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SUPPLEMENT ARTICLE

# The Epidemiology of Carbapenem-Resistant Enterobacteriaceae: The Impact and Evolution of a Global Menace

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Carbapenem-resistant Enterobacteriaceae (CRE) are a serious public health threat. Infections due to these organisms are associated with significant morbidity and mortality. Mechanisms of drug resistance in gram-negative bacteria (GNB) are numerous; β-lactamase genes carried on mobile genetic elements are a key mechanism for the rapid spread of antibiotic-resistant GNB worldwide. Transmissible carbapenem-resistance in Enterobacteriaceae has been recognized for the last 2 decades, but global dissemination of carbapenemase-producing Enterobacteriaceae (CPE) is a more recent problem that, once initiated, has been occurring at an alarming pace. In this article, we discuss the evolution of CRE, with a focus on the epidemiology of the CPE pandemic; review risk factors for colonization and infection with the most common transmissible CPE worldwide, *Klebsiella pneumoniae* carbapenemase–producing *K. pneumoniae*; and present strategies used to halt the striking spread of these deadly pathogens.

**Keywords.** epidemiology; gram-negative bacteria; Enterobacteriaceae infections; carbapenemases; drug resistance; antibacterial agents; carbapenems; adult; child; global health.

The prevalence of multidrug-resistant organisms (MDROs), a major public health threat, continues to increase on a global level and is associated with significant morbidity and mortality. Historically, MDROs have affected patients in hospital settings, where exposure to antibiotics, frequent and/or long-term hospitalization, use of in-dwelling devices, and host factors provide risks for acquisition [1, 2]. However, the distinction between multidrug-resistant healthcare-acquired and community-onset bacterial infections has become blurred over the last 2 decades, with an explosion in antibiotic resistance genes located on mobile genetic elements (MGEs) capable of efficient spread between bacteria and hosts in and out of hospitals [3].

These trends are highlighted in Enterobacteriaceae, a family of gram-negative bacteria (GNB) responsible for a variety of community and healthcare-acquired infections. In GNB, the major driving force of resistance is the presence of β-lactamases (encoded by *bla*), a rapidly expanding list of β-lactam–hydrolyzing enzymes for which the number of unique protein sequences as currently cataloged has surpassed 2100 [4]. Many of these organisms carry additional plasmid-borne genes active against other classes of antibiotics, rendering bacteria resistant to multiple drugs [5, 6].

There is a dearth of drugs capable of treating MDR GNB infections [7]. As carbapenem-resistant Enterobacteriaceae (CRE) have become increasingly prevalent worldwide, carbapenems, long a last line of defense, more and more are challenged by MGEs harboring carbapenemases and other drug resistance genes [8]. As the molecular mechanisms of resistance continue to evolve, the epidemiology of CRE is changing, and growing numbers of people worldwide are being affected by these dangerous organisms.

## MOLECULAR MECHANISMS OF CARBAPENEM RESISTANCE IN ENTEROBACTERIACEAE

Phenotypic resistance to carbapenems is typically caused by 2 main mechanisms: (1) β-lactamase activity combined with structural mutations and (2) production of carbapenemases, enzymes that hydrolyze carbapenem antibiotics (Table 1) [6, 9]. The former mechanism includes extended-spectrum β-lactamases (ESBLs), which are generally encoded by plasmids, and AmpC cephalosporinases (AmpC), for which expression in Enterobacteriaceae is most often associated with hyperproduction of enzymes from inducible or derepressed chromosomal genes [6]. ESBLs and AmpC are capable of conferring carbapenem resistance when combined with the mutation of porins, a family of proteins of the outer membrane of GNB that, when altered or lost, can retard diffusion of antibiotics across the bacterial membrane to a rate slow enough to facilitate the action of ESBL and AmpC enzymes [9, 17, 18]. Other mechanisms associated with carbapenem-resistance in GNB include drug efflux pumps and alterations in penicillin-binding proteins [8].

