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Trends in Incidence of Carbapenem-Resistant Enterobacterales in 7 US Sites, 2016–2020

Nadezhda Duffy,^{1,✉} Rongxia Li,¹ Christopher A. Czaja,² Helen Johnston,² Sarah J. Janelle,² Jesse T. Jacob,^{3,4,✉} Gillian Smith,^{3,4,5} Lucy E. Wilson,⁶ Elisabeth Vaeth,⁶ Ruth Lynfield,⁷ Sean O'Malley,⁷ Paula Snippes Vagnone,⁷ Ghinwa Dumyati,^{8,✉} Rebecca Tsay,⁸ Sandra N. Bulens,¹ Julian E. Grass,¹ Rebecca Pierce,⁹ P. Maureen Cassidy,⁹ Heather Hertzler,⁹ Christopher Wilson,¹⁰ Daniel Muleta,¹⁰ Jacquelyn Taylor,¹⁰ and Alice Y. Guh¹

¹Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia, USA, ²Division of Disease Control and Public Health Response, Colorado Department of Public Health and Environment, Denver, Colorado, USA, ³Department of Medicine, Emory University School of Medicine, Atlanta, Georgia, USA, ⁴Georgia Emerging Infections Program, Atlanta, Georgia, USA, ⁵Atlanta Veterans Affairs Medical Center, Decatur, Georgia, USA, ⁶Maryland Department of Health, Infectious Disease Epidemiology and Outbreak Response Bureau, Baltimore, Maryland, USA, ⁷Minnesota Department of Health, Saint Paul, Minnesota, USA, ⁸New York Emerging Infections Program at the University of Rochester Medical Center, Rochester, New York, USA, ⁹Public Health Division, Oregon Health Authority, Portland, Oregon, USA, and ¹⁰Tennessee Department of Health, Nashville, Tennessee, USA

Background. We described changes in 2016–2020 carbapenem-resistant Enterobacterales (CRE) incidence rates in 7 US sites that conduct population-based CRE surveillance.

Methods. An incident CRE case was defined as the first isolation of *Escherichia coli*, *Klebsiella* spp., or *Enterobacter* spp. resistant to ≥ 1 carbapenem from a sterile site or urine in a surveillance area resident in a 30-day period. We reviewed medical records and classified cases as hospital-onset (HO), healthcare-associated community-onset (HACO), or community-associated (CA) CRE based on healthcare exposures and location of disease onset. We calculated incidence rates using census data. We used Poisson mixed effects regression models to perform 2016–2020 trend analyses, adjusting for sex, race/ethnicity, and age. We compared adjusted incidence rates between 2016 and subsequent years using incidence rate ratios (RRs) and 95% confidence intervals (CIs).

Results. Of 4996 CRE cases, 62% were HACO, 21% CA, and 14% HO. The crude CRE incidence rate per 100 000 was 7.51 in 2016 and 6.08 in 2020 and was highest for HACO, followed by CA and HO. From 2016 to 2020, the adjusted overall CRE incidence rate decreased by 24% (RR, 0.76 [95% CI, .70–.83]). Significant decreases in incidence rates in 2020 were seen for HACO (RR, 0.75 [95% CI, .67–.84]) and CA (0.75 [.61–.92]) but not for HO CRE.

Conclusions. Adjusted CRE incidence rates declined from 2016 to 2020, but changes over time varied by epidemiologic class. Continued surveillance and effective control strategies are needed to prevent CRE in all settings.

Keywords. carbapenem-resistant Enterobacterales; CRE; trends in incidence.

Carbapenem-resistant Enterobacterales (CRE) have been deemed an urgent public health threat in the Centers for Disease Control and Prevention (CDC) Antibiotic Resistance Treat Report [1]. CRE caused an estimated 13 100 cases and 1100 deaths among hospitalized US patients in 2017. During the coronavirus disease 2019 (COVID-19) pandemic, US hospital-onset (HO) CRE rates increased 35% in 2020, emphasizing the need to contain further CRE spread [2]. Although CRE in the United States are mainly associated with healthcare [3], their emergence in the community has been described [4, 5]. Particularly concerning are CRE that produce carbapenemases (ie, carbapenemase-producing CRE [CP-CRE]) because the genes that encode the carbapenemases are located on mobile genetic elements that can be transferred horizontally

to other gram-negative bacteria thus contributing to rapid spread [6]. Treatment options for CRE are limited, as these organisms are resistant to most antibiotic classes, thus often resulting in difficult-to-manage infections associated with significant morbidity and mortality rates [7].

