# Carbapenem-Resistant *Enterobacteriaceae*: Epidemiology and Prevention

**Neil Gupta,[1,2] Brandi M. Limbago,[2] Jean B. Patel,[2] and Alexander J. Kallen[2]**

[1]Epidemic Intelligence Service and [2]Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, Atlanta, Georgia

**Over the past 10 years, dissemination of *Klebsiella pneumoniae* carbapenemase (KPC) has led to an increase in the prevalence of carbapenem-resistant *Enterobacteriaceae* (CRE) in the United States. Infections caused by CRE have limited treatment options and have been associated with high mortality rates. In the previous year, other carbapenemase subtypes, including New Delhi metallo-β-lactamase, have been identified among *Enterobacteriaceae* in the United States. Like KPC, these enzymes are frequently found on mobile genetic elements and have the potential to spread widely. As a result, preventing both CRE transmission and CRE infections have become important public health objectives. This review describes the current epidemiology of CRE in the United States and highlights important prevention strategies.**

Resistance to broad-spectrum antimicrobials, such as the extended-spectrum cephalosporins, is a well-recognized problem among *Enterobacteriaceae* [1]. Carbapenems have served as an important antimicrobial class for the treatment of these organisms and, until recently, resistance to carbapenems has been uncommon among *Enterobacteriaceae* in the United States. However, the emergence of novel β-lactamases with direct carbapenem-hydrolyzing activity has contributed to an increased prevalence of carbapenem-resistant *Enterobacteriaceae* (CRE). CRE are particularly problematic given the frequency with which *Enterobacteriaceae* cause infections [2], the high mortality associated with infections caused by CRE [3–5], and the potential for widespread transmission of carbapenem resistance via mobile genetic elements [6, 7].

Although CRE have primarily been recognized in health care settings [3, 8], *Enterobacteriaceae* are common causes of both health care and community infections, raising the possibility of spread of CRE into the community. These issues, combined with the limited therapeutic options available to treat patients infected with these organisms, have made CRE of epidemiologic importance nationally. In this brief review, we will describe the epidemiology of CRE in the United States, with an emphasis on carbapenemase-producing strains, and discuss strategies for prevention.

## EPIDEMIOLOGY

CRE appear to have been uncommon in the United States before 1992. Using data from the National Nosocomial Infection Surveillance (NNIS) system from 1986 to 1990, Gaynes et al found that only 2.3% of 1825 *Enterobacter* isolates tested nonsusceptible to imipenem [9]. However, over the last decade CRE have been reported more commonly. In the Meropenem Yearly Susceptibility Test Information Collection Program, meropenem resistance among clinical isolates of *Klebsiella pneumoniae* increased significantly from 0.6% in 2004 to 5.6% in 2008 [10]. Among isolates reported to the National Healthcare Safety Network (NHSN) in 2006–2007, carbapenem resistance was reported in up to 4.0% of *Escherichia coli* and 10.8% of *K. pneumoniae* isolates that were associated with certain device-related infections [2].

Received 28 December 2010; accepted 1 March 2011.

Correspondence: Neil Gupta, MD, Division of Healthcare Quality Promotion, Centers for Disease Control and Prevention, 1600 Clifton Road NE, MS A-35, Atlanta, GA, 30333 (ngupta1@cdc.gov).

**Clinical Infectious Diseases 2011;53(1):60–67**
Published by Oxford University Press on behalf of the Infectious Diseases Society of America 2011.
1058-4838/2011/531-0011$14.00
DOI: 10.1093/cid/cir202