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**Table 1. Characteristics of Common Acquired Carbapenem-Hydrolyzing β-Lactamases in Enterobacteriaceae**

| Ambler Structural Class | Functional Class[a] | Active Site[b] | Inhibitor(s) | Notable Gene[c] | Mobile Genetic Elements[d] | Multilocus STs[e] | Retained β-Lactam Susceptibility[f] |
|---|---|---|---|---|---|---|---|
| A | 2f | Serine | Commercially available β-lactamase inhibitors | KPC | IncFIIK$_2$, IncF1A, IncI2, multiple types; Tn*4401*[g] | CC258 (ST258) dominant,[h] others | Carbapenems (low-to-high–level hydrolysis) |
| | | | | GES | Class I integrons[i] | . . . | Carbapenems (low-level hydrolysis) |
| B | 3 | Zinc | Metal-chelating agents (eg, EDTA) | VIM | IncN, IncI1, multiple types; class I integrons | ST147, ST11, others | Monobactams spared |
| | | | | IMP | IncL/M, IncA/C, multiple types; class I integrons | . . . | |
| | | | | NDM | IncA/C, multiple; IS*Aba125* | ST101, ST11, several others | |
| D | 2d | Serine | NaCl (in vitro) | OXA-48 | IncL/M, Tn*1999*, IS*1999* | ST147, ST11, ST101, ST405, ST395, others | PCN (high-level hydrolysis), carbapenems (low-level hydrolysis), extended-spectrum cephalosporins spared |
| | | | | OXA-181 | ColE plasmids, Tn*2013*, IS*Ecp1* | . . . | |

Data are adapted from [8–16].

Abbreviations: CG, clonal group; EDTA, ethylenediaminetetraacetic acid; GES, Guiana extended spectrum; IMP, active on imipenem; Inc, plasmid incompatibility type; IS, insertion sequence; KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase-type carbapenem-hydrolyzing β-lactamase; PCN, penicillin; ST, sequence type; VIM, Verona integron-encoded metallo-β-lactamase.

[a] Bush-Jacoby-Medeiros functional classification scheme.

[b] Hydrolytic mechanism. Class B carbapenem-hydrolyzing β-lactamases represent metallo-β-lactamases, and class D represent oxacillinases.

[c] The most common acquired genes are included and may vary by region. Only certain variants harbor carbapenemase genes (ie, GES-5). Several other genes exist in each class.

[d] The most common mobile genetic elements are included and may vary by region.

[e] Only *Klebsiella pneumoniae*– and *Escherichia coli*–associated STs are listed.

[f] The phenotypic profile may vary depending on the genetic variant type and/or if multiple β-lactamase genes are present in an isolate.

[g] Tn*4401* is a Tn*3*-based transposon and is associated with multiple plasmid types. Tn*1999* is associated with IncL/M plasmids.

[h] CC258 contains 43 STs, including the ST258 pandemic strains (2 major clades exist). Several non-CC258 strains (eg, ST147, ST442, and ST14) harbor *bla*$_{KPC}$.

[i] These are often embedded in conjugative plasmids and/or transposons, facilitating horizontal transfer.

Carbapenemases are classified by their molecular structures and belong to 3 classes of β-lactamases: class A, B, and D of the Ambler classification system [6, 10]. Class A and D carbapenemases require serine at their active site, while class B, the metallo-β-lactamases (MBLs) require zinc for β-lactam hydrolysis [6]. Notable class A carbapenemase genes include *Klebsiella pneumoniae* carbapenemases (KPCs), Guiana extended spectrum (GES), imipenem resistant (IMI), non–metallo-carbapenemase-A (NMC-A), *Serratia marcescens* enzyme (SME), and *Serratia fonticola* carbapenemase (SFC), of which the KPCs are the most common transmissible class A genes circulating in Enterobacteriaceae worldwide [8]. KPCs are capable of hydrolyzing all β-lactams, and strains harboring *bla*$_{KPC}$ often have acquired resistance to fluoroquinolones, aminoglycosides, and trimethoprim-sulfamethoxazole, creating MDROs [19].

The international spread of KPC-producing Enterobacteriaceae is primarily due to clonal expansion of strains of *K. pneumoniae* belonging to clonal complex 258 (CC258) and, more specifically, to multilocus sequence type (ST) 258 strains harboring a *bla*$_{KPC-2}$ or *bla*$_{KPC-3}$ gene located on a Tn*3*-based transposon, Tn*4401* [20, 21]. However, the propagation of *bla*$_{KPC}$ is much more complex. Circulating ST258 *K. pneumoniae* strains comprise 2 distinct genetic clades (I and II), and several additional sequence types have been found to carry *bla*$_{KPC}$, which is associated with a variety of plasmids [8, 11, 22]. Additionally, KPC-producing strains have low to high level carbapenem resistance with corresponding minimum inhibitory concentrations ranging from susceptible to >16 μg/mL, related to increased *bla*$_{KPC}$ gene copy number, deletions directly upstream of the *bla*$_{KPC}$ gene, and/or outer membrane porin losses (OmpK35 and/or OmpK36) [8, 23].

