



Epidemiological Profile of Carbapenem-resistant *Enterobacteriaceae* (CRE) — South Dakota, 2013-2016



2013-2016 CRE Epidemiological Profile authors
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Summary

BACKGROUND

CRE, which stands for Carbapenem-resistant *Enterobacteriaceae*, are a family of germs that are difficult to treat because they have high levels of resistance to carbapenems. CRE are an important emerging threat to public health due to limited treatment options for patients infected with them.

Carbapenem resistance among *Enterobacteriaceae* can be due to several different mechanisms. Some CRE possess a β -lactamase [e.g., AmpC or extended spectrum β -lactamase (ESBL)] which, when combined with porin mutations, can render an organism nonsusceptible to carbapenems. Some CRE possess a carbapenemase (carbapenemase-producing CRE or CP-CRE) that directly breaks down carbapenems. Carbapenemases are often contained on mobile genetic elements that facilitate the transfer of resistance among *Enterobacteriaceae* and other gram-negative organisms. CP-CRE were first identified in the United States from an isolate collected in 1996 and have disseminated widely since that time. Much of the increase in CRE since 2000 has been due to the spread of CRE that produce the carbapenemase *Klebsiella pneumoniae* Carbapenemase (KPC). In addition to KPC, several other types of carbapenemases have been identified in the United States since 2009.

Until recently carbapenems have been successfully used for the treatment of infections caused by *Enterobacteriaceae*, including those producing extended-spectrum beta-lactamases. However, carbapenemases confer resistance to broad-spectrum antibiotics, usually including carbapenems, and therefore, the majority of carbapenemase-producing *Enterobacteriaceae* are carbapenem resistant (CRE)¹. According to recent data from the Centers for Disease Control and Prevention in the United States, the percentage of CRE increased from 1.2% in 2001 to 4.2% in 2011². The highest increase in proportion, from 1.6% to 10.4%, was observed for *Klebsiella spp.* during the same period³.

In studies evaluating risk factors for CRE acquisition or infection, exposure to health care and antimicrobials are among the most prominent risks ³. Invasive infections with carbapenem-resistant *K. pneumoniae* (CRKP)—likely primarily KPC-producers—were independently associated with recent organ or stem-cell transplantation, receipt of mechanical ventilation, exposure to antimicrobials, and longer length of stay when compared with patients with carbapenem-susceptible *K. pneumoniae* (CSKP) ³. Other risk factors associated with the acquisition of CRKP include poor functional status, intensive care unit (ICU) stay, and use of several classes of antimicrobials including carbapenems, cephalosporins, fluoroquinolones, and vancomycin³.

In 2013 South Dakota experienced an outbreak of CRE in the northeast region of the state. This outbreak prompted the South Dakota Department of Health (SD DOH) to initiate activities to limit the spread and development of CRE. Those activities included:

- Adding CRE to the reportable diseases list. This activity allowed SD DOH to monitor CRE prevalence in the state and identify basic epidemiologic characteristics of CRE positive cases.
- Creating an electronic database of CRE positive cases with variables of interest.
- Initiating an antimicrobial stewardship program to lower pressure exercised by antibiotics to limit development of CRE and other multi-drug resistant organisms (MDROs) in a community.
- Developing close regional partnerships and providing communication and technical assistance to healthcare facilities on case management and screening protocols of patients.
- Training infection preventionists on appropriate care for patients with CRE.

The current epidemiologic profile is a summary of reported CRE cases to the SD DOH during 2013-2016. The report summarizes major characteristics of isolates as well as characteristics of

infected/colonized patients in South Dakota. The intent of this document is to help South Dakota clinicians and public health professionals understand the epidemiology of CRE cases.

CRE Definitions:

During the reporting period two case definitions have been used:

1. Before 2015 the CDC CRE definition (nonsusceptible to imipenem, meropenem, or doripenem, AND resistant to all third-generation cephalosporins tested) was designed to be more specific for CP-CRE; however, it has proven to be complicated, difficult to implement, and has been found to miss some CP-CRE.
2. In January 2015, CDC modified the surveillance definition for CRE to the current definition (resistant to imipenem, meropenem, doripenem, or ertapenem OR documentation that the isolate possess a carbapenemase).

