Carbapenemase production among less-common Enterobacterales genera: 10 US sites, 2018

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Background: Historically, United States’ carbapenem-resistant Enterobacterales (CRE) surveillance and mechanism testing focused on three genera: Escherichia, Klebsiella, and Enterobacter (EsKE); however, other genera can harbour mobile carbapenemases associated with CRE spread.

Objectives: From January through May 2018, we conducted a 10 state evaluation to assess the contribution of less common genera (LCG) to carbapenemase-producing (CP) CRE.

Methods: State public health laboratories (SPHLs) requested participating clinical laboratories submit all Enterobacterales from all specimen sources during the surveillance period that were resistant to any carbapenem (Morganellaceae required resistance to doripenem, ertapenem, or meropenem) or were CP based on phenotypic or genotypic testing at the clinical laboratory. SPHLs performed species identification, phenotypic carbapenemase production testing, and molecular testing for carbapenemases to identify CP-CRE. Isolates were categorized as CP if they demonstrated phenotypic carbapenemase production and ≥1 carbapenemase gene (blaKPC, blaNDM, blaVIM, blaIMP, or blaOXA-48-like) was detected.

Results: SPHLs tested 868 CRE isolates, 127 (14.6%) were from eight LCG. Overall, 195 (26.3%) EsKE isolates were CP-CRE, compared with 24 (18.9%) LCG isolates. LCG accounted for 24 (11.0%) of 219 CP-CRE identified. Citrobacter spp. was the most common CP-LEC; the proportion of Citrobacter that were CP (11/42, 26.2%) was similar to the proportion of EsKE that were CP (195/741, 26.3%). Five of 24 (20.8%) CP-LCG had a carbapenemase gene other than blaKPC.

Conclusions: Participating sites would have missed approximately 1 in 10 CP-CRE if isolate submission had been limited to EsKE genera. Expanding mechanism testing to additional genera could improve detection and prevention efforts.
Introduction

Enterobacterales (which has now replaced the former Family Enterobacteriaceae) is a large taxonomic Order encompassing seven families and more than 80 genera of Gram-negative bacteria.\(^1\) It includes pathogens from three genera associated with 30% of healthcare-associated infections (HAIs) in adults in the United States: Escherichia coli, Klebsiella spp., and Enterobacter spp.,\(^4\) and many less-common pathogens that can cause complicated infections, such as Proteus spp., Citrobacter spp., and Serratia spp.\(^5\) Carbenapenem are broad-spectrum antibiotics and a mainstay of treatment for serious Enterobacteriales infections; however, their efficacy can be compromised by multiple distinct resistance mechanisms.\(^8\)\(^-\)\(^11\) Carbenapenemase enzymes, the most concerning of these mechanisms, are β-lactamas that inactivate most or all β-lactam antibiotics. Most carbenapenemases are encoded by genes located on mobile genetic elements (MGEs), which can be efficiently transferred between bacterial taxa.\(^8\)\(^-\)\(^13\) These MGEs also frequently carry additional genes that confer resistance to non-β-lactam antibiotics, further limiting treatment options for carbenapenem-producing carbenapenem-resistant Enterobacteriales (CP-CRE) infections.\(^8\)\(^,\)\(^10\)\(^,\)\(^14\) Owing to the potential for rapid spread of multidrug resistance, CP-CRE surveillance and prevention has been a US public health priority since cases were first identified domestically.\(^11\)\(^,\)\(^12\)\(^,\)\(^15\) Overall, 34.7% of CRE from US patients have a carbenapenemase gene detected.\(^15\) Among CP-CRE tested through the Antibiotic Resistance (AR) Laboratory Network, Klebsiella pneumoniae carbenapenem (bla\(_{KPC}\)) is the most-common gene identified by far, found in 85.7% of CP-CRE isolates. Other carbenapenemase genes are more rare: 9.8% of CP-CRE isolates harbour New Delhi metallo-β-lactamase (bla\(_{NDM}\)), 3.9% carry oxacillinase (bla\(_{OXA-48\text{-like}}\)), 1.3% carry active-on-imipenem (bla\(_{IMP}\)), and 0.8% carry Verona integron-encoded metallo-β-lactamase (bla\(_{VIM}\)).\(^15\)

