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Reviewed work(s):
Source: *Infection Control and Hospital Epidemiology*, (-Not available-), p. 000
Published by: The University of Chicago Press on behalf of The Society for Healthcare Epidemiology of America
Stable URL: http://www.jstor.org/stable/10.1086/669523
Accessed: 06/02/2013 12:35

ORIGINAL ARTICLE

Trends in Resistance to Carbapenems and Third-Generation Cephalosporins among Clinical Isolates of *Klebsiella pneumoniae* in the United States, 1999–2010

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OBJECTIVE. Multidrug-resistant *Enterobacteriaceae* pose a serious infection control challenge and have emerged as a public health threat. We examined national trends in the proportion of *Klebsiella pneumoniae* isolates resistant to carbapenems (CRKP) and third-generation cephalosporins (G3CRKP).

DESIGN AND SETTING. Retrospective analysis of approximately 500,000 *K. pneumoniae* isolates cultured between January 1999 and July 2010 at 287 clinical laboratories throughout the United States.

METHODS. Isolates were defined as CRKP if they were nonsusceptible to 1 or more carbapenems and were defined as G3CRKP if they were nonsusceptible to ceftazidime, ceftriaxone, or related antibiotics. A multivariable analysis examined trends in the proportion of resistant isolates, adjusting for age, sex, isolate source, patient location, and geographic region.

RESULTS. The crude proportion of CRKP increased from less than 0.1% to 4.5% between 2002 and 2010; the frequency of G3CRKP increased from 5.3% to 11.5% between 1999 and 2010. G3CRKP and CRKP were more common among elderly patients (those greater than 65 years of age); the adjusted odds ratio (aOR) relative to pediatric patients (those less than 18 years of age) was 1.2 for G3CRKP (95% confidence interval [CI], 1.2–1.3) and 3.3 for CRKP (95% CI, 2.6–4.2). G3CRKP and CRKP were also more common among patients from the northeastern United States (aOR, 2.9 [95% CI, 2.8–3.0] and 9.0 [95% CI, 7.9–10.4]) than among those from the western United States. The prevalence of outpatient CRKP isolates increased after 2006, reaching 1.9% of isolates in our sample in 2010 (95% CI, 1.6%–2.1%).

CONCLUSIONS. The frequency of G3CRKP and CRKP is increasing in all regions of the United States, and resistance is emerging among isolates recovered in the outpatient setting. This underscores the need for enhanced laboratory capacity and coordinated surveillance strategies to contain the further spread of these emerging pathogens.

Infect Control Hosp Epidemiol 2013;34(3):000-000

Infections with multidrug-resistant gram-negative pathogens impose a significant and increasing burden on both patients and healthcare providers.[1,2] After widespread adoption of broad-spectrum cephalosporins in the 1980s, *Enterobacteriaceae*-producing extended-spectrum β-lactamases (ESBLs) have become endemic in hospitals and communities worldwide.[3,4] Infection with an ESBL-producing gram-negative pathogen, particularly *Escherichia coli* or *Klebsiella pneumoniae*, is associated with greater mortality, an increase in the length of hospital stay and hospitalization costs, and delays in treatment, compared with infection due to non-ESBL organisms.[5,6] Carbapenems are reserved as the treatment of choice for serious infections caused by ESBL-producing organisms, which makes the global emergence of carbapenem-resistant *Enterobacteriaceae* (CRE) strains a cause of great concern for public health.[7,8]

Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) outbreaks have been described worldwide,[7,9] and CRKP is the most common type of CRE in North America.[10,11] Previously confined to hospitals in New York City and the surrounding Middle Atlantic region,[12,13] CRKP prevalence is increasing in all US regions according to summary data from the National

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Received July 9, 2012; accepted October 23, 2012; electronically published January 23, 2013.

 0899-823X/2013/3403-00XX$15.00. DOI: 10.1086/669523

TABLE 1. Characteristics of *Klebsiella pneumoniae* Isolates Included in the Analysis, 1999–2010

Variable	No. (%) of isolates	
	G3CRKP (n = 553,250)	CRKP (n = 441,343)
Positive[a]	47,076 (8.5)	5,558 (1.3)
Age, years		
<18	29,396 (5.3)	23,549 (5.3)
18–40	127,174 (23)	101,576 (23)
41–65	124,184 (22.4)	102,002 (23.1)
>65	272,496 (49.3)	214,216 (48.6)
Sex		
Female	377,857 (68.3)	294,574 (66.7)
Male	175,393 (31.7)	146,769 (33.3)
Isolate source		
Urine	388,485 (70.2)	295,739 (67)
Wound	67,763 (12.2)	58,644 (13.3)
Lower respiratory tract	54,571 (9.9)	48,830 (11.1)
Blood	38,406 (6.9)	34,642 (7.8)
Other[b]	4,025 (0.7)	3,488 (0.8)
Patient location		
Outpatient	282,977 (51.1)	221,457 (50.2)
Inpatient	208,114 (37.6)	166,074 (37.6)
ICU inpatient	49,410 (8.9)	43,657 (9.9)
Nursing home	12,749 (2.3)	10,155 (2.3)
Region		
Midwest	124,284 (22.5)	107,803 (24.4)
West	119,368 (21.6)	94,526 (21.4)
South Atlantic	118,397 (21.4)	95,594 (21.7)
Northeast	108,073 (19.5)	85,052 (19.3)
South Central	83,128 (15)	58,369 (13.2)