The class D OXA β-lactamases, named somewhat ironically for their oxacillin-hydrolyzing capabilities, are a diverse and heterogeneous group of enzymes found in *Acinetobacter* species and, increasingly, especially the OXA-48 variants, in Enterobacteriaceae [24, 25]. The backbone most commonly associated with the spread of OXA-48–producing Enterobacteriaceae is an IncL/M-type plasmid with integration of the bla$_{OXA-48}$ gene through the acquisition of a Tn1999 composite transposon [12, 24–26]. OXA-48 enzymes hydrolyze penicillins at a high level and carbapenems at a low level, while sparing extended-spectrum cephalosporins; however, strains may express multiple ESBLs, rendering them resistant to all β-lactams [12].

The class B MBLs are a complex group of enzymes that hydrolyze all β-lactams, save monobactams, and are not inhibited by commercially available β-lactamase inhibitors [6, 8]. They

differ from the serine carbapenemases in the requirement of zinc for β-lactam hydrolysis; thus, their activity is inhibited by metal-chelating agents such as ethylenediaminetetraacetic acid (EDTA) [6, 8]. Notable transmissible MBL genes in Enterobacteriaceae include IMP (active on imipenem), VIM (Verona integron-encoded MBL), and NDM (New Delhi MBL) [6, 8, 27]. There are 3 MBL subclasses (B1–B3), which differ by amino acid sequence homology; almost all clinically important, acquired MBLs belong to subclass B1 [8, 28]. VIM-type and IMP-type MBLs are most commonly embedded in class I integrons and are associated with transposons or plasmids, which facilitate spread.

Although the rapid dissemination of NDM-producing Enterobacteriaceae resembles that of KPC-producing Enterobacteriaceae, the spread of NDM-type MBLs does not appear to be associated with dominate clonal strains and is mediated by several different plasmid incompatibility (*Inc*) types. The current theory is that the most common circulating NDM MBL gene in Enterobacteriaceae ($bla_{\text{NDM-1}}$) evolved from *Acinetobacter baumannii*. This view is based on the complete or variant insertion sequence IS*Aba*125 upstream of the $bla_{\text{NDM-1}}$ gene in both $bla_{\text{NDM}}$-harboring *A. baumannii* and Enterobacteriaceae and the similar coexpression in both genera of $bla_{\text{NDM}}$ with $ble_{\text{MBL}}$, a gene responsible for resistance to the cancer drug bleomycin [29, 30]. NDM-type MBL genes have been found in several epidemic clones, including *K. pneumoniae* ST11 and ST147 and *Escherichia coli* ST131 and ST101, which are known to harbor other β-lactamase genes and antibiotic resistance determinants [8, 27, 30]. It is thought that the rapid and dramatic spread of NDM MBLs is facilitated by the genetic elements' bacterial promiscuity.

The differentiation between carbapenemase-producing (CP) CRE and non-CP CRE is important epidemiologically and clinically; however, providers need mainly susceptibility patterns and treatment recommendations for patient care. The Centers for Disease Control and Prevention (CDC) has provided updated definitions that can help direct definitions and testing considerations in the diagnosis and management of CRE [31].

## THE GLOBAL DISTRIBUTION AND PREVALENCE OF THE MOST COMMON TRANSMISSIBLE CARBAPENEMASE GENES IN ENTEROBACTERIACEAE, BY REGION

Figure 1 represents a global map that highlights the dramatic worldwide dissemination of carbapenemase genes in Enterobacteriaceae, by country and region. While the first identification of chromosomally based carbapenemase genes was in gram-positive bacilli, by the mid-to-late 1980s, "metalloenzymes," now referred to as MBLs, were recognized in gram-negative non–lactose-fermenting bacteria [13]. This was followed shortly by description of another set of carbapenem-hydrolyzing enzymes (using serine at their active site) in Enterobacteriaceae [13]. This landscape radically changed in the early 1990s, when plasmid carriage of these originally chromosomally based, species-specific enzymes was recognized in multiple species found in clinical isolates [8, 13]. To date, the most common species of Enterobacteriaceae harboring transmissible carbapenemase genes are *K. pneumoniae*.

