM} were the most common genes in CP-CRE and CP-CRPA isolates, respectively, but regional differences in the frequency of carbapenemase genes detected were apparent. In CRE and CRPA isolates tested for carbapenemase production and the presence of the targeted genes, 97% had concordant results; 3% of CRE and 2% of CRPA isolates were carbapenemase production positive but PCR negative for those genes. Isolates harboring bla_{NDM} showed the highest frequency of resistance across the carbapenems tested, and those harboring bla_{IMP} and $bla_{OXA\text{-}48\text{-}like}$ genes showed the lowest frequency of carbapenem resistance. The AR Lab Network provides a national snapshot of rare and emerging carbapenemase genes, delivering data to inform public health actions to limit the spread of these antibiotic resistance threats.

KEYWORDS AR Lab Network, carbapenemase producing, Gram negative, carbapenem resistant

Carbapenems are critically important β-lactam drugs for treating patients with severe infections caused by Gram-negative bacilli, and resistance to this class of antibiotics is an evolving, global public health problem. Many of these carbapenem-resistant pathogens are common in health care environments and of particular concern because of high mortality rates and treatment failures among infected patients (1–3). In 2019, the Centers for Disease Control and Prevention (CDC) published its second report on antibiotic resistance threats in the United States and estimated that antibiotic-resistant infections sicken over 2.8 million people each year in the United States, and more than 35,000 people die from these infections (4). The report reconfirmed carbapenem-resistant *Enterobacterales* (CRE) and multidrug-resistant *Pseudomonas aeruginosa* as urgent and serious threats to human health and promoted carbapenem-resistant *Acinetobacter baumannii* (CRAB) as an urgent threat (5).

Production of carbapenemase β-lactamases represent one mechanism by which organisms may acquire carbapenem resistance. They are enzymes that can hydrolyze

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carbapenems and other β-lactam drugs, rendering them ineffective. Some carbapenemase genes may be carried on mobile genetic elements, facilitating transmission among bacterial genera and species, which may also spread between patients and across health care facilities (6). In the United States, the five most common carbapenemase genes circulating among health care-associated Gram-negative bacilli are those coding for *Klebsiella pneumoniae* carbapenemase (bla_{KPC}), New Delhi metallo-β-lactamase (MBL) (bla_{NDM}), Verona integron-encoded MBL (bla_{VIM}), oxacillinase-48-like carbapenemases ($bla_{OXA\text{-}48\text{-}like}$), and the MBL active on imipenem (bla_{IMP}).

In 2017, CDC outlined their new Containment Strategy, which encouraged health care facilities and public health authorities to implement aggressive response activities when new or rare genes and germs are identified so that transmission can be contained (7). For example, colonization screening and contact tracing are important pillars to containing spread. The same year, CDC established the Antibiotic Resistance Laboratory Network (AR Lab Network) to enhance national laboratory capacity to rapidly identify and characterize such AR threats. This laboratory infrastructure works in conjunction with CDC's Containment Strategy to support faster outbreak detection and response to contain the spread of AR threats. Herein, we summarize findings from the AR Lab Network's first 3 years of testing CRE, carbapenem-resistant *P. aeruginosa* (CRPA), CRAB, and colonization screens.

RESULTS

From January 2017 through December 2019, the AR Lab Network tested 76,887 CRE, CRPA, CRAB, and colonization screening specimens. Among the 42,006 CRE isolates tested, the genera identified most frequently were the three prioritized for AR Lab Network testing: *Klebsiella* spp., *E. coli*, and *Enterobacter* spp. (Table 1). Fifty-one public health laboratories (PHLs) conducted testing of additional *Enterobacterales* families and genera, accounting for 14% (n = 5,804) of all CRE isolates tested in the AR Lab Network. At least one targeted carbapenemase gene was detected in 35% (n = 14,562) of CRE isolates tested (Table 1); bla_{KPC} was the most common gene detected (86%; n = 12,540), followed by bla_{NDM} (9%; n = 1,378). The proportion of carbapenemase gene-positive CRE (CP-CRE) isolates and the frequency of specific carbapenemase genes varied by genus (Table 1). The most common genes detected among CP-CRE isolates, by genus, were bla_{KPC} in *Klebsiella* (92%; n = 9,224), *Enterobacter* (88%; n = 1,520), *Citrobacter* (92%; n = 431), and *Serratia* (98%; n = 190), bla_{NDM} in *Escherichia coli* (35%; n = 578), and bla_{IMP} in *Providencia* (79%; n = 81) and *Proteus* (54%; n = 61). More than one targeted gene was identified in 190 (<1%) of the CP-CRE isolates tested. The most common combinations were bla_{NDM} with $bla_{OXA\text{-}48\text{-}like}$ (60%; n = 114) and bla_{KPC} with bla_{NDM} (26%; n = 50). A single isolate harbored bla_{NDM}, bla_{VIM}, and $bla_{OXA\text{-}48\text{-}like}$ genes.