NOTE. Third-generation cephalosporin–resistant *K. pneumoniae* (G3CRKP) included all isolates tested against either ceftriaxone (88.5% of isolates), ceftazidime (73.9%), aztreonam (57.5%), cefotaxime (29.9%), or ceftizoxime (6.3%). Carbapenem-resistant *K. pneumonia* (CRKP) included all isolates tested against either imipenem (76.3%), meropenem (27.4%), ertapenem (26.4%), or doripenem (<0.1%). ICU, intensive care unit.

[a] Includes all isolates reported to be nonsusceptible to 1 or more drugs included in the sample.

[b] Other sources include upper respiratory tract and skin cultures.

Healthcare Safety Network (NHSN). The spread of CRKP between healthcare settings is aided by interfacility transfers, particularly from long-term care facilities, which are a reservoir of drug-resistant strains.[14,15]

Because of the prevalence of and therapeutic challenges posed by drug-resistant *Enterobacteriaceae*, it is essential to monitor their spread through comprehensive national and regional surveillance.[16] However, there is a paucity of recent national studies on the prevalence of *K. pneumoniae* strains that are resistant to extended-spectrum cephalosporins and carbapenems. The most recent data come from local outbreak reports,[9,12,13,15,17] or NHSN summaries that are limited to device- and procedure-associated infections acquired in a sample of self-selected, acute-care hospitals that were not designed to be representative of facilities nationwide.[18]

In this study, we examine trends in the resistance of clinical *K. pneumoniae* isolates from acute care, long-term care, and outpatient settings across different US geographic regions. Using nationally representative surveillance data that encompass a longer time span and larger isolate count than has been used to date, we characterize the epidemiology of third-generation cephalosporin–resistant and carbapenem-resistant phenotypes of *K. pneumoniae* between 1999 and 2010. Results are stratified by patient care settings, including nursing homes, which allows the first national and regional analysis of the association between resistance patterns and isolate source, geographic region, patient location, and demographic characteristics.

METHODS

Antimicrobial susceptibility data were obtained from The Surveillance Network Database–USA (TSN; Eurofins-Medinet). The data are described in detail elsewhere and have been widely used to characterize national antibiotic susceptibility trends.[19-22] Briefly, the microbiological laboratories in the network were selected on the basis of geographic and demographic criteria to be representative of hospitals in each of 9 US Census Bureau regional divisions. Results for all routine susceptibility tests performed on-site are electronically validated and merged into a central database. Categorical results are based on Clinical Laboratory Standards Institute interpretative criteria adopted by the facility at the time of testing and reflect susceptibilities as reported to clinicians.[22]

The analysis considered all isolates from patients in outpatient, inpatient non–intensive care unit (ICU; referred to as inpatient), ICU, and nursing home settings between January 1, 1999, and July 1, 2010, that were identified as *K. pneumoniae.* The third-generation cephalosporin-resistant *K. pneumoniae* (G3CRKP) phenotype included all isolates nonsusceptible to 1 or more of the 5 agents recommended for ESBL screening (aztreonam, cefotaxime, ceftizoxime, ceftazidime, and ceftriaxone).[23] The carbapenem-resistant *K. pneumoniae* (CRKP) phenotype was defined as all isolates nonsusceptible to 1 or more carbapenem (doripenem, ertapenem, imipenem, and meropenem). For each analysis, the data were filtered to retain isolates that were tested against at least 1 drug included in each phenotype definition. To avoid bias from duplicate cultures, we considered only the first isolate from a patient in a rolling 30-day period.

Individual susceptibility results were stratified by isolate source (blood, urine, lower respiratory tract, wound, and other, which included upper respiratory tract and skin), patient location (inpatient, ICU, outpatient, and nursing home), age (less than 18, 18-40, 41–65, and greater than 65 years), sex, and year. The site-level breakdown was collapsed into 5 broad regions, equivalent to the 4 US census regions (North-

