Gram-Negative Bacteria Harboring Multiple Carbapenemase Genes, United States, 2012–2019

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Reports of organisms harboring multiple carbapenemase genes have increased since 2010. During October 2012–April 2019, the Centers for Disease Control and Prevention documented 151 of these isolates from 100 patients in the United States. Possible risk factors included recent history of international travel, international inpatient healthcare, and solid organ or bone marrow transplantation.

Carbapenems have been standard treatments for multidrug-resistant gram-negative bacilli infections since 1985, when they were approved for clinical use in the United States (https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/050587s074lbl.pdf). Carbapenem-resistant organisms (CROs) are a growing public health concern as carbapenemase-producing CROs become more common (*1*). Several recent reports describe CROs carrying multiple carbapenemase genes (multi-CPOs) (*2*–*8*). We describe multi-CPOs reported to the Centers for Disease Control and Prevention (CDC; Atlanta, GA, USA) during 2012–2019.

The Study

CDC receives reports of carbapenemase-producing CROs from health departments, public health laboratories, healthcare facilities, and isolates sent to CDC for confirmatory testing. In 2016, CDC established the Antibiotic Resistance Laboratory Network (AR Lab Network), a national network of 55 public health laboratories that test carbapenem-resistant Enterobacterales (CRE), carbapenem-resistant *Pseudomonas aeruginosa* (CRPA), and carbapenem-resistant *Acinetobacter baumannii* (CRAB) isolates for carbapenemase genes.

We reviewed CDC and AR Lab Network reports of multi-CPOs identified during January 1, 2010–April 30, 2019. We defined a multi-CPO case as Enterobacterales, *Pseudomonas* spp., or *A. baumannii* isolated from any specimen source and carrying genes encoding >1 carbapenemase routinely tested for at CDC and the AR Lab Network (CRE, CRPA, and CRAB isolates were tested for *Klebsiella pneumoniae* carbapenemase [KPC], New Delhi metallo-β-lactamase [NDM], Verona integron-encoded metallo-β-lactamase [VIM], active-on-imipenem metallo-β-lactamase [IMP], and oxacillinase [OXA]-48–like β-lactamases; CRAB isolates also were tested for OXA-23, OXA-24/40, and OXA-58–like β-lactamases). Whole-genome sequencing (WGS) was conducted on a subset of isolates (Appendix, https://wwwnc.cdc.gov/EID/article/27/9/21-0456-App1.pdf). We defined an incident case as the first isolation of a unique organism–carbapenemase combination in each patient.

As part of routine public health investigations, health departments reviewed medical records and laboratory reports for patient demographic data and risk factors for exposure. We conducted descriptive analyses using SAS version 9.4 (https://www.sas.com) and calculated Pearson χ^2 score using SPSS Statistics 21.0 (IBM, https://www.ibm.com).

During January 2010–April 2019, a total of 151 multi-CPO isolates, including those from 105 incident cases, were identified in 100 unique patients; the first case was identified in October 2012 (Table 1; Appendix Tables 1,2). Among 89 (84.8%) incident cases

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Table 1. Incident cases of gram-negative bacilli harboring multiple carbapenemase genes, United States, January 2012–April 2019*

Organism	Carbapenemase combinations								
	NDM + OXA-48–like	KPC + NDM	KPC + VIM	NDM + VIM	KPC + OXA-48–like	NDM + IMP	NDM + OXA-23	NDM + OXA-48–like + VIM	Total, N = 105
Enterobacterales	64	23	6	0	2	0	0	1	96
Citrobacter freundii	0	0	1	0	1	0	0	0	2
Enterobacter cloacae	0	8	1	0	0	0	0	0	9
Escherichia coli	17	3	0	0	0	0	0	0	20
Klebsiella aerogenes	0	0	1	0	0	0	0	0	1
K. oxytoca	0	0	1	0	0	0	0	0	1
K. pneumoniae	46	12	2	0	1	0	0	1	62
Providencia rettgeri	1	0	0	0	0	0	0	0	1
Pseudomonadales	0	0	1	4	0	2	2	0	9
Pseudomonas aeruginosa	0	0	1	3	0	2	0	0	6
Pseudomonas fluorescens	0	0	0	1	0	0	0	0	1
Acinetobacter baumannii	0	0	0	0	0	0	2	0	2