### The MBLs

The first major description of a transmissible carbapenemase gene in a clinical Enterobacteriaceae isolate occurred >2 decades ago when a gene, subsequently named IMP-1 MBL, was discovered on an integron in *Serratia marcescens* in Okazaki, Japan, associated with a plasmid-mediated outbreak in 7 Japanese hospitals. Widespread dissemination of $bla_{\text{IMP-1}}$-harboring Enterobacteriaceae throughout Japan followed [41]. At present, there have been at least 52 variants of IMP genes identified in multiple species with worldwide distribution; however, to date, IMP-type MBL-containing Enterobacteriaceae are endemic only in Japan and Taiwan [32]. For example, a Taiwanese study from a 900-bed hospital in Southern Taiwan in 2002 assessed 9082 clinical Enterobacteriaceae isolates (other than *Klebsiella* species) for MBL genes and found that 29 of 1261 *Enterobacter cloacae* isolates (2.9%) harbored $bla_{\text{IMP-8}}$, a variant of $bla_{\text{IMP-2}}$ [42]. Descriptions of IMP MBLs in other countries are mostly of sporadic outbreaks or single reports [8, 9, 32].

The VIM-type MBLs were described in 1996 and 1997 in *P. aeruginosa* from Verona, Italy (VIM-1), and Marseilles, France (VIM-2) [43, 44]. By the late 1990s to early 2000s, there were several reports of VIM-type MBLs in Enterobacteriaceae [13]. Currently, VIM-2 is the most common VIM-type MBL worldwide, with at least 46 $bla_{\text{VIM}}$ variants now cataloged [45]. The epicenter of VIM-type Enterobacteriaceae is Greece, where *K. pneumoniae* and *E. coli* containing $bla_{\text{VIM-1}}$ predominate [46]. A study in the intensive care units (ICUs) of 3 teaching hospitals in Athens, Greece, in 2002 recovered 17 *K. pneumoniae* isolates harboring $bla_{\text{VIM-1}}$ over a 3-month period; at least 12 isolates were clinically relevant [47]. Since that time, several other VIM types have been recovered from gram-negative bacilli in Greece; globally, the majority of regions have reported outbreaks with VIM-producing Enterobacteriaceae [32, 33, 46, 47].

Attention to the epidemic of MBL-producing Enterobacteriaceae increased dramatically in 2008 with the discovery of an ST14 *K. pneumoniae* with a new MBL gene, $bla_{\text{NDM-1}}$, from a Swedish patient who received healthcare in New Delhi, India [48]. Since then, there has been global dissemination of NDM MBLs with rapid gene transfer between species. In regions of endemicity, such as the Indian subcontinent, NDM-type MBLs predominate over other carbapenemases. In most other regions (except the Middle East and Balkan countries), NDM-type MBLs are described mostly as sporadic occurrences [30]. There are currently 16 cataloged variants of NDM-type MBLs, $bla_{\text{NDM-1}}$ to $bla_{\text{NDM-16}}$ [49].