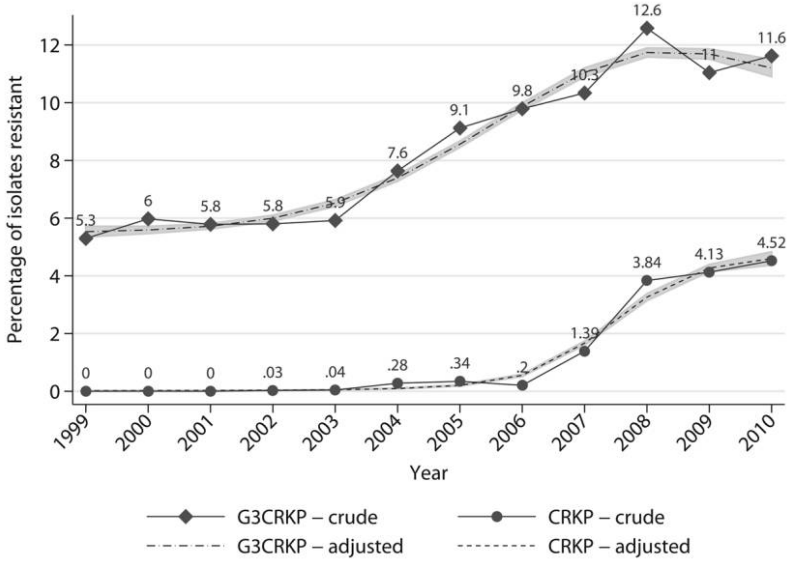

FIGURE 1. Crude and adjusted percentage of *Klebsiella pneumoniae* isolates resistant to third-generation cephalosporins (G3CRKP) and carbapenems (CRKP), 1999–2010. Numbers and solid lines correspond to the crude percentage values for each year. Dashed lines correspond to fitted (adjusted) model values, estimated using logistic regression that included year, patient, and isolate characteristics, and a 4-knot restricted cubic spline to smooth trend lines. Shaded area represents 95% confidence intervals. Data for 2010 were only available through July 1.

east, Midwest, South, and West), with the South region separated into South Atlantic and South Central to account for its larger population and greater number of reported isolates.

Crude (unadjusted) susceptibility rates for each year were calculated as the number of positive phenotypes as a proportion of the number of tested isolates. A multivariable logistic regression was used to model the prevalence of resistant phenotypes and control for available isolate and patient characteristics, including age, sex, isolate source, patient location, and geographic region. Restricted cubic splines with 4 knots were used to smooth the data and account for nonlinearity in trends. The number and placement of spline knots was based on a previously published method by Sauerbrei.[24] Fitted values were used to plot stratified estimates of the percentage of isolates resistant. The Cochran-Armitage χ^2 test for linear trend was used to assess significance of unadjusted yearly trends. Statistical significance was determined at the 5% level. Data analysis was conducted using Stata software, version 11 (StataCorp).

RESULTS

Table 1 summarizes isolate and patient characteristics for the cohort. Between January 1, 1999, and July 1, 2010, results for 553,250 *K. pneumoniae* isolates tested for G3CRKP and 441,343 isolates tested for CRKP were submitted by 287 sites. The difference between samples (111,907 isolates) resulted from G3CRKP cultures that were not tested against any carbapenems. Figure 1 presents the crude (unadjusted) percentage of each phenotype. Between 1999 and 2003, the unadjusted proportion of G3CRKP remained statistically unchanged ($P = .24$ by χ^2). After 2003, the prevalence of G3CRKP increased significantly, reaching a high of 12.6% in 2008 ($P = .011$). The proportion of CRKP isolates, which were not reported before 2002 and remained rare until 2004, increased from less than 0.1% to 4.5% in the 2002–2010 period ($P = .001$).

The frequency of G3CRKP and CRKP was modeled using multivariable logistic regression, which controlled for time, patient, and isolate characteristics and included a 3-knot cubic spline to smooth predicted trends. Results are shown in Figure 1, and Table 2 summarizes model estimates. The coefficients for linear time and restricted cubic spline knots were significant in each model, which confirmed the overall upward trajectory and hypothesized nonlinearity in trends. All variables were statistically significant and were retained in subsequent models.

After the data were adjusted and smoothed, elderly patients (older than 65 years of age) showed the highest prevalence of carbapenem resistance among *K. pneumoniae* isolates, with nearly 3.3 times the rate for isolates from pediatric patients (those less than 18 years of age; adjusted odds ratio [aOR], 3.29 [95% confidence interval (CI), 2.6–4.15]), whereas adult patients between 41 and 65 years of age had a greater frequency of G3CRKP (aOR, 1.39 [95% CI, 1.32–1.47]; Table 2). Plotting the fitted values for each year revealed different age trends for the 2 phenotypes: for most of the period, rates of G3CRKP were highest among the 41–65-year-old age group and began to decrease in 2008, as did those among

TABLE 2. Logistic Model of *Klebsiella pneumoniae* Resistance to Third-Generation Cephalosporins (G3CRKP) and Carbapenems (CRKP) Adjusted for Patient and Isolate Characteristics, 1999–2010

