Emerging Infections Program (EIP) Network Report
Healthcare-Associated Infections Community Interface Activity
Multi-site Gram-negative Surveillance Initiative
Carbapenem-Resistant Enterobacterales (CRE) Surveillance, 2019

Case Definition:

A carbapenem-resistant Enterobacterales (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 current Clinical and Laboratory Standards Institute clinical breakpoints (1);
- Isolated from 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 2019.

Surveillance Catchment Areas:

California (3 county San Francisco area), Colorado (5 county Denver area); Connecticut (statewide); 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 area represents 23,019,707 persons.
Source: National Center for Health Statistics bridged-race vintage 2019 file.

Methods:

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=823) was collected from 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 Carbapenem Inactivation Method (mCIM), real-time polymerase chain reaction (PCR) screening for carbapenemase-encoding genes, including bla_{KPC}, bla_{NDM}, and $bla_{\text{OXA-48-like}}$ genes, and PCR testing for other carbapenemase genes (i.e., bla_{VIM}) if MBL screen positive and negative for bla_{KPC}, bla_{NDM}, and $bla_{\text{OXA-48-like}}$ genes.

Incidence rates for incident CRE cases were calculated using the 2019 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 2/2/2022 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 CRE Cases by Organism, 2019 (N=1309)

Organism	Total	Urine No.	Urine %	Blood[a] No.	Blood[a] %	Other Sterile Sites No.	Other Sterile Sites %
Enterobacter cloacae complex	495	432	87.3	40	8.1	23	4.6
Escherichia coli	338	302	89.3	29	8.6	7	2.1
Klebsiella pneumoniae	347	315	90.8	24	6.9	8	2.3
Klebsiella aerogenes	105	98	93.3	4	3.8	3	2.9
Klebsiella oxytoca	24	19	79.2	5	20.8	0	0.0
Total	**1309**	**1166**	**89.1**	**102**	**7.8**	**41**	**3.1**

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

Table 2 Incidence Rates of CRE Cases by Sex, Race and Age, 2019 (N=1309)

Sex	No. of Cases	%	Incidence Rate[a]
Female	814	62.2	6.92
Male	494	37.7	4.39
Unknown	1	0.1	-

Race	No. of Cases	%	Incidence Rate[a]
White	790	60.4	4.97
Black or African American	260	19.9	5.91
Other[b]	68	5.2	2.50
Unknown	191	14.6	-

Age groups, years	No. of Cases	%	Incidence Rate[a]
0–18	43	3.3	0.81
19–49	181	13.8	1.81
50–64	260	19.9	5.93
65–79	452	34.5	17.39
≥80	373	28.5	46.83
Invasive cases[c]	151	11.5	0.66
All cases	1309	100.0	5.69

[a] Cases per 100,000 population for EIP areas (crude rates)

[b] Other race includes Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, or ≥2 races reported

[c] 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 3. CRE Cases by Race and Ethnicity, 2019 (N=1309)

Race/Ethnicity	No. of Cases	%
Hispanic, any race	100	7.6
Not known to be Hispanic[a] – White[b]	726	55.5
Not known to be Hispanic[a] – Black or African American[c]	256	19.6
Not known to be Hispanic[a] – Asian[d]	61	4.7
Not known to be Hispanic – Other or multiple races[e]	10	0.8
Not known to be Hispanic[a,f]– Unknown race	156	11.9

[a] Records either indicated ethnicity was non-Hispanic, or ethnicity was not known

[b] 63 CRE cases with unknown ethnicity

[c] 16 CRE cases with unknown ethnicity

[d] 2 CRE cases with unknown ethnicity

[e] American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, or ≥2 races reported; 3 CRE cases with unknown ethnicity

[f] Of cases with unknown race, 135 CRE cases had unknown ethnicity

Table 4. Selected Characteristics of CRE, 2019 (N=1309)

Location of patient on the 3rd calendar day before incident specimen collection	No. of Cases	%
Private residence or other location	775	59.2
Long-term care facility	229	17.5
Acute-care hospital (inpatient)	216	16.5
Long-term care acute care hospital	22	1.7
Homeless	5	0.4
Unknown	62	4.7