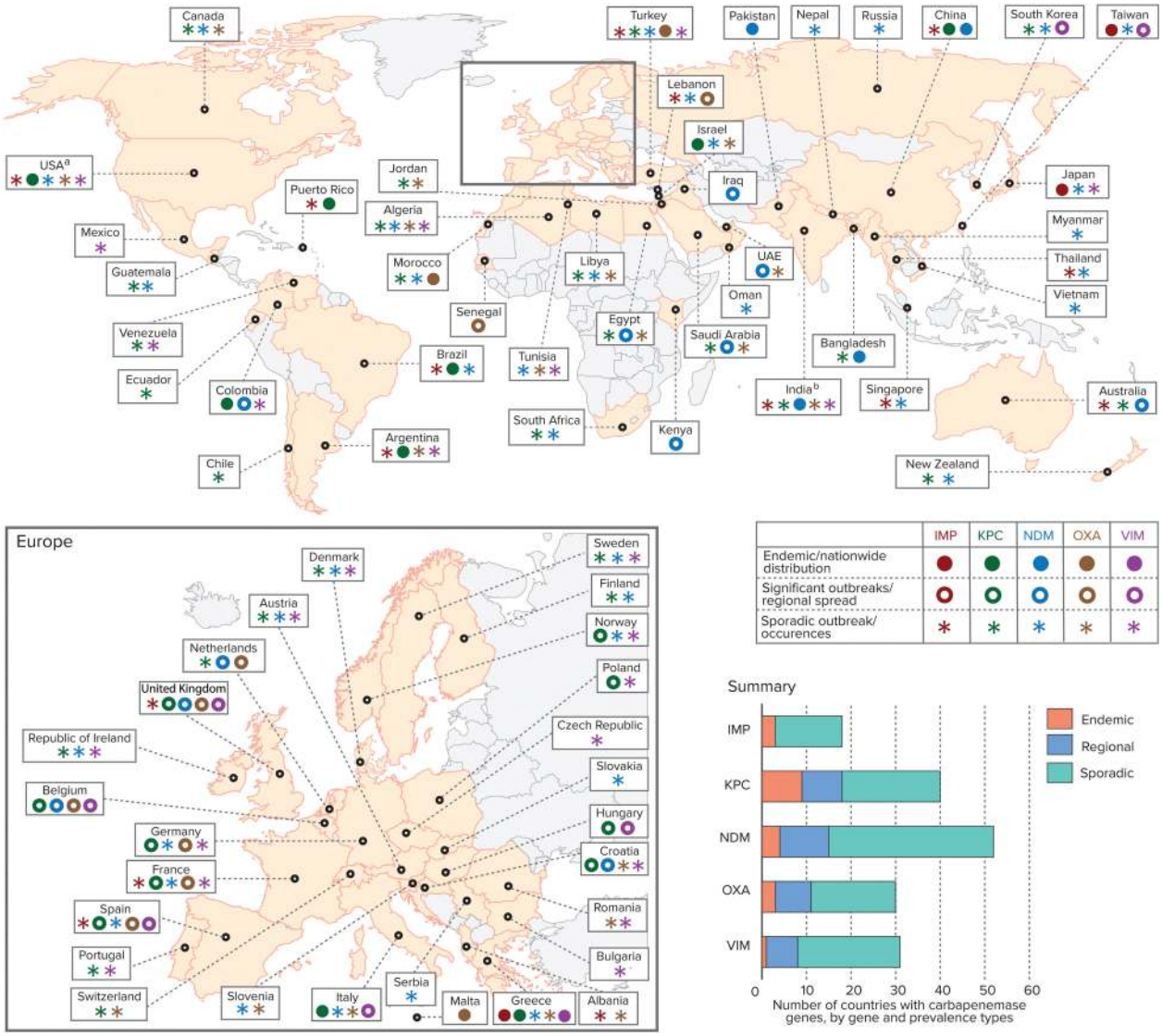


**Figure 1.** Global distribution of carbapenemases in Enterobacteriaceae, by country and region. Data are adapted from [8, 12, 13, 15, 25, 32–40]. [a]KPCs are endemic in some US states; [b]OXA mainly refers to OXA-48, except in India, where it refers to OXA-181. Abbreviations: IMP, active on imipenem metallo-β-lactamase; KPC, *Klebsiella pneumoniae* carbapenemase; NDM, New Delhi metallo-β-lactamase; OXA, oxacillinase-type carbapenem-hydrolyzing β-lactamase; VIM, Verona integron-encoded metallo-β-lactamase.

Increasing colonization rates with $bla_{NDM}$-producing bacteria have been noted in patients in several Indian and Pakistani hospitals, where reported prevalence rates of carriage of $bla_{NDM}$-producing bacteria in ICUs range from 2% to 13.5% [50–53]. Additionally, data from the SENTRY Antimicrobial Surveillance Program (SENTRY) suggest that $bla_{NDM}$ may have been circulating in bacteria in India as early as 2006 [54]. In the Study for Monitoring Antimicrobial Resistance Trends 2009 program, of the 235 isolates tested from India, 66 (28%) carried ≥1 carbapenemase gene; the most common gene carried—in 50% of these isolates—was $bla_{NDM-1}$ [55]. An additional concern particular to the NDM-type MBLs is spread via environmental sources in community settings in lower-income countries. A point-prevalence survey of public tap water and seepage water in India in 2011 found that a striking 4% of drinking water samples and 30% of seepage samples contained $bla_{NDM-1}$-positive bacteria [56].