In the United States, increased reports of carbenapenem-resistant Klebsiella pneumoniae and E. coli HAIs in the early 2000s, followed by more recent decreases, have been attributed in part to the initial spread of, and subsequent public health efforts to control, CP-CRE.\(^11\)\(^,\)\(^12\)\(^,\)\(^16\) These control efforts prioritize early detection of clinical cases and contact screening to identify asymptomatic carriage, even for single cases of emerging carbenapenemases.\(^11\)\(^,\)\(^12\)\(^,\)\(^16\) Public health surveillance programmes have been especially critical to detection and control of CP-CRE because of limited clinical laboratory testing. In a national survey of US hospitals, only half reported being served by a laboratory that tests CRE for mechanism testing (i.e., a combination of phenotypic testing for carbenapenemase enzymatic activity and molecular testing for carbenapenemase genes), less-common Enterobacteriales species were accepted. Ad hoc submissions over the first 9 months of isolate collection in 2017 identified carbenapenemases in 21% of CRE from LCG, suggesting carbenapenemases of public health concern might be more common in these organisms than previously recognized.\(^11\)\(^,\)\(^13\) We conducted a 5 month, 10 state surveillance project to determine what proportion of CRE from LCG were carbenapenemase-producing, and the overall contribution of LCG to the burden of CP-CRE in the areas under surveillance.

Materials and methods

From 1 January through 31 May, 2018, 10 state public health laboratories (SPHLs) volunteered to conduct systematic surveillance, aligned with US public health laboratory capabilities and mission (https://www.cdc.gov/drugresistance/laboratories.html), to assess carbenapenemase production in all species of carbenapenem-resistant Enterobacteriales identified at clinical laboratories. Arizona, Minnesota, Nebraska and Wisconsin included isolates from all clinical laboratories statewide. The remaining states identified a total of 25 sentinel clinical laboratories to participate, including four laboratories in Indiana, six in Maryland, two in Michigan, four in North Carolina, six in Tennessee, and four in Washington.

All states except for North Carolina had a public health CRE reporting mandate during the study period and six states required isolate submission to the SPHL; however, CRE definitions and target organism (e.g., CRE versus CP-CRE) varied by jurisdiction.

We defined CRE as any Enterobacteriales resistant to any carbenapenem antibiotic (MIC ≥4 mg/L for doripenem, imipenem, and meropenem, and ≥2 mg/L for ertapenem)\(^9\) or demonstrating the presence of a carbenapenemase by a phenotypic or genotypic test at the clinical laboratory. For organisms from the Morganellaceae family with intrinsic low-level imipenem resistance, resistance to doripenem, ertapenem, or meropenem was required for submission. SPHLs requested their participating clinical laboratories to submit all CRE isolated from any specimen source; in addition to clinical cultures, CRE isolated from active surveillance cultures at facilities served by the participating laboratories may have been forwarded to SPHLs.

SPHLs performed species identification using MALDI-ToF MS [nine SPHLs used Bruker (Billerica, MA); the MD SPHL used bioMérieux (Marcy-l’Étoile, France)]. Confirmed Enterobacteriales species underwent phenotypic carbenapenemase production testing using the modified carbenapenem inactivation method (mCIM)\(^23\) and broth microdilution AST using Sensititre\(^{TM}\) GNX2F or GN4F plates (Thermo Fisher Scientific, Waltham, MA). Isolates with carbenapenemase activity were tested by PCR for genes encoding KPC, NDM, OXA-48-like, VIM, and IMP carbenapenemases.\(^24\)\(^,\)\(^25\) PCR-based methods varied by state and included in-house laboratory developed assays, CDC-developed assays, and GeneXpert Carba-R\(^{TM}\) (Cepheid, Sunnyvale, CA). Isolates that demonstrated carbenapenemase activity via the mCIM test, but did not have a carbenapenemase gene detected, were re-tested at CDC by PCR for the five common carbenapenemases; S. marcescens and Enterobacter
spp. were additionally tested by conventional PCR for the presence of \( \beta \text{LAM}_{\text{ES}} \) and imipenem-hydrolysing-\( \beta \text{-lactamase} \) (\( \beta \text{LAM}_{\text{IM}} \))/non-metallo-\( \beta \text{-lactamase} \) (\( \beta \text{LAM}_{\text{NN}} \)) genes, respectively (CDC, unpublished data).

