Emerging Infections Program (EIP) Network Report
Healthcare-Associated Infections Community Interface Activity
Multi-site Gram-negative Surveillance Initiative
Carbapenem-Resistant Enterobacterales (CRE) Surveillance,
2021

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 specimen (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 2021.

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 23,111,016 persons.
Source: Starting with the 2021 surveillance year, population estimates were obtained from the U.S. Census Bureau, Population Division, Vintage 2021 Special Tabulation. This file includes population estimates for the five single-race categories and a multiple-race category specified in the 1997 Office of Management and Budget (OMB) standards for racial categories. The population estimates for previous reports were obtained from the National Center for Health Statistics, which bridged the multiple-race group population counts to the four single-race categories specified in the 1977 OMB standards.

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.

Standardized case report forms were completed for incident cases 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=711) 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 Carbapenem Inactivation Method (mCIM), real-time polymerase chain reaction (PCR) screening for carbapenemase-encoding genes, including bla_{KPC}, bla_{NDM}, and $bla_{OXA-48-like}$ genes, and PCR testing for other carbapenemase genes (i.e., $bla_{VIM,}$ bla_{imp}) if MBL screen positive and negative for bla_{KPC}, bla_{NDM}, and $bla_{OXA-48-like}$ genes.

Incidence rates for CRE cases were calculated using the 2021 U.S. 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 7/7/2023 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:

Note: The numbers of cases and denominators used for incidence rate calculations and case descriptions vary from table to table.

Tables 1 and 2 include all incident cases identified in 10 surveillance catchments areas (n=1417). Incidence rates were calculated using the total population in the 10-site surveillance catchments area.

Tables 3–7 include 1271 incident cases with completed case report forms (n=1236) or unavailable charts (n=34) in 10 EIP sites. This number differs from the total number of incident cases (n=1417) because chart review was attempted for only 33% of cases in 2021 in 1 of the 10 EIP sites.

Table 1. Specimen Sources for CRE Cases by Organism, 2021 (N=1417)

Organism	Total	Urine No.	Urine %	Blood[a] No.	Blood[a] %	Other sterile specimens No.	Other sterile specimens %
Enterobacter cloacae complex	569	498	87.5	44	7.7	27	4.7
Klebsiella pneumoniae	391	332	84.9	48	12.3	11	2.8
Escherichia coli	314	281	89.5	25	8.0	8	2.5
Klebsiella aerogenes	102	88	86.3	11	10.8	3	2.9
Klebsiella oxytoca	41	33	80.5	6	14.6	2	4.9
Total	**1417**	**1232**	**86.9**	**134**	**9.5**	**51**	**3.6**

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

Table 2. Incidence Rates of CRE Cases by Sex, Race and Age, 2021 (N=1417)

Sex	No. of Cases	%	Incidence Rate[a]
Female	827	58.4	7.0
Male	588	41.5	5.2
Unknown	2	0.1	-

Race	No. of Cases	%	Incidence Rate[a]
White	800	56.5	5.2
Black or African American	289	20.4	6.8
Other[b]	55	3.9	1.6
Unknown	273	19.3	-

Age groups, years	No. of Cases	%	Incidence Rate[a]
0–18	32	2.3	0.6
19–49	160	11.3	1.6
50–64	316	22.3	7.1
65–79	545	38.5	19.7
≥80	364	25.7	48.1
Invasive cases[c]	195	13.8	0.8
All cases	1417	100.0	6.1

[a] Cases per 100,000 population for EIP sites (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, 2021 (N=1271)

Race/Ethnicity	No. of Cases	%
Hispanic, any race	128	10.1
Not known to be Hispanic[a] – White[b]	726	57.1
Not known to be Hispanic[a] – Black or African American[c]	281	22.1
Not known to be Hispanic[a] – Asian[d]	46	3.6
Not known to be Hispanic – Other or multiple races[e]	14	1.1
Not known to be Hispanic[a,f]– Unknown race	76	6.0

Note: Table includes data from ten EIP sites; case report form data were available for only 33% of cases in one EIP site
[a] Records either indicated ethnicity was non-Hispanic, or ethnicity was not known
[b] 32 CRE cases with unknown ethnicity
[c] 19 CRE cases with unknown ethnicity
[d] 1 CRE case with unknown ethnicity
[e] American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, or ≥2 races reported; 1 CRE case with unknown ethnicity
[f] Of cases with unknown race, 63 CRE cases had unknown ethnicity

Table 4. Selected Characteristics of CRE Cases, 2021 (N=1271)