Problematic issues in CRE surveillance:

Surveillance of CRE in South Dakota faced the following challenges during the reporting period:

- Differentiating colonized cases from infections and ascertaining the epidemiologic and public health importance of colonizations.
- Problematic and complicated case definitions with changing minimal inhibitory concentrations (MIC) limits that have not been adopted by all laboratories in the state.
- Varied screening protocols in affected facilities. No clear directions exist on the frequency and duration of screening as well as when to initiate screening.
- Communication between facilities and CRE case management.
- Duration of shedding organism and requirements of contact precautions for healthcare personnel handling CRE positive cases.

RESULTS:

The analysis covered 145 CRE cases reported to the SD DOH during 2013-2016 calendar years (cumulative incidence rate for 4 years: 16.9 per 100,000 population). Seventy five (52%) were female and the median age was 68 (range 0-95 years). American Indians (AIs) accounted for 28 (19%) cases while the majority, 114 (79%) were white. One hundred and fourteen patients (79%) had no previous CRE history indicated, while 31 (21%) had a previous history of CRE infection or colonization.

Eighty two specimens (57%) were obtained from hospitalized patients and 63 (43%) from non-hospitalized patients.

The number of cases increased beginning in 2013. All reported cases were residents of SD.

Figure 1. Number of CRE cases reported to the SDDOH by year — South Dakota, 2013-2016