SPHLS submitted testing data to CDC for collation and analysis. We excluded isolates not tested according to the specified algorithm and included only the first isolate per organism–mechanism combination per patient. Organisms reported as Enterobacter aerogenes were re-
categorized as Klebsiella aerogenes.\(^2\) Two VIM-producing isolates without a definitive species identification, reported to CDC as either Klebsiella oxytoca or Raoultella amylolytica, were categorized as K. oxytoca. Isolates were defined as carbapenemase-producing if they showed carbapenemase activity by mCIM test and had a KPC, NDM, OXA-48-like, VIM, or IMP-encoding gene identified. For the primary analysis, S. marcescens with \( \beta \text{LAM}_{\text{ES}} \) and Enterobacter spp. with \( \beta \text{LAM}_{\text{ES}} \) were grouped with non-CP-CRE because these genes are not associated with the same risk for spread of carbapenem resistance; these genes have generally not been associated with spread outside of their host organisms and therefore the recommended public health and infection control response is more similar to non-CP-CRE than to CP-CRE with one of the five targeted carbapenemase genes.\(^3,13,20,26\) We then performed a secondary sensitivity analysis grouping these isolates with CP-CRE to reflect their genotypic classification.

For patients with CP-CRE from LCG, state health departments reported to CDC age, inpatient healthcare history, and international travel history for the 12 months prior to specimen collection. These data are routinely collected during public health investigations of CP-CRE.\(^6\)

State health departments reported to CDC known or suspected CRE outbreaks from submitting healthcare facilities during the surveillance period. We performed a sensitivity analysis excluding outbreak-associated isolates to assess their impact on our findings.

Differences in frequency were assessed using the Chi-square test, or Fisher's exact test for cell sizes \( \leq 5 \), with significance assessed at \( P < 0.05 \) using a two-tailed test. Analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC).

This activity was reviewed by the human subjects’ advisors in the National Center for Emerging and Zoonotic Infectious Diseases at the CDC and was determined to constitute public health surveillance.

**Results**

Overall, 877 CRE isolates were submitted and 868 (99.0%) were tested according to the project algorithm. Among the 868 isolates, 127 (14.6%) were LCG (Table 1). In total, 219 (25.2%) CRE isolates met the definition of CP. The proportion of CP-CRE did not differ significantly between EsKE and LCG (195/741, 26.3%, versus 24/127, 18.9%). Among the 219 CP-CRE identified, 24 (11.0%) were LCG.

SPHLS each contributed a median of 62 CRE isolates, ranging from 21 isolates from Nebraska to 187 isolates from Wisconsin (Table 1). SPHLS that conducted statewide surveillance (AZ, MN, NE, WI) accounted for 59.8% (519/868) of CRE isolates and 67.7% (86/127) of LCG identified, but only 37.0% (81/219) of all CP-CRE. Although laboratories that did statewide surveillance had a greater proportion of CRE from LCG (86/519, 16.6%) than SPHLS that did sentinel surveillance (41/349, 11.7%, \( P = 0.049 \)), their proportion of LCG that were CP-CRE was lower (statewide 11/86, 12.8%, versus sentinel, 13/41, 31.7%, \( P = 0.011 \)). SPHLS in the Midwest census division (IN, MI, MN, NE, and WI) identified more LCG among submitted CRE (84/454, 18.5%) than SPHLS outside the Midwest (43/414, 10.4%, \( P = 0.003 \)). Midwestern SPHLS also found that LCG accounted for a greater proportion of CP-CRE (14/78, 17.9%) compared with the other sites (10/141, 7.1%),

