

# Carbapenem-Resistant *Klebsiella pneumoniae* Infection in Three New York City Hospitals Trended Downwards From 2006 to 2014

Sun O. Park,<sup>1,4</sup> Jianfang Liu,<sup>2</sup> E. Yoko Furuya,<sup>3</sup> and Elaine L. Larson<sup>1,2</sup>

<sup>1</sup>Mailman School of Public Health, <sup>2</sup>School of Nursing, and <sup>3</sup>College of Physicians and Surgeons, Columbia University, New York; <sup>4</sup>Department of Medicine, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, New York

**Background.** Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infection is a rising public health threat since its first outbreaks in New York City (NYC) in the early 2000s. We investigated annual trends of CRKP infection in hospital-acquired infections (HAIs) and community-onset infections (COIs) treated in 3 NYC hospitals from 2006 to 2014.

**Methods.** We extracted *K pneumoniae* infection data including carbapenem susceptibility and anatomical sites, compared clinical characteristics between CRKP and carbapenem-susceptible *K pneumoniae* infections, and determined CRKP infection proportions in total *K pneumoniae* infections in HAI and COI to identify statistically significant trends from 2006 to 2014 using the Cochran-Armitage trend test.

**Results.** Carbapenem-resistant *K pneumoniae* contributed 17.3% (601 of 3477) of hospital-acquired *K pneumoniae* infection compared with 7.7% (149 of 1926) in COI from 2006 to 2014. Carbapenem-resistant *K pneumoniae* proportions in HAI and COI were positively correlated over time ( $r = 0.83$ ,  $P < .01$ ), and there were downward annual trends of CRKP proportions from 2006 to 2014 in both HAI and COI (25.8% to 10.5% in HAI,  $P < .001$ ; 13.6% to 3.1% in COI,  $P < .001$ ). By anatomical site, significant downward annual trends were present only in urinary tract infection ( $P < .001$  for both HAI and COI) from 2006 to 2014.

**Conclusions.** Annual trends of CRKP proportions from 2006 to 2014 were downward in both HAI and COI, and HAI and COI were positively correlated. Efforts to reduce and prevent CRKP infections in both hospital and community settings were successful and warrant continuation.

**Keywords.** carbapenem-resistant *Klebsiella pneumoniae* (CRKP); carbapenem-susceptible *Klebsiella pneumoniae* (CSKP); community-onset infection (COI); hospital-acquired infection (HAI).

Carbapenems are considered the antibiotics of choice for Gram-negative bacteria that produce plasmid-encoded extended-spectrum  $\beta$ -lactamases (ESBL) or chromosomal cephalosporinases [1]. Since imipenem became the first carbapenem available in 1985, there have been no new classes of antibiotics targeting drug-resistant Gram-negative bacteria [2, 3]. During the past decade, carbapenem-resistant *Enterobacteriaceae* (CRE) have become a public health threat and economic burden due to lack of effective antibiotics, wide transmission, and high mortality rate of up to 50% in blood stream infections (BSIs) [4, 5]. Carbapenem-resistant *Enterobacteriaceae* represent 1 of the 3 urgent antibiotic resistance threats ranked by the Centers for Disease Control and Prevention ([CDC] the other 2 are *Clostridium difficile*

and drug-resistant *Neisseria gonorrhoeae* [<http://www.cdc.gov/drugresistance/threat-report-2013>]). The most common mechanism for carbapenem resistance in CRE is production of carbapenemases [5, 6]. Carbapenemases are commonly expressed from mobile genetic elements such as plasmids or transposons, which frequently contain multiple drug-resistant genes and have the potential for widespread transmission to other bacteria via horizontal gene transfer [6, 7]. Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) is one of the most commonly reported CRE in healthcare settings in the United States [8, 9].

Although *K pneumoniae* carbapenemase (KPC) was first identified in a *K pneumoniae* from a clinical specimen of a patient in North Carolina in 1996 [6, 10], CRKP was rarely reported until the early 2000s in the United States [11]. After the outbreaks of KPC-producing CRKP in New York City (NYC) hospitals in the early 2000s, KPC-producing CRKP has spread throughout the United States and worldwide [6, 7, 12–16]. Carbapenem-resistant *K pneumoniae* that produce other types of carbapenemases such as New Delhi metallo- $\beta$ -lactamase (NDM) and oxacillinase-48 have also been increasingly reported [6] (<http://www.cdc.gov/hai/organisms/cre/TrackingCRE.html>). In 2000, less than 1% of *Klebsiella* isolates reported to the CDC were CRKP, the prevalence then increased to 8% in 2007 [17]. In 2009–2010, CRKP

Received 26 July 2016; editorial decision and accepted 13 October 2016.

Correspondence: Sun Park, MD, MS, 1250 Waters Place Tower 2, 11th Floor, Bronx, NY 10461 (spark@montefiore.org).

## Open Forum Infectious Diseases®

© The Author 2016. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs licence (<http://creativecommons.org/licenses/by-nc-nd/4.0/>), which permits non-commercial reproduction and distribution of the work, in any medium, provided the original work is not altered or transformed in any way, and that the work is properly cited. For commercial re-use, please contact [journals.permissions@oup.com](mailto:journals.permissions@oup.com).

DOI: 10.1093/ofid/ofw222

proportions that were associated with certain device-related infections were greater than 12% according to a report from the National Healthcare Safety Network (NHSN) [9]. Within the past few years, CRKP proportions have been trending down according to the NHSN's online report (<http://gis.cdc.gov/grasp/PSA/MapView.html>); the percentage of carbapenem-resistant *Klebsiella* isolates decreased from 9.8% to 7.8% in the nation and 16.2% to 14.2% in New York state (NYS) from 2011 to 2014, based on the collected data for hospital-acquired infections (HAIs). Besides the national studies [8, 9, 18, 19] and short-term studies of CRKP in NYC hospitals [13, 14, 20], there is limited literature on temporal trends of CRKP in NYC hospitals. Literature is similarly limited regarding temporal trends of community-onset CRKP, and association between trends of CRKP in HAIs and in community-onset infections (COIs) has not been studied. Knowledge of temporal trends of CRKP in NYC hospitals is critical because (1) information of temporal trends would inform decisions for antimicrobial stewardship and infection control policymaking and (2) temporal trends of CRKP in NYC hospitals would likely predict temporal trends in various other locations. Hence, we investigated annual CRKP proportions trends in HAI and COI treated in 3 NYC hospitals over a 9-year period (2006–2014) and their correlation in the same period. We also investigated annual CRKP proportions trends by anatomical sites (respiratory, urinary tract, bloodstream, and surgical site) and clinical characteristics of CRKP infections.