	G3CRKP (n = 553,250)		CRKP (n = 441,343)	
Isolate characteristic	aOR (95% CI)	P	aOR (95% CI)	P
Linear trend, 1999–2010[a]	1.027 (1.011–1.043)	.001	1.213 (1.059–1.389)	.005
Second spline knot[b]	1.220 (1.175–1.266)	<.001	2.158 (1.878–2.479)	<.001
Third spline knot[c]	0.565 (0.509–0.629)	<.002	0.905 (0.897–0.911)	<.001
Age, years (reference, <18)				
18–40	1.284 (1.217–1.354)	<.001	2.656 (2.09–3.376)	<.001
41–65	1.394 (1.323–1.47)	<.001	3.167 (2.503–4.009)	<.001
>65	1.232 (1.171–1.297)	<.002	3.289 (2.606–4.152)	<.002
Patient location (reference, outpatient)				
Inpatient	2.209 (2.158–2.262)	<.001	3.036 (2.456–2.82)	<.001
ICU	2.818 (2.726–2.913)	<.001	3.265 (2.769–3.328)	<.001
Nursing home	3.902 (3.713–4.101)	<.001	2.632 (2.878–3.703)	<.001
Sex (reference, female)				
Male	2.635 (2.564–2.708)	<.001	2.351 (2.168–2.549)	<.001
Isolate source (reference, urine)				
Lower respiratory tract	2.390 (2.277–2.509)	<.001	3.239 (2.85–3.682)	<.001
Blood	2.988 (2.863–3.118)	<.001	3.956 (3.526–4.439)	<.001
Wound	1.908 (1.833–1.985)	<.001	2.568 (2.313–2.851)	<.001
Other[d]	2.781 (2.419–3.198)	<.001	3.675 (2.571–5.254)	<.001
Isolate source × sex (reference, urine × female)				
Lower respiratory tract × male	0.396 (0.371–0.424)	<.001	0.369 (0.308–0.442)	<.001
Blood × male	0.344 (0.326–0.363)	<.001	0.358 (0.309–0.415)	<.001
Wound × male	0.484 (0.458–0.511)	<.001	0.482 (0.415–0.56)	<.001
Other × male	0.411 (0.34–0.497)	<.001	0.37 (0.221–0.62)	<.001
Region (reference, West)				
Northeast	2.897 (2.8–2.997)	<.001	9.034 (7.863–10.379)	<.001
Midwest	1.927 (1.861–1.996)	<.001	7.711 (6.71–8.861)	<.001
South Atlantic	2.296 (2.219–2.376)	<.001	3.102 (2.68–3.589)	<.001
South Central	1.253 (1.202–1.305)	<.001	1.533 (1.264–1.859)	<.001

NOTE. Four-knot restricted cubic splines used to model time, with number and placement of knots chosen on the basis of the lowest Akaike Information Criterion value of tested models. Data for 2010 were available through July 1. aOR, adjusted odds ratio; CI, confidence interval; ICU, intensive-care unit.

[a] First and fourth knot placed at 1999 and 2010 and estimate a linear relationship.

[b] Second knot placed at 2003 for G3CRKP and 2005 for CRKP.

[c] Third knot placed at 2008 for G3CRKP and CRKP.

[d] Other isolate sources include upper respiratory tract and skin cultures.

the 18–40-year-old age group (Figure 2). In contrast, resistance to CRKP isolates increased faster for older age groups. By 2010, the resistance rate for the elderly group (5.9% [95% CI, 5.4%–6.5%) was more than 5 times higher than the pediatric rate (1.01% [95% CI, 0.47%–1.54%]). Resistance among pediatric isolates increased for both phenotypes, reaching 7.1% (95% CI, 5.9%–8.3%) in the G3CRKP sample.

The prevalence and trends of resistant phenotypes among *K. pneumoniae* isolates varied with patient location at the time of isolation: cultures obtained at nursing homes were associated with the highest G3CRKP prevalence, nearly 4 times as high as the prevalence among cultures from outpatient (aOR, 3.9 [95% CI, 3.71–4.1]). Similarly, isolates obtained at ICUs had the highest CRKP prevalence (aOR, 3.27 [95% CI, 2.87–3.7]; Table 2). For G3CRKP, the prevalence of resistance was greatest among isolates obtained at nursing homes, followed by isolates obtained at ICUs and then isolates obtained from inpatients, although the rate of increase in all 3 groups appears to have slowed after 2008, whereas the rate among isolates obtained from outpatients may still be increasing (Figure 3). For CRKP, the prevalence of resistance first increased among isolates obtained at ICUs and isolates obtained from inpatients, going from approximately 0.1% in 2004 to slightly more than 5% in 2010. The prevalence of CRKP among isolates in the nonacute care group started increasing later and increased at a slower pace; however, the prevalence of CRKP increased among cultures from both outpatients and nursing home residents between 2006 and 2010 and reached levels of 1.85% (95% CI, 1.63%–2.07%) and 3.1% (95% CI, 0.47%–5.8%), respectively.