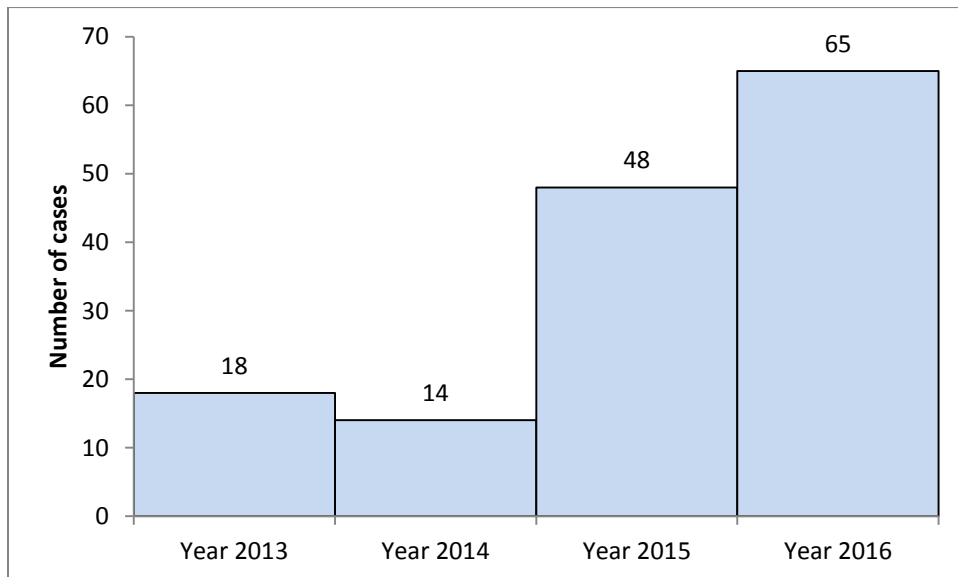
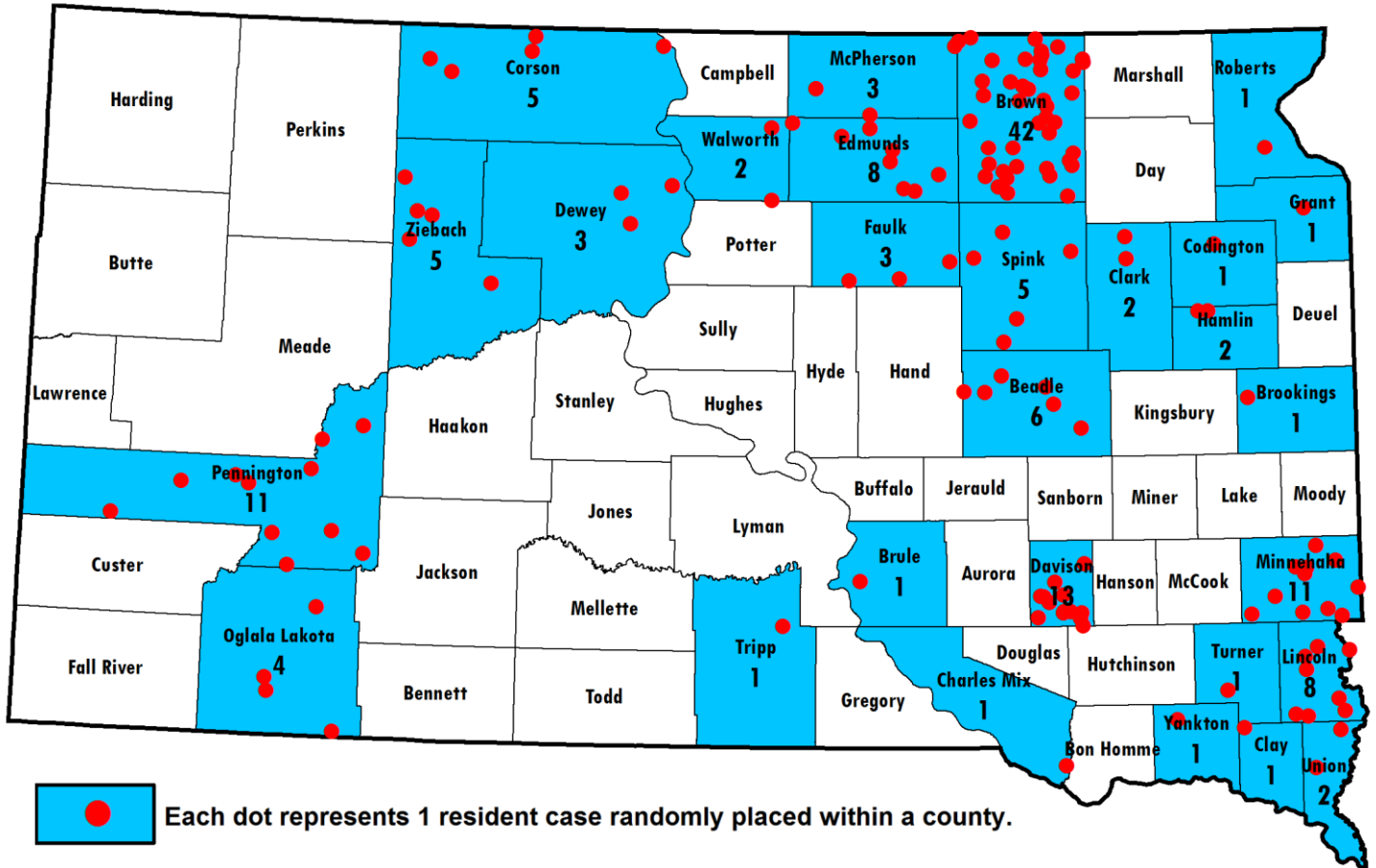
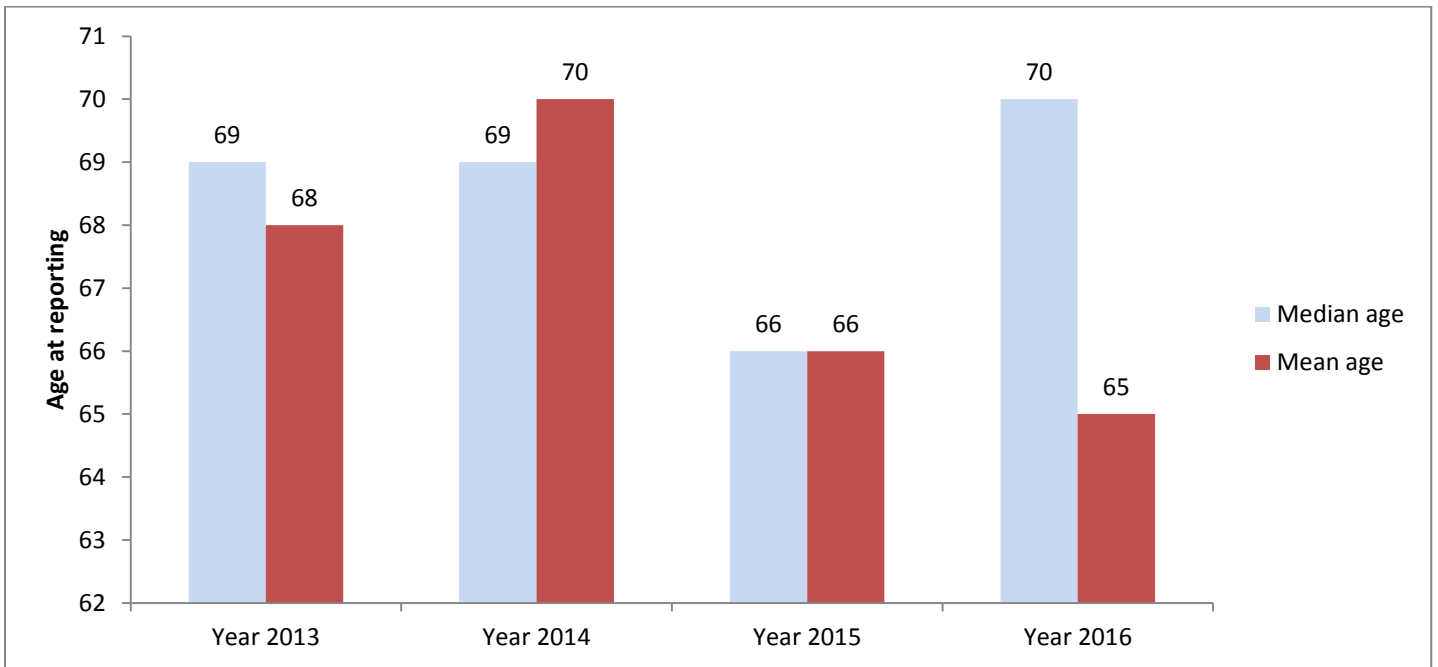


