

# Epidemiology of Carbapenem-Resistant Enterobacteriaceae in 7 US Communities, 2012-2013

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## IMPORTANCE

Carbapenem-resistant Enterobacteriaceae (CRE) are a worldwide clinical and public health problem. These multidrug-resistant organisms cause infections associated with high mortality and limited treatment options, and are increasingly recognized as an important cause of health care-associated infections.<sup>1-5</sup> In the United States, much of the initial dissemination of CRE can be attributed to organisms producing the *Klebsiella pneumoniae* carbapenemase, a type of  $\beta$ -lactamase enzyme that confers resistance to carbapenem antimicrobials.

Since the first case was reported in North Carolina in 2001, cases of *Klebsiella pneumoniae* carbapenemase-producing CRE have been reported in almost every state and it remains the carbapenemase most commonly identified in isolates sent to the US Centers for Disease Control and Prevention (CDC).<sup>6</sup> To date, 23 states have required some form of CRE reporting; however, requirements and definitions vary by state. The current US reporting requirements are available online.<sup>7</sup>

To describe CRE epidemiology in the catchment areas and inform prevention efforts, the CDC formally initiated population-based surveillance in 2012 in select US geographical areas using the Emerging Infections Program (EIP). This surveillance system provides the most extensive US population-based evaluation of CRE to date, allowing for the monitoring of the burden of disease over time, identification of risk factors, and characterization of strains. We present the population-

based

ing of serial dilutions of imipenem with and without chelators at fixed concentrations. A decrease in the minimum inhibitory concentration of the drug by 2 or more doubling dilutions in the presence of chelators was considered a positive metallo- $\beta$ -lactamase screening.<sup>11</sup> Any isolate positive for metallo- $\beta$ -lactamase but negative for New Delhi metallo- $\beta$ -lactamase was further tested by polymerase chain reaction for genes encoding Verona integron-encoded metallo- $\beta$ -lactamase and Imipenemase metallo- $\beta$ -lactamase. The modified Hodge test was performed on all submitted isolates using both ertapenem and meropenem; a positive result for either carbapenem was considered indicative of carbapenemase production.

### Statistical Analyses

Annual incidence rates for CRE cases and case-patients were calculated using the 2012 and 2013 US census estimates of the surveillance area population as the denominator. Standardized incidence ratio, which is an indirect standardization, was calculated to compare incident CRE rates among EIP sites. Standardized incidence ratio was used for this analysis because the relatively small number of CRE cases produced stratum-specific estimates (by age and race) that were too low to allow accurate direct standardization for disease rate comparison.<sup>13</sup> Missing values for race were imputed based on the distribution of known race by age, sex, and surveillance site.

The standardized incidence ratio was calculated by dividing the number of observed cases by the number of predicted cases. The number of predicted cases was estimated from a multivariable negative binomial regression predicting CRE infection incidence, adjusted by age (0-18 years, 19-49 years, 50-64 years, and  $\geq 65$  years) and race (white and nonwhite), and constructed from CRE surveillance data during 2012-2013 using surveillance site US census data as the denominator.<sup>13</sup>

The CRE incidence estimates aggregated across all participating sites during this same period represent the population used to standardize CRE incidence (standard population). The 95% confidence intervals for the standardized incidence ra-

tios were constructed using the site-specific predicted case counts from each EIP site. A standardized incidence ratio of less than 1.0 indicates fewer observed CRE cases than predicted compared with the standard population, whereas a ratio greater than 1.0 indicates more observed CRE cases than predicted compared with the standard population.

Descriptive analyses were performed to summarize specimen information, health care exposures, outcomes, and mi-

#### Incidence Rates and Standardized Incidence Ratios

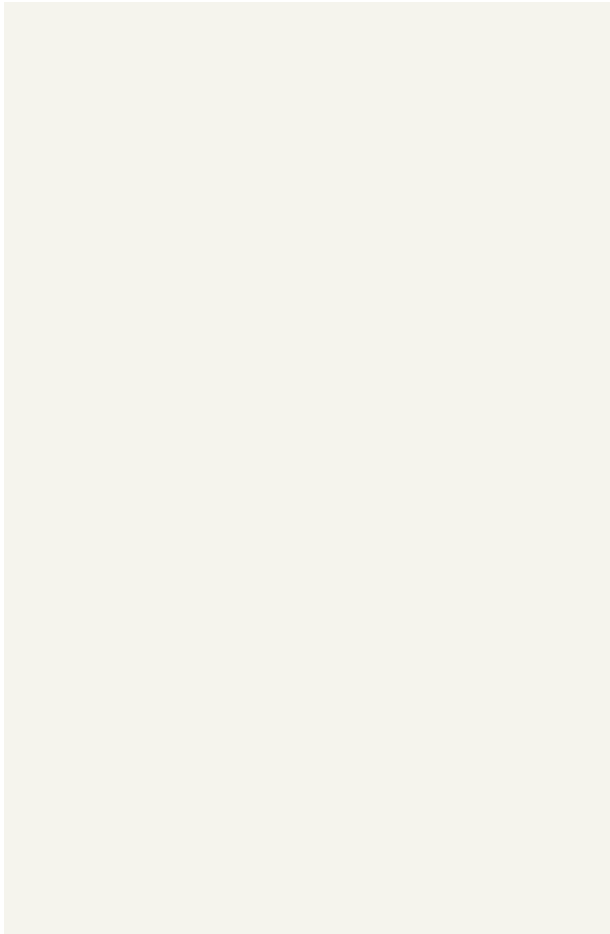
The overall crude annual CRE incidence across the EIP sites during the 2-year period was 2.93 (95% CI, 2.65-3.23) per 100 000 population. Site-specific crude incidence rates in 2012 ranged from 0.35 (95% CI, 0.14-0.74) per 100 000 population in Oregon to 4.58 (95% CI, 3.94-5.30) per 100 000 population in Georgia (Table 2). The site-specific crude incidence rates in 2013 ranged from 0.82 (95% CI, 0.47-1.34) per 100 000 population in Oregon to 4.80 (95% CI, 3.89-5.85) per 100 000 population in Maryland.