Preventing CRE spread remains a public health priority [8], and the monitoring of CRE incidence is important for assessing the effectiveness of prevention interventions [9]. However, most reports on CRE trends have been limited to hospitalized patients or a single region [10, 11]. To our knowledge, trends in CRE incidence rates using population-based surveillance data have not been previously described. We describe changes in 2016–2020 CRE incidence rates in 7 diverse US sites that conduct active laboratory and population-based CRE surveillance for the Multi-site Gram-negative Surveillance Initiative, which is part of the CDC's Emerging Infections Program (EIP) [12].

METHODS

Surveillance Population and Case Definition

We included data from 7 EIP sites, consisting of selected counties in Colorado, Georgia, Maryland, Minnesota, New York,

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Correspondence: Nadezhda Duffy, MD, MPH, Division of Healthcare Quality Promotion, MS H16-3, Centers for Disease Control and Prevention, 1600 Clifton Rd NE, Atlanta, GA 30329-4027 (nduffy@cdc.gov).

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Oregon, and Tennessee that continuously participated in CRE surveillance during 2016–2020 with no known changes in CRE testing practices among surveillance site laboratories [12]. In 2020, the total estimated surveillance population was 15 144 382 persons.

Starting in 2016, an incident CRE case was defined as the first isolation of *Escherichia coli*, *Klebsiella aerogenes*, *Enterobacter cloacae* complex, *Klebsiella pneumoniae*, or *Klebsiella oxytoca* resistant to ≥ 1 carbapenem (imipenem, meropenem, doripenem, ertapenem) from a sterile site (blood, cerebrospinal fluid, pleural fluid, pericardial fluid, peritoneal fluid, joint/synovial fluid, bone, internal body site [eg, lymph node, brain, heart, liver spleen, vitreous fluid, kidney, pancreas, or ovary], muscle, deep tissue, or other normally sterile site) or urine in a surveillance area resident in a 30-day period. Colonization screening cultures were excluded. The case definition before 2016 was more specific for CP-CRE and required nonsusceptibility (ie, intermediate or resistant) to carbapenems (excluding ertapenem) and resistance to all third-generation cephalosporins tested (ceftazidime, ceftriaxone, and cefotaxime) [13].

Data Collection and Epidemiologic Classification

EIP staff routinely contacted clinical laboratories serving the surveillance area for reports of CRE identified through a query of minimum inhibitory concentration values from automated testing instruments. Site staff performed medical record review and completed a standardized case report form for all incident CRE cases to record patient demographic data, location of culture collection, selected healthcare exposures and risk factors, and clinical characteristics, including types of infection associated with the CRE culture.

Based on medical record review, incident CRE cases were epidemiologically classified as HO CRE if the incident culture was obtained ≥ 3 days after admission to a hospital; as healthcare-associated community-onset (HACO) CRE if the incident culture was obtained in a nonhospital setting or < 3 days after hospital admission in a person with a history of hospitalization, surgery, residence in a long-term care facility, or residence in a long-term acute-care hospital in the year before culture or from a patient on long-term dialysis or with an indwelling device or external urinary catheter in the 2 days before culture collection; and as community-associated (CA) CRE if no healthcare risk factors in the prior year were documented in the medical record.

Statistical Analysis

Analysis was performed using SAS software, version 9.4 (SAS Institute). Incidence rates were calculated using case counts and the 2016–2020 US census population estimates. Multiple imputation was performed for missing race/ethnicity and epidemiologic class variables by using the fully conditional specification method [14] based on the distributions of the following variables: age, sex, race/ethnicity, epidemiologic classification,

EIP site, and year. To assess changes in the overall incidence of CRE and by epidemiologic class, we used Poisson mixed effects regression models, adjusting for sex, race/ethnicity, and age, with the EIP site used as a random effect. Adjusted incidence rates between 2016 and subsequent years were compared using incidence rate ratios (RRs) and 95% confidence intervals (CIs). Since the current case definition has led to increased detection of non-CP-CRE [15, 16], we repeated the above analyses using the pre-2016 CRE case definition. In addition, the 1-tailed Mann-Kendall test was used to determine whether there was a significant increasing or decreasing trend in the crude incidence rates of CRE organisms and infection types. Differences were considered statistically significant at $P < .05$.