Figure 2. Cumulative number of reported CRE cases to SD DOH — South Dakota, 2013-2016



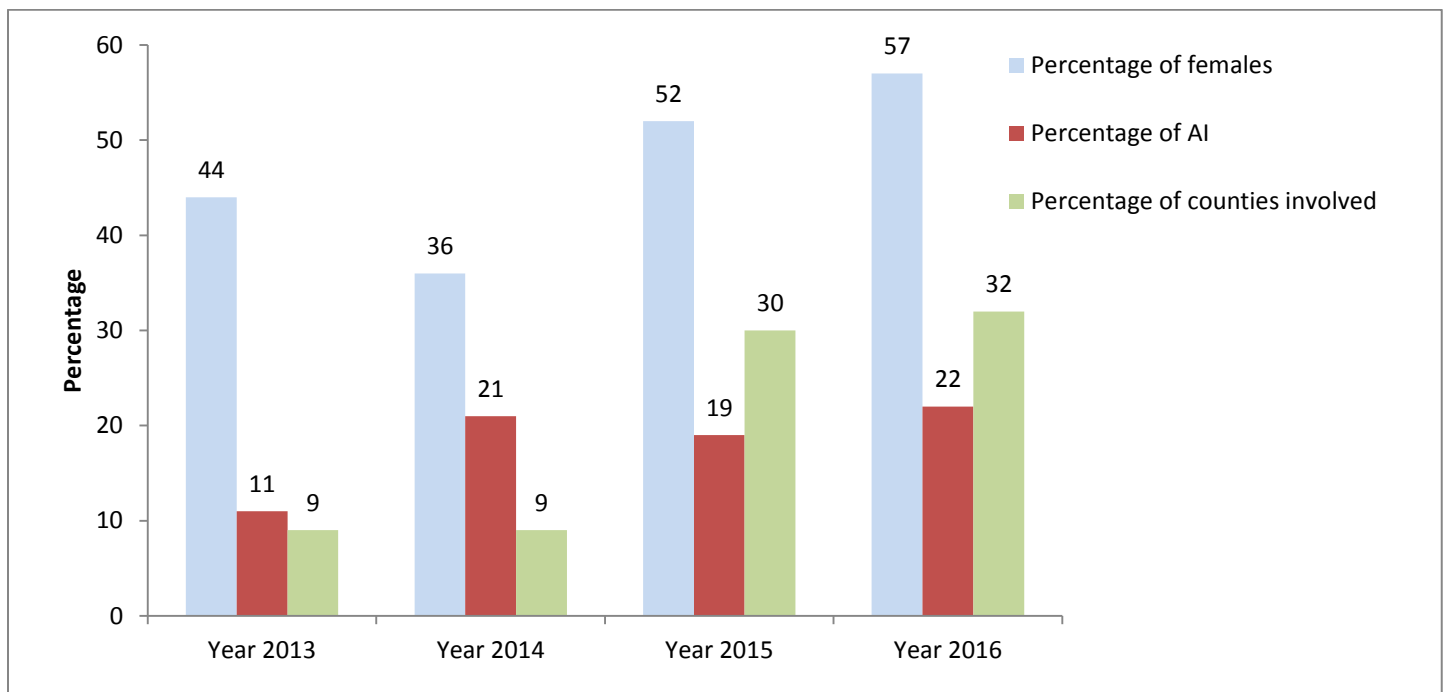
Cases were not stratified by age group because the median age of cases was 68 years. Rather, median and mean ages were presented by year. Figure 3 below indicates that in 2016 younger patients were identified as opposed to previous years (the difference between median and mean is 5 years). The mean age is affected by the influx of younger patients.