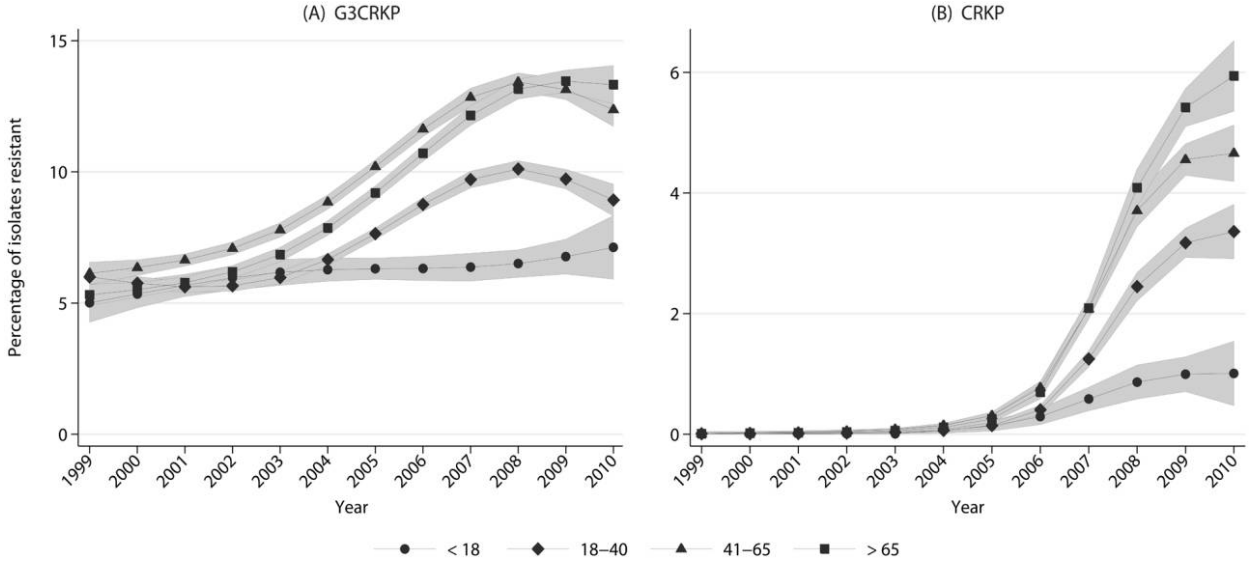

FIGURE 2. Fitted values of *Klebsiella pneumoniae* resistance to (*A*) third-generation cephalosporins (G3CRKP) and (*B*) carbapenems (CRKP), 1999–2010, stratified by age group. The proportion of resistant isolates for each phenotype was estimated using logistic regression adjusted for year, patient, and isolate characteristics and smoothed using a 4-knot restricted cubic spline. Shaded area represents 95% confidence intervals. Data for 2010 were only available through July 1.

Isolates from male patients had significantly higher adjusted odds of being G3CRKP (aOR, 2.63 [95% CI, 2.56–2.7]) and CRKP (aOR, 2.35 [95% CI, 2.16–1.54]; Table 2). Isolates from urinary cultures dominated the sample (Table 1), and their share relative to isolates from other anatomical sites was notably higher among female patients than among male patients (80.3% vs 48.5% for G3CRKP and 77.9% vs 45.1% for CRKP). Examining the interaction of sex with anatomical site revealed that, with the exception of urinary isolates, all other culture sources had lower resistance values among males than among females (Table 2). Stratified sex trends by the anatomical site of the isolate can be seen in Figure 4. Across both sex and phenotype, isolates obtained from the lower respiratory tract had the highest levels of resistance. Compared with isolates from female patients, respiratory isolates from male patients had significantly lower CRKP levels starting in 2007, with the difference reaching 4.2% (95% CI, 3.27%–5.15%) in 2010. However, urinary cultures from men showed notably higher levels of both G3CRKP and CRKP, with the sex difference increasing over time.

K. pneumoniae isolates from the northeastern United States were more than 9 times as likely to be CRKP (aOR, 9.03; 95% CI, 7.86–10.37) and nearly 3 times as likely to be G3CRKP (aOR, 2.9 [95% CI, 2.8–3.0]) compared with those from the western United States (Table 2). However, there were significant differences in the regional emergence and spread of phenotypes (Figure 5). G3CRKP levels in the northeastern United States exceeded levels in other regions by a significant margin for the majority of years (2000–2007), after which they decreased to 9.9% (95% CI, 9.28–10.51) in 2010. South Atlantic states experienced the largest increase (a 3.9-fold increase) in G3CRKP, from 3.45% (95% CI, 3.13%–3.78%) in 1999 to 13.46% (95% CI, 12.81%–14.1%) in 2010. CRKP emerged in the northeastern United States in 2003–2004 and spread to the Midwest and South Atlantic states after 2007 and to the South Central region after 2008. In 2010, CRKP rates in the Northeast and Midwest had reached 6.16% (95% CI, 5.55%–6.77%) and 5.9% (95% CI, 5.33%–6.46%), respectively, which is approximately twice as high as rates in the South Central (2.17% [95% CI, 1.39%–2.95%]) and South Atlantic (2.49% [95% CI, 2.15%–2.82%]) regions. For both phenotypes, resistance in the South Central states began increasing later than in other parts of the country. Detailed trends and maps of regional resistance patterns are available from the authors.

DISCUSSION

Recent reports of a carbapenem-resistant *K. pneumonia* outbreak at the National Institutes of Health Clinical Center have highlighted the importance of CRKP as a major infection control challenge.[25] These pathogens, which were endemic only in hospitals in the northeastern United States in the early 2000s, have spread to neighboring regions and are emerging in or being exported to nonacute care settings.

Additionally, resistance to extended-spectrum cephalosporins more than doubled in the 1999–2010 period, with particularly high levels among isolates from the Northeast and South Atlantic regions that were recovered from respiratory or blood sites of adult patients in ICUs or nursing homes.