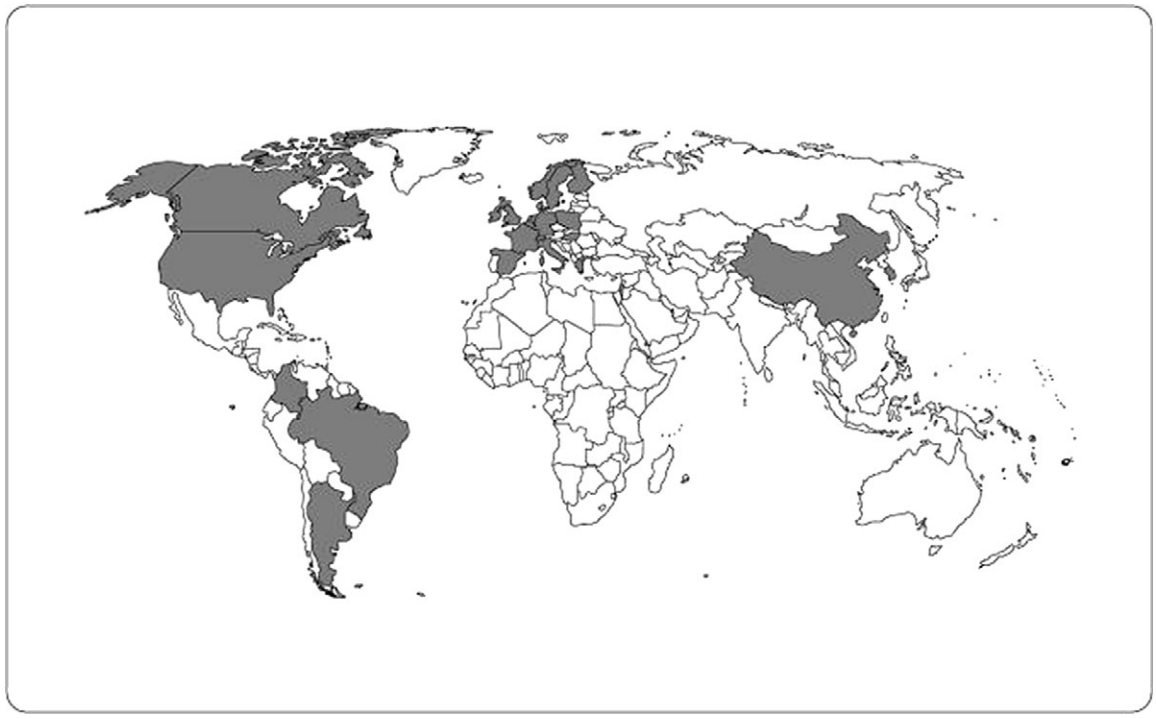

**Figure 1.** International dissemination of *Klebsiella pneumoniae* carbapenemase (KPC)–producing *Enterobacteriaceae*. This map indicates countries where KPC-producing *Enterobacteriaceae* have been described in published reports available as of 11 February, 2011. Because of lack of systematic surveillance for these organisms, countries not highlighted in this figure might also have unreported KPC-producing *Enterobacteriaceae*.

### The Emergence of *Klebsiella pneumoniae* Carbapenemases

Although initial reports described that carbapenem resistance among *Enterobacteriaceae* was due to overproduction of Amp C-mediated β-lactamases or extended-spectrum β-lactamases (ESBLs) in organisms with porin mutations [11–13], carbapenemases have now become another mechanism for carbapenem resistance among CRE in the United States. The most common carbapenemase in the United States is *Klebsiella pneumoniae* carbapenemase (KPC), an Ambler molecular class A enzyme that utilizes serine at the active site to facilitate hydrolysis of a broad variety of β-lactams [14].

KPC-producing *Enterobacteriaceae* were first reported in a clinical specimen from a patient in North Carolina in 2001 [7]. Subsequently, outbreaks and transmission of KPC-producing organisms were reported, predominantly from the northeastern United States [3, 8]. In a 2002–2003 surveillance study in New York City, 9 of 602 *K. pneumoniae* isolates were found to contain the $bla_{KPC}$ gene. In the following year, 20 additional KPC-producing isolates were identified from 2 hospital outbreaks in the city [3]. Since that time, KPC-producing isolates have become more widespread nationally. Although the Centers for Disease Control and Prevention (CDC) does not yet perform systematic surveillance for these organisms, as of December 2010, KPC-producing isolates have been received or identified from 36 states, Washington, DC, and Puerto Rico (unpublished CDC data).

In addition, reports of KPC-producing *Enterobacteriaceae* have emerged from other parts of the world—some associated with receipt of medical care in the United States—suggesting intercontinental spread of these organisms [15]. In Israel, a number of facilities reported increases in KPC-producing *Enterobacteriaceae* beginning in 2006 [16, 17]. Pulsed-field gel electrophoresis (PFGE) analysis of KPC-producing *K. pneumoniae* from 8 hospitals and 5 chronic care centers demonstrated a clonal relationship between many of these isolates, some of which appeared to be genetically related to strains reported from outbreaks in the United States [17]. These organisms have now spread widely; countries from which KPCs have been reported since 2001 are shown in Figure 1.

In the United States, much of the dissemination of KPC-producing CRE isolates also appears to be clonal [18]. A sample of KPC-producing *K. pneumoniae* isolates sent to the CDC for reference testing from 1996 to 2008 was characterized using PFGE and multilocus sequence typing (MLST). This analysis revealed that a dominant strain, ST258, accounted for approximately 70% of all KPC-producing *K. pneumoniae* isolates sent to the CDC during that time period [18].