Location of incident specimen collection	No. of Cases	%
Outpatient setting or emergency department	826	63.1
Acute care hospital	303	23.1
Long-term care facility	145	11.1
Long-term acute care hospital	22	1.7
Unknown	13	1.0

Infection types[a]	No. of Cases	%
Urinary tract infection	890	68.0
Bacteremia[b]	134	10.2
Septic shock	55	4.2
Other	106	8.1
None[c]	169	12.9
Unknown	92	7.0

[a] Patients could have more than one type of infection reported

[b] Bacteremia includes cases with a positive blood specimen (incident or non-incident) or a documented diagnosis of sepsis, septicemia, bacteremia, or blood stream infection

[c] No infection types reported

Table 5. Selected Clinical Characteristics of CRE, 2019[a] (N=1309)

Charlson comorbidity index	No. of Cases	%
0	269	20.6
1	226	17.3
≥2	747	57.1
Unknown	67	5.1
Median (IQR)	2	1–14

Underlying conditions	No. of Cases	%
Cardiovascular disease[b]	471	36.0
Diabetes mellitus	455	34.8
Urinary tract problems/abnormalities	425	32.5
Neurologic condition, any	422	32.2
Chronic renal disease	318	24.3
Chronic pulmonary disease[c]	272	20.8
Skin condition	250	19.1
Malignancy (hematologic or solid organ)	224	17.1
Gastrointestinal disease[d]	168	12.8
Transplant (hematopoietic stem cell or solid organ)	60	4.6
Unknown	67	5.1

[a] Patients could have more than one underlying condition reported

[b] Defined as myocardial infarction, congestive heart failure, congenital heart disease, stroke, transient ischemic attack, or peripheral vascular disease

[c] Defined as cystic fibrosis or any chronic respiratory condition resulting in symptomatic dyspnea

[d] Defined as diverticular disease, inflammatory bowel disease, peptic ulcer disease, short gut syndrome, or liver disease

Table 6. Selected Healthcare Exposures or Risk Factors of CRE Cases, 2019[a] (N=1309)

Healthcare facility stay in the year before the date of incident specimen collection	No. of Cases	%
Acute care hospitalization	806	61.6
Long-term care facility residence	426	32.5
Long-term acute care hospitalization	46	3.5

Exposure	No. of Cases	%
Surgery in the year before the date of incident specimen collection	360	27.5
Specimen collected ≥3 days after hospital admission	188	14.4
Chronic dialysis	54	4.1

Selected medical device(s) in place in the 2 calendar days before the date of incident specimen collection	No. of Cases	%
Urinary catheter	397	30.3
Central venous catheter	182	13.9
Other[b]	236	18.0
None of the above healthcare exposures[c]	266	20.3
Healthcare exposures are unknown	43	3.3
International travel in the 2 months prior to date of incident specimen	38	2.9

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

[b] Other medical devices: 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

Table 7. Outcomes of Incident CRE Cases, 2019 (N=1309)

Outcomes	**No. of Cases**	**%**
Hospitalized on the day of or in the 29 days after the date of incident specimen collection	665	50.8
ICU admission in the 6 days after the date of incident specimen collection	101	7.7

Discharge location among hospitalized	**No. of Cases**	**%**
Private residence or other location	332/665	49.9
Long-term care facility	237/665	35.6
Died during hospitalization	74/665	11.1
Long-term acute care hospital	19/665	2.9
Unknown	3	0.2
Died within 30 days of incident specimen collection date	66	5.0
Cases with an incident sterile site specimen	26/143	18.2
Cases with an incident urine specimen[a]	40/1166	3.4

[a] Two incident CRE cases had a subsequent non-incident blood specimen collected on the date of incident specimen collection or in the 29 days after

Laboratory Characterization:

Table 8a. Antimicrobial Susceptibility and Molecular Characteristics of CRE Isolates Based on Testing Performed at CDC, 2019(N=823)

Organism	Isolates Submitted to CDC	Carbapenemase-producing, [a,b,c] - N	%
Enterobacter cloacae complex	333	19	5.7
Escherichia coli	191	34	17.8
Klebsiella pneumoniae	215	91	42.3
Klebsiella aerogenes	69	0	0.0
Klebsiella oxytoca	15	8	53.3
Total	**823**	**152**	**18.5**