Geographic region was among the most important isolate

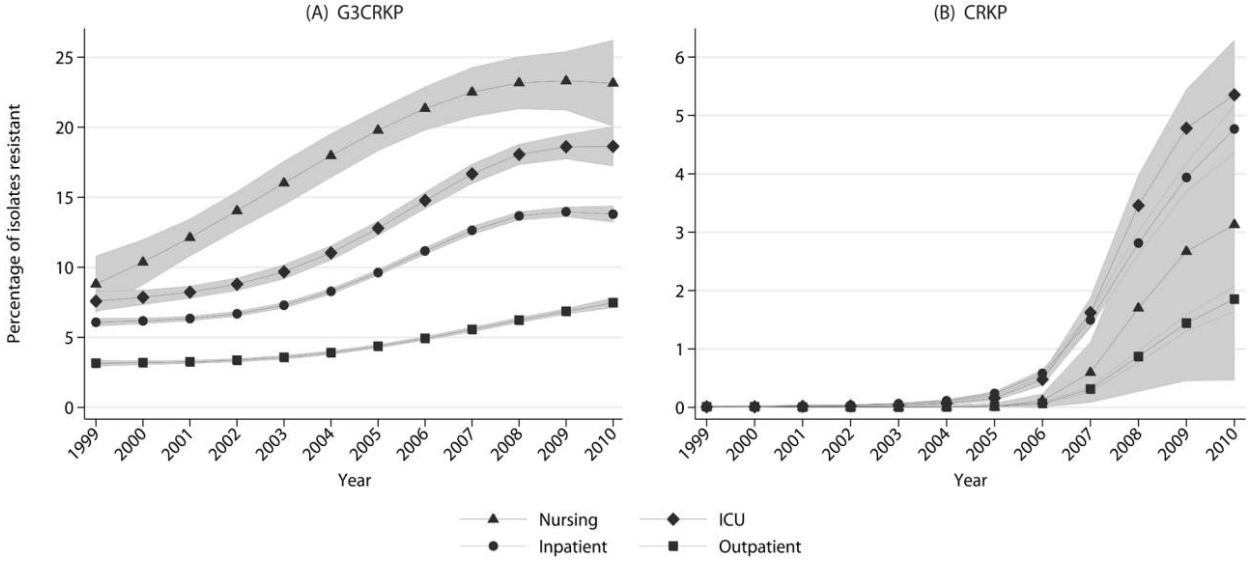

FIGURE 3. Fitted values of *Klebsiella pneumoniae* resistance to (*A*) third-generation cephalosporins (G3CRKP) and (*B*) carbapenems (CRKP), 1999–2010, stratified by patient location. The proportion of resistant isolates for each phenotype was estimated using logistic regression adjusted for year, patient, and isolate characteristics and smoothed using a 4-knot restricted cubic spline. Inpatient includes only cultures from non-ICU ward patients. Shaded area represents 95% confidence intervals. Data for 2010 were only available through July 1. ICU, intensive care unit.

characteristics in our model, particularly for CRKP. We found notably higher levels of carbapenem resistance in the Northeast, followed by the South Atlantic and Midwest regions. This is consistent with multiple outbreak reports from the past decade[3,9,13,17] as well as with reports from larger surveillance studies.[26] These data represent the spread of CRKP west and south from New York City, where initial outbreaks occurred in the early 2000s.[13] The only region without a marked increase in CRKP prevalence was the West, although recent reports from California indicate the spread of CRKP to the Pacific states after 2010.[27] The uncertain drivers of the observed variation across regions and patient settings is a topic that merits more research, particularly with regard to the role of interfacility transfers and local antibiotic use patterns.[14,15,28]

Male sex was associated with an increased prevalence of resistant phenotypes among urinary isolates, which is likely because urinary tract infections in men tend to be more complicated and to end in hospitalization more frequently than urinary tract infections in women.[29]

The noted increase in the prevalence of resistance among *Klebsiella* isolates expands upon smaller surveillance studies.[18,26,30-32] Recent US data from the SENTRY Antimicrobial Surveillance Program found that 16.9% of 7,162 *K. pneumoniae* isolates were resistant to third-generation cephalosporins in 2006.[31] The Meropenem Yearly Susceptibility Test Information Collection (MYSTIC) Program found that 15% of 416 inpatient *K. pneumoniae* isolates from participating sites were resistant to ceftazidime in 2008.[32] These numbers are similar to the increasing frequency of G3CRKP, from 5.3% to 11.5% of isolates, observed from 1999 to 2010 in our study. Our findings also support previous reports that showed a global increase in carbapenem resistance in the late 2000s.[30] A MYSTIC report found that CRKP rates in the United States between 2006 and 2007 exceeded 8% but decrease to 4.3% in 2008. This is in contrast to the uninterrupted upward trend for isolates from inpatient and outpatient settings seen in our sample. The difference is likely attributable to the smaller sample size and geographic diversity of the MYSTIC data. The 2006–2007 NHSN summary of antimicrobial trends reported that 8.7% of approximately 1,300 pathogenic isolates were carbapenem resistant during the period 2006–2007.[18] The prevalence decreased to 5% after New York hospitals were excluded. These estimates are higher than the percentage of CRKP in our data using all isolates (2.45% with and 1.6% without isolates from New York). This is not surprising, given that our numbers are based on all inpatient and outpatient cultures, whereas NHSN isolates are obtained from patients with healthcare-associated infections at acute-care facilities.