In addition to β-lactams, KPC-producing isolates demonstrate resistance to many agents commonly used to treat gram-negative bacteria, including quinolones and aminoglycosides [19, 20]. Among 344 isolates of KPC-producing *Enterobacteriaceae* sent

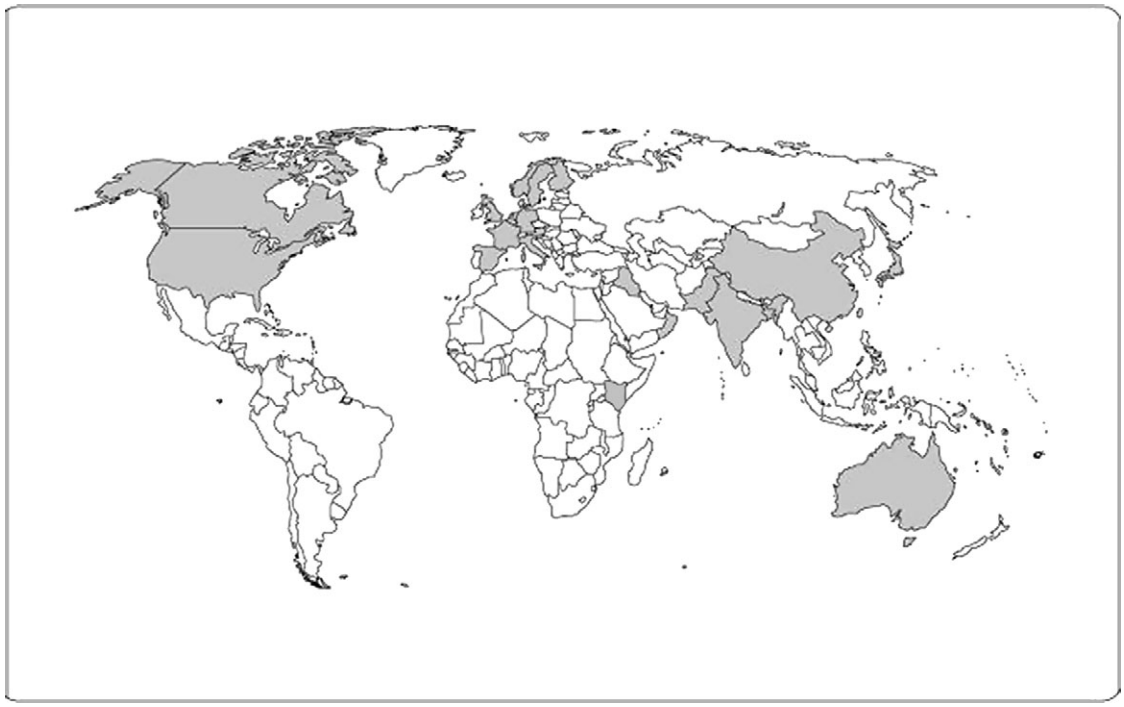

**Figure 2.** International dissemination of New Delhi metallo-β-lactamase (NDM)–producing *Enterobacteriaceae*. This map indicates countries where NDM-producing *Enterobacteriaceae* have been described in published reports available as of 11 February, 2011. Because of lack of systematic surveillance for these organisms, countries not highlighted in this figure might also have unreported NDM-producing *Enterobacteriaceae*.

to CDC for evaluation from January 2007 through October 2009, 312 (91%) had a colistin minimum inhibitory concentration (MIC) ≤ 2μg/mL, and 304 (88%) had a tigecycline MIC ≤ 2μg/mL. Only 2 isolates were nonsusceptible to both colistin and tigecycline (unpublished CDC data). "Pan-resistance" to antimicrobials agents has also been reported [21].

### Novel Phenotypes: The Metallo-β-Lactamases

The Ambler class B metallo-β-lactamases (MBLs) differ from other carbapenemases by the utilization of zinc at the active site to facilitate hydrolysis [14]. Although MBLs have been described in *Pseudomonas species* [22], they have only rarely been reported among *Enterobacteriaceae* in the United States. In other parts of the world, however, MBL-producing *Enterobacteriaceae* are more common. Until recently, the most common MBLs found worldwide in *Enterobacteriaceae* were VIMs (Verona integron-encoded MBLs) and IMPs (active on imipenem).

In 2009, a novel MBL, the New Delhi MBL (NDM), was described [23, 24]. NDM was first recognized in a *K. pneumoniae* isolate from a Swedish patient who had received medical care in India [24] and was soon recognized as an emerging mechanism of resistance in multiple species of *Enterobacteriaceae* in the United Kingdom [23]. Many of the early cases in the United Kingdom were associated with receipt of medical care in India or Pakistan [23, 25].

NDM has also been recognized among *Enterobacteriaceae* in India. In 1 study of *Enterobacteriaceae* from a tertiary care center in Mumbai, 22 of 24 consecutively collected CRE isolates contained $bla_{NDM}$, the gene encoding NDM [26]. Kumarasamy et al found that among a convenience sample of *Enterobacteriaceae* obtained from patients in India, between 31% and 55% of CRE isolates were NDM-producers [25]. Many of the NDM-producing isolates from India were from patients with community-onset infections. Countries that have reported NDM-producing *Enterobacteriaceae* since 2009 are shown in Figure 2.

In the United States, between January 2009 and February 2011, 7 NDM-producing *Enterobacteriaceae* have been identified among clinical isolates sent to CDC (Table 1). In addition, 6 *Enterobacteriaceae* containing VIMs or IMPs have also been identified between November 2009 and November 2010 (Table 1). Of these 13 MBL-containing *Enterobacteriaceae,* 8 were in patients whose primary risk was exposure to health care in countries where these organisms are more common.