Among 30,390 CRPA isolates tested; 2% (n = 672) were CP-CRPA (Table 1). The most frequently detected carbapenemase gene among CP-CRPA isolates was bla_{VIM} (62%; n = 414), followed by bla_{KPC} (25%; n = 171). No CRPA isolate harboring the $bla_{OXA\text{-}48\text{-}like}$ gene was detected. Fifteen CP-CRPA isolates were positive for more than one targeted gene; these isolates carried bla_{IMP} and bla_{VIM} (n = 6), bla_{KPC} and bla_{VIM} (n = 4), bla_{NDM} and bla_{VIM} (n = 3), or bla_{NDM} and bla_{IMP} (n = 2).

Regional sentinel surveillance tested 4,491 CRAB isolates from 41 states. Targeted carbapenemase genes were detected in 39 (<1%) of the CRAB isolates submitted. Among CP-CRAB isolates, bla_{NDM} (69%; n = 27) and bla_{KPC} (31%; n = 12) were detected; bla_{IMP}, bla_{VIM} or $bla_{OXA\text{-}48\text{-}like}$ genes were not (Table 1).

Regional laboratories also tested 31,001 colonization screening swabs. Eight percent (n = 2,503) of screens were positive for at least one targeted gene, and bla_{KPC} (84%; n = 2,103) and bla_{NDM} (11%; n = 281) were the genes most frequently detected (Table 1). More than one carbapenemase gene was detected in 132 colonization screens; nine of these were positive for three carbapenemase genes. The most common gene combination among screens was bla_{KPC} and bla_{VIM} (37%; 49/132).

TABLE 1 Carbapenemase genes detected in carbapenem-resistant *Enterobacterales*, carbapenem-resistant *Pseudomonas aeruginosa*, and carbapenem-resistant *Acinetobacter baumannii* isolates and colonization screens according to the Antibiotic Resistance Laboratory Network, 2017 to 2019

Specimen type and organism	No. of specimens tested	No. (%) of specimens with ≥1 carbapenemase gene detected[a]	No (%) of specimens with carbapenemase gene[b]				
			bla$_{KPC}$	*bla*$_{NDM}$	*bla*$_{VIM}$	*bla*$_{IMP}$	*bla*$_{OXA-48-like}$
Carbapenem-resistant clinical isolates	76,887	15,273 (20)	12,723 (83)	1,452 (10)	531 (3)	225 (1)	549 (4)
Enterobacterales	42,006	14,562 (35)	12,540 (86)	1,378 (9)	117 (<1)	169 (1)	549 (4)
Enterobacteriaceae	37,418	13,883 (37)	12,064 (87)	1,342 (10)	105 (<1)	19 (<1)	534 (4)
Klebsiella spp.	16,753	10,004 (60)	9,224 (92)	573 (6)	40 (<1)	4 (<1)	289 (3)
Enterobacter spp.	12,191	1,734 (14)	1,520 (88)	173 (10)	39 (2)	13 (<1)	2 (<1)
Escherichia coli	7,258	1,641 (23)	865 (53)	578 (35)	8 (<1)	0 (0)	226 (14)
Citrobacter spp.	1,136	468 (41)	431 (92)	17 (4)	18 (4)	2 (<1)	6 (1)
Other[c]	80	36 (45)	24 (67)	1 (3)	0 (0)	0 (0)	11 (31)
Yersiniaceae							
Serratia spp.	1,101	194 (18)	190 (98)	1 (<1)	3 (2)	0 (0)	1 (<1)
Morganellaceae	2,291	239 (10)	62 (26)	22 (9)	7 (3)	149 (62)	2 (<1)
Proteus spp.	1,181	113 (10)	42 (37)	7 (6)	2 (2)	61 (54)	1 (<1)
Providencia spp.	482	103 (21)	6 (6)	11 (11)	5 (5)	81 (79)	1 (<1)
Morganella spp.	628	23 (4)	14 (61)	4 (17)	0 (0)	7 (33)	0 (0)
Hafniaceae							
Hafnia spp.	104	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Erwiniaceae							
Pantoea spp.	18	4 (22)	4 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Unknown/blank[d]	1,021	243 (24)	220 (91)	13 (5)	2 (<1)	1 (<1)	12 (5)
P. aeruginosa	30,390	672 (2)	171 (25)	47 (7)	414 (62)	56 (8)	0 (0)
A. baumannii	4,491	39 (<1)	12 (31)	27 (69)	0 (0)	0 (0)	0 (0)
Colonization screens	31,001	2,503 (8)	2,103 (84)	281 (11)	205 (8)	5 (<1)	51 (2)

[a]Carbapenemase gene detected if PCR positive for ≥1 of the five targeted carbapenemase genes tested.
[b]Genes are arranged by carbapenemase class; class B metallo-β-lactamase genes include *bla*$_{NDM}$, *bla*$_{VIM}$, and *bla*$_{IMP}$. Specimens with multiple carbapenemase genes detected were counted once in each gene category.
[c]Other genera included *Cronobacter*, *Kosakonia*, *Kluyvera*, *Leclercia*, *Pluralibacter*, *Raoultella*, and *Yokenella*.
[d]Isolates submitted to the public health laboratory as *Enterobacterales*, but genus and species not reported to CDC.