**Table 1.** Total carbapenem-resistant Enterobacterales (CRE) submitted and carbapenemase-producing (CP\(^{a}\)) CRE identified, with isolates grouped by the three most-common genera (EsKE; Escherichia, Klebsiella, and Enterobacter) and less-common genera (LCG), by submitting state, \( N = 868 \)

| State  | Total N | N % | N % | LCG N % | LCG N % |
|--------|---------|-----|-----|---------|---------|
| AZ     | 150     | 131 | 87.3 | 19      | 12.7    |
| IN     | 37      | 29  | 78.4 | 8       | 21.6    |
| MD     | 108     | 99  | 91.7 | 9       | 8.3     |
| MI     | 48      | 39  | 81.3 | 9       | 18.8    |
| MN     | 161     | 130 | 80.7 | 31      | 19.3    |
| NC     | 55      | 52  | 96.6 | 2       | 3.4     |
| NE     | 21      | 17  | 81.0 | 4       | 19.0    |
| TN     | 64      | 54  | 84.4 | 10      | 15.6    |
| WA     | 33      | 30  | 90.9 | 3       | 9.1     |
| WI     | 187     | 155 | 82.9 | 32      | 17.1    |
| Total  | 868     | 741 | 85.4 | 127     | 14.6    |

\(^{a}\)Isolates were defined as carbapenemase-producing if they had both carbapenemase activity by mCIM test and had a \( \beta \text{LAM}_{\text{ES}} \), \( \beta \text{LAM}_{\text{NN}} \), or \( \beta \text{LAM}_{\text{IM}} \) gene identified.

\(^{b}\)Four Serratia spp. with \( \beta \text{LAM}_{\text{ES}} \) outbreak isolates were identified at one facility.

\(^{c}\)Two non-CP-Klebsiella spp. outbreak isolates were identified at one facility.

\(^{d}\)Three Klebsiella spp. with \( \beta \text{LAM}_{\text{ES}} \) outbreak isolates identified at one facility.

\(^{e}\)Three states, IN, NE, WI, additionally reported 80 isolates with intermediate susceptibility to carbapenems. Of these, 11/80 (13.8%) isolates were LCG and 2 (2.5%) isolates, both EsKE, were CP-CRE. A sensitivity analysis in which these isolates were included found no significant difference in the frequency of carbapenemase-production between EsKE (197/810, 24.3%) and LCG (24/138, 17.4%).
Table 2. Frequency of carbapenemase-production and carbapenemase genes with known epidemiological significance to public health detected among carbapenem-resistant Enterobacteriales (CRE) isolates by genus, N = 868

| Organisms            | No. CP-CREb/Total No. CRE n/N (%) | bla<sub>KPC</sub> | bla<sub>OXA-48-like</sub> | bla<sub>NDM</sub> | bla<sub>VIM</sub> | bla<sub>IMP</sub> | bla<sub>NDM/bla<sub>OXA-48-like</sub></sub> | bla<sub>KPC/bla<sub>VIM</sub></sub> |
|----------------------|-----------------------------------|-------------------|------------------------|-----------------|-----------------|-----------------|--------------------------------|--------------------------|
| More-common genera<sup>a</sup> | 195/741 (26.3) | 154 | 16 | 15 | 6 | 1 | 2 | 1 |
| **Enterobacter**     | 29<sup>2</sup>/308 (9.4) | 25 | 1 | 2 | 1 |
| **Escherichia**      | 36/136 (26.5) | 18 | 9 | 9 | 2 | 1 |
| **Klebsiella**       | 130<sup>3</sup>/297 (43.8) | 111 | 7 | 5 | 4 | 2 | 1 |
| Less-common genera<sup>a</sup> | 24/127 (18.9) | 19 | 1 | 3 | 1 |
| **Citrobacter**      | 11/42 (26.2) | 10 | 1 | 1 |
| **Hafnia**           | 0/4 (0.0) | 0 |
| **Morganella**       | 0/13 (0.0) | 0 |
| **Proteus**          | 2/19 (10.5) | 1 | 1 |
| **Providencia**      | 3/8 (37.5) | 2 | 1 |
| **Raoultella**       | 0/5 (0.0) | 0 |
| **Serratia**         | 8/<sup>b</sup>/36<sup>c</sup> (22.2) | 8<sup>d</sup> | 17 | 15 | 6 | 4 | 3 | 1 |
| **Total**            | 219/868 (25.2) | 173 | 17 | 15 | 6 | 4 | 3 | 1 |

<sup>a</sup>Some laboratories employed hierarchical molecular testing for isolates showing carbapenemase activity by mCIM test. 147 isolates (67.1%) were tested for four of five genes (bla<sub>KPC</sub>, bla<sub>NDM</sub>, bla<sub>OXA-48-like</sub> and bla<sub>VIM</sub>); 8 isolates (3.7%) were tested for bla<sub>KPC</sub> and bla<sub>NDM</sub> only; 2 isolates (1.0%) were tested for bla<sub>KPC</sub> only; and 1 isolate (0.5%) was tested for bla<sub>NDM</sub>, bla<sub>OXA-48-like</sub> and bla<sub>VIM</sub> genes only.