Our study has several limitations. First, as with most laboratory-based surveillance studies, we cannot control for patient clinical characteristics or distinguish between confirmed infection and colonization. Second, patient location entered in laboratory information systems may not correspond to the clinical setting where patients ultimately received care (eg, culture specimens obtained in the emergency department may be counted as outpatient cultures, even if the patient was ultimately admitted to the ICU). Third, results for nursing homes combine isolates from long-term acute care hos-

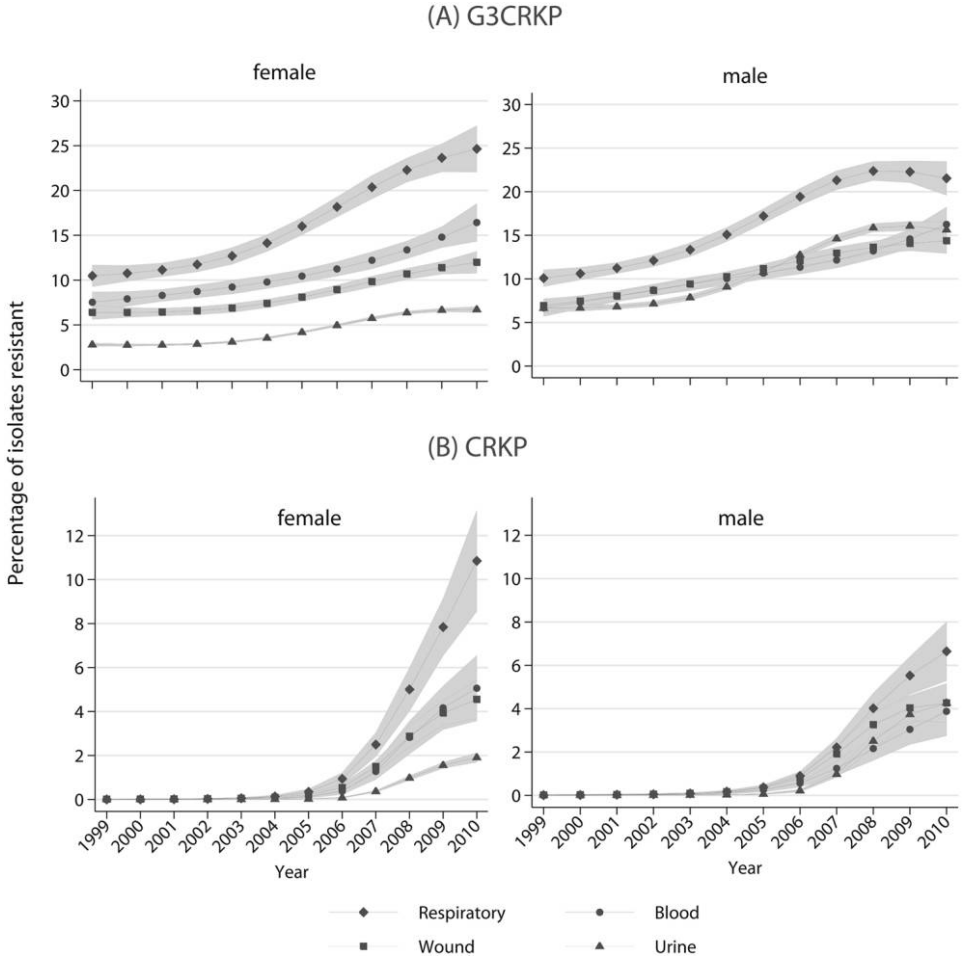

FIGURE 4. Fitted values of *Klebsiella pneumoniae* resistance to (*A*) third-generation cephalosporins (G3CRKP) and (*B*) carbapenems (CRKP), 1999–2010, stratified by sex and isolate source site. The proportion of resistant isolates for each phenotype was estimated using logistic regression adjusted for year, patient, and isolate characteristics and smoothed using a 4-knot restricted cubic spline. Shaded area represents 95% confidence intervals. Data for 2010 were only available through July 1.

pitals and traditional skilled nursing facilities, which masks potentially important differences between these environments. Fourth, changes in surveillance practices (eg, introducing active ESBL surveillance or routine carbapenem testing of urine cultures at institutions with a high prevalence of such infections) during the study period could influence reported trends. Fifth, routine testing may fail to identify carbapenemase-producing *Enterobacteriaceae* below established breakpoints,[33] which suggests that the true frequency of CRKP is likely higher than reported. Finally, interpretative criteria for cephalosporins and aztreonam were lowered in January 2010, followed by a revision of carbapenem breakpoints in June 2010.[23] An analysis of national data found that the revision would increase cephalosporin resistance rates by approximately 3% for the same isolates.[34] Although use of the new breakpoints by TSN participants could not be ascertained, the effect was likely minor, because carbapenem breakpoints were revised only a month before the end of our analysis period, and many clinical laboratories delayed the adoption of cephalosporin breakpoints because of implementation difficulties.[35] Specifically, the vast majority (greater than 80%) of TSN sites used automated testing systems that are regulated by the US Food and Drug Administration,[36] which did not provide updated breakpoints until after the end of our study.