Patient Consent Statement

This activity was reviewed by the CDC and was conducted consistent with applicable federal law and CDC policy (see, eg, 45 CFR part 46, 21 CFR part 56; 42 USC §241(d); 5 USC §552a; 44 USC §3501 et seq). It was also reviewed by EIP sites and either was deemed nonresearch or received an institutional review board approval with a waiver of informed consent. This activity did not include factors necessitating patient consent.

RESULTS

CRE Characteristics and Crude Incidence Rates

During 2016–2020, we identified 4996 incident CRE cases among 4321 patients; 291 (7%) patients had 2 incident cases, and 64 (2%) had 3. Of 4996 incident CRE cases reported in 2016–2020, *E. cloacae* complex was the predominant organism, followed by *K. pneumoniae* and *E. coli* (Supplementary Table 1). Most cases were identified from urine (89%) or blood (8%) samples (Supplementary Table 2), and most patients were female (62%) and of non-Hispanic, white race (46%); the median patient age (interquartile range) was 69 (56–80) years (Table 1). Of the 4996 CRE cases, 3093 (62%) were HACO, 1041 (21%) were CA, and 703 (14%) were HO; the epidemiologic class was unknown in 159 (3%).

The crude overall CRE incidence rate per 100 000 population was 7.51 in 2016 and 6.08 in 2020 and was highest for HACO CRE, followed by CA and HO CRE (Figure 1). Over this 5-year period, *K. pneumoniae* was the only organism to have a significant decreasing trend in crude incidence rate ($P = .04$) (Figure 2). Over the same period, urinary tract infections also showed a significant decreasing trend in crude incidence rate ($P = .04$), whereas sterile-site infections showed a significant increasing trend ($P = .04$) (Figure 3).

Adjusted CRE Incidence Rates

Compared with 2016, the adjusted overall CRE incidence rate significantly decreased by 20% in 2018 (RR, 0.80 [95% CI, .73–.87]), 17% in 2019 (0.83 [.76–.91]), and 24% in 2020 (0.76

Table 1. Selected Descriptive Characteristics of Incident Carbapenem-Resistant Enterobacterales Cases at 7 Emerging Infections Program Sites, United States, 2016–2020

Characteristic	Incident Case Patients, No. (%) ^a (N = 4996)
Age, median (IQR), y	69 (56–80)
Age group	
0–18 y	135 (2.7)
19–49 y	764 (15.3)
50–64 y	1042 (20.9)
65–79 y	1751 (35.1)
≥80 y	1304 (26.1)
Female sex	3104 (62.1)
Race/ethnicity	
Hispanic, any race	253 (5.1)
Non-Hispanic, white race	2318 (46.4)
Non-Hispanic, other race ^b	1396 (27.9)
Unknown race or ethnicity	1029 (20.6)
EIP site	
Colorado	583 (11.7)
Georgia	1639 (32.8)
Maryland	1031 (20.6)
Minnesota	691 (13.8)
New York	487 (9.8)
Oregon	207 (4.1)
Tennessee	358 (7.2)
Epidemiologic classification	
HACO CRE	3093 (61.9)
CA CRE	1041 (20.8)
HO CRE	703 (14.1)
Unknown	159 (3.2)

Abbreviations: CA, community-associated; CRE, carbapenem-resistant Enterobacterales; EIP, Emerging Infections Program; HACO, healthcare-associated community-onset; HO, hospital-onset; IQR, interquartile range.

^aData represent no. (%) of incident case patients unless otherwise specified.

^b“Other race” included non-Hispanic black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, or ≥2 races reported.

[.70–.83]) (Figure 4). Compared with 2016, the adjusted incidence rates for each epidemiologic class decreased annually since 2018. However, for HO CRE, only the 23% decrease in 2019 (RR, 0.77 [95% CI, .61–.98]) was significant. HACO CRE significantly decreased by 19% in 2018 (RR, 0.81 [95% CI, .73–.91]), 15% in 2019 (0.85 [.76–.94]), and 25% in 2020 (0.75 [.67–.84]). CA CRE significantly decreased by 23% in 2018 (RR, 0.77 [95% CI, .63–.93]) and 25% in 2020 (0.75 [.61–.92]).

When the pre-2016 case definition was applied, similar trends with larger annual decreases in CRE incidence rates were observed from 2016 to 2020 (Supplementary Figure). However, the decreases in the adjusted incidence rate of CA CRE were not statistically significant.