<sup>b</sup>Isolates were defined as carbapenemase-producing if they had both carbapenemase activity by mCIM test and had a bla<sub>KPC</sub>, bla<sub>NDM</sub>, bla<sub>OXA-48-like</sub>, bla<sub>VIM</sub>, or bla<sub>IMP</sub> gene identified.

<sup>c</sup>More common genera species included E. cloacae complex (304), E. coli (137), K. aerogenes (63), K. oxytoca (16), E. faecalis (16), and E. coli (214), and K. variicola (2). Six Enterobacter spp. isolates and 6 Klebsiella spp. isolates could not be definitively speciated.

<sup>d</sup>One Enterobacter spp. with bla<sub>NDM</sub>/bla<sub>OXA-48-like</sub> and 7 S. marcescens with bla<sub>NDM</sub> carbapenemases are excluded from CP-CRE calculations. If E. cloacae with bla<sub>NDM</sub> and S. marcescens with bla<sub>NDM</sub> were categorized as CP, then 26.5% (196/741) of EsKE and 24.4% (31/127) LCG would have been CP-CRE.

<sup>e</sup>Two non-CP-Klebsiella spp. outbreak isolates identified at one facility.

<sup>f</sup>Less common genera species included Citrobacter amalonaticus (2), C. freundii complex (36), C. koseri (2), Hafnia alvei (4), Morganella morganii (13), Proteus mirabilis (18), P. vulgaris (2), Providencia rettgeri (5), P. stuartii (3), Raoultella ornithinolytica (3), R. planticola (1), Serratia marcescens (35), and S. urealytica (1). Two Citrobacter spp., one Raoultella spp., and one Serratia spp. could not be definitively speciated.

<sup>g</sup>Four Serratia spp. with bla<sub>KPC</sub> were identified at one facility.

P = 0.014; Indiana had the highest proportion of CP-CRE that were LCG (6/22, 27.3%) (Table 1).

Table 2 describes, by genus, the proportion of isolates that were CP-CRE and the carbapenemase genes identified. The proportion of isolates that were CP-CRE among three less-common genera, Providencia (3/8, 37.5%), Citrobacter (11/42, 26.2%), and Serratia (8/36, 22.2%), was similar to that of the EsKE genera overall (195/741, 26.3%) and greater than the proportion among Enterobacter (29/308, 9.4%; Enterobacter versus Providencia P = 0.037; versus Citrobacter P = 0.001; versus Serratia P = 0.019) (Table 2). Among CP-CRE from the LCG, 11 (46%) isolates were Citrobacter spp., of which 10 harboured bla<sub>KPC</sub>. bla<sub>IMP</sub> was more commonly identified in the LCG (3/24, 12.5%) compared with the EsKE genera (1/194, 0.5%, P = 0.004) (Table 2); the distribution of other carbapenemases did not differ. Of the 219 CP-CRE, 72 (32.9%) underwent hierarchical PCR testing for carbapenemase genes, which may have decreased detection of isolates carrying ≥1 carbapenemase gene. Overall, 61 (27.9%) CP-CRE were tested for four of five genes, but not bla<sub>IMP</sub>, and 11 (5.0%) CP-CRE were tested for fewer than four genes. Ten isolates showed carbapenemase activity by mCIM test, but had none of the five common carbapenemase genes detected; of these, seven Serratia isolates harboured bla<sub>NDM</sub>, one Enterobacter isolate harbour<br> bla<sub>NDM</sub>/bla<sub>IMP</sub>, and two Enterobacter isolates had unknown mechanisms of carbapenemase production, although one AST phenotype was consistent with hyper-AmpC production (i.e., carbapenem-resistant, cefta-<br><br>pime-susceptible).