### The Class D OXA Carbapenem-Hydrolyzing β-Lactamases

The worldwide spread of OXA-type carbapenemases is mainly attributed to the success of OXA-48–producing clones and, to a lesser extent, OXA-181 in certain regions (eg, the Indian subcontinent) [24, 26, 32]. The $bla_{OXA-48}$ element was discovered in Turkey in 2001 in *K. pneumoniae*, and since then OXA-producing bacteria have become endemic in that country [57]. Several countries have reported outbreaks with OXA-producing Enterobacteriaceae, but few countries report endemicity. Because of the variable susceptibility profiles of

OXA—heterogeneity of hydrolysis of carbapenems, broad-spectrum cephalosporins, and aztreonam and lack of inhibition by EDTA or clavulanic acid—the prevalence of these enzymes may be underestimated [24, 32].

### The Class A KPCs

The global rise of KPC-producing Enterobacteriaceae remains one of the most successful MDRO pandemics in the history of GNB. A major focus of the propagation and persistence of KPC-harboring Enterobacteriaceae is the successful ST258 lineage, MDR strains of *K. pneumoniae* that are endemic in an increasing number of countries and are responsible for many major outbreaks worldwide [8, 34].

## KPC-ENDEMIC REGIONS

### Greece

Greece has experienced some of the highest carbapenem resistance rates among GNB globally. Prior to 2001, the Greek System for the Surveillance of Antimicrobial Resistance reported carbapenem resistance prevalence of <1%; this increased to 30% in hospital wards and to 60% in ICUs by 2008 [58]. Data from the European Centre for Disease Prevention and Control EARS-Net revealed that, in 2014, of 1088 Greek *K. pneumoniae* isolates, 678 (62.3%) were resistant to carbapenems [35]. Before 2006, the predominant carbapenemase genes in Enterobacteriaceae recovered in Greece were VIM-1–type MBLs. This changed after the introduction and rapid dissemination of $bla_{\text{KPC-2}}$-producing *K. pneumoniae* isolates throughout the country in 2007; by the end of 2008, a surveillance study of 21 hospitals found $bla_{\text{KPC-2}}$-producing *K. pneumoniae* in 18 hospitals across Crete, Thessaloniki, and Athens, with 96% of isolates a single pulsotype and the ST258 lineage [59]. More-recent surveys confirm the ongoing dominance of ST258 *K. pneumoniae* strains; however, several other ST types harboring $bla_{\text{KPC}}$ are circulating among the almost 40% of *K. pneumoniae* currently harboring $bla_{\text{KPC}}$ in Greece [34, 36].

### Israel

Israel was the second country (after the United States) to report outbreaks of infection due to KPC-producing *K. pneumoniae*. A study of carbapenem-resistant *K. pneumoniae* in Tel-Aviv during 2004–2006 disclosed epidemic $bla_{\text{KPC-2}}$- or $bla_{\text{KPC-3}}$-carrying strains. The peak of the outbreak occurred in 2007, with 55.5 incident nosocomial cases of carbapenem-resistant *K. pneumoniae* infection per month per 100 000 patient-days [60, 61]. A nationally implemented intervention, employed in 2007–2008, resulted in a decrease in the monthly incidence to 11.7 cases per 100 000 patient-days [61].

Two cross-sectional, point-prevalence national surveys of CP Enterobacteriaceae (CPE) in post-acute-care Israeli hospitals in 2008 and 2013 (before and after the intervention) showed a significant decrease in the overall prevalence of carbapenem resistance among Enterobacteriaceae isolates (184 of 1147 isolates [16%] and 127 of 1287 isolates [9.9%], respectively). Notably, in 2008, all CPE surveyed were KPC-containing *K. pneumoniae*, while during the 2013 survey, additional carbapenemase genes were found (including $bla_{\text{NDM}}$ and $bla_{\text{OXA}}$). However, KPC-carrying *K. pneumoniae* persisted as the predominant CPE, with an increasing proportion of ST258 *K. pneumoniae* strains (120 of 184 [65%] in 2008 vs 91 of 113 [80%] in 2013) [37].