Table 8b. Molecular Characteristics of CRE Isolates Based on Testing Performed at CDC, 2019 (N=823) by Carbapenemase Gene

Organism	***bla*$_{KPC}$ - N**	***bla*$_{KPC}$ - %**	***bla*$_{NDM}$ - N**	***bla*$_{NDM}$ - %**	***bla*$_{OXA-48-like}$ - *N***	***bla*$_{OXA-48-like}$ - *%***	***bla*$_{vim}$[e] - *N***	***bla*$_{vim}$[e] - *%***	***bla*$_{imp}$[e] - N**	***bla*$_{imp}$[e] - %**
Enterobacter cloacae complex	16	4.8	2	0.6	0	0.0	1	0.3	0	0.0
Escherichia coli	9	4.7	13	6.8	14	7.3	0	0.0	0	0.0
Klebsiella pneumoniae	82	38.1	7	3.3	2	0.9	0	0.0	0	0.0
Klebsiella aerogenes	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Klebsiella oxytoca	6	40.0	2	13.3	0	0.0	0	0.0	0	0.0
Total	**113**	**13.7**	**24**	**2.9**	**16**	**1.9**	**1**	**0.1**	**0**	**0.0**

Table 8c. Confirmatory Antimicrobial Susceptibility Results of CRE Isolates Submitted to CDC

Organism	**Carbapenem-resistant - N**	**Carbapenem-resistant - %**	**Difficult to treat[f] - N**	**Difficult to treat[f] - %**
Enterobacter cloacae complex	154	46.2	15	4.5
Escherichia coli	94	49.2	13	6.8
Klebsiella pneumoniae	135	62.8	50	23.3
Klebsiella aerogenes	28	40.6	0	0.0
Klebsiella oxytoca	10	66.7	1	6.7
Total	**421**	**51.2**	**79**	**9.6**

[a] Testing was performed by PCR

[b] Carbapenemase-producing isolates were collected from urine (n=131/152; 86.2%), blood (n=19/152; 12.5%), and other normally sterile site (n=2/152; 1.3%)

[c] All isolates that were mCIM positive were also PCR positive, except for four isolates that were mCIM positive and PCR negative

[d] Two isolates had *bla*$_{NDM}$ and *bla*$_{OXA-48-like}$ gene

[e] Testing was not done prior to 2019

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

Summary:

Surveillance data from 2019 represent the eighth full year of population-based surveillance for CRE through the Emerging Infections Program. The overall crude incidence rate of CRE in 2019 was 5.69 cases per 100,000 persons. The incidence rate increased with age and was higher in women than in men and higher in persons of Black or African American race than in persons of other races. More CRE were isolated from a urine source than from normally sterile body sites. Underlying conditions were commonly reported, with more than half of CRE cases having a Charlson comorbidity index of ≥2. Prior healthcare exposures were reported for most cases, with hospitalization in the prior year, presence of indwelling medical devices, and prior long-term care facility residency being the most common exposures. Approximately half of the CRE cases required hospitalization, and overall crude 30-day mortality was 5.0%, with a higher 30-day mortality observed in cases with a sterile-site specimen source compared to those with a urine specimen source.

Among the 823 CRE isolates submitted to CDC, 18.5% were carbapenemase-producing. KPC was detected in 13.7% of the isolates, NDM in 2.9% of the isolates, and OXA-48-like in 1.9% of the isolates.

References:

1. Clinical and Laboratory Standards Institute (CLSI). Performance Standards for Antimicrobial Susceptibility Testing. 29th ed. CLSI supplement M100 (ISBN 978-1-68440-032-4). Clinical and Laboratory Standards Institute, 950 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087 USA, 2019.

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 Outcome of Resistance to All First-line Agents. Clin Infect Dis. 2019 Nov 28;67(12):1803-14.

Citation:

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For more information, visit our web sites:

- Multi-site Gram-negative Surveillance Initiative (MuGSI) (https://www.cdc.gov/hai/eip/mugsi.html)
- Healthcare-Associated Infections - Community Interface Data Visualization (https://www.cdc.gov/hai/eip/haicviz.html)