## METHODS

### Study Setting and Data Collection

We extracted data from a large healthcare system in NYC, which includes a community hospital, a pediatric hospital, and a tertiary care hospital totaling 575 373 admissions in 2006–2014. The 3 hospitals share a clinical data warehouse that integrates data from over 20 clinical electronic sources [21]. The data included the following: (1) patients' locations, prior hospitalization, length of stay, and admission source; (2) patients' comorbid conditions including dementia, diabetes, malignancy, acquired immune deficiency syndrome, cardiac, cerebrovascular, liver, kidney, and pulmonary disease (to calculate a weighted Charlson Comorbidity Index); (3) accounts of administered antibiotics; and (4) results of microbiologic tests.

### Case Definitions and Study Subjects

As part of an National Institutes of Health-funded project (5R01NR010822), whose methods were described in Apte et al [21], a team of clinicians and researchers developed electronic algorithms to define BSI, urinary tract infection (UTI), pneumonia (PNU), surgical site infection (SSI), the causative organisms, and antibiotic susceptibility. Surgical site infection was defined using the surveillance definition from the CDC's NHSN [21]. We defined COI as an infection that occurred before or on the 3rd hospital day without being admitted from another healthcare

setting and without history of admission to one of the study hospitals within the previous 30 days, and we defined HAI as an infection that occurred after the 3rd hospital day or occurred in persons who were admitted from another healthcare setting or admitted to one of the study hospitals within the previous 30 days.

One microbiology laboratory processed all clinical specimens and performed carbapenem susceptibility tests primarily by Vitek 2 (bioMérieux Inc., Durham, NC). When Etest (bioMérieux Inc.) for meropenem or imipenem was also performed (usually upon a clinician's request or due to a discrepancy in susceptibilities between carbapenems by Vitek 2), the result of Etest was used over Vitek 2 to determine carbapenem susceptibilities. The microbiology laboratory used the latest Clinical Laboratory Standards Institute (CLSI) interpretive criteria and adopted the revised (June 2010) CLSI interpretive criteria for *Enterobacteriaceae* in January 2011. We categorized the laboratory reports of imipenem- or meropenem-susceptible as carbapenem-susceptible, and we categorized reports of imipenem- or meropenem-resistant or -intermediate as carbapenem-resistant. When there was a discrepant report on susceptibility test for imipenem and meropenem (imipenem was susceptible but meropenem was resistant, or vice versa), we categorized it as resistant. Study subjects were patients with *K pneumoniae* infection in 1 of 4 anatomical sites, BSI, UTI, PNU, or SSI in 2006–2014. Each patient was eligible only once. If *K pneumoniae* was isolated from multiple anatomical sites either through 1 hospitalization or multiple hospitalizations, only the first infection was counted.

### Measures

We measured annual CRKP proportions (cases of CRKP infection divided by cases of *K pneumoniae* [KP] infection and multiplied by 100) at each of the 4 anatomical sites of infection (BSI, UTI, PNU, and SSI). Overall, CRKP proportions combined the above 4 sites. Carbapenem-resistant *K pneumoniae* proportions (HAI and COI) of the 3 individual hospitals and 3 hospitals combined were examined from 2006 to 2014 annually. We measured differences in various clinical characteristics between CRKP and CSKP (Table 1) and the strength of linear associations between CRKP proportions in HAI and COI.

### Statistical Analysis

To compare clinical characteristics between CRKP and CSKP, we performed bivariate analyses using  $\chi^2$  test for categorical variables and Student *t* test or Wilcoxon rank-sum test for continuous variables, dependent on the validity of normality assumption. We performed multiple logistic regression to determine associations between CRKP proportions and variables that were statistically significant from bivariate analyses.

We used Cochran-Armitage trend test [18] to determine statistical significance in annual CRKP proportions trends and used Pearson's correlation coefficient, *r*, to indicate linear associations between HAI and COI CRKP proportions. We performed all statistical analyses using SAS version 9.4 (SAS

**Table 1. Clinical Characteristics of Patients With Carbapenem-Resistant vs Carbapenem-Susceptible *Klebsiella pneumoniae* in Hospital-Acquired and Community-Onset Infections**