DISCUSSION

From 2016 to 2020, the adjusted CRE incidence rate across 7 US sites decreased significantly, by 24%; however, decreases varied

by epidemiologic class. We observed similar trends using the pre-2016 case definition, which supports a decline in CRE, presumably a combination of CP-CRE and non-CP-CRE. Notably, a significant decline was seen with *K pneumoniae*, which is more likely to be a carbapenemase producer than other CRE organisms [16, 17]. Concerted national prevention efforts likely contributed to the decrease in CRE, including improved surveillance for CRE, prompt implementation of recommended prevention measures, and continued emphasis on antibiotic stewardship [18]. In addition, efforts to reduce urinary catheter use and inappropriate urine cultures may have contributed to the decrease in urinary tract infection rates. Although our findings are consistent with national CRE declines seen across US Veteran Affairs medical centers [19], they conflict with the increased CRE rates reported in the Houston area during the same period, suggesting variation in regional CRE trends despite observed national decreases [10].

Our finding that HO CRE incidence significantly declined in 2019 but not in 2020, and in fact increased between 2019 and 2020, complements other CDC reports that demonstrated a decrease in US hospital CRE rates during 2018–2019 followed by an increase in 2020 during the COVID-19 pandemic [1, 2]. Multiple factors during the pandemic might have reversed some of the progress in CRE prevention and contributed to an increase in HO as well as sterile-site infections in 2020, including increased hospitalizations of patients with comorbid conditions, high antimicrobial use, hospital staffing shortages, and challenges adhering to infection prevention and control guidance [2]. In contrast, CA and HACO CRE significantly declined in 2020, likely owing to decreases in outpatient health-care utilization during the pandemic.

Interestingly, we found the decline in CA CRE was not significant when using the pre-2016 case definition. The reasons for this are unclear but could reflect a low statistical power (fewer CA CRE identified by the pre-2016 definition) or a greater decline in non-CP-CRE than CP-CRE among CA cases. It is possible that CP strains have become more prevalent among CA CRE. Although data are limited, in an earlier multisite study from 2012–2015, 5 (42%) of 12 CA CRE isolates that were evaluated by whole-genome sequencing had harbored a carbapenemase [5]. Another multicenter study conducted among hospitalized patients in 2016–2017 found that 81% of CA CRE were carbapenemase producers [4]; however, differences in study designs limit comparability.

Our analysis has several limitations. First, the CRE case definition changed in 2016, and thus the analysis was restricted to more recent years, limiting our ability to understand long-term trends. Second, we included cases detected by automated testing instruments, which can sometimes misclassify isolates as ertapenem resistant (eg, ertapenem monoresistance) [20], resulting in the inclusion of some cases that might not be confirmed as carbapenem resistant on further testing [16, 21]. However, we