### CRE Risk Factors and Associated Mortality

In studies evaluating risk factors for CRE acquisition or infection, exposure to health care and antimicrobials are among the most prominent risks [4, 5, 20, 27]. Patel et al found that invasive infections with carbapenem-resistant *K. pneumoniae* (CRKP)—likely primarily KPC-producers—were independently associated with recent organ or stem-cell transplantation, receipt

**Table 1. Cases of Metallo-β-Lactamase–Producing *Enterobacteriaceae* in the United States Reported to CDC, 2009–2010**

| Case | MBL type | Culture date | Organism | Culture site | Received medical care outside United States | Additional patient information |
|---|---|---|---|---|---|---|
| 1 | NDM | Apr 2009 | *Enterobacter cloacae* | Urine | Yes | Hospitalization in India |
| 2 | NDM | Dec 2009 | *Klebsiella pneumoniae* | Urine | Yes | Hospitalization in India |
| 3 | NDM | May 2010 | *Escherichia coli* | Urine | No | Travel in India, history of multiple comorbidities, indwelling medical device |
| 4 | NDM | Sep 2010 | *K. pneumoniae* | Respiratory | Yes | Hospitalization in Pakistan |
| 5 | NDM | Sep 2010 | *E. coli* | Respiratory | Yes | Received medical care in India, no hospitalizations |
| 6 | NDM | Dec 2010 | *K. pneumoniae* | Urine | Yes | Hospitalization in India |
| 7 | NDM | Feb 2011 | *K. pneumoniae* | Respiratory | Yes | Hospitalization in India |
| 8 | IMP | Nov 2009 | *K. pneumoniae* | Urine | No | No known travel outside United States |
| 9 | IMP | May 2010 | *K. pneumoniae* | Urine | No | No known travel outside United States |
| 10 | IMP | Jun 2010 | *K. pneumoniae* | Urine | No | No known travel outside United States |
| 11 | VIM | Jul 2010 | *K. pneumoniae* | Blood | Yes | Hospitalization in Greece |
| 12 | VIM | Sep 2010 | *K. pneumoniae* | Urine | Yes | Hospitalization in Italy |
| 13 | VIM | Oct 2010 | *K. pneumoniae* | JP drain | No | Overlapping ICU stay with case-patient 11 during United States hospitalization |

**NOTE.** MBL, metallo-β-lactamase; NDM, New Delhi metallo-β-lactamase; IMP, ''active on imipenem''; VIM, Verona integron-encoded metallo-β-lactamase; ICU, intensive care unit.

of mechanical ventilation, exposure to antimicrobials, and longer length of stay when compared with patients with carbapenem-susceptible *K. pneumoniae* (CSKP) [4]. Other risk factors associated with the acquisition of CRKP include poor functional status and intensive care unit (ICU) stay [5]. Of note, use of several classes of antimicrobials has been associated with CRKP carriage or infection, including carbapenems [4, 20], cephalosoprins [4], fluoroquinolones [5, 20], and vancomycin [27].

When outcomes for patients with CRKP are compared with those for patients with CSKP, carbapenem resistance has been independently associated with an increase in mortality [4, 5, 28]. Age, mechanical ventilation, malignancy, heart disease, and ICU stay have been associated with increased mortality among those with CRKP infections [4, 5, 28], whereas removal of the focus of infection (eg, catheter removal, debridement, or drainage) was independently associated with survival [4].

### Long-term Care and CRE

The presence of CRE carriage has been described in a number of investigations involving patients from postacute care facilities [29–31], particularly long-term acute care hospitals (LTACHs) [29, 30]. Perez et al found that greater than 50% of patients with carbapenem-resistant gram-negative organisms were admitted from postacute care facilities, suggesting that these settings may be important reservoirs for the transmission and dissemination of these organisms [30]. In addition, small numbers of CRE clinical cases may be associated with larger reservoirs of colonized patients in these settings. In an investigation of 3 patients with KPC-producing CRE infection transferred to a hospital from a LTACH, active surveillance cultures from residents in the same LTACH unit as the case-patients identified CRE colonization among 49% of residents (unpublished CDC data).

## PREVENTION

Although antimicrobial development efforts remain a cornerstone of CRE response efforts [32], interventions aimed at preventing the transmission of, and infections with, these organisms are also important. Delaying the emergence of carbapenem resistance, particularly in areas where this resistance is still uncommon, can decrease the impact of these organisms as we await additional treatment options. More research is needed to determine the best ways to prevent CRE transmission, but single-center studies and 1 national effort [33] have suggested that bundled prevention strategies can be successful in outbreak [34–36] and endemic [37] settings. The next section highlights important prevention activities and describes the CDC's current recommendations for preventing CRE transmission in acute care facilities [38].