### Latin America

KPC-producing bacteria disseminated throughout Colombia in the late 2000s after the discovery of *K. pneumoniae* harboring $bla_{\text{KPC-2}}$ in 2005 in patients with no travel history, followed by an outbreak of infection due to *K. pneumoniae* carrying $bla_{\text{KPC-3}}$, which was traced to an index patient who had travelled recently to Israel [62–64]. In 2006, Colombia was the first country to report a KPC-producing *Pseudomonas aeruginosa* [65]. Since that time, other countries, including Argentina, Chile, and Mexico, have reported the introduction of KPC-producing Enterobacteriaceae; the highest prevalence of $bla_{\text{KPC}}$-positive bacteria outside of Colombia is in Brazil, with dissemination throughout the country and reports of KPC-producing isolates in all states [64]. The spread in Brazil has been associated mostly with CC258 *K. pneumoniae*, including ST258, ST11, and ST437; these strains harbor a $bla_{\text{KPC-2}}$ gene associated with Tn*4401b* and multiple plasmid (IncFII, IncL/M, and IncN) types [66–68]. Of 70 CRE submitted to SENTRY from Latin hospitals in 2010, 56 strains contained $bla_{\text{KPC-2}}$; 44 (78.6%) were from Brazil, and among 19 Brazilian *K. pneumoniae* strains tested, 17 (89.5%) were grouped within CC258 [38].

### United States

The first KPC-producing *K. pneumoniae* was discovered in a patient in a North Carolina hospital in 1996 [69]. By 2001, there was an explosion of reports in northeastern United States (with a focus in New York) of KPC-producing bacteria in hospitalized patients [34, 70]. In 2006, the Meropenem Yearly Susceptibility Test Information Collection surveillance program described 57 isolates, with 9.5% of the collection characterized as clonal $bla_{\text{KPC}}$-producing *Klebsiella* strains, representing a 2-fold increase from the prior year; most isolates were from states in the Mid-Atlantic US Census division, and hospital prevalence rates ranged from 2.4% in Ohio to 50.8% in New York [71, 72].

A nationwide survey by SENTRY in 2007–2009 studied 42 medical centers for CP *K. pneumoniae* and found an overall $bla_{\text{KPC}}$-positive bacteria prevalence of 5.5%, with significant regional increases in KPC genes detected in *K. pneumoniae* over the period in the Mid-Atlantic (28.6% overall and 33% in 2009) and East North Central (2.4% overall, 3.8% in 2009) US Census divisions [73]. The expansion of KPC-producing bacteria across the United States is clearly evident; the same surveillance program reported that, by 2010, 28 of 195 Enterobacteriaceae isolates (14.4%) surveyed from 26 US medical centers harbored $bla_{\text{KPC-2}}$ or $bla_{\text{KPC-3}}$; 9 of the 28 were found in Texas [74].

Most recently, a population- and laboratory-based active surveillance study of 7 US metropolitan areas during 2012–2013 found an overall annual CRE incidence of 2.93 cases per 100 000 population; of 188 CRE isolates tested, 90 (47.3%) were identified as CPE, all of which were found to contain $bla_{KPC}$ [75]. As of April 2016, the CDC reported that KPC-producing bacteria have been identified in 48 states, the District of Columbia, and Puerto Rico; however, the endemicity of KPC-producing bacteria within the United States is still focused in regional hot spots [34, 76].

In children, there have been notable increases in CRE prevalence, although few genotypic data are available [14]. A recent study of CRE prevalence in US children, using antimicrobial susceptibility data for Enterobacteriaceae reported to 300 laboratories participating in the Surveillance Network–USA database during January 1999–July 2012, found an overall low pediatric prevalence of CRE (266 of 316 253 isolates [0.08%]); however, there was a significant increase in CRE detected in children over the study period (from 0% in 1999–2000 to 0.47% in 2011–2012) [77]. The highest increases were seen in *Enterobacter* species, blood culture isolates, and isolates from patients in the ICU (0.0% in 1999–2000 and 5.2%, 4.5%, and 3.2%, respectively, in 2011–2012). While the increases in *Enterobacter* species may be related to nosocomial ecology and not reflect true carbapenemase production, there were also significant increases in CR *E. coli* and *K. pneumoniae* (both 0% in 1999–2000 and 0.14% and 1.7%, respectively, in 2011–2012), which more likely represent CPE [77]. Colonization and infection with KPC and MBL-producing Enterobacteriaceae are being reported increasingly across the United States in pediatric settings [14, 78–82].