Characteristics	Hospital-Acquired Infection (n = 3477)			Community-Onset Infection (n = 1926)		
	CRKP (n = 601)	CSKP (n = 2876)	PValue	CRKP (n = 149)	CSKP (n = 1777)	PValue
Age (year), mean ± SD	62.3 ± 20.0	61.6 ± 24.1	.24	68.5 ± 17.7	65.2 ± 22.4	0.31
Female sex	330 (54.9)	1639 (57.0)	.35	79 (53.0)	1220 (68.7)	<.001
Hospital			<.001 <sup>a</sup>			.09 <sup>a</sup>
1 (tertiary)	466 (77.5)	2134 (74.2)		106 (71.1)	1234 (69.4)	
2 (community)	112 (18.6)	430 (15.0)		40 (26.9)	429 (24.1)	
3 (children's)	23 (3.8)	312 (10.8)		3 (2.0)	114 (6.4)	
Anatomical site			<.001 <sup>a</sup>			.12 <sup>a</sup>
UTI	372 (61.9)	1897 (66.0)		124(83.2)	1448 (81.5)	
PNU	148 (24.6)	473 (16.4)		13(8.7)	104 (5.8)	
BSI	66 (11.0)	421 (14.6)		12(8.1)	225 (12.7)	
SSI	15 (2.5)	85 (3.0)				
Year of infection			<.001 <sup>a</sup>			<.001 <sup>a</sup>
2006	102 (17.0)	294 (10.2)		30 (20.1)	190 (10.7)	
2007	101 (16.8)	308 (10.7)		35 (23.5)	224 (12.6)	
2008	89 (14.8)	283 (9.8)		29 (19.5)	165 (9.3)	
2009	62 (10.3)	390 (13.6)		16 (10.7)	237 (13.3)	
2010	40 (6.7)	355 (12.3)		16 (10.7)	220 (12.4)	
2011	48 (8.0)	236 (8.2)		4 (2.7)	122 (6.9)	
2012	49 (8.2)	333 (11.6)		5 (3.4)	185 (10.4)	
2013	72 (12.0)	352 (12.2)		7 (4.7)	216 (12.2)	
2014	38 (6.3)	325 (11.3)		7 (4.7)	218 (12.3)	
Diabetes	201 (33.4)	880 (30.6)	.17	46 (30.9)	612 (34.5)	.38
Malignancy	93 (15.5)	602 (20.9)	<.01	23 (15.4)	258 (14.5)	.76
Dialysis	91 (15.1)	182 (6.3)	<.001	6 (4.0)	64 (3.6)	.79
History of transplant	28 (4.7)	123 (4.3)	.68	8 (5.4)	71 (4.0)	.42
Charlson Comorbidity Index, mean ± SD	2.9 ± 2.4	2.9 ± 2.6	.46	2.6 ± 2.5	2.5 ± 2.4	.22
Prior hospitalization <sup>b</sup>	348 (57.9)	1743 (60.6)	.22	69 (46.3)	979 (55.1)	.04
Hospital LOS before KP infection, mean ± SD	13.7 ± 18.7	9.7 ± 15.2	<.001	N/A	N/A	N/A
ICU stay before KP infection	261 (43.4)	939 (32.7)	<.001	N/A	N/A	N/A
ICU days before KP infection, mean ± SD	14.9 ± 18.2	10.7 ± 16.3	<.001	N/A	N/A	N/A
Antibiotics before KP infection <sup>c</sup>	382 (63.6)	1325 (46.1)	<.001	N/K	N/K	N/K

Abbreviations: BSI, blood stream infection; CRKP, carbapenem-resistant *K pneumoniae*; CSKP, carbapenem-susceptible *K pneumoniae*; ICU, intensive care unit; LOS, length of stay; N/A, not applicable; N/K, not known; PNU, pneumonia; SD, standard deviation; SSI, surgical site infection; UTI, urinary tract infection.

Note: Data are No. (%), unless indicated. P values were obtained from bivariate analyses.

<sup>a</sup>Overall P value for a variable with multiple categories.

<sup>b</sup>Prior hospitalization at the study in New York City hospitals.

<sup>c</sup>Longer than 1 day of any oral or parenteral antibiotic use including β-lactams, β-lactam-β-lactamase inhibitor, fluoroquinolones, and aminoglycosides.

Institute, Inc., Cary, NC). A 2-sided  $P < .05$  was considered statistically significant.

## RESULTS

### Data's Clinical Characteristics

Table 1 shows clinical characteristics of patients who were hospitalized at one of the study institutions with *K pneumoniae* infection in 2006–2014. Mean age was older in COI compared with HAI (65.5 vs 61.7 years,  $P < .01$ ). Females contributed 54.9% (330 of 601) of CRKP in HAI and 53.0% of CRKP in COI, but they had smaller CRKP proportions compared with males (females 16.8% vs males 18.0% in HAI; 6.1% vs 11.2% in COI) because female KP infection population was larger than male's (Table 1).

In bivariate analyses of HAI, the anatomical site was significantly associated with CRKP infection; the odds of CRKP infection in PNU is greater than the odds of CRKP infection in BSI (the odds ratio [OR] = 2.0,  $P < .01$ ) and in UTI (OR = 1.60,  $P < .01$ ). In bivariate analyses of HAI, CRKP infection was positively associated with dialysis status (OR = 2.64,  $P < .001$ ), longer hospital stay (OR = 1.01,  $P < .001$ ), intensive care unit (ICU) stay (OR = 1.58,  $P < .001$ ), longer ICU days (OR = 1.01,  $P < .001$ ), and antibiotic use (OR = 2.04,  $P < .001$ ), whereas it was negatively associated with history of malignancy (OR = 0.69,  $P < .01$ ) (Table 1). In multivariable analysis of HAI, dialysis status, longer hospital stay, and antibiotic use were independently positively associated, whereas history of malignancy was independently negatively associated with CRKP infection (Table 2).

**Table 2. Multivariable Analyses for Carbapenem-Resistant vs Carbapenem-Susceptible *Klebsiella pneumoniae* in Hospital-Acquired and Community-Onset Infections**