### Laboratory Detection

Accurately identifying CRE in the clinical laboratory is an important first step in prevention. Early studies have demonstrated that some KPC-producing isolates have carbapenem MICs that

**Table 2. Clinical and Laboratory Standards Institute Interpretive Criteria for Carbapenems and *Enterobacteriaceae* [41]**

| | Previous breakpoints (M100-S19)MIC (μg/mL) | | | Revised breakpoints (M100-S20)MIC (μg/mL) | | |
|---|---|---|---|---|---|---|
| Agent | Susceptible | Intermediate | Resistant | Susceptible | Intermediate | Resistant |
| Doripenem | … | … | … | ≤1 | 2 | ≥4 |
| Ertapenem | ≤2 | 4 | ≥8 | ≤0.25 | 0.5 | ≥1 |
| Imipenem | ≤4 | 8 | ≥16 | ≤1 | 2 | ≥4 |
| Meropenem | ≤4 | 8 | ≥16 | ≤1 | 2 | ≥4 |

**NOTE.** MIC, minimum inhibitory concentration.

remain in the susceptible range [39]. As a result, failure to detect these organisms may have underestimated CRE prevalence in early reports. To improve the detection of carbapenemase-producing *Enterobacteriaceae*, in 2008 the Clinical Laboratory and Standards Institute (CLSI) recommended that *Enterobacteriaceae* with elevated MICs to carbapenems (2–4 μg/mL) or reduced disk diffusion zones be tested for production of a carbapenemase using the modified Hodge test (MHT) [40]. If test results were positive, it was recommended that the presence of a carbapenemase be noted in the medical record. CLSI reevaluated the carbapenem breakpoints for *Enterobacteriaceae* and in 2010 recommended lowering the carbapenem breakpoints for ertapenem, imipenem, and meropenem and established new breakpoints for doripenem [41] (Table 2). These new breakpoints were established to more accurately predict carbapenem treatment outcomes without the need for a special test to detect carbapenemase production.

Although the CLSI breakpoint changes were recommended in 2010, the Food and Drug Administration (FDA)–approved breakpoints have not been changed, so the manufacturers of automated testing devices have not been able to provide clinical laboratories with tests whose performance has been validated against the new CLSI breakpoints. Thus, it appears that many clinical laboratories continue to rely on the older, higher breakpoints combined with phenotypic tests for determining carbapenem nonsusceptibility among *Enterobacteriaceae*.

In addition to the issues described previously, the identification of CRE is complicated by the fact that different definitions exist. Current definitions may include different bacterial species, different carbapenem susceptibility results, or results of additional testing (eg, carbapenemase testing). A conservative definition used at the CDC is nonsusceptibility to imipenem, meropenem, or doripenem using the revised 2010 CLSI breakpoints. Although this definition can be used for all *Enterobacteriaceae,* including the most common carbapenemase-producing strains (eg, *Klebsiella* species and *E. coli*), it might not apply equally to genera with higher baseline MICs to imipenem (eg, *Providencia* species, *Proteus* species, and *Morganella morganii*).

### Recognizing CRE Cases

It is important for health care facilities to understand how common CRE are in their institutions. In investigations conducted by the CDC, failure to recognize CRE infections when they first occur in a facility has resulted in a missed opportunity to intervene before these organisms are transmitted more widely. This omission is often related to 2 issues: first, a failure to recognize CRE as an epidemiologically important organism that requires specific attention, and second, the lack of an established communication mechanism between infection-prevention personnel and the clinical laboratory. Based on current recommendations for the control of multidrug-resistant organisms (MDROs), the CDC recommends that, in areas where CRE are not endemic, acute care facilities review microbiology records for the preceding 6–12 months to determine whether CRE have been isolated at the facility [38]. If previously unrecognized cases are identified, a round of surveillance cultures (ie, a point-prevalence survey) in high-risk areas (eg, ICUs or wards where previous cases have been detected) should be considered to identify unrecognized cases. In addition, facilities should ensure a system is in place to promptly notify infection-prevention personnel when CRE are identified in the laboratory. All identified CRE case-patients should be placed on contact precautions, and some experts have also recommended patient cohorting and use of dedicated staff for these patients [42].

### Surveillance Cultures

If previously unrecognized CRE cases or hospital-onset CRE infections are identified via either clinical cultures or point-prevalence surveys, facilities should consider surveillance cultures from patients with epidemiologic links to CRE case-patients. The goal of these cultures is to identify additional unrecognized CRE-colonized patients who are a potential source for transmission. If additional CRE-colonized patients are recognized, appropriate isolation precautions should be implemented.

Data from several studies have suggested that clinical cultures identify only a portion of patients colonized with CRE. In a point-prevalence study reporting a 5.4% carriage rate of CRKP among inpatients at a hospital in Israel [27], fewer than one-

third of these patients had positive clinical cultures for CRKP. In another study, surveillance cultures were responsible for identifying more than one-third of the patients infected or colonized with CRKP, resulting in an estimated 1400 days saved from unprotected exposure through early detection and implementation of contact precautions [43].