*IMP, active-on-imipenem metallo-β-lactamase; KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase; VIM, Verona integron-encoded metallo-β-lactamase.

reported since AR Lab Network testing began in 2017, a total of 15 were reported in 2017, 51 in 2018, and 23 in the first 4 months of 2019. Among the isolates tested through the AR Lab Network during 2017–2019, a total of 111/28,390 (0.391%) CRE, 5/19,609 (0.025%) CRPA, and 2/2,443 (0.082%) CRAB isolates harbored multiple carbapenemase genes; we included CRAB isolates tested only during January 2018–April 2019. Incident cases were reported in 29 US states and the District of Columbia. Enterobacterales accounted for 96 (91.4%) of the incident multi-CPO cases; in addition, 7 (6.7%) were *Pseudomonas* spp. and 2 (1.9%) were *A. baumannii*. Among 96 incident Enterobacterales cases, the most common (46; 47.9%) organism–gene combination was *K. pneumoniae* harboring bla_{NDM} and $bla_{OXA-48-like}$.

WGS was conducted on 46 isolates from incident cases, identifying 6 sequence types of *Enterobacter cloacae*, 9 of *Escherichia coli*, and 11 of *K. pneumoniae*. WGS identified 21 isolates harboring bla_{NDM-1}, 16 harboring bla_{NDM-5}, 16 harboring $bla_{OXA-181}$, and 11 harboring bla_{KPC-3} (Appendix Table 2). In total, 8 incident cases were associated with 2 separate clusters at acute care hospitals.

The median age of patients at the time of multi-CPO identification was 63 years (range 2–94 years). Among 93 incident cases with available data, 62 (66.7%) occurred in patients who had traveled internationally in the 12 months before their incident culture. Among patients with a history of international travel, most (89.5%) had received inpatient healthcare while abroad. Association with international travel varied by carbapenemase combination; among 59 incident cases with available data that harbored bla_{NDM} and $bla_{OXA-48-like}$, 47 (79.7%) occurred in patients who reported international travel; only 5/19 (26.3%; $p<0.01$) incident cases that harbored bla_{KPC} and bla_{NDM} occurred in patients who reported international travel. Among the 80 incident cases with available data, 14 (17.5%) occurred in patients with a history of solid organ or bone marrow transplantation before their incident culture (Table 2).

Multi-CPOs in this convenience sample were identified in many states and included diverse organisms, sequence types, and carbapenemase gene combinations and variants, suggesting that clonal spread is not responsible for their emergence. Variants harboring bla_{KPC-4} and bla_{NDM-4}, which are uncommon in the United States, were identified (*9*–*11*). Most incident cases of CROs harboring multiple carbapenemase genes occurred in patients who had a recent history of international travel and inpatient healthcare outside the United States; we also identified history of solid organ or bone marrow transplant as a potential risk factor.

Receiving healthcare abroad and, more recently, international travel without medical care are risk factors for acquiring carbapenemase-producing organisms among patients in the United States (*9*). However, in this study, one third of cases occurred in persons without known recent travel outside the United States. For some carbapenemase combinations, such as isolates harboring bla_{KPC} and $bla_{NDM,}$ most cases occurred in patients who had not recently traveled internationally. In addition, identifying facility clusters raises further concerns about dissemination of these multidrug-resistant organisms among healthcare facilities in the United States.

The emergence of multi-CPOs has clinical, laboratory testing, and public health implications. The ceftazidime/avibactam, meropenem/vaborbactam, and imipenem/cilastatin/relebactam combination therapies have increased treatment options for CREs that produce KPC and OXA-48–like carbapenemases; growth in the proportion of isolates that co-harbor

Table 2. Characteristics and exposures of incident cases of gram-negative bacilli harboring multiple carbapenemase genes, United States, January 2012–April 2019*