Two states reported three suspected or confirmed CRE outbreaks at participating sites during the surveillance period. Nine outbreak-associated isolates were reported: three OXA-48-like-producing Klebsiella spp. and two non-CP-Klebsiella spp., from North Carolina, and four KPC-producing Serratia spp. from Indiana. Excluding these nine isolates, 16.3% (20/123) of LCG were CP-CRE compared with 26.1% (192/736) of EsKE genera and the difference between the proportions reached statistical significance (P = 0.019). Also in the sensitivity analysis, the difference in proportions of LCG that were CP-CRE that varied by surveillance method-
Among the 24 patients with CP-CRE from LCG, median patient age was 59.5 years (range: 21–88 years). Excluding outbreak isolates, the most common specimen sources were respiratory (n = 6, 30%) and urine (n = 6, 30%), followed by wounds (n = 5, 25%), blood (n = 1, 5%), ear (n = 1), and rectum (n = 1). Compared with CP-CRE from the EsKE genera, CP-CRE from LCG were more likely to be from respiratory specimens (18, 12.2%, P = 0.032) and wounds (13, 8.8%, P = 0.044) and less likely to be from urine (86, 58.1%, P = 0.018). Two (8.3%) patients, one with OXA-48-like-producing Citrobacter koseri and one with NDM- and OXA-48-like-producing Providencia rettgeri, had a history of inpatient hospitalization outside of the United States in the 12 months prior to specimen collection; both had been hospitalized in India. Among the 22 remaining patients, 20 (90.9%) had been hospitalized in the United States in the 12 months prior to specimen collection. Two patients (8.3%), one with IMP-producing Proteus mirabilis and one with KPC-producing Citrobacter freundii complex, had no prior inpatient healthcare exposures identified during medical record review.

### Discussion

Among participating laboratories, if CRE mechanism testing had been limited to the EsKE genera that were targeted by the US national testing programme in 2018, approximately one in 10 CP-CRE identified during the surveillance period would have been missed. We observed geographic variability in the contribution of LCG to the total burden of CP-CRE, consistent with the heterogeneous epidemiology of CRE in the United States. The highest burden of CP-CRE from LCG was observed among Midwestern states, but there was considerable variability even within this region. Among both carbapenem-resistant and CP-LCG organisms, Citrobacter was the most common genus, with a frequency of CP-CRE no different than E. coli and substantially higher than Enterobacter. Other LCG, such as Providencia and Serratia, although identified less often, were similarly likely to harbour transmissible carbapenemase genes. To our knowledge, this is the first formal assessment of carbapenemase production across a broad range of Enterobacteriales species. Taken together, these findings suggest that strategic CRE testing beyond the three most-common genera, accounting for local epidemiology and targeting specific organisms, could improve CP-CRE detection and control.

Ten SPHLs volunteered to participate in this evaluation: half from the Midwestern census region (IN, MI, MN, NE, WI), three from the South (MD, NC, TN), two from the West (AZ, WA), and none from the Northeast. This geographic subset did not include several major metropolitan areas where KPC-producing CRE are endemic, which might explain why the overall proportion of CP-CRE (25.2%) in our assessment was lower than the 32% identified through the AR Lab Network nationally. Our systematic evaluation found 18.9% of LCG were CP-CRE, similar to the proportion (21%) identified from a convenience sample of 346 LCG isolates submitted to the AR Lab Network, confirming that carbapenemase production in these organisms is not uncommon. We observed variation within and between geographic regions, including in neighbouring states. Wisconsin and Minnesota had similar overall proportions of CRE that were CP (27/187, 14.4%, and 16/161, 9.9%, respectively) and both used statewide surveillance. However, in Wisconsin, nearly one in five CP-CRE were from LCG, almost 50% more than the burden in Minnesota. The variable burden of CP-CRE from the LCG within the Midwest, which was overrepresented in our assessment, and across states from other regions, is consistent with the diversity of CP-CRE nationally. It also highlights that the burden of CP-CRE from LCG varies geographically and cannot be generalized even within broad geographic areas.