The ideal anatomic site to screen for resistant *Enterobacteriaceae* with surveillance cultures has been investigated in a number of studies. Among these, perianal and rectal cultures are generally the most reliable [27, 44]. The CDC has primarily obtained surveillance cultures for *Enterobacteriaceae* from the perirectal area and wounds during outbreak investigations. A laboratory protocol for processing of these swabs is available on the CDC's Web site (http://www.cdc.gov/ncidod/dhqp/pdf/ar/Klebsiella_or_Ecoli.pdf).

Active surveillance cultures have been used as part of a comprehensive strategy to interrupt transmission of KPC-producing *K. pneumoniae* in several investigations [34–36]. Evaluation of the impact of this intervention has generally taken on a quasi-experimental design and has often involved multiple interventions that make it difficult to understand the impact of surveillance cultures alone. During a CRKP outbreak, Ben-David and colleagues obtained active surveillance cultures from ICU patients on admission and weekly thereafter, and from non-ICU patients with epidemiologic links to CRKP case-patients, as part of their intervention. They reported a 4.7-fold reduction in the incidence of CRKP infections following implementation of their prevention effort [34]. Similarly, Kochar et al found a decrease in the incidence of CRKP in an ICU with endemic CRE using a multifaceted intervention that included rectal surveillance cultures obtained at admission and weekly [37]. Although the exact role for active surveillance cultures is not known, screening patients coming from highly endemic settings at admission for these organisms might be a consideration for some facilities.

In addition to active surveillance, Zuckerman et al assessed the eradication of CRE carriage using oral gentamicin. They achieved a 66% CRE eradication rate; however, more research is needed before this can be recommended more widely [45].

### Antimicrobial Stewardship and Minimizing Devices

Antimicrobial stewardship has been suggested as an important part of efforts to control MDROs [46]. However, multiple antimicrobial classes have been identified as possible risk factors for infection or colonization with CRE [4, 5, 20, 27]. Therefore, antimicrobial stewardship might be most effective if efforts are directed toward an overall decrease in antimicrobial use rather than targeting a specific antimicrobial class. Carbapenem restriction has been associated with lower rates of carbapenem-resistant *Pseudomonas aeruginosa* [47]; however, more research is needed to clarify the effect on CRE.

Limiting use of invasive devices is another potentially important intervention for CRE prevention. CRE have been identified from device-associated infections, particularly catheter-associated urinary tract infections. Therefore, strategies to prevent device-related infections, as described in previously published guidelines [48], should be implemented. For urinary catheters, prevention efforts include inserting catheters only in those patients with appropriate indications and removing them as soon as possible, using aseptic technique and sterile equipment for insertion, and maintaining a sterile closed drainage system [48].

### Prevention Beyond Acute Care and Role of Public Health

Although much of the effort surrounding CRE control has focused on acute care facilities, nonacute care settings also provide care for patients colonized or infected with these organisms [29–31]. Limiting prevention efforts to acute care settings fails to take into account the presence of MDROs across different health care settings. Broadening the approach to prevention requires employing setting-specific infection prevention strategies in all health care arenas but also requires a method for enhanced communication to ensure that proper infection-control practices [46] are continued when patients are transferred between levels of care.

CRE can become an issue not only in individual institutions but also across an entire community, thus highlighting a role for public health in CRE-prevention efforts. Public health has the ability to reach across the spectrum of health care to improve community situational awareness with respect to CRE and to assist with coordinating prevention efforts. Toward this end, a number of states have added, or are considering adding, CRE to the state's reportable conditions list. In support of this approach, a review of the experience in Israel suggests that centrally coordinated efforts to prevent these organisms have been associated with large decreases in the incidence of CRKP [33].

## Acknowledgments

We thank Carolyn V. Gould, MD, MSCR, and Arjun Srinivasan, MD, for their thoughtful review of the manuscript.

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

***Potential conflicts of interest.*** A. J. K. reports that his spouse has served as a consultant for Kimberly-Clark. All other authors: no conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed in the Acknowledgments section.