Location of patient on the 3rd calendar day before incident specimen collection	No. of Cases	%
Private residence or other location	793	62.4
Acute-care hospital (inpatient)	223	17.5
Long-term care facility	175	13.8
Long-term care acute care hospital	42	3.3
Homeless/other location	8	0.6
Unknown	30	2.4

Location of incident specimen collection	No. of Cases	%
Outpatient setting or emergency department	785	61.8
Acute care hospital	317	24.9
Long-term care facility	104	8.2
Long-term acute care hospital	37	2.9
Unknown	28	2.2

Infection types[a]	No. of Cases	%
Urinary tract infection	891	70.1
Bacteremia[b]	151	11.9
Septic shock	49	3.9
Other	95	7.5
None[c]	146	11.5
Unknown	71	5.6

Note: Table includes data from ten EIP sites; case report form data were available for only 33% of cases in one EIP site

[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 Cases, 2021 (N=1271)

Charlson comorbidity index	No. of Cases	%
0	218	17.2
1	218	17.2
≥2	796	62.6
Unknown	40	3.1
Median (IQR)	2	1–4

Underlying conditions [a]	No. of Cases	%
Urinary tract problems/abnormalities	495	38.9
Diabetes mellitus	492	38.7
Cardiovascular disease[b]	486	38.2
Neurologic condition, any	471	37.1
Chronic renal disease	407	32.0
Chronic pulmonary disease[c]	293	23.1
Skin condition	286	22.5
Malignancy (hematologic or solid organ)	237	18.6
Gastrointestinal disease[d]	173	13.6
Transplant (hematopoietic stem cell or solid organ)	56	4.4
Unknown	40	3.1

SARS-CoV-2 testing	No. of Cases	%
Positive test for SARS-CoV-2 during hospitalization and on or before date of incident specimen collection[e]	96/530	18.1

Note: Table includes data from ten EIP sites; case report form data were available for only 33% of cases in one EIP site

[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

[e] Among patients in the hospital on the date of incident specimen collection. Excludes patients who were admitted to the hospital after the date of incident specimen collection. A positive SARS-CoV-2 test was defined as any positive viral test for SARS-CoV-2, including antigen and nucleic acid amplification tests. Serologic tests were excluded

Table 6. Selected Healthcare Exposures or Risk Factors of CRE Cases, 2021[a] (N=1271)

Exposure	No. of Cases	%
Healthcare facility stay in the year before the date of incident specimen collection – any healthcare facility stay	802	63.1
Healthcare facility stay in the year before the date of incident specimen collection – acute care hospitalization	753	59.2
Healthcare facility stay in the year before the date of incident specimen collection – long-term care facility residence	316	24.9
Healthcare facility stay in the year before the date of incident specimen collection – long-term acute care hospitalization	67	5.3
Surgery in the year before the date of incident specimen collection	398	31.3
Specimen collected ≥3 days after hospital admission	203	16.0
Chronic dialysis	62	4.9
Selected medical device(s) in place in the 2 calendar days before the date of incident specimen collection – urinary catheter	437	34.4
Selected medical device(s) in place in the 2 calendar days before the date of incident specimen collection – central venous catheter	184	14.5
Selected medical device(s) in place in the 2 calendar days before the date of incident specimen collection – other [b]	266	20.9
None of the above healthcare exposures [c]	254	20.0
Healthcare exposures are unknown	38	3.0
International travel in the 12 months prior to date of incident specimen	24	1.9

Note: Table includes data from ten EIP sites; case report form data were available for only 33% of cases in one EIP site
[a] Patients could have more than one prior healthcare or exposure 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, 2021 (N=1271)

Outcomes	No. of cases	%
Outcomes – hospitalized on the day of or in the 29 days after the date of incident specimen collection[a,b]	634	49.9
Outcomes – ICU admission in the 6 days after the date of incident specimen collection[a]	90	7.1
Discharge location among hospitalized patients – private residence or other location	354/634	55.8
Discharge location among hospitalized patients – long-term care facility	172/634	27.1
Discharge location among hospitalized patients – died during hospitalization	85/634	13.4
Discharge location among hospitalized patients – long-term acute care hospital	18/634	2.8
Discharge location among hospitalized patients – unknown/other	5/634	0.8
Died within 30 days of incident specimen collection date	68	5.4
Cases with an incident sterile site specimen	34/159	21.4
Cases with an incident urine specimen[c]	34/1112	3.1