The volume of CRE and CRPA isolates tested and the percentage of isolates positive for any given targeted carbapenemase gene varied by region (Table 2). For example, the Northeast region detected the highest frequency of CP-CRE isolates (49%; n = 2,225), and the Central region detected the lowest (18%; n = 599). *bla*$_{VIM}$ (2%; n = 79) and *bla*$_{IMP}$ (8%; n = 50) genes were most frequently detected in the Midwest and Central regions, respectively, whereas *bla*$_{NDM}$ (16%; n = 351) was most frequently detected in the Northeast region. Among CRPA isolates, the West region detected *bla*$_{VIM}$ (76%; n = 60) most frequently, but *bla*$_{KPC}$ (54%; n = 27) and *bla*$_{NDM}$ (17%; n = 4) were detected most frequently in the Mid-Atlantic and Central regions, respectively. Among colonization screens, *bla*$_{KPC}$ (91%; n = 575) and *bla*$_{IMP}$ (1%; n = 5) were most frequently detected in the Mid-Atlantic region. In contrast, screens with *bla*$_{VIM}$ (13%; n = 69) were most frequently detected from the Southeast region, and screens with *bla*$_{NDM}$ (40%; n = 27) were most frequently detected from the Central region.

The carbapenem resistance profile among carbapenemase gene-positive CRE and CRPA is presented in Table 3. Generally, isolates with *bla*$_{NDM}$ showed the highest frequency of resistance across the different carbapenem drugs, whereas isolates with *bla*$_{IMP}$ and *bla*$_{OXA-48-like}$ showed lower frequencies of carbapenem resistance. Apart from imipenem resistance among *bla*$_{IMP}$ isolates, resistance to doripenem was the least predictive of carbapenemase presence among CRE. CRPA isolates harboring one of the metallo-β-lactamase (MBL) genes *bla*$_{IMP}$, *bla*$_{NDM}$, or *bla*$_{VIM}$, showed the highest frequency of resistance across carbapenems tested.

Among isolates tested for carbapenemase production and targeted carbapenemase genes, 97% of both CRE and CRPA isolates had concordant findings between the phenotypic and PCR tests (Table 4). A small subset of CRE (3%; n = 443) and CRPA (2%; n = 117) isolates were carbapenemase production positive, but PCR

TABLE 2 Regional distribution of carbapenemase genes detected in carbapenem-resistant *Enterobacterales*, carbapenem-resistant *Pseudomonas aeruginosa*, and carbapenem-resistant *Acinetobacter baumannii* isolates and colonization screens according to the Antibiotic Resistance Laboratory Network, 2017 to 2019