Characteristics	Hospital-Acquired Infection		Community-Onset Infection	
	Multivariable		Multivariable	
	CRKP vs CSKP		CRKP vs CSKP	
Variables	OR (95% CI)	P Value	OR (95% CI)	P Value
Sex (male vs female)	N/A	N/A	2.11 (1.50–3.00)	<.001
Prior hospitalization	N/A	N/A	0.89 (0.63–1.27)	.53
Year of infection		<.001 <sup>a</sup>		<.001 <sup>a</sup>
2006	1		1	
2007	0.89 (0.64–1.24)		1.04 (0.61–1.78)	
2008	0.86 (0.61–1.21)		1.14 (0.65–2.01)	
2009	0.42 (0.29–0.61)		0.44 (0.23–0.83)	
2010	0.31 (0.21–0.47)		0.47 (0.25–0.91)	
2011	0.55 (0.37–0.82)		0.23 (0.08–0.67)	
2012	0.41 (0.28–0.61)		0.16 (0.06–0.44)	
2013	0.54 (0.38–0.78)		0.20 (0.09–0.48)	
2014	0.31 (0.21–0.47)		0.21 (0.09–0.49)	
Hospital		<.001 <sup>a</sup>		N/A
1 (tertiary)	1		N/A	
2 (community)	1.45 (1.14–1.88)		N/A	
3 (children's)	0.29 (0.19–0.47)		N/A	
Anatomical site		.65 <sup>a</sup>		N/A
UTI	1		N/A	
PNU	1.10 (0.86–1.41)		N/A	
BSI	0.89 (0.66–1.20)		N/A	
SSI	1.14 (0.63–2.06)		N/A	
Malignancy	0.72 (0.56–0.93)	.01	N/A	N/A
Dialysis	1.87 (1.39–2.50)	<.001	N/A	N/A
Hospital LOS before KP infection	1.01 (1.003–1.02)	<.01	N/A	N/A
ICU stay before KP infection	1.004 (0.80–1.30)	.97	N/A	N/A
Antibiotics before KP infection	1.84 (1.46–2.32)	<.001	N/A	N/A

Abbreviations; BSI, blood stream infection; CI, confidence interval; CRKP, carbapenem-resistant *K pneumoniae*; CSKP, carbapenem-susceptible *K pneumoniae*; ICU, intensive care unit; KP, *K pneumoniae*; LOS, length of stay; N/A, not applicable; OR, odds ratio; PNU, pneumonia; SSI, surgical site infection; UTI, urinary tract infection.

Note: Multivariable analyses included variables with statistical significance ( $P < .05$ ) from the Table 1.

<sup>a</sup>Overall  $P$  value for a variable with multiple categories.

In bivariate analyses of COI, CRKP infection was positively associated with male sex (OR = 1.94,  $P < .01$ ), whereas it was negatively associated with prior hospitalization (OR = 0.70,  $P = .04$ ) (Table 1). In multivariable analysis of COI, male sex was independently positively associated with CRKP infection. In both HAI and COI, data year was independently associated with CRKP infection (Table 2).

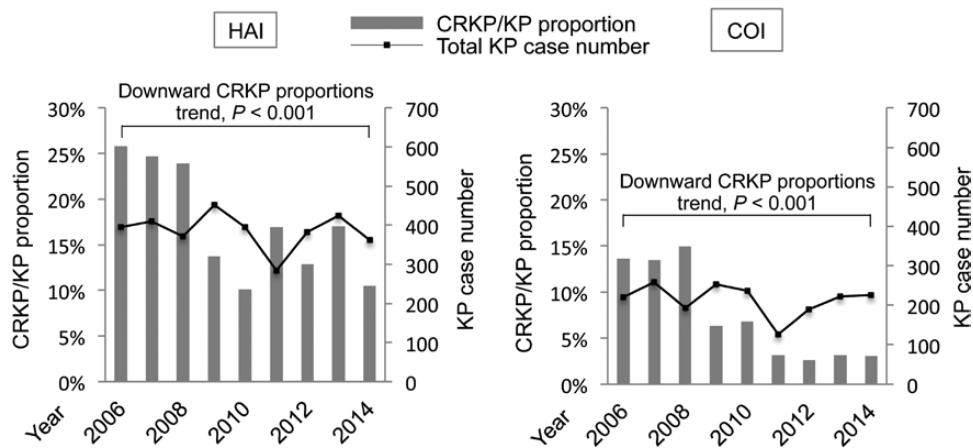
#### Downward Trends of Carbapenem-Resistant *Klebsiella pneumoniae*

In 2006–2014, 17.3% of total *K pneumoniae* in HAI and 7.7% of total *K pneumoniae* in COI was CRKP. There were downward annual CRKP proportions trends in both HAI (from 25.8% to 10.5%) and COI (from 13.6% to 3.1%) from 2006 to 2014 (Figure 1). Furthermore, downward annual CRKP proportions trends were found in each study hospital from 2006 to 2014 in both HAI (from 27.8% to 12.2% in Hospital 1; from 32.9% to 4.8% in Hospital 2; from 8.3% to 0.0% in

Hospital 3) and COI (from 11.8% to 4.2% in Hospital 1; from 19.7% to 1.6% in Hospital 2; from 6.7% to 0.0% in Hospital 3) (Figure S1).

In HAI, PNU had the highest CRKP proportions followed by UTI, SSI, and BSI (23.8%, 16.4%, 15%, 13.6%, respectively), similarly in COI, PNU had the highest CRKP proportions followed by UTI and BSI (11.1%, 7.9%, 5.1%, respectively). Downward CRKP proportions trends in UTI were significant in both HAI (from 25.1% to 8.3%) and COI (from 15.2% to 2.6%) in 2006–2014 (Figure 2). There were no statistically significant CRKP proportions trends in BSI and PNU in either HAI or COI in 2006–2014 (Figure 2). There were no cases of CRKP in SSI from 2006 to 2011, but significant upward CRKP proportion trends were identified from 2011 to 2014 (from 0% to 18.2%;  $P = .03$ ).

Hospital-acquired infections and COI CRKP proportions were positively correlated in 2006–2014 ( $r = 0.83$ ,  $P < .01$ ). In 2006–2014, there was significant positive correlation between



**Figure 1.** Trend analyses of annual carbapenem-resistant *Klebsiella pneumoniae* (CRKP) proportions. Carbapenem-resistant *K pneumoniae* proportions (CRKP infections/*K pneumoniae* [KP] infections) and total case numbers of KP infections are presented annually from 2006 to 2014 as marked. Downward CRKP proportions trends and the corresponding *P* values in hospital-acquired infection (HAI) and community-onset infection (COI), as indicated, were determined by Cochran-Armitage trend test. Trends with *P* < .05 are considered statistically significant.