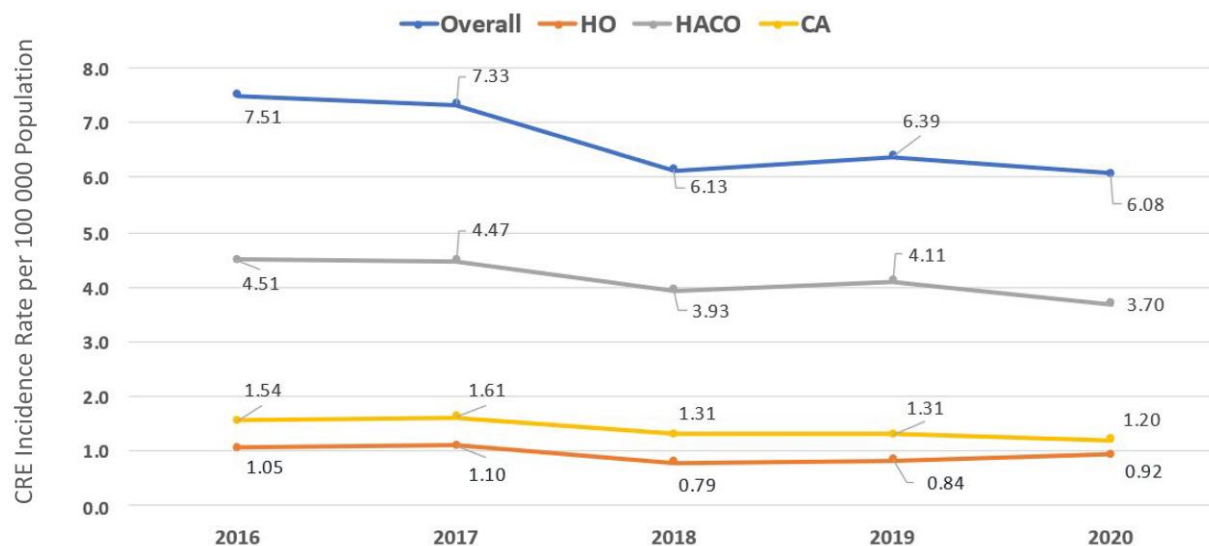


Figure 1. Crude carbapenem-resistant Enterobacterales (CRE) incidence rates, overall and by epidemiologic class, 2016–2020. Abbreviations: CA, community-associated; HACO, healthcare-associated community-onset; HO, hospital-onset.

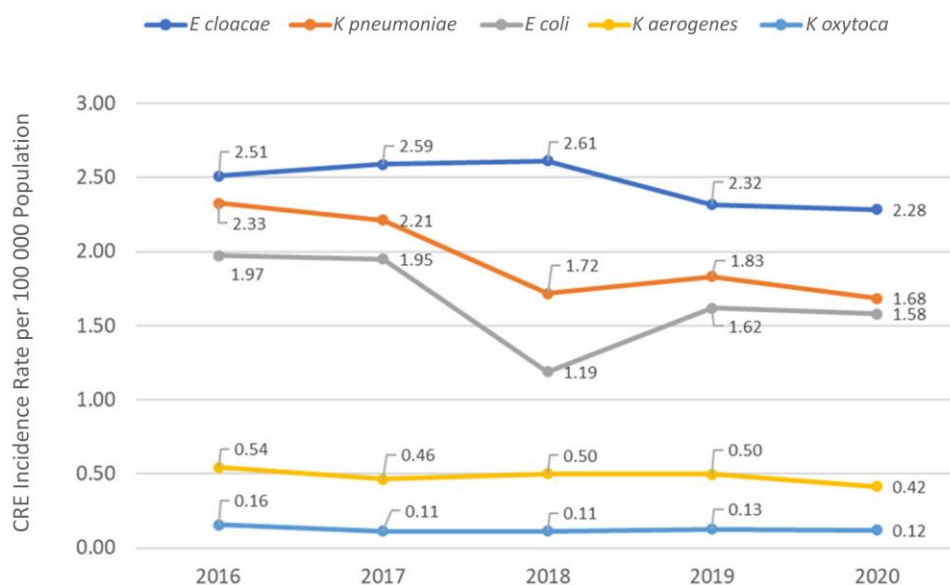


Figure 2. Crude carbapenem-resistant Enterobacterales (CRE) incidence rates by organism type, 2016–2020. A significant decreasing trend in incidence rate was seen for *Klebsiella pneumoniae* ($P = .04$) but not for *Enterobacter cloacae* complex ($P = .23$), *Escherichia coli* ($P = .11$), *Klebsiella aerogenes* ($P = .16$), or *Klebsiella oxytoca* ($P = .50$).

repeated our analysis using the pre-2016 case definition, which excluded ertapenem, and observed generally similar trends. Third, only a convenience sample of CRE isolates were submitted to CDC for carbapenemase testing. The selection of isolates for carbapenemase testing was determined by individual EIP sites and was not necessarily representative of the geographic or species distribution of cases; thus, we were unable to determine the incidence of CP-CRE. Fourth,

although we included geographically diverse sites, our results may not be representative of the entire country. Notably, CRE prevalence and carbapenemase production have been reported to vary widely by region [16]. In addition, we did not analyze site-specific trends, and it is possible the overall CRE decrease might be driven by selected sites; however, we accounted for variability in incidence among sites by including EIP site as a random effect in our analysis. Fifth, because this