Characterizing the molecular epidemiology behind the noted trends was outside the scope of this study, because our data do not report the necessary phenotype or genotype test results. Isolates resistant to third-generation cephalosporins are often presumed to carry an ESBL.[19,31] However, using such a phenotypic marker may carry low positive predictive value (40%–80%), particularly in regions with a low prevalence and in the presence of AmpC enzymes.[26,37,38] The majority of CREs in North America are due to *K. pneumoniae* carba-

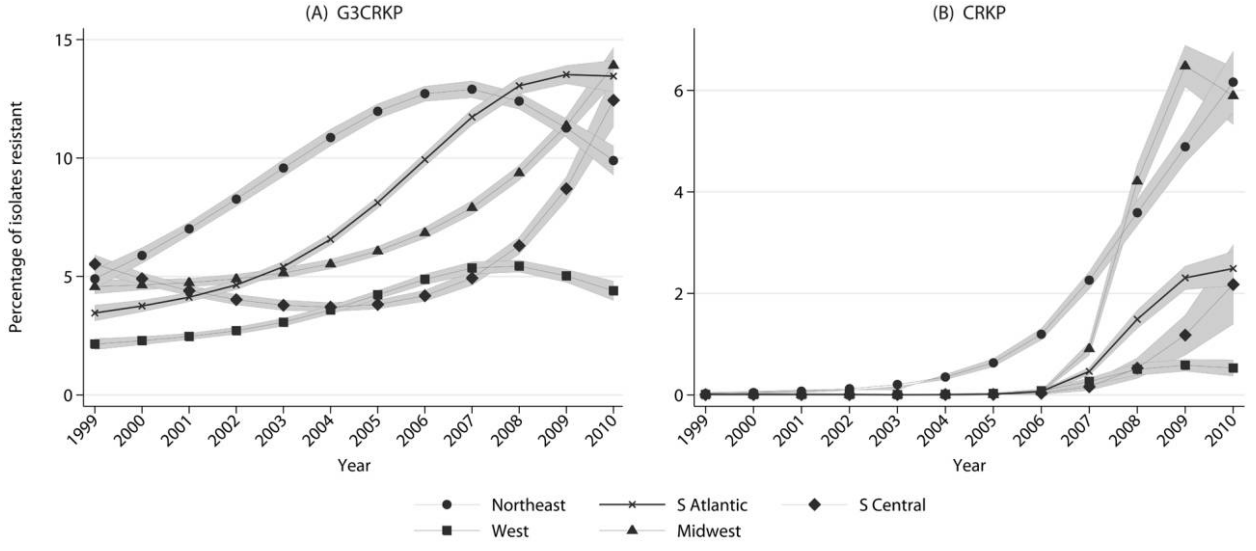

FIGURE 5. Fitted values of *Klebsiella pneumoniae* resistance to third-generation cephalosporins (G3CRKP) and carbapenems (CRKP), 1999–2010, stratified by 5 geographic regions. The geographic breakdown is equivalent to US Census regions (Northeast, Midwest, South, West), with the South region divided into South Atlantic (S Atlantic) and South Central (S Central). The proportion of resistant isolates for each phenotype was estimated using logistic regression adjusted for year, patient, and isolate characteristics and smoothed using a 4-knot restricted cubic spline. Shaded area represents 95% confidence intervals. Data for 2010 were only available through July 1.

penemases (KPCs),[9,17] with sporadic outbreaks involving other enzymes, including New Delhi metallo-β-lactamase (NDM-1).[39] Future investigations should include data on the prevalence of emerging resistance mechanisms, particularly those that present difficulties in routine detection.

In summary, we found a significant increase in the prevalence of CRKP and G3CRKP isolates across regions and patient settings. The increase in CRKP in the nonacute setting is especially troubling, because it could indicate the arrival of a community-based epidemic of carbapenemase-producing *Enterobacteriaceae*.[7] Public health authorities should take notice of successful locally and nationally coordinated strategies for managing outbreaks and consider making CRKP a reportable disease, particularly for highly transmissible strains carrying KPC or NDM-1 genes.[39,40] Clinicians and hospital epidemiologists need to assure that, in addition to routine susceptibility testing, their laboratories can detect these resistance mechanisms for epidemiological purposes in areas where these organisms are emerging.

ACKNOWLEDGMENTS

Financial support. The Extending the Cure Project, funded by a Pioneer Portfolio grant of the Robert Wood Johnson Foundation, and the Health Grand Challenges Program at Princeton University.

Potential conflicts of interest. All authors report no conflicts of interest relevant to this article. All authors submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest, and the conflicts that the editors consider relevant to this article are disclosed here.

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Presented in part: IDWeek 2012, a Joint Meeting of the Infectious Diseases Society of America, Society for Healthcare Epidemiology of America, HIV Medicine Association, and Pediatric Infectious Diseases Society; San Diego, California; October 17–21, 2012 (Abstracts 683 and 685).

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