CRKP proportions in UTIs in HAI and COI ( $r = 0.87, P < .01$ ), but no significant correlations between CRKP proportions in BSIs in HAI and COI ( $r = 0.08, P = .83$ ), and between CRKP proportions in PNUs in HAI and COI ( $r = 0.25, P = .52$ ). There were significant positive correlations between CRKP proportions in BSI and PNU ( $r = 0.80, P = .01$ ), UTI and PNU ( $r = 0.70, P = .04$ ), but no significant correlation between CRKP proportions in BSI and UTI ( $r = 0.60, P = .09$ ) in HAI. There were no significant correlations between CRKP proportions in BSI and PNU ( $r = -0.17, P = .67$ ), UTI and PNU ( $r = 0.59, P = .09$ ), and BSI and UTI ( $r = 0.27, P = .50$ ) in COI.

## DISCUSSION

### Carbapenem-Resistant *Klebsiella pneumoniae* Proportions in Hospitals and Community Settings Are Positively Correlated

*Klebsiella pneumoniae* is a normal intestinal flora in humans and animals and a common microorganism in the environment, which can become carbapenem-resistant by acquiring genes coding for carbapenemase, or loss of outer membrane porin concurrently with ESBL or AmpC  $\beta$ -lactamase production [1]. In the United States, majority of dissemination of KPC-producing CRKP is clonal with a common strain type, ST258 [6, 10, 11].

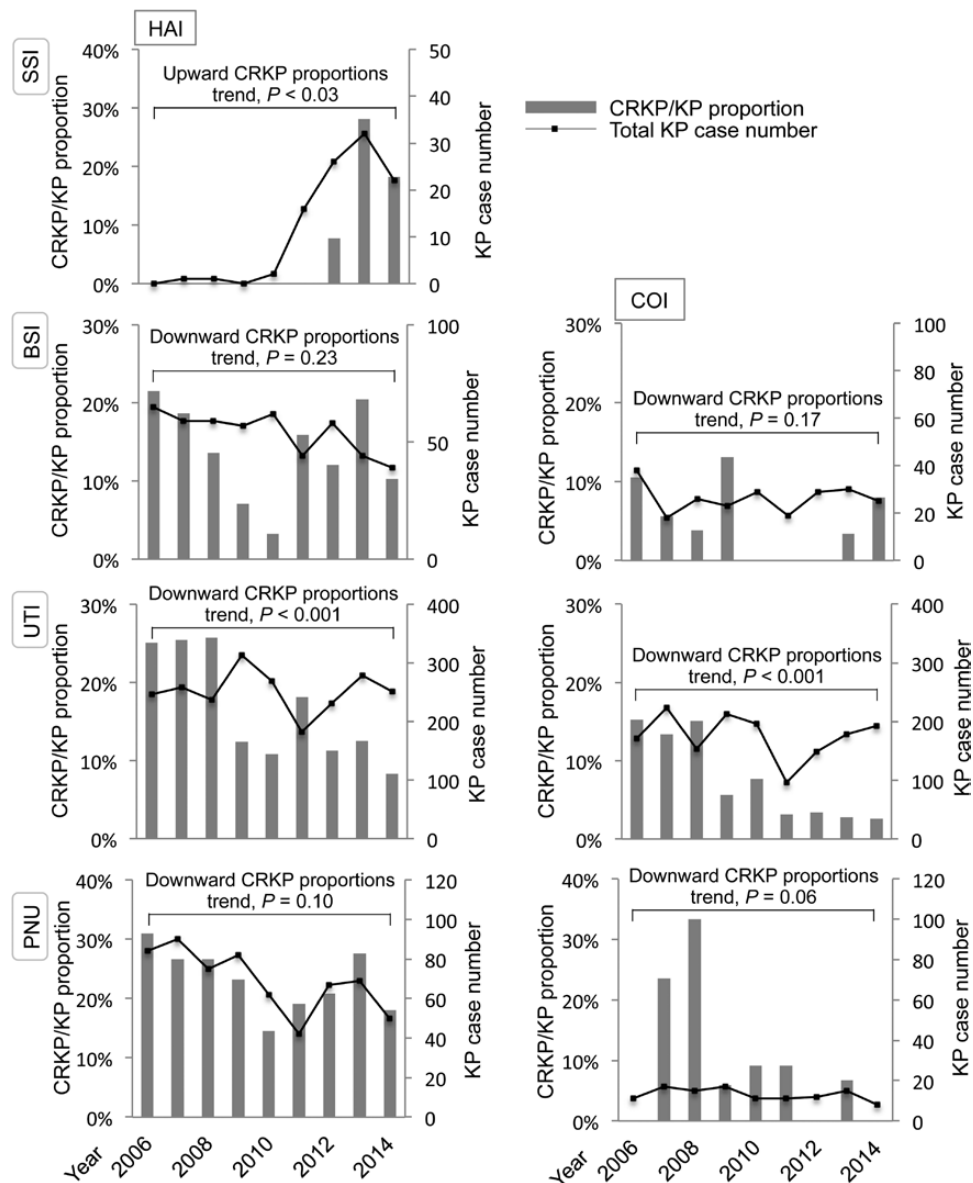
Carbapenem-resistant *K pneumoniae* infections have been predominantly reported in healthcare settings such as acute care hospitals, long-term acute care hospitals (LTACHs), and nursing homes [10, 19, 22], where broader spectrum antibiotics are used for longer duration [23] and odds of contacts with CRKP are higher. Furthermore, LTACHs and nursing homes have been known to be major reservoirs in dissemination of CRKP in multiple regions, where populations with complex comorbidities require prolonged care [24, 25]. Our study supports the conventional knowledge that CRKP is more prevalent in the hospital settings than in the community settings. We note

that CRKP proportion in COI (mean 7.7%, range 2.6%–14.9%) is unlikely explained alone by personal use of antibiotics; other mechanisms such as person-to-person transmission must have played an important role.