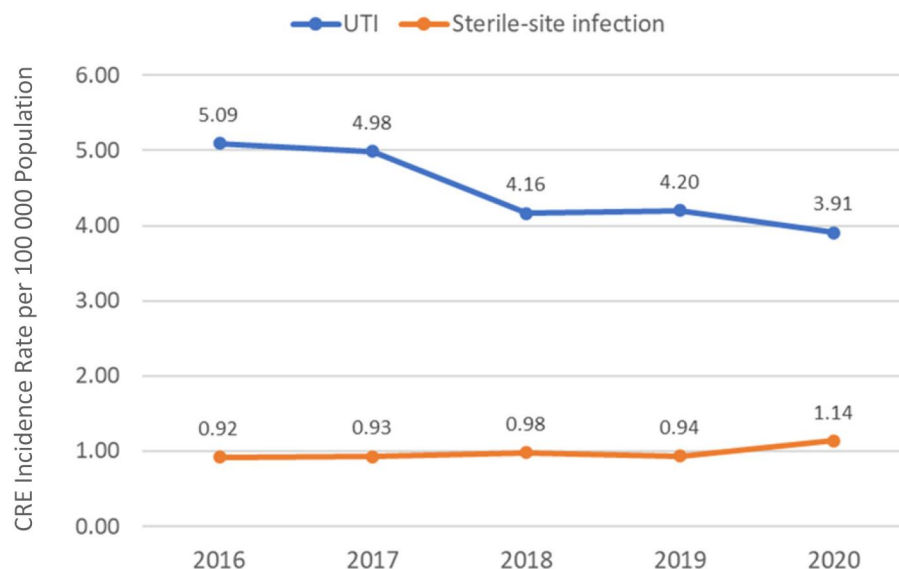


Figure 3. Crude incidence rates for the infection types associated with the incident carbapenem-resistant Enterobacterales (CRE) culture, 2016–2020. A significant decreasing trend in incidence rate was seen for urinary tract infection (UTI; $P = .04$), whereas a significant increasing trend was seen for sterile-site infection ($P = .04$).

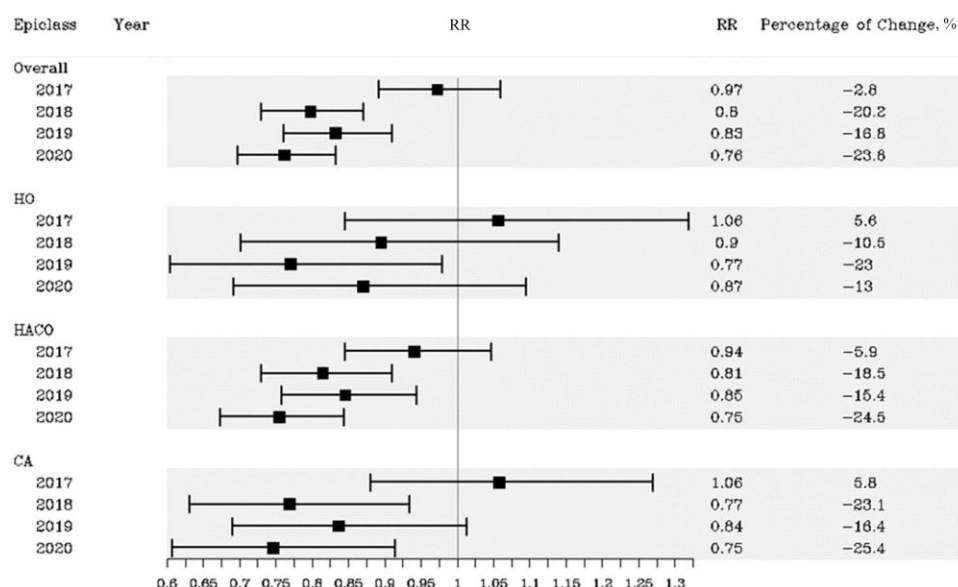


Figure 4. Adjusted rate ratios (RRs) with 95% confidence intervals comparing annual 2017–2020 carbapenem-resistant Enterobacterales (CRE) incidence rates with the 2016 CRE incidence rate, using the current surveillance case definition (which was applied to all years starting in 2016). RRs were adjusted for case sex, race/ethnicity, and age. Abbreviations: CA, community-associated; HACO, healthcare-associated community-onset; HO, hospital-onset.

CRE surveillance is primarily intended to capture clinical infections, certain specimens that are difficult to distinguish between infection versus colonization, such as respiratory cultures and wound cultures that were not collected intraoperatively, were excluded from surveillance. Thus, this could have resulted in an underestimation of CRE incidence rates. Finally, data were extracted from retrospective record reviews

and may be incomplete for some variables, including health-care risk factors, which could have resulted in the misclassification of some cases as CA.

In conclusion, adjusted CRE incidence rates declined from 2016 to 2020 using current and prior surveillance case definitions, although changes varied by epidemiologic class. Further surveillance is needed to understand post-COVID-19 pandemic

changes to CRE incidence. Continued CRE prevention across both healthcare and community settings is critical and will require a better understanding of the epidemiology of CA CP-CRE.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Data availability. The data are not publicly available.

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