Figure 3. Patient's age at reporting by year — South Dakota, 2013-2016



Frequency of females, AIs and counties of residence became more uniform with years and closely reflected current South Dakota population characteristics. That might indicate increased prevalence of CRE affecting increasing number of all segments of South Dakota population.

Figure 4. Percentage of females, AIs, and counties involved based on the patient’s county of residence by year of reporting — South Dakota, 2013-2016



The majority of isolates were obtained at hospitals (57%) and clinics (23%). However long-term care facilities accounted for 8% and 12% of isolates respectively.

During 2013-2015 eighty cases of CRE were reported. Those cases came from two different sources: 1. Rectal swab (as part of a screening process) and 2. As a culture obtained from urine, wound, tissue, etc. The second segment of CRE positive cases were further stratified as “infections” (symptomatic patients) or “colonizations” (non-symptomatic patients). Overall, rectal swabs and colonizations (asymptomatic cases) made up 31% of total number (25 cases) and were later classified as “colonizations”, while symptomatic CRE cases accounted for 69% (55 cases) and were later classified as “CRE infections”.

This protocol has been modified in 2016. In 2016 a total of 65 cases have been reported. Those cases were classified as “colonizations” if they were coming from a rectal swab performed as part of the active screening process (7 cases, 11%) or “CRE cases”. The latter category included cases coming from all other sources regardless of their symptomatology (58 cases, 89%).

Initially South Dakota initiated screening of patients in an attempt to halt a regional outbreak. Later county incidence rate or outbreak in a county determined whether or not a facility introduced screening using predetermined screening criteria.

The most frequent site of CRE isolation among symptomatic patients was urine (62%) and sputum (13%). Site variations indicate the presence of CRE in other anatomical locations as well.

Table 1. Site of CRE isolation among infected (symptomatic) patients — South Dakota, 2013-2016.

Site of a specimen collection	Frequency (%)
Blood	1 (1)
Non-surgical wound	7 (6)
Abdominal Cavity	2 (2)
Intra-abdominal abscess	1 (1)
Peritoneal fluid	1 (1)
Sputum	15 (13)
Surgical wound	10 (9)
Non-surgical wound	1 (1)
Tracheal/broncho-alveolar lavage	4 (4)
Urine	70 (62)
Gallbladder	1 (1)

Table 2. Site of CRE isolation among all patients — South Dakota, 2013-2016

Site of a specimen collection	Frequency (%)
Blood	1 (1)
Non-surgical wound	7 (5)
Other - Abdominal cavity	2 (1)
Other - intra-abdominal abscess	1 (1)
Rectal swab	19 (13)
Peritoneal fluid	1 (1)
Sputum	15 (10)
Surgical wound	10 (7)
Tissue (undetermined)	1 (1)
Tracheal/broncho-alveolar lavage	4 (3)
Urine	83 (57)
Gallbladder	1 (1)
Total	145