## References

1. Jacoby GA, Munoz-Price LS. The new beta-lactamases. N Engl J Med **2005**; 352:380–91.
2. 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.
3. 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.
4. Patel G, Huprikar S, Factor SH, Jenkins SG, Calfee DP. Outcomes of carbapenem-resistant Klebsiella pneumoniae infection and the impact of antimicrobial and adjunctive therapies. Infect Control Hosp Epidemiol **2008**; 29:1099–106.
5. Schwaber MJ, Klarfeld-Lidji S, Navon-Venezia S, Schwartz D, Leavitt A, Carmeli Y. Predictors of carbapenem-resistant *Klebsiella pneumoniae* acquisition among hospitalized adults and effect of acquisition on mortality. Antimicrob Agents Chemother **2008**; 52:1028–33.
6. Watanabe M, Iyobe S, Inoue M, Mitsuhashi S. Transferable imipenem resistance in *Pseudomonas aeruginosa*. Antimicrob Agents Chemother **1991**; 35:147–51.
7. Yigit H, Queenan AM, Anderson GJ, et al. Novel carbapenem-hydrolyzing beta-lactamase, KPC-1, from a carbapenem-resistant strain of *Klebsiella pneumoniae*. Antimicrob Agents Chemother **2001**; 45:1151–61.
8. Bratu S, Brooks S, Burney S, et al. Detection and spread of *Escherichia coli* possessing the plasmid-borne carbapenemase KPC-2 in Brooklyn, New York. Clin Infect Dis **2007**; 44:972–5.
9. Gaynes RP, Culver DH. Resistance to imipenem among selected gram-negative bacilli in the United States. Infect Control Hosp Epidemiol **1992**; 13:10–4.
10. Rhomberg PR, Jones RN. Summary trends for the Meropenem Yearly Susceptibility Test Information Collection program: A 10-year experience in the United States (1999–2008). Diagn Microbiol Infect Dis **2009**; 65:414–26.
11. Bradford PA, Urban C, Mariano N, Projan SJ, Rahal JJ, Bush K. Imipenem resistance in *Klebsiella pneumoniae* is associated with the combination of ACT-1, a plasmid-mediated AmpC beta-lactamase, and the foss of an outer membrane protein. Antimicrob Agents Chemother **1997**; 41:563–9.
12. Chow JW, Shlaes DM. Imipenem resistance associated with the loss of a 40 kDa outer membrane protein in Enterobacter aerogenes. J Antimicrob Chemother **1991**; 28:499–504.
13. MacKenzie FM, Forbes KJ, Dorai-John T, Amyes SG, Gould IM. Emergence of a carbapenem-resistant *Klebsiella pneumoniae*. Lancet **1997**; 350:783.
14. Queenan AM, Bush K. Carbapenemases: The versatile beta-lactamases. Clin Microbiol Rev **2007**; 20:440–58, table of contents.
15. Naas T, Nordmann P, Vedel G, Poyart C. Plasmid-mediated carbapenem-hydrolyzing beta-lactamase KPC in a *Klebsiella pneumoniae* isolate from France. Antimicrob Agents Chemother **2005**; 49:4423–4.
16. Leavitt A, Navon-Venezia S, Chmelnitsky I, Schwaber MJ, Carmeli Y. Emergence of KPC-2 and KPC-3 in carbapenem-resistant *Klebsiella pneumoniae* strains in an Israeli hospital. Antimicrob Agents Chemother **2007**; 51:3026–9.
17. Navon-Venezia S, Leavitt A, Schwaber MJ, et al. First report on a hyperepidemic clone of KPC-3-producing *Klebsiella pneumoniae* in Israel genetically related to a strain causing outbreaks in the United States. Antimicrob Agents Chemother **2009**; 53:818–20.
18. Kitchel B, Rasheed JK, Patel JB, et al. Molecular epidemiology of KPC-producing *Klebsiella pneumoniae* isolates in the United States: Clonal expansion of multilocus sequence type 258. Antimicrob Agents Chemother **2009**; 53:3365–70.
19. Castanheira M, Sader HS, Jones RN. Antimicrobial susceptibility patterns of KPC-producing or CTX-M-producing *Enterobacteriaceae*. Microb Drug Resist **2010**; 16:61–5.
20. Hussein K, Sprecher H, Mashiach T, Oren I, Kassis I, Finkelstein R. Carbapenem resistance among *Klebsiella pneumoniae* isolates: Risk factors, molecular characteristics, and susceptibility patterns. Infect Control Hosp Epidemiol **2009**; 30:666–71.
21. Elemam A, Rahimian J, Mandell W. Infection with panresistant *Klebsiella pneumoniae*: A report of 2 cases and a brief review of the literature. Clin Infect Dis **2009**; 49:271–4.
22. Lolans K, Queenan AM, Bush K, Sahud A, Quinn JP. First nosocomial outbreak of *Pseudomonas aeruginosa* producing an integron-borne metallo-beta-lactamase (VIM-2) in the United States. Antimicrob Agents Chemother **2005**; 49:3538–40.
23. Health Protection Agency. Multi-resistant hospital bacteria linked to India and Pakistan. Health Protection Report **2009**; 3. Available at: http://www.hpa.org.uk/hpr/archives/2009/news2609.htm. Accessed 17 February 2011.
24. Yong D, Toleman MA, Giske CG, et al. Characterization of a new metallo-beta-lactamase gene, bla(NDM-1), and a novel erythromycin esterase gene carried on a unique genetic structure in *Klebsiella pneumoniae* sequence type 14 from India. Antimicrob Agents Chemother **2009**; 53:5046–54.
25. Kumarasamy KK, Toleman MA, Walsh TR, et al. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: A molecular, biological, and epidemiological study. Lancet Infect Dis **2010**; 10:597–602.
26. Deshpande P, Rodrigues C, Shetty A, Kapadia F, Hedge A, Soman R. New Delhi Metallo-beta lactamase (NDM-1) in *Enterobacteriaceae*: Treatment options with carbapenems compromised. J Assoc Physicians India **2010**; 58:147–9.
27. Wiener-Well Y, Rudensky B, Yinnon AM, et al. Carriage rate of carbapenem-resistant *Klebsiella pneumoniae* in hospitalised patients during a national outbreak. J Hosp Infect **2010**; 74:344–9.
28. Daikos GL, Petrikkos P, Psichogiou M, et al. Prospective observational study of the impact of VIM-1 metallo-beta-lactamase on the outcome of patients with *Klebsiella pneumoniae* bloodstream infections. Antimicrob Agents Chemother **2009**; 53:1868–73.
29. Endimiani A, Depasquale JM, Forero S, et al. Emergence of blaKPC-containing *Klebsiella pneumoniae* in a long-term acute care hospital: A new challenge to our healthcare system. J Antimicrob Chemother **2009**; 64:1102–10.
30. Perez F, Endimiani A, Ray AJ, et al. Carbapenem-resistant *Acinetobacter baumannii* and *Klebsiella pneumoniae* across a hospital system: Impact of post-acute care facilities on dissemination. J Antimicrob Chemother **2010**; 65:1807–18.
31. Urban C, Bradford PA, Tuckman M, et al. Carbapenem-resistant *Escherichia coli* harboring *Klebsiella pneumoniae* carbapenemase beta-lactamases associated with long-term care facilities. Clin Infect Dis **2008**; 46:e127–30.
32. Infectious Diseases Society of America. The 10x20 Initiative: Pursuing a global commitment to develop 10 new antibacterial drugs by 2020. Clin Infect Dis **2010**; 50:1081–3.
33. 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.
34. Ben-David D, Maor Y, Keller N, et al. Potential role of active surveillance in the control of a hospital-wide outbreak of carbapenem-resistant *Klebsiella pneumoniae* infection. Infect Control Hosp Epidemiol **2010**; 31:620–6.
35. Munoz-Price LS, De La Cuesta C, Adams S, et al. Successful eradication of a monoclonal strain of *Klebsiella pneumoniae* during a *K. pneumoniae* carbapenemase-producing *K. pneumoniae* outbreak in a surgical intensive care unit in Miami, Florida. Infect Control Hosp Epidemiol **2010**; 31:1074–7.
36. 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.
37. Kochar S, Sheard T, Sharma R, et al. Success of an infection control program to reduce the spread of carbapenem-resistant *Klebsiella pneumoniae*. Infect Control Hosp Epidemiol **2009**; 30:447–52.