Our findings indicate that overall CRKP proportions in HAI and COI are positively correlated in 2006–2014, whereas CRKP UTIs were the only anatomic sites infections that were significantly correlated. It is possible that our study did not have the statistical power to detect correlations between CRKP proportions of BSIs or PNUs in HAI and COI because of small sample sizes of CRKP in COI.

### Antibiotic Use in Food Animals Could Contribute to Drug-Resistance Pattern

Antibiotic use selects for preexisting resistant populations of bacteria in nature [26]. Eighty percent of all antibiotics used in the United States are administered to food animals [2]. Subtherapeutic levels of antibiotics are frequently administered for infection prophylaxis or growth promotion, which are believed to promote drug resistance [27]. A direct correlation between drug-resistant bacteria in farm animals and their colonization or infection in humans has been reported [28]. Ninety percent of antibiotics given to animals are released in excreta and widely dispersed [2], potentially facilitating emergence of drug-resistant bacteria in our environment. As examples, NDM-producing bacteria was detected in drinking water (2 of 50 samples) and seepage water (51 of 171 samples) in New Delhi [29], and KPC-producing *Escherichia coli* was recovered from river water (1 of 5 samples), despite the fact that there were no prior reported cases of KPC-producing bacteria in Portugal [10]. Although we have not found similar studies for CRE in NYC, ampicillin- or tetracycline-resistant bacteria including *Enterobacteriaceae* were detected at all 10 sampling sites around NYC and throughout the lower Hudson River Estuary in 2010 [30].



**Figure 2.** Annual carbapenem-resistant *Klebsiella pneumoniae* (CRKP) proportions trend analyses for various anatomical sites. Carbapenem-resistant *K pneumoniae* proportions (CRKP infections/*K pneumoniae* [KP] infections) and total case numbers of KP infections in 4 anatomical sites, as marked, are presented annually from 2006 to 2014. Upward or downward CRKP proportions trends and the corresponding *P* values in hospital-acquired infection (HAI) and community-onset infection (COI), as indicated, were determined by Cochran-Armitage trend test. By definition, there was no surgical site infection (SSI) in COI. Abbreviations: BSI, blood stream infection; PNU, pneumonia; UTI, urinary tract infection.

### Carriage of Carbapenem-Resistant *Klebsiella pneumoniae* (CRKP) Might Affect CRKP Prevalence

Asymptomatic carriage of CRKP silently transmits pathogens and increases risk for subsequent symptomatic infections [31]. Hence, knowledge in prevalence and duration of CRKP carriage is important to predict trends of CRKP infection and control. Surveillance rectal swab cultures were positive for CRKP in 15.3% of 301 asymptomatic residents in a long-term care facility in NYC [31]. A retrospective cohort study from a tertiary medical center in Israel described that the carrier status persisted for 2 years in 15% of 163 CRKP carriers [32]. Although studies regarding prevalence of CRKP carriage in the community settings are limited, reports of high prevalence of drug-resistant

*E coli* carriage in community settings where there were populations without previous antibiotic exposure [33, 34] raise the possibility of high prevalence of CRKP carriage in the community as well. Some of the patients in our study who rarely received antibiotics before CRKP infection might have acquired CRKP from carriers in the community.

### Existing Knowledge of Carbapenem-Resistant *Klebsiella pneumoniae* Proportion and Prevalence in New York City Hospitals and Infection Control Efforts

Defining whether there are trends in CRKP infection is a prerequisite to understanding the epidemiology of CRKP. Carbapenem-resistant *K pneumoniae*s are distributed heterogeneously in the

United States, and most states (48 of 50 states; <https://www.cdc.gov/hai/organisms/cre/TrackingCRE.html>) reported cases of CRKP infection [6].

In NYC, CRKP proportion was 1.5% (9 of 602 isolates) in a study involving 11 hospital-based microbiology laboratories in Brooklyn conducted in 2002–2003 [13]. In 2004, 4 hospitals in Brooklyn found that 24% (62 of 257 isolates) of *K pneumoniae* isolates were KPC producers [14]. Surveillance studies conducted for a 3-month period in 2006 and 2009 in 14 hospitals in Brooklyn showed a decline in proportions of KPC-producing *K pneumoniae* from 38% (302 of 1024 isolates) in 2006 to 29% (379 of 997 isolates) in 2009 [20, 35]. Active surveillance testing of perianal swab culture and clinical culture at a tertiary hospital in Manhattan in 2005–2007 showed that CRKP prevalence was 2% (215 of 11 236 patients) in study ICUs [36]. Active surveillance testing at 2 tertiary hospitals in Manhattan in 2009–2010 showed that CRE prevalence (84.7% was *K pneumoniae*) was 5.4% (306 of 5676 patients) in study inpatient units [23].

Literature and national reports showed sharp increases of CRKP proportions in 2000s [6, 11, 22], then slight decreases in 2011–2014 (<http://gis.cdc.gov/grasp/PSA/MapView.html>). Our results indicate downward annual CRKP proportions trends in both HAI and COI in 2006–2014. Decreasing CRKP proportions trends were sturdier in COI than in HAI. Trends in CRKP proportions of HAIs fluctuated in 2011–2014 after significant decreasing trends in 2006–2010.

Several factors could have affected the results of trends analyses. First, we considered the possibility that breakpoint changes on carbapenem susceptibility for *K pneumoniae* affected our trends analyses. Because some carbapenemase-producing *K pneumoniae* were susceptible to carbapenems, the CLSI in June 2010 lowered carbapenem breakpoints to capture all carbapenemase producers without the use of the Modified Hodge test [11, 37]. The literature suggests that the percentage change of CRKP proportions after the CLSI breakpoint changes was less than 1% [37, 38]. Thus, it is unlikely that the revision of the CLSI interpretive criteria significantly affected our results. Second, infection control efforts at the local and national level might have contributed to decreases in CRKP proportions. In 2012, the CDC introduced a CRE Toolkit as guidance for control of CRE, which was associated with a reduction in the incidence rate of CRE [39]. In April 2012, the US Food and Drug Administration issued a guidance to phase out unsupervised use of medically important antimicrobial drugs in food-producing animals, followed by a guidance in December 2013 for voluntary removal of growth enhancement as an indication for antibiotic use ([www.fda.gov](http://www.fda.gov)). In NYS, CRE became a statewide reportable condition on July 1, 2013 ([www.apic.org](http://www.apic.org)), which has encouraged hospitals to proactively control CRE. Our study hospitals used an antimicrobial stewardship program since 2000 [40] and have a robust infection prevention and control program that implements

staff education, bundled interventions, and isolation protocol. Whether these proactive steps can explain the downward trends of CRKP requires further studies.