Specimen type and region[a]	No. of specimens tested	No. (%) of specimens with carbapenemase gene detected[b]	No. (%) of specimens with carbapenemase gene[c]				
			bla_{KPC}	bla_{NDM}	bla_{VIM}	bla_{IMP}	$bla_{OXA-48-like}$
Carbapenem-resistant *Enterobacterales*	42,006	14,562 (35)	12,540 (86)	1,378 (9)	117 (<1)	169 (1)	549 (4)
Central	3,419	599 (18)	457 (76)	61 (10)	(0)	50 (8)	36 (6)
Mid-Atlantic	7,941	3,427 (43)	3,079 (88)	238 (7)	7 (<1)	18 (<1)	139 (4)
Midwest	10,724	3,230 (30)	2,785 (86)	229 (7)	79 (2)	73 (2)	85 (3)
Mountain	4,318	1,322 (31)	1,111 (83)	150 (11)	9 (<1)	9 (<1)	59 (4)
Northeast	4,539	2,225 (49)	1,794 (81)	351 (16)	1 (<1)	4 (<1)	114 (5)
Southeast	6,166	2,209 (36)	2,035 (91)	143 (6)	16 (1)	6 (<1)	39 (2)
West	4,899	1,550 (32)	1,279 (81)	206 (13)	5 (<1)	9 (<1)	77 (5)
Carbapenem-resistant *P. aeruginosa*	30,390	672 (2)	171 (25)	47 (7)	414 (62)	56 (8)	0 (0)
Central	3,370	23 (<1)	4 (17)	4 (17)	12 (50)	4 (17)	0 (0)
Mid-Atlantic	3,122	50 (2)	27 (54)	7 (14)	13 (26)	3 (6)	0 (0)
Midwest	5,445	49 (<1)	10 (20)	6 (12)	33 (66)	1 (2)	0 (0)
Mountain	6,667	194 (3)	19 (10)	12 (6)	132 (67)	33 (17)	0 (0)
Northeast	3,890	129 (3)	51 (40)	10 (8)	67 (52)	1 (<1)	0 (0)
Southeast	3,838	154 (4)	58 (36)	3 (2)	97 (61)	2 (1)	0 (0)
West	4,058	73 (2)	2 (3)	5 (6)	60 (76)	12 (15)	0 (0)
Carbapenem-resistant *A. baumannii*	4,491	39 (<1)	12 (31)	27 (69)	0 (0)	0 (0)	0 (0)
Central	272	1 (<1)	1 (100)	0 (0)	0 (0)	0 (0)	0 (0)
Mid-Atlantic	708	19 (3)	2 (11)	17 (89)	0 (0)	0 (0)	0 (0)
Midwest	781	7 (<1)	2 (29)	5 (71)	0 (0)	0 (0)	0 (0)
Mountain	1,369	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Northeast	320	3 (<1)	2 (67)	1 (33)	0 (0)	0 (0)	0 (0)
Southeast	702	5 (<1)	2 (40)	3 (60)	0 (0)	0 (0)	0 (0)
West	339	4 (1)	3 (75)	1 (25)	0 (0)	0 (0)	0 (0)
Colonization screens	31,001	2,503 (8)	2,103 (84)	281 (11)	205 (8)	5 (<1)	51 (2)
Central	3,301	68 (2)	41 (60)	27 (40)	2 (3)	0 (0)	1 (1)
Mid-Atlantic	4,998	632 (13)	575 (91)	37 (6)	11 (2)	5 (<1)	22 (3)
Midwest	5,741	720 (13)	605 (84)	106 (15)	76 (11)	0 (0)	13 (2)
Mountain	2,504	144 (6)	119 (83)	4 (3)	16 (11)	0 (0)	5 (3)
Northeast	2,191	211 (10)	149 (71)	63 (30)	10 (5)	0 (0)	5 (2)
Southeast	9,923	543 (5)	457 (84)	34 (6)	69 (13)	0 (0)	5 (<1)
West	2,343	185 (8)	157 (85)	10 (5)	21 (11)	0 (0)	0 (0)

[a]Antibiotic Resistance Laboratory Network Regions are as follows: Central, AR, IA, KS, MN, MO, ND, NE, OK, and SD; Mid-Atlantic, DC, DE, MD, NC, PA, Philadelphia, SC, VA, and WV; Midwest, IL, IN, KY, MI, OH, and WI; Mountain, AZ, CO, Houston, ID, MT, NM, TX, UT, and WY; Northeast, CT, MA, ME, NH, NJ, NY, New York City, RI, and VT; Southeast, AL, FL, GA, LA, MS, Puerto Rico, and TN; and West, AK, CA, HI, LA County, NV, OR, and WA.

[b]Carbapenemase gene detected if PCR positive for ≥1 of the five targeted carbapenemase genes tested.

[c]Genes are arranged by carbapenemase class; class B metallo-β-lactamase genes include bla_{NDM}, bla_{VIM}, and bla_{IMP}. Specimens with multiple carbapenemase genes detected were counted once in each gene category.

negative. Antimicrobial susceptibility testing (AST) phenotypes suggested that 49% (n = 219) of these discordant CRE isolates were likely explained by the presence of hyperproduction of AmpC in *Enterobacter* (n = 114) or bla_{SME} (*Serratia marcescens* enzyme) in *Serratia* (n = 105). PCR testing and whole-genome sequencing of a subset of additional discrepant CRE and CRPA isolates identified additional mechanisms: two bla_{IMI} (imipenem-hydrolyzing β-lactamase) genes and a variety of β-lactamase genes were found among 8 CRE isolates; bla_{GES} (Guiana extended-spectrum β-lactamase) genes and/or other bla_{OXA} variants were detected in all 93 CRPA isolates sequenced. Less than 1% (n = 76) of CRE and CRPA isolates tested were carbapenemase production negative but PCR positive for the targeted carbapenemase genes. These discrepant PCR-positive isolates were reported from 27 different PHLs and across all targeted genes.