Characteristics and exposures	Enterobacterales†				*Pseudomonas* spp.,‡ KPC + VIM, NDM + VIM, or NDM + IMP	*Acinetobacter baumannii*, NDM + OXA-23	Total
	NDM + OXA-48§	KPC + NDM	KPC + VIM	KPC + OXA-48			
Total no. (%) cases	65 (100.0)	23 (100.0)	6 (100.0)	2 (100.0)	7 (100.0)	2 (100.0)	105 (100.0)
Region of specimen collection¶							
South	22/65 (33.8)	9/23 (39.1)	2/6 (33.3)	0	3/7 (42.9)	1/2 (50.0)	37/105 (35.2)
West	22/65 (33.8)	3/23 (13.0)	2/6 (33.3)	0	1/7 (14.3)	0	28/105 (26.7)
Northeast	14/65 (21.5)	5/23 (21.7)	0	0	2/7 (28.6)	0	21/105 (20.0)
Midwest	7/65 (10.8)	6/23 (26.1)	2/6 (33.3)	2/2 (100.0)	1/7 (14.3)	1/2 (50.0)	19/105 (18.1)
Location of specimen collection							
Acute care hospital	51/57 (89.5)	18/22 (81.8)	3/4 (75.0)	2/2 (100.0)	5/7 (71.4)	0	79/94 (84.0)
Outpatient facility	5/57 (8.8)	1/22 (4.5)	0	0	2/7 (28.6)	1/2 (50.0)	9/94 (9.6)
Long-term acute care hospital	0	1/22 (4.5)	1/4 (25.0)	0	0	1/2 (50.0)	3/94 (3.2)
Skilled nursing facility	0	2/22 (9.1)	0	0	0	0	2/94 (2.1)
Joint acute care hospital/ inpatient rehabilitation facility	1/57 (1.8)	0	0	0	0	0	1/94 (1.1)
Hospitalization in previous 12 mo, United States#	44/56 (78.6)	19/23 (82.6)	4/5 (80.0)	2/2 (100.0)	4/7 (57.1)	2/2 (100.0)	75/95 (78.9)
International travel in previous 12 mo**							
Yes	47/59 (79.7)††	5/19 (26.3)††	1/4 (25.0)	1/2 (50.0)	7/7 (100.0)	1/2 (50.0)	62/93 (66.7)
International inpatient healthcare‡‡	40/43 (93.0)	3/4 (75.0)	0/1	0/1	6/7 (85.7)	1/1 (100.0)	51/57 (89.5)
India	29/39 (74.4)	1/3 (33.3)		1/1 (100.0)	3/6 (50.0)	1/1 (100.0)	35/50 (70.0)
Other§§	5/39 (12.8)	2/3 (66.7)		0	2/6 (33.3)	0/1	9/50 (18.0)
Pakistan	3/39 (7.7)	0/3		0/1	0/6	1/1 (100.0)	4/50 (8.0)
Egypt	2/39 (5.1)	0/3		0/1	0/6	0/1	2/50 (4.0)
Vietnam	1/39 (2.6)	0/3		0/1	1/6 (16.7)	0/1	2/50 (4.0)
No	12/59 (20.3)	14/19 (73.7)	3/4 (75.0)	1/2 (50.0)	0/7	1/2 (50.0)	31/93 (33.3)
US hospitalization	11/12 (91.7)	12/14 (85.7)	3/3 (100.0)	1/1 (100.0)		1/1 (100.0)	28/31 (90.3)
Transplant recipient¶¶	11/48 (22.9)	4/17 (23.5)	0/5	1/2 (50.0)	1/6 (16.7)	0/2	17/80 (21.3)
Before incident case	8/11 (72.7)	4/4 (100.0)		1/1 (100)	1/1 (100.0)		14/17 (82.4)
Transplant to incident case, d, median (IQR)							44 (15–446)
After incident case	3/11 (27.3)	0/4		0/1	0/1		3/17 (17.6)
Incident case to transplant, d, median (IQR)							96 (28–188)
Type of transplant##							
Solid organ	11/11 (100.0)	2/4 (50.0)		0/1	0/1		13/17 (76.5)
Kidney	7/11 (63.6)	0/2					7/13 (53.8)
Liver	3/11 (27.3)	1/2 (50.0)					4/13 (30.8)
Lung	1/11 (9.1)	1/2 (50.0)					2/13 (15.4)
Bone marrow	0/11	2/4 (50.0)		1/1 (100.0)	1/1 (100.0)		4/17 (23.5)