### Limitations

There are several limitations, which should be considered when interpreting our findings. (1) We retrospectively obtained our data from electronic databases, which has a limitation in differentiating between colonization and clinical infection. (2) Due to lack of data from outside of the study hospitals, patients who were admitted within 30 days of discharge or surgical procedures performed outside of the study hospitals would have been misclassified as COI or not counted for SSI. (3) Microbiology laboratory did not routinely report or check ertapenem or doripenem susceptibility, so ertapenem- or doripenem-resistant *K pneumoniae* might have been misclassified as carbapenem-susceptible. (4) Information regarding the mechanisms of carbapenem-resistance is not available, limiting the depth of our analyses of CRKP infections. (5) NYC, the largest metropolitan in the nation, has a dense population that share environments such as public transportation that are different from many other parts in the United States. Therefore, our findings might not apply to other hospitals in less populated cities. Whether our findings are applicable to other hospitals in NYC also awaits further study.

### CONCLUSIONS

In summary, we show that CRKP proportions trends in HAI and COI are positively and statistically significantly associated. We further present evidence for downward CRKP proportions trends in HAI and COI in 3 NYC hospitals. To extend these downward trends, judicious antibiotic use and infection control efforts should be continued in both hospital and community settings. Higher CRKP proportions in HAI compared with COI in 2006–2014 warrant enhanced efforts to control CRKP in hospitals. Lastly, studies to understand and reduce CRKP carriage are indicated to enlighten the epidemiology of CRKP infections.

### Supplementary Data

Supplementary material is available at *Open Forum Infectious Diseases* online.

### Acknowledgments

**Financial support.** This study was funded in part by Health Information Technology to Reduce Healthcare-Associated Infections (Project no. 5R01NR010822).

**Potential conflicts of interest.** All authors report no conflicts of interests that the editors consider relevant to the content of this manuscript. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