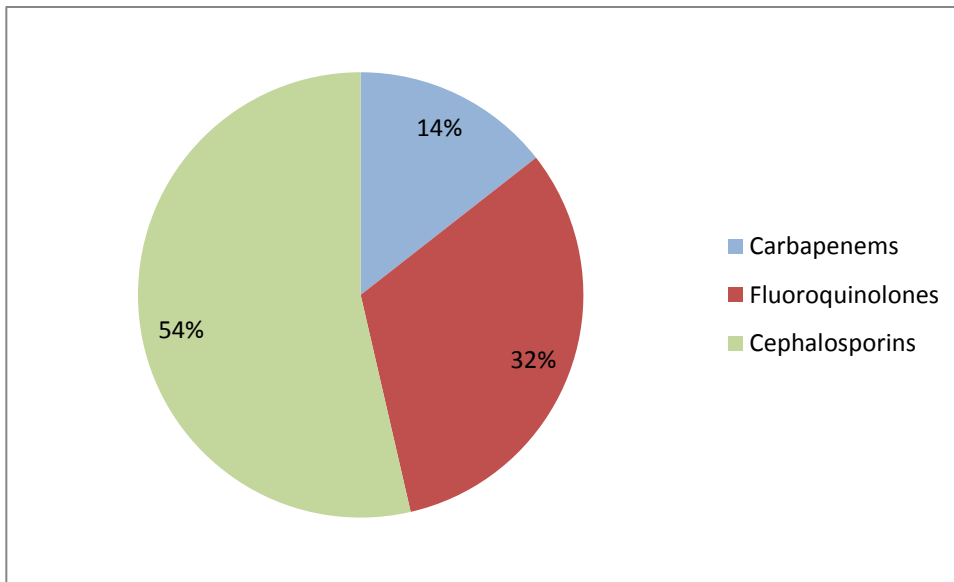
A history of receiving medical care outside of the U.S. within 6 months prior to diagnosis was known in 115 cases and all denied receiving medical care outside of the US. This finding underscores the fact that CRE in South Dakota is part of a US epidemic and not brought from elsewhere.

Among 119 patients whose previous medical history was known, 49 (41%) were hospitalized during the previous 12 months, 38 (32%) had a surgery, 18 (15%) had a history of an ICU stay, and 29 (24%) had a scope procedure (bronchoscopy, endoscopy, colonoscopy, cystoscopy) during the previous 12 months. The difference in those metrics was not statistically significant among different racial groups. The dataset does not include a reference group; therefore, it is problematic to draw conclusions based on cases only without taking into account a control population. However, consistent with the national profile, a high rate of medical procedures within a year prior to CRE diagnosis makes medical procedures and hospitalization a probable risk-factor of acquiring CRE. Another possibility could be the patient exposure to a long-term care facility. Sixty two patients (53%) reported a history of living in a long-term care facility within the preceding twelve months.

Among the patients that tested positive from urine (83 patients), 19 of those (23%) had an indwelling catheter at the time of specimen collection. Interestingly, among those patients where a specimen was obtained from other sites (62 cases), 15 (24%) patients had a urinary catheter in place, suggesting possible cross-contamination of other anatomical sites and a urinary catheter as a possible risk-factor for other locations.

Antibiotic exposure is one of the biggest risk-factors for creating multidrug-resistant organisms⁵. Seventy two patients (50%) reported exposure to cephalosporins, carbapenems, fluoroquinolones or combination of those three antibiotics three months prior to testing positive for CRE.

Figure 5. Exposure to commonly used broad spectrum antibiotics 3 months prior to testing positive for CRE — South Dakota, 2013-2016



Laboratory results:

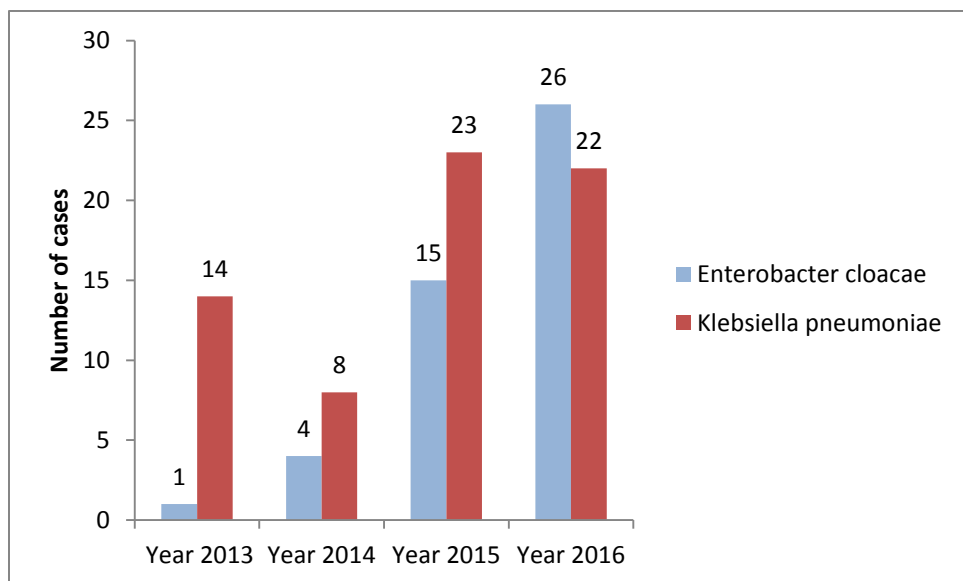
The most commonly cultured CRE was *Klebsiella pneumoniae* followed by *Enterobacter cloacae*.