*Values are no. cases/total no. in category (%) except as indicated. Three incident cases occurred in 3 patients who reported no international travel or hospitalization in the United States during the previous 12 mo (1 case of *E. coli* harboring *bla*$_{NDM}$ and *bla*$_{KPC}$, 1 case of *K. pneumoniae* harboring *bla*$_{NDM}$ and *bla*$_{KPC}$, and 1 case of *E. coli* harboring *bla*$_{NDM}$ and *bla*$_{OXA-48-like}$). Among these patients, 1 was a nursing home resident, 1 did not have additional information provided, and 1 had a spouse who had traveled to India and returned ≈1 mo before their incident case. Exposures are described for the 12 mo before identification of incident case. IMP, active-on-imipenem metallo-β-lactamase; KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase; VIM, Verona integron-encoded metallo-β-lactamase.
†*Citrobacter freundii*, *Enterobacter cloacae*, *Escherichia coli*, *Klebsiella aerogenes*, *K. oxytoca*, *K. pneumoniae*, and *Providencia rettgeri* isolates.
‡*Pseudomonas aeruginosa* and *Pseudomonas fluorescens* isolates.
§Includes 1 *K. pneumoniae* isolate harboring *bla*$_{NDM}$, *bla*$_{OXA-48-like}$, and *bla*$_{VIM}$.
¶Based on census regions of residence (US Census Bureau, https://www2.census.gov/geo/pdfs/maps-data/maps/reference/us_regdiv.pdf).
#Of 90 unique patients who contributed 95 incident cases with complete data.
**Of 88 unique patients who contributed 93 incident cases with complete data.
††Significant difference; p<0.01. Exclusion of incident cases associated with an outbreak or cluster did not change this association: 47/56 (83.9%) incident cases harboring *bla*$_{NDM}$ and *bla*$_{OXA-48-like}$ occurred in patients who reported international travel, compared with 4/14 (28.6%; p<0.01) with *bla*$_{KPC}$ and *bla*$_{NDM}$.
‡‡Two patients reported international inpatient healthcare in 2 countries.
§§One hospitalization in Bangladesh, 1 in Columbia, 1 in Iraq, 1 in Mexico, 1 in Nigeria, 1 in Tajikistan, 1 in Thailand, 1 in Turkey, and 1 in Yemen.
¶¶Solid organ or bone marrow transplants; of 75 unique patients who contributed 80 incident cases with complete data.
##Of includes 17 unique patients who contributed 17 incident cases with complete data.

bla_{NDM} jeopardizes the usefulness of these therapies. We noted 1 *P. aeruginosa* isolate harboring bla_{NDM-1} and bla_{IMP-1}; this isolate was panresistant to all antimicrobial drugs tested (*12*). A high proportion (17.5%) of cases occurred among patients with history of solid organ or bone marrow transplantation before their index culture, a population for whom CRO infections are associated with worse outcomes than patients without transplants (*13*,*14*). In comparison, only 3.1% of patients with CRE reported to the Multi-Site Gram-Negative Surveillance Initiative at CDC during 2012–2019 had a history of transplant before their positive culture (*15*; I. See, CDC, pers. comm., 2021 Jan 19); whether multi-CPOs are emerging in this population requires careful monitoring. Finally, hierarchical testing algorithms, in which testing is halted after detection of an initial carbapenemase, might not identify additional, less common carbapenemases (e.g., hierarchical testing might not identify bla_{VIM} in an isolate with bla_{KPC} and bla_{VIM}).

The first limitation of our analysis is that these data represent a passively reported convenience sample during a period in which multiple changes in testing practices, including the establishment of the AR Lab Network, occurred. For this reason, we cannot determine whether multi-CPOs became more common during the evaluation period. Second, CROs from patients with a history of healthcare abroad might have been selected for mechanism testing, biasing detection toward this risk factor; bias might have been more influential early in the investigation period, when testing resources were limited. Finally, this analysis did not systematically document outpatient healthcare exposures and residence in long-term care facilities, which also might be relevant sources of exposure; 1 case in this analysis was associated with invasive urologic procedures abroad (*7*).