Citrobacter and Serratia commonly carried blaKPC, which is the most widely disseminated carbapenemase gene among CRE overall in the United States. These two genera are already intrinsically multidrug resistant. With the addition of blaKPC, which we observed in approximately 1 in 4 isolates, these organisms have potential to cause infections with few treatment options. Additionally, both KPC-producing Citrobacter spp. and KPC-producing Serratia spp. have caused outbreaks in healthcare settings. Mechanism testing of these organisms could help to prevent further spread of blaKPC in the United States. Half (n = 4) of the KPC-producing Serratia we identified were from a single facility respiratory outbreak. Notably, even when this outbreak is excluded, the proportion of Serratia that were CP (4/32, 12.5%) still exceeded that of Enterobacter. Although the outbreak may have elevated the frequency of CP-Serratia relative to a random sample, it underscores the propensity for CP-Serratia to cause healthcare-associated outbreaks, and the role for expanded carbapenemase testing to facilitate a public health response to prevent spread.

The frequency of blaIMP carriage was notably different between LCG and EsKE genera. Three of the four IMP-producing CRE were among the LCG, all within the Morganellaceae family. Although these organisms with intrinsic low-level imipenem resistance contribute a relatively small number of isolates to the burden of CP-CRE, data from this and other studies indicate Morganellaceae frequently harbour transmissible carbapenemase genes, most commonly metallo-β-lactamases such as blaIMP. The number of Providencia isolates was very small, but more than a third were CP-CRE. Although Morganellaceae are associated with a small proportion of healthcare-associated infections in hospitals, they are epidemiologically important in other healthcare settings such as nursing homes, where they can cause complex, persistent infections and have been associated with large outbreaks.

We did not collect extensive medical histories for patients with CP-CRE in LCG and the overall numbers are small, but the assessed risk factors yielded some interesting observations. First, two patients (8.3%) had no known recent healthcare exposures, indicating they might be community-associated cases. Cases of community-associated CP-CRE have been documented, but overall, community-associated CRE are rare. Second, among the five patients with CP-LGG producing carbapenemases other than KPC, only two had been hospitalized outside the United States. Hospitalization outside the United States has historically been a risk factor for non-KPC carbapenemases; however, our findings are consistent with recent reports of domestic acquisition and transmission of metallo-β-lactamases. As carbapenemase testing among LGG increases, it will better inform the epidemiology of these organisms.

This analysis is subject to multiple limitations. We conducted CRE mechanism testing for a relatively short timeframe in ten states, therefore, these results are not nationally generalizable. Additionally, in states that conducted sentinel surveillance, participating clinical laboratories might have served catchments with different underlying epidemiology from the state overall. Clinical
laboratories’ adherence to the isolate submission protocol could have varied by state, clinical laboratory, and organism submitted, and may have caused unrecognized biases. Although most states have a legal requirement for healthcare facilities to report outbreaks to public health authorities, it is possible that outbreaks, especially of non-CP-CRE, might have been underrecognized and underreported. When sensitivity analysis was performed by removing known outbreak isolates, the proportion of LCG that were CP-CRE declined from 18.9% to 16.3%, and the difference in proportions of EsKε and LCG that were CP-CRE became statistically significant. This illustrates that outbreaks can be highly influential in analyses such as this, but also emphasizes the importance of early detection and response to limit CP-CRE spread. Finally, hierarchical molecular testing of some isolates, wherein PCR testing for less commonly identified carbapenemase genes (e.g., \textit{blaOmpK}) may not be conducted if a more common gene is identified first, may have limited our ability to detect CP-CRE carrying multiple carbapenemase genes. Further characterization, including whole genome sequencing, is required to determine the distribution of carbapenemase gene variants and assess the contribution of species’ clones to outbreaks and expansion of CP-CRE among the LCG.

Based on these findings, we recommend that clinical and public health laboratories consider strategic expansion of carbapenem resistance mechanism testing to additional genera that frequently harbour carbapenemase genes, such as \textit{Citrobacter} and \textit{Providencia}. As of January 2019, AR Lab Network jurisdictions were encouraged to expand mechanism testing to include all CRE genera overall, and \textit{Providencia}, \textit{Proteus}, \textit{Morganella}, \textit{Citrobacter}, and \textit{Serratia}, in particular. Testing from additional sites over a longer timeframe will expand our knowledge of the relative frequency of carbapenemase genes circulating in these LCG as well as our understanding of regional differences and temporal variations. Most importantly, however, these actions are anticipated to enhance rapid identification of CP-CRE, which when coupled with prompt implementation of appropriate infection control measures, is critical to preventing spread.\textsuperscript{11,12}

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None to declare.

**Disclaimer**

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