38. Centers for Disease Control and Prevention. 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.
39. Anderson KF, Lonsway DR, Rasheed JK, et al. Evaluation of methods to identify the *Klebsiella pneumoniae* carbapenemase in *Enterobacteriaceae*. J Clin Microbiol **2007**; 45:2723–5.
40. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing; 18th informational supplement. CLSI document M100-S18. Wayne, PA: CLSI, 2008.
41. Clinical and Laboratory Standards Institute (CLSI). Performance standards for antimicrobial susceptibility testing; Twentieth informational supplement (June 2010 update). CLSI document M100-S20-U Vol 30. Wayne, PA: Clinical and Laboratory Standards Institute, 2010.
42. Bilavsky E, Schwaber MJ, Carmeli Y. How to stem the tide of carbapenemase-producing *Enterobacteriaceae*?: Proactive versus reactive strategies. Curr Opin Infect Dis **2010**; 23:327–31.
43. 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.
44. Buehlmann M, Fankhauser H, Laffer R, Bregenzer T, Widmer AF. The inguinal skin: An important site of colonization with extended-spectrum beta-lactamase-producing *Enterobacteriaceae*. Infect Control Hosp Epidemiol **2010**; 31:427–8.
45. Zuckerman T, Benyamini N, Sprecher H, et al. SCT in patients with carbapenem resistant *Klebsiella pneumoniae*: A single center experience with oral gentamicin for the eradication of carrier state. Bone Marrow Transplant **2010**. first published online 8 November, 2010; doi:10.1038/bmt.2010.279.
46. Siegel JD, Rhinehart E, Jackson M, Chiarello L, and Healthcare Infection Control Practices Advisory Committee. Management of multidrug-resistant organisms in health care settings, 2006. Am J Infect Control **2007**; 35:S165–93.
47. Pakyz AL, Oinonen M, Polk RE. Relationship of carbapenem restriction in 22 university teaching hospitals to carbapenem use and carbapenem-resistant *Pseudomonas aeruginosa*. Antimicrob Agents Chemother **2009**; 53:1983–6.
48. Gould CV, Umscheid CA, Agarwal RK, Kuntz G, Pegues, DA, and Healthcare Infection Control Practices Advisory Committee Guideline for prevention of catheter-associated urinary tract infections 2009. Infect Control Hosp Epidemiol **2010**; 31:319–26.