Conclusions

Multi-CPOs in healthcare facilities are an emerging concern in the United States. Although hospitalization outside the United States was the most common risk factor, we found a substantial proportion of cases that were probably acquired in healthcare facilities in the United States. Several measures might slow further spread. First, screening patients who were recently hospitalized outside the United States can help prevent additional introductions of carbapenemase genes not commonly found in the United States. Second, molecular testing to identify carbapenemase genes should not use hierarchical algorithms. Finally, when a multi-CPO is identified, public health officials should assess for potential transmission (https://www.cdc.gov/hai/containment/guidelines.html).

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Appendix

Appendix Methods

Laboratory Methods for Molecular Detection of Carbapenemase Genes

Molecular detection of targeted carbapenemase genes was conducted using ≥1 PCR-based protocols and platforms, namely the Centers for Disease Control and Prevention (CDC)'s laboratory-developed and validated methods, Gene Xpert Carba-R (Cepheid, https://www.cepheid.com), ARM-D β-Lactamase (Streck, https://www.streck.com), and Verigene Gram-Negative Blood Culture System (Nanosphere, http://www.nanosphere.us). Laboratories used the modified carbapenem inactivation method (mCIM) or CarbaNP as phenotypic tests to determine whether an organism is carbapenemase-producing (https://arpsp.cdc.gov/resources/arln-psp-technical-appendix.pdf).

Changes in Laboratory Testing Protocols During Investigation Period

Beginning in January 2017, laboratories in the Antibiotic Resistance Laboratory Network tested for New Delhi metallo-β-lactamase, *Klebsiella pneumoniae* carbapenemase, Verona integron-encoded metallo- β-lactamase, active-on-imipenem metallo-β-lactamase, and oxacillinase-48–like β-lactamases. Not all laboratories initially tested all isolates for all gene targets. Some laboratories instituted hierarchical testing algorithms; if *bla*$_{KPC}$ and *bla*$_{NDM}$ were not detected, the isolates were tested for additional targets validated in their testing menu. If carbapenemase-producing (i.e., testing positive by the modified carbapenem inactivation method or CarbaNP) isolates were negative for all targets tested, the laboratories forwarded the isolate to their regional laboratory or CDC for additional characterization. In November 2017, CDC deployed PCR specific to additional *bla*$_{IMP}$ variants not identified by Gene Xpert Carba-R. In November 2018, CDC deployed PCR that detects additional oxacillinases commonly associated

with *Acinetobacter* spp. (i.e., *bla*$_{\text{OXA-23}}$, *bla*$_{\text{OXA-24/40}}$, *bla*$_{\text{OXA-58}}$). After approval, these the assays were made available to the Antibiotic Resistance Laboratory Network and were validated and implemented at different times by laboratories in the network.

Whole-Genome Sequencing (WGS) Methods

Results were obtained from CDC and 4 state public health laboratories (SPHLs) that commonly performed WGS on carbapenemase-producing, carbapenem-resistant organisms harboring multiple carbapenemase genes. We report results on carbapenemase gene variants and sequence types determined by multilocus sequence typing (MLST).

WGS at SPHL 1

Isolates were extracted using the Qiagen DNeasy Blood & Tissue kit (QIAGEN, https://www.qiagen.com) and DNA libraries were prepared using the PulseNet Illumina Nextera XT protocol before being loaded on the Illumina MiSeq (Illumina, https://www.illumina.com). Carbapenemase variants were identified using ABRicate (https://github.com/tseemann/abricate). MLST was performed at CDC.

WGS at SPHL 2

DNA was extracted with the Qiagen DNeasy Blood & Tissue Kit (QIAGEN and libraries were prepared with the Illumina Nextera XT Kit and sequenced with a MiSeq version 3.0 600-cycle Kit (Illumina). Reads were assembled with CLC Genomics Workbench (QIAGEN), and assemblies were submitted to the ResFinder tool for antimicrobial resistance gene prediction or the MLST tool for in silico MLST.

