Emerging Infections Program (EIP) Network Report Healthcare-Associated Infections Community Interface Multi-site Gram-negative Surveillance Initiative Carbapenem-Resistant Enterobacteriaceae (CRE) Surveillance, 2016

EIP Areas
Colorado (5 county Denver area); Georgia (8 county Atlanta area); Maryland (4 county Baltimore area); Minnesota (2 county Minneapolis – St. Paul area); New Mexico (1 county Albuquerque area); New York (1 county Rochester area); Oregon (3 county Portland area); and Tennessee (8 county Nashville area).

Population
The surveillance areas represent 15,370,591 persons.
Source: National Center for Health Statistics bridged-race vintage 2016 postcensal file.

Case Definition
The CRE case definition changed for the 2016 surveillance year and subsequent years with the inclusion of ertapenem resistance and removal of the requirement for resistance to all third generation cephalosporins tested.

A CRE case was defined as isolation of *Escherichia coli*, *Enterobacter aerogenes* (now *Klebsiella aerogenes*), *Enterobacter cloacae* complex, *Klebsiella pneumoniae,* or *Klebsiella oxytoca* with the following criteria:

- Carbapenem-resistant (doripenem, imipenem, meropenem, or ertapenem) using the 2016 Clinical and Laboratory Standards Institute clinical breakpoints (1);
- Isolated from either a normally sterile body site (e.g., blood, cerebrospinal fluid, pleural fluid, pericardial fluid, peritoneal fluid, joint/synovial fluid, bone, internal body sites, or muscle) or urine;
- Identified in residents of the surveillance area in 2016.

This case definition uses a different antimicrobial susceptibility phenotype from what was used for MuGSI CRE surveillance from 2012-2015, which was non-susceptible to doripenem, imipenem, or meropenem and resistant to all tested third generation cephalosporins.

Methodology
Case finding was active, laboratory-based, and population-based. Clinical laboratories that serve residents of the surveillance area were routinely contacted for case identification through a query of minimum inhibitory concentration (MIC) values from automated testing instruments. When possible, the MIC values obtained directly from the automated testing instruments were used to determine if an isolate met the phenotypic case definition. An incident CRE case was defined as the first CRE isolate meeting the case definition from a patient during a 30-day period.

A standardized case report form was completed for each incident case through review of medical records. Inpatient and outpatient medical records were reviewed for information on patient demographics, clinical syndrome, outcome of illness, and relevant healthcare exposures.

A convenience sample of CRE isolates (N=548) was collected from EIP sites and submitted to CDC for additional testing including species confirmatory testing, antimicrobial susceptibility testing by reference broth microdilution with a metallo-β-lactamase (MBL) screen, screening for carbapenemase production using the Modified Hodge Test (MHT), polymerase chain reaction (PCR) screening for KPC, NDM, and OXA-48-like carbapenemase genes, and PCR testing for other carbapenemase genes (i.e., VIM) if MBL screen positive and negative for KPC, NDM, and OXA-48-like genes.

Incidence rates for CRE cases were calculated using the 2016 US Census estimates of the surveillance area population as the denominator. Assessment of vital status in patients admitted to a hospital occurred at the time of discharge from the acute care hospital. For patients in a long-term care facility, long-term acute care facility, or in an outpatient dialysis center, vital status was assessed 30 days after culture collection. For all other patients, vital status was assessed using medical records from the healthcare facility encounter associated with the culture.

CRE surveillance data underwent regular data cleaning to ensure accuracy and completeness. Patients with complete case report form data as of 3/4/2020 were included in this analysis. Because data can be updated as needed, analyses of datasets generated on a different date may yield slightly different results.

Results

Table 1. Specimen Sources for Incident CRE Cases by Organism (N=1218), 2016

CRE Organism	Total	Urine No.	Urine %	Blood[a] No.	Blood%	Other Sterile Sites No.	Other Sterile Sites %
Enterobacter Klebsiella aerogenes	84	78	92.9	3	3.6	3	3.6
Enterobacter cloacae complex	409	372	91.0	22	5.4	15	3.7
Escherichia coli	341	329	96.5	10	2.9	2	0.6
Klebsiella pneumoniae	359	321	89.4	32	8.9	6	1.7
Klebsiella oxytoca	25	20	80.0	5	20.0	0	0
Total	1218	1120	92.0	72	5.9	26	2.1

[a] Category includes 6 cases with both a positive blood and urine specimen collected.