DISCUSSION

CDC established the AR Lab Network to provide nationwide laboratory capacity to rapidly detect antibiotic resistance and inform local responses to help contain the

TABLE 3 Carbapenem susceptibility testing data for carbapenem-resistant *Enterobacterales* and carbapenem-resistant *Pseudomonas aeruginosa* isolates, characterized by carbapenemase genes detected according to the Antibiotic Resistance Laboratory Network, 2018 to 2019

	No. (%) of isolates with carbapenemase gene[a]														
	bla_{KPC}			bla_{NDM}			bla_{VIM}			bla_{IMP}			$bla_{OXA-48-like}$		
Organism and drug	Tested	R	I	Tested	R	I	Tested	R	I	Tested	R	I	Tested	R	I
Carbapenem-resistant *Enterobacterales*[b]															
Ertapenem	7,279	6,501 (89)	615 (8)	796	789 (99)	6 (1)	69	55 (80)	12 (17)	106	88 (83)	11 (10)	279	224 (80)	47 (17)
Meropenem	7,160	5,868 (82)	605 (8)	803	787 (98)	9 (1)	73	63 (86)	2 (3)	95	67 (71)	9 (9)	273	124 (45)	36 (13)
Imipenem	6,026	4,806 (80)	859 (14)	714	694 (97)	15 (2)	71	65 (92)	2 (3)	91	42 (46)	35 (38)	236	95 (40)	53 (22)
Doripenem	4,140	2,097 (51)	1,091 (26)	345	321 (93)	17 (5)	19	11 (58)	2 (11)	49	28 (57)	11 (22)	200	54 (27)	30 (15)
Carbapenem-resistant *P. aeruginosa*[c]															
Meropenem	121	114 (94)	1 (1)	29	28 (97)	0 (0)	231	223 (97)	5 (2)	39	39 (100)	0	ND	ND	ND
Imipenem	111	104 (94)	1 (1)	28	28 (100)	0 (0)	228	225 (99)	2 (1)	37	36 (97)	0	ND	ND	ND
Doripenem[d]	55	48 (87)		21	21 (100)		131	128 (98)		33	33 (100)		ND	ND	ND

[a]Abbreviations: ND, not detected; R, resistant; I, intermediate. Genes are arranged by carbapenemase class; class B metallo-β-lactamase genes include bla_{NDM}, bla_{VIM}, and bla_{IMP}. Excluded are isolates with >1 carbapenemase gene detected. Not all isolates were tested for all drugs listed.

[b]Carbapenem-resistant *Enterobacterales* isolates tested at public health laboratories were defined as any clinical isolate of *Enterobacterales* resistant to ertapenem, imipenem, meropenem, or doripenem (MICs of $\geq$4 μg/ml for imipenem, meropenem, and doripenem or $\geq$2 μg/ml for ertapenem) at the submitting clinical laboratory. Interpretations were based on Clinical Laboratory and Standards Institute breakpoints.

[c]Carbapenem-resistant isolates of *Pseudomonas aeruginosa* tested at public health laboratories were defined as any clinical isolate of *P. aeruginosa* resistant to imipenem, meropenem, or doripenem (MICs of $\geq$8 μg/ml) at the submitting clinical laboratory. Interpretations were based on Clinical Laboratory and Standards Institute breakpoints.

[d]Excludes data from laboratories using commercial broth microdilution panels where intermediate and resistant doripenem interpretations could not be distinguished.

TABLE 4 Comparison of carbapenemase production and molecular testing results for carbapenem-resistant *Enterobacterales* and carbapenem-resistant *Pseudomonas aeruginosa* isolates according to the Antibiotic Resistance Laboratory Network, 2017 to 2019

Isolate characteristic(s)	No. (%) of carbapenem-resistant isolates	
	Enterobacterales[a]	*P. aeruginosa*
Total[a]	16,980	4,759
Carbapenemase production$^+$, PCR$^+$	9,638 (57)	468 (10)
Carbapenemase production$^-$, PCR$^-$	6,841 (40)	4,156 (87)
Carbapenemase production$^+$, PCR$^-$	443 (3)	117 (2)
Carbapenemase production$^-$, PCR$^+$	58 (<1)	18 (<1)

[a]Excludes *Serratia* isolates with AST phenotypes consistent with the presence of bla_{SME} (*Serratia marcescens* enzyme) (defined as resistant to carbapenems and susceptible to third-generation cephalosporins), *Enterobacter* species isolates with AST phenotypes suggestive of hyperproduction of AmpC (defined as resistant to cefotaxime, ceftriaxone, and ceftazidime and susceptible to cefepime), and isolates with missing modified carbapenem inactivation method (mCIM) or PCR testing results.

spread of resistance in the United States. By implementing state-of-the-art methods in PHLs, the AR Lab Network has improved our national infrastructure to detect and characterize novel and emerging resistance threats like carbapenemase gene-positive CRE, CRPA, and CRAB.