WGS at SPHL 3

Genomic DNA was extracted from isolates using the DNeasy Blood & Tissue Kit on a QIAcube (QIAGEN). Sequence libraries were prepared using the Nextera XT DNA Sample Preparation Kit and sequenced on the Illumina MiSeq system (Illumina).

Raw Illumina reads were processed with Trimmomatic version 0.38 (*1*) and paired, 250 bp reads were then de novo assembled into contigs with SPAdes version 3.12.0 (*2*). Assembly quality was assessed using quantitative measurements, including BUSCO version 3.1.0 (*3*,*4*), before MLST with mlst v2.16.2 (https://github.com/tseemann/mlst) and AR gene identification with ABRicate version 0.8.13 (https://github.com/tseemann/abricate). Final analysis of the AR

genes in the genome assembly compared gene identification between the National Center for Biotechnology Information Bacterial Antimicrobial Resistance Reference Gene Database (*5*), ResFinder (*6*), and Comprehensive Antibiotic Resistance Database (*7*) to determine the best matches.

WGS at SPHL 4

DNA extraction was performed on the Magnapure 24 automated platform (Roche Molecular Systems, https://www.roche.com). Whole genome sequencing was performed using Illumina Miseq (Illumina). Following sequencing, de novo assembly was performed using CLC Genomics Workbench (QIAGEN), and the resistance gene profile is analyzed through CGE's Resfinder database. MLST was performed using the Linux-based program MLST by Torsten Seeman, which uses the available schemes found in pubmlst (https://github.com/tseemann/mlst).

WGS at CDC

Genomic DNA was extracted using Promega Maxwell 16 MDx Instrument and Maxwell 16 Cell Low Elution volume DNA Purification Kit (Promega Corporation, https://www.promega.com). WGS was performed using the Illumina MiSeq System and MiSeq Reagent version 2.0 kit, generating 2 × 250 paired-end reads (Illumina).

The WGS data was processed with the QuAISAR-H pipeline (Quality, Assembly, species Identification, Sequence typing, Annotation, Resistance mechanisms for Healthcare pathogens, https://github.com/DHQP/QuAISAR_singularity/). The pipeline includes species verification using pyani (*8*), identification of MLST using PubMLST definitions (*9*), and antibiotic resistance gene calling using GAMMA (https://github.com/rastanton/GAMMA) against a database constructed from the nonredundant entries in the ARG-ANNOT (*10*), NCBI AMRFinder (*5*), and ResFinder (*11*) antimicrobial resistance databases.

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Appendix Table 1. Specimen sources of incident cases of gram-negative bacilli harboring multiple carbapenemase genes, United States, January 2012–April 2019*

	Carbapenemase combinations								
Source	NDM + OXA-48–like	KPC + NDM	KPC + VIM	NDM + VIM	KPC + OXA-48–like	NDM + IMP	NDM + OXA-23	NDM + OXA-48–like + VIM	Total, N = 105
Urine	37	8	3	3	0	2	1	1	55
Blood	7	3	1	1	1	0	0	0	13
Respiratory	5	6	2	0	0	0	0	0	13
Rectal swab	5	5	0	0	0	0	1	0	11
Other†	6	0	0	0	0	0	0	0	6
Wound	2	1	1	0	0	0	0	0	4
Peritoneal fluid	1	0	0	0	1	0	0	0	2
Unknown	1	0	0	0	0	0	0	0	1

*IMP, active-on-imipenem metallo-β-lactamase; KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase; VIM, Verona integron-encoded metallo-β-lactamase.
†Comprises 1 sample from abdomen, 1 from an abscess, 1 from penile exudate, 1 from a foot, 1 from the peritoneal cavity, and 1 from pleural fluid.