[a] Patients could have more than one outcome

[b] Data include 223 cases considered to be hospital-onset

[c] No 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 8.a. Antimicrobial Susceptibility and Molecular Characteristics of CRE Isolates Based on Testing Performed at CDC, 2021 (N=711)

Organism	Isolates Submitted to CDC	Carbapenemase-producing, [a,b,c] - N	%
Enterobacter cloacae complex	312	26	8.3
Klebsiella pneumoniae[d]	170	79	46.5
Escherichia coli	142	39	27.5
Klebsiella aerogenes	68	2	2.9
Klebsiella oxytoca	19	10	52.6
Total	**711**	**156**	**21.9**

Table 8.b. Molecular Characteristics of CRE Isolates Based on Testing Performed at CDC by Carbapenemase Gene[e], 2021 (N=711)

Organism	bla_{KPC} - N	bla_{KPC} - %	bla_{NDM} - N	bla_{NDM} - %	$bla_{OXA\text{-}48\text{-like}}$ - N	$bla_{OXA\text{-}48\text{-like}}$ - %	bla_{vim}[f] - N	bla_{vim}[f] - %	bla_{imp}[f] - N	bla_{imp}[f] - %
Enterobacter cloacae complex	22	7.1	5	1.6	0	0.0	0	0.0	0	0.0
Klebsiella pneumoniae[d]	62	36.5	8	4.7	12	7.1	0	0.0	0	0.0
Escherichia coli	17	12.0	16	11.3	6	4.2	1	0.7	0	0.0
Klebsiella aerogenes	2	2.9	0	0.0	0	0.0	0	0.0	0	0.0
Klebsiella oxytoca	8	42.1	1	5.3	1	5.3	0	0.0	0	0.0
Total	**111**	**15.6**	**30**	**4.2**	**19**	**2.7**	**1**	**0.1**	**0**	**0.0**

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

Organism	Carbapenem-resistant - N	Carbapenem-resistant - %	Difficult to treat[g] - N	Difficult to treat[g] - %
Enterobacter cloacae complex	173	55.4	12	3.8
Klebsiella pneumoniae[d]	121	71.2	49	28.8
Escherichia coli	72	50.7	13	9.2
Klebsiella aerogenes	39	57.4	1	1.5
Klebsiella oxytoca	14	73.7	1	5.3
Total	**419**	**58.9**	**76**	**10.7**

[a] Testing was performed by PCR

[b] Carbapenemase-producing isolates were collected from urine (n=125/156; 80.1%), blood (n=24/156; 15.4%), and other normally sterile specimens (n=7/156; 4.5%)

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

[d] Includes *Klebsiella pneumoniae* and *Klebsiella variicola*

[e] Two isolates had bla_{kpc} and bla_{NDM} genes; three isolates had $bla_{OXA\text{-}48}$ and bla_{NDM} genes; two isolates carrying a $bla_{OXA\text{-}48}$ gene were not carbapenem-resistant

[f] Testing was not done prior to 2019

[g] 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 2021 represent the tenth full year of population-based surveillance for CRE (2011 was a pilot year) through the Emerging Infections Program. The overall crude incidence rate of CRE in 2021 was 6.1 cases per 100,000 persons. The incidence rate increased with increasing age, was higher in women than in men, and higher in persons of Black or African American race than in persons of other races. More cases of 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 an admission to a healthcare setting in the prior year, presence of indwelling medical devices, and surgery in the prior year being the most common exposures. Approximately half of the CRE cases were hospitalized, and overall crude 30-day mortality was 5.4%, with a higher 30-day mortality observed in cases with a sterile-site specimen source compared to those with a urine specimen source. Eighteen percent of patients in the hospital on the date of incident specimen collection had a positive viral test for SARS-CoV-2 during their hospitalization and on or before date of incident CRE specimen collection.

Among the 711 CRE isolates submitted to CDC, 21.9% were carbapenemase-producing. KPC was detected in 15.6% of the isolates, NDM in 4.2% of the isolates, OXA-48-like in 2.7% of the isolates, IMP in 0.0% of the isolates, and VIM in 0.1% of the isolates.

References:

1. CLSI. *Performance Standards for Antimicrobial Susceptibility Testing.* 31st ed. CLSI supplement M100. Wayne, PA: Clinical and Laboratory Standards Institute; 2022.

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/healthcare-associated-infections/php/haic-eip/mugsi.html)
- Healthcare-Associated Infections - Community Interface Data Visualization (https://www.cdc.gov/healthcare-associated-infections/php/haic-eip/haicviz.html)