Significantly higher than predicted CRE standardized incidence ratios adjusted for age and race, which were independently associated with increased risk of CRE, for the 2-year period were observed for Georgia ( $P < .001$ ), Maryland ( $P = .001$ ), and New York ( $P = .048$ ). Significantly lower than predicted standardized incidence ratios were observed for Colorado ( $P < .001$ ), New Mexico ( $P = .01$ ), and Oregon ( $P < .001$ ).

#### Specimen Information and Prior Health Care Exposures of Incident CRE Cases

Data on the health care location of specimen collection (eg, out-





reflect the degree to which carbapenemase-producing strains have emerged within and across regions of the United States. Carbapenemase-producing CRE carry antimicrobial resistance genes on mobile plasmids that can move between organisms, potentially facilitating a wider and more rapid spread, adding to the background of non-carbapenemase-producing CRE. Failure to address the spread of carbapenemase-producing CRE could lead to further increases in CRE incidence in areas in which they are already present and wider spread of CRE to areas that have not seen these organisms regularly.

Recommended control measures (eg, contact precautions) should be generally implemented to prevent further spread of all CRE, with more aggressive interventions used for carbapenemase-producing CRE (eg, surveillance cultures of hospitalized roommates).<sup>3,19</sup> Regionwide control measures also have been recommended to achieve maximal benefit.<sup>19</sup> Only half of all submitted CRE isolates meeting

incidence of 2.93 per 100 000 population. This estimate is substantially lower than the incidence of infections due to other pathogens traditionally associated with health care exposures, including methicillin-resistant *S a c c a e* (25.1 per 100 000 population),<sup>16</sup> invasive candidiasis (13.3-26.2 per 100 000),<sup>17</sup> and *C d d f f c e* (147.2 per 100 000).<sup>18</sup> We found variation by site for the distribution of species, annual incidence, and the percentage of isolates that produced carbapenemase. Ninety-one percent of CRE cases were in individuals with preceding health care exposures and underlying comorbidities.

Although most cases were from cultures collected outside a short-stay acute care hospital, almost half were among individuals hospitalized within 30 days after their initial culture. The majority of hospitalized cases resulted in a discharge directly to a long-term care facility or long-term acute care hospital. Urine was the most common source of CRE, which likely accounted for the low overall mortality observed.

The variability in CRE incidence and the frequency with which different species are represented in EIP sites might



Fifth, although a broad set of catchment areas are included in this surveillance system, it is not designed to be representative of the United States. In addition, isolates from only one-third of all cases were available for molecular characterization. Although attempts were made to systematically collect isolates, a nonrepresentative sample might have been selected at some sites.

In summary, the results of this investigation further inform local efforts to prevent CRE transmission. The low CRE incidence in the catchment areas, compared with other more established resistant organisms, highlights that CRE are emerging and suggests that control interventions implemented now could have a substantial effect.

The fact that heterogeneity exists (with respect to the incidence and the types of CRE found in these different surveillance areas) further highlights the need to understand the local epidemiology to tailor prevention efforts in individual

regions of the United States. The frequency with which individuals with CRE are transferred between facilities emphasizes the need for regional control efforts in all the facilities. In addition, the finding that many CRE do not produce a carbapenemase suggests the potential need for a tiered response to these organisms as well as the need for more rapid and readily available laboratory tests to differentiate these strains.

## Conclusions

In this population- and laboratory-based active surveillance system in 7 states, the incidence of CRE was 2.93 per 100 000 population. Most CRE cases were isolated from a urine source, and were associated with high prevalence of prior hospitalizations or indwelling devices, and discharge to long-term care settings.

### ARTICLE INFORMATION

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**Author Contributions:** Dr Guh and Ms Bulens had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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**Additional Contributions:**

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