Although carbapenemase gene-positive organisms are not reportable throughout the United States, some systems do collect surveillance data on CRE, CRPA, and CRAB. For instance, health care settings report health care-associated infections caused by these organisms to the National Healthcare and Safety Network (NHSN). In 2018, carbapenem resistance was detected in 39.2%, 14.3%, and 2.7% of *A. baumannii*, *P. aeruginosa*, and *Enterobacterales* isolates tested, respectively (8). CDC's Multisite Gram-negative Surveillance Initiative (MuGSI), an active population- and laboratory-based surveillance activity that is part of the Emerging Infections Program, detected carbapenemase producers in 30% (n = 94/312) of CRE isolates tested from January 2011 to January 2014 and <1% (n = 1/391) of CRPA isolates tested from August 2016 to July 2017 (9, 10). Unlike NHSN and MuGSI, the AR Lab Network was not designed to be a traditional surveillance system, yet the frequency with which the AR Lab Network detected carbapenemase genes was similar to that of MuGSI, detecting at least one carbapenemase gene in 35% of CRE and 2% of CRPA isolates. Thus, the nationwide testing in the AR Lab Network is not only detecting carbapenemase genes in CRE and CRPA isolates at comparable frequencies to MuGSI, but also testing higher volumes of these relatively rare threats, thereby providing a wealth of data on the targeted mechanisms and the spread of these less common organisms domestically.

Data from the AR Lab Network not only substantiate existing literature that bla_{KPC} is the most common carbapenemase gene circulating in the United States (11, 12), but also highlight its dissemination into CRPA, CRAB, and the less common CRE genera, like *Citrobacter* and *Serratia* (13–16). Among jurisdictions routinely testing all CRE isolates, 20% of isolates from the less common genera were carbapenemase gene positive. This finding supports the concern that other genera can harbor and spread carbapenemase genes and highlights that testing less common CRE genera is important for detecting and controlling the spread of resistance (17, 18). As a result of these and other data collected through the AR Lab Network, some states subsequently implemented or updated their reporting laws to include additional CRE genera beyond *E. coli*, *Klebsiella*, and *Enterobacter* spp.

The five targeted carbapenemase genes were detected in only 39 of 4,491 CRAB isolates tested. Although still rare, the frequency of these carbapenemases in CRAB has increased annually in the AR Lab Network. Continued vigilance by rapid detection is essential for containing the spread of these genes in these already highly resistant organisms and preventing the difficult-to-treat infections they cause.

Currently, few FDA-approved drugs are available to treat infections caused by MBL-producing Gram-negative organisms (19–23). MBL genes were detected in only 3% of

all isolates tested, but their frequency varied by specimen type: they were present in 77% of CP-CRPA isolates, 69% of CP-CRAB isolates, 20% of positive colonization screens, and 11% of CP-CRE isolates detected. This is concerning because in addition to hydrolyzing carbapenems, MBLs are unaffected by newer β-lactamase inhibitors such as avibactam, vaborbactam, and relebactam. MBL producers do not hydrolyze the monobactam aztreonam; however, some also coexpress extended-spectrum β-lactamases (ESBLs) or AmpC, which inactivate monobactams, rendering aztreonam ineffective. This limits the treatment options for these highly resistant infections. Cefiderocol is one such option, and aztreonam-avibactam, which is still in phase 3 clinical trials but can be achieved through administration of two FDA-approved drugs (ceftazidime-avibactam and aztreonam), has also shown potent *in vitro* activity against bla_{NDM}-producing *Enterobacterales* (24).

A small subset of specimens tested in the AR Lab Network were found to carry multiple targeted carbapenemase genes. These specimens may represent novel threats for public health because the presence of more than one gene and/or more than one plasmid may provide increased opportunity for spread. In addition, although the clinical implications of these multimechanism organisms are not fully known, they could have negative implications for treatment (25). Organisms harboring genes from different Ambler classes of β-lactamases could further limit available treatment options for patients, particularly because most of these multimechanism isolates harbored at least one MBL gene. Additional studies have demonstrated increased MIC values associated with such multimechanism isolates and suggest they display increased virulence (26, 27).

Ninety-seven percent of CRE and CRPA isolates had concordant findings for carbapenemase production and targeted gene detection. Most of the observed differences in isolates with discordant findings could be explained by their AST profiles, false-negative carbapenemase production results, variations in the modified carbapenem inactivation method (mCIM) protocols used, and the presence of other resistance mechanisms. These findings not only support the sensitivity and specificity of mCIM for the detection of CP-CRE and CP-CRPA isolates, including its performance in the presence of weaker carbapenemase genes and variants, but also highlight its potential value in laboratories with limited resources (28–30). Facilities without molecular platforms to detect carbapenemase genes could use these tests for phenotypic detection of carbapenemase production to inform containment response efforts.