Appendix Table 2. Sequence types and gene variants of incident cases of gram-negative bacilli harboring multiple carbapenemases, United States, January 2012–April 2019*

	Carbapenemase combinations (no.)					
STs and gene variants†	NDM + OXA-48–like	KPC + NDM	KPC + VIM	NDM + VIM	NDM + IMP	NDM + OXA-48–like + VIM
Enterobacterales						
Enterobacter cloacae						
ST78		KPC-4, NDM-1 (1)				
ST91		KPC-3, NDM-7 (1)				
ST114		KPC-3, NDM-1 (1)				
ST171		KPC-3, NDM-1 (1)				
ST597		KPC-4, NDM-7 (2)				
ST729		KPC-3, NDM-1 (2)				
Escherichia coli						
ST2	NDM-5, OXA-181 (1)					
ST39		KPC-3, NDM-4 (1)				
ST167/2		KPC-4, NDM-5 (1)				
ST361	OXA-181 (1)‡					
ST398		KPC-3, NDM-5 (1)				
ST635	NDM-5, OXA-181 (1)					
ST648	NDM-7, OXA-181 (1)					
ST940	NDM-7, OXA-181 (1)					
ST8346	NDM-5, OXA-181 (1)					
Klebsiella pneumoniae						
ST14	NDM-1, OXA-232 (1)					
ST15	NDM-1, OXA-181 (1); NDM-1 (1)§	KPC-3, NDM-1 (1)				
ST16	NDM-5, OXA-181 (1)					

STs and gene variants†	Carbapenemase combinations (no.)					
	NDM + OXA-48–like	KPC + NDM	KPC + VIM	NDM + VIM	NDM + IMP	NDM + OXA-48–like + VIM
ST147	NDM-5, OXA-181 (4); NDM-5, OXA-232 (2)	KPC-3, NDM-1 (1)				
ST163		KPC-3, NDM-1 (1)				
ST231	NDM-1, OXA 181 (2); NDM-5, OXA-232 (1)					
ST395	NDM-5, OXA-232 (1)					
ST859	NDM-1, OXA-181 (1)					
ST983	NDM-5, OXA-48 (1)					
ST2497	NDM-1, OXA-232 (1)					
ST3392	NDM-1, OXA-232 (1)					
Novel			KPC-2, VIM-4 (1)			NDM-5, OXA-232, VIM-2 (1)
Unknown		KPC-3, NDM-1 (1)	KPC-2, VIM-4 (1)			
Providencia rettgeri						
Unknown	NDM-1, OXA-181 (1)					
Pseudomonadales						
Pseudomonas aeruginosa						
ST244					IMP-1, NDM-1 (1)	
Unknown					IMP-15, NDM-1 (1)	
Pseudomonas fluorescens (unknown ST)				NDM-1, VIM-2 (1)		

*Three *K. pneumoniae* incident cases harboring *bla*$_{NDM}$ and *bla*$_{OXA-48-like}$ were associated with an outbreak at an acute care hospital. Of the 3 isolates, 2 underwent WGS; they were identified as ST147 harboring *bla*$_{NDM-5}$ and *bla*$_{OXA-181}$. In a separate cluster at an acute care hospital, an additional 5 incident cases harboring *bla*$_{KPC}$ and *bla*$_{NDM}$ (3 *E. cloacae* and 2 *K. pneumoniae*) were identified during a 16-mo period. WGS of 4 of these 5 isolates demonstrated that all harbored *bla*$_{KPC-3}$ and *bla*$_{NDM-1}$ and that 2 isolates were *E. cloacae* ST729, 1 was *E. cloacae* ST114, and 1 was *K. pneumoniae* ST163. Excluding these 8 cases linked to clusters, 97 incident cases were identified in 29 US states and the District of Columbia; only 19 (19.6%) incident cases with the same organism–mechanism combination were identified from the same state within the same 90-d period, making it unlikely that small outbreaks were the primary cause of cases. IMP, active-on-imipenem metallo-β-lactamase; KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase; ST, sequence type; VIM, Verona integron-encoded metallo-β-lactamase; WGS, whole-genome sequencing.

†Determined by WGS.

‡WGS did not detect *bla*$_{NDM}$. The mobile genetic element carrying *bla*$_{NDM}$ might have been lost before sequencing, which was conducted ≈3–5 wks after initial characterization.

§WGS did not detect *bla*$_{OXA-48-like}$. The mobile genetic element carrying *bla*$_{OXA-48-like}$ might have been lost before sequencing, which was conducted ≈3–5 wks after initial characterization.