Table 3. Genus and species of CRE isolates — South Dakota, 2013-2016

Genus and species	Number of isolates (%)
<i>Enterobacter aerogenes</i>	9 (6)
<i>Acinetobacter baumannii</i>	1 (1)
<i>Enterobacter cancerogenus</i>	1 (1)
<i>Enterobacter cloacae</i>	46 (32)
<i>Escherichia coli</i>	9 (6)
<i>Citrobacter freundii</i>	2 (1)
<i>Citrobacter koseri</i>	1 (1)
<i>Serratia marcescens</i>	3 (2)
<i>Proteus mirabilis</i>	1 (1)
<i>Klebsiella oxytoca</i>	1 (1)
<i>Klebsiella pneumoniae</i>	67 (46)
<i>Citrobacter spp</i>	1 (1)
<i>Citrobacter youngae</i>	1 (1)
Unknown	2 (1)
Total	145

The number of *Klebsiella pneumoniae* isolates was relatively stable across the years while the number of reported *Enterobacter cloacae* was dramatically increased.

Figure 6. Reported *Klebsiella pneumoniae* and *Enterobacter cloacae* cases by year of reporting — South Dakota, 2013-2016



PCR test was used in 55 cases. Among those 47 (85%) were positive and 8 (15%) were negative.

Modified Hodge test was used in 55 cases. Among those 23 (42%) were positive and 32 (58%) were negative. Among all isolates tested (83 in total), 49 (59%) were carbapenemase producers and 34 (41%) non-producers. Among those that have been tested for carbapenemase, the highest rate (69%) of carbapenemase production was observed among *Klebsiella pneumoniae* strains (34 out of total 49 positive isolates).

History of having a MDRO in the past was available for 135 (93%) patients. Among those, 63 (47%) had a history of a previous MDRO infection. Among those 63 patients, 19 (35%) have tested positive for ESBL (Extended-spectrum beta-lactamases), 19 (35%) for MRSA (Methicillin-resistant *Staphylococcus aureus*), 9 (16%) for VRE (Vancomycin-resistant enterococci), and 8 (15%) for other MDROs cultured.

LIMITATIONS:

The current report has several limitations:

- Information is unavailable on case-control studies that might uncover potential risk-factors of CRE in the state. High frequency of exposure to antibiotics, indwelling catheters, and common medical procedures warrants case-control studies in the future.
- Changes in case definition might create a problem in comparing the data across several years.
- Making CRE a reportable condition in 2013 may have created an artifact in surveillance, resulting in a higher number of cases reported.

CONCLUSIONS:

- CRE is becoming more common and widespread. There are several indications of this statement based on the presented data:
 - The most frequent site of CRE isolation among symptomatic patients was urine (62%) and sputum (13%). However, a wide variety of sites indicates that CRE is no longer concentrated in specific locations.
 - A wide variety of isolated organisms indicates an involvement in multiple genus and species. However old reports describe *Enterobacter spp.* and *Klebsiella pneumoniae* as the only CREs isolated (in 1986-1990 and 2004 – 2008 respectively)⁶.
 - The number of affected counties is increased and the mean age of patients is decreased indicating that younger patients are acquiring CRE.
- Another explanation of the findings may be an artifact of the surveillance system. In 2013 SDDOH made CRE a reportable condition, allowing collection of data on cases that previously remained unknown. The new reporting requirement potentially increased the number of reported cases over time and increased variety of CRE presentations described above.
- American Indians were disproportionately affected. However potential risk factors such as hospitalizations during the previous year, ICU, surgeries, and scope procedures did not differ significantly between American Indians and whites.

- Sixty-three (47%) of patients had a history of MDRO other than CRE infection in the past and 72 (50%) reported exposure to commonly used broad-spectrum antibiotics. This highlight suggests a systemic problem of antibiotic overutilization and underscores the urgent need for antimicrobial stewardship programs statewide.
- High frequency of catheter use among patients alludes to catheters as a potential source of introduction and contamination of the environment with CRE.
- The absence of patients in the dataset reporting medical care outside of the U.S. indicates a domestic rather than imported problem in South Dakota.

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