The AR Lab Network data show all CP-CRPA isolates were highly resistant to all carbapenems tested. In contrast, CRE isolates harboring $bla_{OXA\text{-}48\text{-}like}$ or bla_{IMP} had lower frequencies of resistance across the carbapenems tested. bla_{IMP}-positive CRE isolates displayed lower frequencies of resistance to imipenem (46%), particularly bla_{IMP}-positive *Enterobacter* spp. and species of the *Morganellaceae* family, compared with other genera tested in the Network. This observation has also been noted by others (31). Together, these findings suggest that performing AST using more than one carbapenem can facilitate detection of CP-CRE isolates more efficiently.

One key aspect of CDC's Containment Strategy is to respond to even a single case of an emerging AR threat to prevent its transmission. A pillar of this strategy is to conduct colonization screening of persons exposed to patients with confirmed cases. Eight percent of patient contacts screened from January 2017 through December 2019 were colonized with at least one carbapenemase gene-positive organism. These colonization screens informed infection control measures and detected potentially unrecognized carriers who could spread highly resistant bacteria to other patients and facilities (32).

The data presented in this report have several limitations. First, isolate testing was influenced by clinical laboratory network coverage and jurisdictional reporting and isolate submission laws; therefore, the data reported do not represent all clinical isolates of CRE, CRPA, or CRAB in the United States. Second, not all Network PHLs began testing at the same time. Third, specific assays were staggered in timing of deployment, validation, and implementation across the Network. For example, testing for bla_{IMP} variants beyond those detected by the Cepheid CarbaR was not initiated until 2018. Thus, the

number of bla_{IMP}-positive isolates reported was likely underrepresented during these years. Staggered test implementation also likely hampered the identification of all multimechanism isolates because some PHLs took a stepwise approach to PCR; if one PCR target was positive, no additional PCR targets were tested. Nevertheless, in 2018 CDC recommended comprehensive PCR testing to better detect multimechanism isolates, and 96% (n = 5,737) of mCIM-positive isolates from 2019 were tested against all validated targets. Fourth, characterization of CRAB isolates for sentinel surveillance did not include routine testing of additional oxacillinase genes (i.e., $bla_{OXA\text{-}23\text{-}like}$, $bla_{OXA\text{-}24/40\text{-}like}$, or $bla_{OXA\text{-}58\text{-}like}$) that are more common in *Acinetobacter* spp. Finally, our data include specimens collected for clinical diagnosis, surveillance, and outbreak investigations. Because of the confluence of these various public health activities, outbreak-associated testing and screenings likely increase the proportion of specimens that are carbapenemase gene-positive. But this confluence also points to how AR Lab Network testing has helped identify and contain outbreaks that could have gone otherwise undetected. Two well-publicized examples of large investigations facilitated through the AR Lab Network include an outbreak of bla_{VIM} CRPA infections associated with medical tourism to Tijuana, Mexico, and a regional outbreak of bla_{VIM} CRPA infections around Lubbock, TX (33, 34).

Antibiotic resistance is a global threat, and resistance mechanisms that were once novel are emerging and spreading rapidly in the United States (35, 36). As an essential component of CDC's Containment Strategy, the AR Lab Network offers flexibility with the capacity to incorporate new resistance targets and detection methods as threats emerge and technologies evolve. In 2019, the AR Lab Network deployed aztreonam-avibactam testing at regional laboratories to bridge the gap between clinical use of this drug combination and the availability of commercial susceptibility testing for this combination (19, 37–39). In addition, the Network has incorporated more whole-genome sequencing capacity to better detect and understand known and novel AR threats. By establishing national infrastructure for improved detection of carbapenemase gene-positive organisms in the United States, the AR Lab Network is helping health care facilities and public health partners identify and respond to AR threats quickly and improve patient safety.

MATERIALS AND METHODS

In 2016, CDC began funding the public health laboratories (PHLs) of all 50 states plus several cities and Puerto Rico to enhance their capacity to characterize clinical isolates of CRE and CRPA. Each PHL engages a network of clinical laboratories within their jurisdiction to submit bacterial isolates for phenotypic and molecular testing. The size and coverage of each PHL's network vary based on their jurisdiction's reporting laws and submission criteria for CRE and/or CRPA isolates. For jurisdictions lacking defined submission requirements, CDC recommends testing isolates from skilled nursing facilities with ventilator units, long-term acute care hospitals, or short-stay acute care hospitals because patients admitted to these facilities typically have multiple comorbidities and are at a higher risk of acquiring infections caused by multidrug-resistant Gram-negative bacilli (40).