Table 2a. Molecular Characteristics of CRE Isolates Submitted to CDC Based on Testing Performed at CDC (N=548), 2016

Organism	Isolates Submitted to CDC	Carbapenemase-Producing No.[a, b]	%
Enterobacter (*Klebsiella*) *aerogenes*	42	0	0
Enterobacter cloacae complex	236	10/236	4.2
Escherichia coli	115	15/115	13.0
Klebsiella pneumoniae	147	87/147	59.2
Klebsiella oxytoca	8	2/8	25.0
Total	548	114/548	20.8

[a]Testing was performed by PCR.

[b]Carbapenemase-producing isolates were collected from urine (n=100/114; 87.7%) and blood (n=14/114; 12.3%).

Table 2b. Molecular Characteristics of CRE Isolates Submitted to CDC Based on Testing Performed at CDC (N=548), 2016 by Carbapenemase Gene

Organism	KPC No.	KPC %	NDM No.	NDM %	OXA-48-like No.	OXA-48-like %
Enterobacter (*Klebsiella*) *aerogenes*	0	0	0	0	0	0
Enterobacter cloacae complex	10	4.2	0	0	0	0
Escherichia coli	12	10.4	2	1.7	1	0.9
Klebsiella pneumoniae	83	56.5	4	2.7	1	0.7
Klebsiella oxytoca	2	25.0	0	0	0	0
Total	107	19.5	6	1.1	2	0.4

Table 2c. Confirmatory Antimicrobial Susceptibility Results of CRE Isolates Submitted to CDC

Organism	Carbapenem-resistant, No.[c]	Carbapenem-resistant %[c]	Difficult to Treat, No.[d]	Difficult to Treat %
Enterobacter (*Klebsiella*) *aerogenes*	15	35.7	0	0
Enterobacter cloacae complex	68	28.8	9	3.8
Escherichia coli	45	39.1	8	7.0
Klebsiella pneumoniae	109	74.1	72	49.0
Klebsiella oxytoca	6	75.0	1	12.5
Total	243	44.3	90	16.4

[c]Difficult to treat is defined as non-susceptibility to all first-line agents tested (i.e., carbapenems, extended-spectrum cephalosporins, fluoroquinolones, piperacillin-tazobactam, and aztreonam) (2).

Table 3. Incidence Rates for CRE Cases by Sex, Race, and Age (N=1218), 2016

Sex	No. of Cases	Crude Incidence Rate/ 100,000 Population	95% CI
Female	767	9.74	9.71, 9.76
Male	450	6.00	5.98, 6.03
Unknown	1	N/A	N/A

Race	No. of Cases	Crude Incidence Rate/ 100,000 Population	95% CI
White	654	6.08	6.07, 6.10
Black or African American	338	9.93	9.88, 9.99
Other[a]	36	2.96	2.80, 3.12
Unknown	190	N/A	N/A

Age group, years	No. of Cases	Crude Incidence Rate/ 100,000 Population	95% CI
0–18	35	0.93	0.88, 0.99
19–49	217	3.22	3.19, 3.25
50–64	260	8.91	8.84, 8.98
65–79	405	27.01	26.88, 27.14
≥80	301	64.84	64.42, 65.26
Invasive cases[b]	110	0.72	0.70, 0.73
All cases	1218	7.92	7.91, 7.94

[a]Other race includes Asian and American Indian or Alaska Native.

[b]Invasive cases include cases with a sterile incident specimen source or an incident urine specimen with a subsequent non-incident sterile specimen collected on the date of incident specimen collection or in the 29 days after.

Table 4. Clinical Characteristics and Infection Types for Incident CRE Cases (N=1218), 2016[a]

No. of Immunocompromised[b] Cases	%
69	5.7

Infection types	No. of Cases	%
Urinary tract infection[c]	847	69.5
Bacteremia[d]	96	7.9
Septic shock	33	2.7
Abscess (not skin)	11	0.9
Other infection types	33	2.7
None[e]	172	14.1
Unknown	110	9.0

[a]Patients could have more than one type of infection reported.
[b]Immunocompromised includes solid organ transplant recipients and patients with a documented diagnosis of AIDS or a hematologic malignancy.
[c]Among 847 cases with a documented urinary tract infection (UTI), 410 (48.4%) had signs and symptoms associated with a UTI documented in the medical record. Reported signs and symptoms included fever, dysuria, frequency, urgency, costovertebral angle pain or tenderness, and suprapubic tenderness, urgency, and other symptoms.
[d]Bacteremia includes cases with a positive blood specimen (incident or non-incident) or a documented diagnosis of sepsis, septicemia, bacteremia, or blood stream infection.
[e]No infection types reported.