### References

1. Jacoby GA, Munoz-Price LS. The new beta-lactamases. *N Engl J Med* 2005; 352:380–91.

2. Bartlett JG, Gilbert DN, Spellberg B. Seven ways to preserve the miracle of antibiotics. *Clin Infect Dis* **2013**; 56:1445–50.
3. Papp-Wallace KM, Endimiani A, Taracila MA, Bonomo RA. Carbapenems: past, present, and future. *Antimicrob Agents Chemother* **2011**; 55:4943–60.
4. Nordmann P, Cuzon G, Naas T. The real threat of *Klebsiella pneumoniae* carbapenemase-producing bacteria. *Lancet Infect Dis* **2009**; 9:228–36.
5. Schwaber MJ, Carmeli Y. Carbapenem-resistant *Enterobacteriaceae*: a potential threat. *JAMA* **2008**; 300:2911–3.
6. Guh AY, Limbago BM, Kallen AJ. Epidemiology and prevention of carbapenem-resistant *Enterobacteriaceae* in the United States. *Expert Rev Anti Infect Ther* **2014**; 12:565–80.
7. Arnold RS, Thom KA, Sharma S, et al. Emergence of *Klebsiella pneumoniae* carbapenemase-producing bacteria. *South Med J* **2011**; 104:40–5.
8. Hidron AI, Edwards JR, Patel J, et al. NHSN annual update: antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006–2007. *Infect Control Hosp Epidemiol* **2008**; 29:996–1011.
9. Sievert DM, Ricks P, Edwards JR, et al. Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009–2010. *Infect Control Hosp Epidemiol* **2013**; 34:1–14.
10. Munoz-Price LS, Poirel L, Bonomo RA, et al. Clinical epidemiology of the global expansion of *Klebsiella pneumoniae* carbapenemases. *Lancet Infect Dis* **2013**; 13:785–96.
11. Gupta N, Limbago BM, Patel JB, Kallen AJ. Carbapenem-resistant *Enterobacteriaceae*: epidemiology and prevention. *Clin Infect Dis* **2011**; 53:60–7.
12. Bradford PA, Bratu S, Urban C, et al. Emergence of carbapenem-resistant *Klebsiella* species possessing the class A carbapenem-hydrolyzing KPC-2 and inhibitor-resistant TEM-30 beta-lactamases in New York City. *Clin Infect Dis* **2004**; 39:55–60.
13. Bratu S, Landman D, Haag R, et al. Rapid spread of carbapenem-resistant *Klebsiella pneumoniae* in New York City: a new threat to our antibiotic armamentarium. *Arch Intern Med* **2005**; 165:1430–5.
14. Bratu S, Mooty M, Nichani S, et al. Emergence of KPC-possessing *Klebsiella pneumoniae* in Brooklyn, New York: epidemiology and recommendations for detection. *Antimicrob Agents Chemother* **2005**; 49:3018–20.
15. Schwaber MJ, Klarfeld-Lidji S, Navon-Venezia S, et al. Predictors of carbapenem-resistant *Klebsiella pneumoniae* acquisition among hospitalized adults and effect of acquisition on mortality. *Antimicrob Agents Chemother* **2008**; 52:1028–33.
16. Schwaber MJ, Lev B, Israeli A, et al. Containment of a country-wide outbreak of carbapenem-resistant *Klebsiella pneumoniae* in Israeli hospitals via a nationally implemented intervention. *Clin Infect Dis* **2011**; 52:848–55.
17. Centers for Disease Control and Prevention (CDC). Guidance for control of infections with carbapenem-resistant or carbapenemase-producing *Enterobacteriaceae* in acute care facilities. *MMWR Morb Mortal Wkly Rep* **2009**; 58:256–60.
18. Kaiser RM, Castanheira M, Jones RN, et al. Trends in *Klebsiella pneumoniae* carbapenemase-positive *K. pneumoniae* in US hospitals: report from the 2007–2009 SENTRY Antimicrobial Surveillance Program. *Diagn Microbiol Infect Dis* **2013**; 76: 356–60.
19. Guh AY, Bulens SN, Mu Y, et al. Epidemiology of carbapenem-resistant *Enterobacteriaceae* in 7 US communities, 2012–2013. *JAMA* **2015**; 314:1479–87.
20. Landman D, Babu E, Shah N, et al. Transmission of carbapenem-resistant pathogens in New York City hospitals: progress and frustration. *J Antimicrob Chemother* **2012**; 67:1427–31.
21. Apte M, Neidell M, Furuya EY, et al. Using electronically available inpatient hospital data for research. *Clin Transl Sci* **2011**; 4:338–45.
22. Centers for Disease Control and Prevention (CDC). Vital signs: carbapenem-resistant *Enterobacteriaceae*. *MMWR Morb Mortal Wkly Rep* **2013**; 62:165–70.
23. Swaminathan M, Sharma S, Poliansky Blash S, et al. Prevalence and risk factors for acquisition of carbapenem-resistant *Enterobacteriaceae* in the setting of endemicity. *Infect Control Hosp Epidemiol* **2013**; 34:809–17.
24. Hayden MK, Lin MY, Lolans K, et al. Prevention of colonization and infection by *Klebsiella pneumoniae* carbapenemase-producing *Enterobacteriaceae* in long-term acute-care hospitals. *Clin Infect Dis* **2015**; 60:1153–61.
25. Munoz-Price LS, Hayden MK, Lolans K, et al. Successful control of an outbreak of *Klebsiella pneumoniae* carbapenemase-producing *K. pneumoniae* at a long-term acute care hospital. *Infect Control Hosp Epidemiol* **2010**; 31:341–7.
26. Spellberg B, Bartlett JG, Gilbert DN. The future of antibiotics and resistance. *N Engl J Med* **2013**; 368:299–302.
27. Carlet J, Jarlier V, Harbarth S, et al. Ready for a world without antibiotics? The Pensières Antibiotic Resistance Call to Action. *Antimicrob Resist Infect Control* **2012**; 1:11.
28. Wright GD. Antibiotic resistance in the environment: a link to the clinic? *Curr Opin Microbiol* **2010**; 13:589–94.
29. Walsh TR, Weeks J, Livermore DM, Toleman MA. Dissemination of NDM-1 positive bacteria in the New Delhi environment and its implications for human health: an environmental point prevalence study. *Lancet Infect Dis* **2011**; 11:355–62.
30. Young S, Juhl A, O'Mullan GD. Antibiotic-resistant bacteria in the Hudson River Estuary linked to wet weather sewage contamination. *J Water Health* **2013**; 11:297–310.
31. Prasad N, Labaze G, Kopacz J, et al. Asymptomatic rectal colonization with carbapenem-resistant *Enterobacteriaceae* and *Clostridium difficile* among residents of a long-term care facility in New York City. *Am J Infect Control* **2016**; 44:525–32.
32. Ciobotaro P, Flaks-Manov N, Oved M, et al. Predictors of persistent carbapenem-resistant *Enterobacteriaceae* carriage upon readmission and score development. *Infect Control Hosp Epidemiol* **2016**; 37:188–96.
33. Gurnee EA, Ndao IM, Johnson JR, et al. Gut colonization of healthy children and their mothers with pathogenic ciprofloxacin-resistant *Escherichia coli*. *J Infect Dis* **2015**; 212:1862–8.
34. Woerther PL, Angebault C, Lescat M, et al. Emergence and dissemination of extended-spectrum beta-lactamase-producing *Escherichia coli* in the community: lessons from the study of a remote and controlled population. *J Infect Dis* **2010**; 202:515–23.
35. Landman D, Bratu S, Kochar S, et al. Evolution of antimicrobial resistance among *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Klebsiella pneumoniae* in Brooklyn, NY. *J Antimicrob Chemother* **2007**; 60:78–82.
36. Calfee D, Jenkins SG. Use of active surveillance cultures to detect asymptomatic colonization with carbapenem-resistant *Klebsiella pneumoniae* in intensive care unit patients. *Infect Control Hosp Epidemiol* **2008**; 29:966–8.
37. Cantón R, Canut A, Morosini MI, Oliver A. Breakpoints for carbapenemase-producing *Enterobacteriaceae*: is the problem solved? *Enferm Infecc Microbiol Clin* **2014**; 32(Suppl 4):33–40.
38. Rennie RP, Jones RN. Effects of breakpoint changes on carbapenem susceptibility rates of *Enterobacteriaceae*: results from the SENTRY Antimicrobial Surveillance Program, United States, 2008 to 2012. *Can J Infect Dis Med Microbiol* **2014**; 25:285–7.
39. Enfield KB, Huq NN, Gosseling MF, et al. Control of simultaneous outbreaks of carbapenemase-producing *Enterobacteriaceae* and extensively drug-resistant *Acinetobacter baumannii* infection in an intensive care unit using interventions promoted in the Centers for Disease Control and Prevention 2012 carbapenemase-resistant *Enterobacteriaceae* Toolkit. *Infect Control Hosp Epidemiol* **2014**; 35:810–7.
40. Vora NM, Kubin CJ, Furuya EY. Appropriateness of Gram-negative agent use at a tertiary care hospital in the setting of significant antimicrobial resistance. *Open Forum Infect Dis* **2015**; 2:ofv009.