In January 2017, testing in the AR Lab Network began. CRE is defined as any clinical *Enterobacterales* isolate resistant to ertapenem, imipenem, meropenem, or doripenem according to Clinical Laboratory and Standards Institute (CLSI) M100 guidelines (MICs of $\geq$4 μg/ml for imipenem, meropenem, and doripenem or $\geq$2 μg/ml for ertapenem) (41). The AR Lab Network prioritizes testing of *Escherichia coli*, *Klebsiella oxytoca*, *K. pneumoniae*, and *Enterobacter* spp. but encourages testing of additional *Enterobacterales* species where local capacity allows. CRPA and CRAB are defined, respectively, as any clinical isolate of *P. aeruginosa* or *A. baumannii* resistant to imipenem, meropenem, or doripenem according to CLSI M100 guidelines (MIC of $\geq$8 μg/ml) (41). No isolates are excluded based on specimen source.

PHLs in the Network perform organism identification, antimicrobial susceptibility testing (AST), carbapenemase production testing, and molecular detection of five targeted carbapenemase genes: bla_{KPC}, bla_{NDM}, $bla_{OXA\text{-}48\text{-}like}$, bla_{VIM}, and bla_{IMP}. Testing methods vary by PHL (see Table S1 in the supplemental material). For organism identification, most PHLs use matrix-assisted laser desorption ionization–time of flight (MALDI-TOF); some use Vitek 2 (bioMérieux, Marcy-l'Étoile, France), and/or biochemical methods. AST is most often performed using commercially available broth microdilution panels, disk diffusion, and/or gradient diffusion strips. Isolates are tested once against a range of drugs, including at least two carbapenems and two third-generation cephalosporins. Interpretations are based on the most updated version of CLSI M100 breakpoints where available; U.S. Food and Drug Administration breakpoints are used when no CLSI breakpoints were set (e.g., tigecycline) (41, 42). All but one PHL conducts carbapenemase production testing using the modified carbapenem inactivation method (mCIM); one lab uses CarbaNP exclusively (28, 29, 41).

Molecular detection of targeted carbapenemase genes is conducted using one or more PCR-based protocols and platforms, including CDC's laboratory-developed and validated methods (43–45), Gene Xpert Carba-R (Cepheid, Sunnyvale, CA), the ARM-D kit, β-Lactamase (Streck, Omaha, NE), and/or the Verigene Gram-negative blood culture system (Nanosphere, Northbrook, IL). Testing is conducted in accordance with CDC guidance and Clinical Laboratory Improvement Amendments (CLIA) requirements, when necessary.

Seven state PHLs also serve as "regional laboratories," to conduct sentinel surveillance and colonization screening by testing CRAB isolates and rectal swabs, respectively, from health care facilities in their region. For sentinel surveillance, each PHL recruits at least one clinical laboratory from their jurisdiction to submit all CRAB isolates to their regional laboratory for additional characterization. Screening is not limited to specific health facility types, is used to detect silent transmission of the targeted carbapenemase genes among patients, and includes testing epidemiologically linked contacts of patients found to have infections caused by a carbapenemase-positive organism. For rectal swabs collected for colonization screens, regional laboratories use the Gene Xpert Carba-R (Cepheid, Sunnyvale, CA) in accordance with the manufacturer's guidance to detect the presence of bla_{KPC}, bla_{NDM}, $bla_{OXA\text{-}48\text{-}like}$, bla_{VIM}, and $bla_{IMP\text{-}1}$ genes in rectal swabs collected for colonization screens. Regional laboratories attempt to culture gene-positive screens to identify the organisms carrying the genes detected.

Any testing for which a participating PHL is not validated, including supplemental testing of additional gene targets and drugs, is conducted by a regional laboratory or CDC. Thus, a small subset of isolates tested by state and local PHLs are submitted to their regional laboratory for additional characterization. Regional laboratories also conduct whole-genome sequencing to characterize a subset of isolates, including those with discordant carbapenemase production and PCR results (i.e., carbapenemase production positive but negative for the targeted carbapenemase genes), which may indicate the presence of a novel carbapenemase gene.

PHLs report results back to submitting clinical laboratories within two working days of testing completion. Colonization screening results are reported to submitting facilities and jurisdictional public health departments within one working day of completion. Testing results that require immediate public health actions to contain the spread of resistance are reported to jurisdictional public health departments and CDC within 1 day of completion.

PHLs submit testing results to CDC at least monthly. After each calendar year, data are reconciled to verify the number of isolates tested and the associated testing results. Each isolate is counted once, with testing results from each PHL consolidated with additional results submitted by its regional laboratory into one record. Each targeted carbapenemase gene detected is counted individually; therefore, the number of carbapenemase genes detected exceeds the number of isolates reported because some isolates carried more than one such gene. In all summary reports, organisms reported as *Enterobacter aerogenes* or *Klebsiella oxytoca*/*Raoultella ornithinolytica* are reclassified as *Klebsiella aerogenes* and *Klebsiella oxytoca*, respectively.

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.1 MB.

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