Table 5. Patient Location Before, During, and After Incident Specimen Collection Among Incident CRE Cases (N=1218), 2016

Residence before incident specimen collection	No. of Cases	%
Private residence	684	56.2
Long-term care facility	260	21.3
Acute care hospital inpatient	185	15.2
Long-term acute care hospital	33	2.7
Other	4	0.3
Unknown	52	4.3

Collection location	No. of Cases	%
Outpatient setting or emergency department	714	58.6
Acute care hospital	260	21.3
Long-term care facility	196	16.1
Long-term acute care hospital	37	3.0
Unknown	11	0.9

Hospitalized on the day of or in the 29 days after the date of incident specimen collection	No. of Cases	%
Hospitalized	531	43.6
Not hospitalized	623	51.1
Unknown	64	5.3

Discharge location among hospitalized patients (N=531)	No. of Cases	%
Private residence	261	49.2
Long-term care facility	192	36.2
Died during hospitalization	42	7.9
Long-term acute care hospital	30	5.6
Other or unknown	6	1.1

Table 6. Outcome of CRE Cases (N=1218), 2016

Outcome	No. of Cases	%
ICU admission in the 6 days after the date of incident specimen collection	72	5.9
Died	47	3.9
Cases with a positive incident sterile site specimen (N=98)	19	19.4
Cases with a positive incident urine specimen (N=1120)	28[a]	2.5

[a]None had a subsequent non-incident blood specimen collected on the date of incident specimen collection or in the 29 days after.

Table 7. Selected Characteristics of Incident CRE Cases (N=1218), 2016[a]

Exposure	No. of Cases	%
Healthcare facility stay in the year before the date of incident specimen collection	770	63.2
Acute care hospital	693	56.9
Long-term care facility	375	30.8
Long-term acute care hospital	66	5.4
Surgery in the year before the date of incident specimen collection	292	24.0
In ICU in the 7 days before the date of incident specimen collection	81	6.7
Specimen collected ≥3 days after hospital admission	168	13.8
Chronic dialysis	54	4.4
Selected medical device(s) in place in the 2 calendar days before the date of incident specimen collection	535	43.9
Urinary catheter	410	33.7
Central venous catheter	187	15.4
Other[b]	235	19.3
None of the above healthcare exposures[c]	272	22.3
International travel in the 2 weeks before the date of incident specimen collection	14	1.1

[a]Patients could have more than one prior healthcare risk factor reported.

[b]Other medical devices include: endotracheal or nasotracheal tube, tracheostomy, gastrostomy tube, nephrostomy tube, nasogastric tube.

[c]Defined as having no healthcare exposures in the year before specimen collection, no selected medical devices in place in the 2 days before specimen collection, and specimen collected before calendar day 3 after hospital admission if hospitalized.

Summary

The case definition change in 2016 was associated with a substantially higher incidence rate compared to previous years (7.92 cases per 100,000 persons in 2016 vs. 2.96 cases per 100,000 persons in 2015). As in previous years the incidence rate increased with age, was higher in women than in men, and higher in persons of Black or African American race than persons of other races. Prior healthcare exposures were still reported for most cases, with the most common exposures being acute care hospitalization in the prior year, presence of indwelling medical devices, and prior long-term care facility residence. Less than half of the cases required hospitalization, and overall crude mortality rate was 3.9%, with a higher mortality observed in cases with a sterile site specimen source compared to those with a urine specimen source.

After the 2016 case definition change, only 20.8% of isolates submitted to CDC were carbapenemase-producing (compared to 48.0% in 2015). KPC was detected in over 90% of carbapenemase-producing isolates, NDM was detected in 6 isolates, and OXA-48-like was detected in 2 isolates.

References

1. Clinical and Laboratory Standards Institute. *Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Second Informational Supplement*. CLSI document M100-S25 (ISBN 1-56238-990-4). Wayne, PA 2016.
2. Kadri SS, Adjemian J, Lai YL, Spaulding AB, Ricotta E, Prevots DR, et al. Difficult-to-Treat Resistance in Gram-negative Bacteremia at 173 US Hospitals: Retrospective Cohort Analysis of Prevalence, Predictors, and utcome of Resistance to All First-line Agents. Clin Infect Dis. 2018 Nov 28;67(12):1803-14.

Citation:

Centers for Disease Control and Prevention. Emerging Infections Program Healthcare-Associated Infections – Community Interface Carbapenem-Resistant Enterobacteriaceae (CRE) Surveillance Report, Multi-site Gram-negative Surveillance Initiative (MuGSI), 2016. Posted online on October 4, 2022. Available at: https://www.cdc.gov/hai/eip/pdf/mugsi/2016-CRE-Report-508.pdf.