## CLINICAL EPIDEMIOLOGY OF KPC-PRODUCING ENTEROBACTERIACEAE IN THE UNITED STATES

KPC-producing bacteria in the United States, unlike NDM-type and CTX-M–producing Enterobacteriaceae, generally have not emerged as community pathogens. The majority of CRE infections are mainly a problem for inpatient facilities. CRE infections are associated with mortality rates as high as 40%–50%, and these organisms continue to increase in prevalence in national reports [83, 84]. Because most KPCs (and other carbapenemases) are found in *K. pneumoniae*, the majority of studies assessing factors associated with CRE have been specific to CR *K. pneumoniae* or KPC-producing *K. pneumoniae*. These associations have varied, likely because of differences in study venues and design; risk factors for colonization and/or infection in adults that have been identified in multiple studies include critical illness, comorbid conditions, prolonged hospitalization, multiple invasive medical devices, poor functional status, mechanical ventilation, and receipt of certain antibiotic classes [34, 85–87]. Less is known about the epidemiology of KPC-producing Enterobacteriaceae infections in children; however, similar factors have generally been implicated [14, 82, 88–90].

One important risk for CRE colonization appears to be residence in long-term acute care hospitals (LTACHs), mediated in part by interfacility spread at the time of patient transfers [91]. A point-prevalence study performed in Chicago, Illinois, found that 30.4% of patients (119 of 391) in 7 LTACHs were colonized with KPC-producing Enterobacteriaceae, compared with 3.3% of ICU patients (30 of 910) in 24 short-stay hospitals (prevalence ratio, 9.2; 95% confidence interval, 6.3–13.5) [92]. A recently published case-control study of LTACH patients found that independent factors associated with CRE colonization and infection in this setting included solid organ and stem cell transplantation, mechanical ventilation, fecal incontinence, and exposure in the prior 30 days to carbapenems, vancomycin, and metronidazole [93].

## CONTROLLING THE SPREAD OF CRE IN HEALTHCARE SETTINGS

Interventions to curtail the spread of CRE in healthcare facilities most often have involved bundled infection control measures; so, the success of one individual measure cannot simply be compared directly to another. However, successful solutions based on multiple studies include using patient cohorts, contact isolation, and dedicated staffs; daily bathing of all patients with chlorhexidine; educating and training staff; limiting use of invasive devices; shortening the duration of mechanical ventilation; improving hand hygiene rates and antimicrobial stewardship; and, in some studies, enhancing environmental cleaning [84, 85, 94].

In high-prevalence areas, regional surveillance can be extremely useful when paired with the sharing of patient information among facilities; a strategy recommended by the CDC is to "detect and protect" through early identification of patients infected with CRE, followed by prevention of transmission through implementation of infection control precautions [95]. An example of this is the statewide registry of extensively drug-resistant organisms in Illinois, an interactive public health informatics tool that provides a mechanism for standardized reporting of CRE-carrier patients from all healthcare facilities throughout the state. This unique partnership of public health, academia, and non-profit organizations aids in decreasing spread of CRE through communication, which allows for early detection and intervention by receiving facilities [96].

Potential interventions in US facilities where CRE rates are still low include screening high-risk patients for CRE carriage on admission, such as patients transferred from long-term care facilities; while awaiting screening results, hospitals may use preemptive contact precautions for such admissions, especially if rates are high in referring facilities.

## LOOMING THREATS

In November 2015, Liu et al reported a new public health threat, transmissible polymyxin resistance in Enterobacteriaceae

associated with the plasmid-mediated colistin resistance gene, *mcr-1*, a member of the phosphoethanolamine transferase enzyme family [97]. *E. coli* and *K. pneumoniae* that harbored *mcr-1* were found in contaminated retail meat and in colonized food animals and inpatients in 5 Chinese provinces [97]. Shortly after recognition of the threat of plasmid-mediated polymixin resistance, a clinical isolate from a Swiss patient, with no travel history, was discovered to coharbor plasmid-mediated $bla_{\text{MCR-1}}$ and MBL ($bla_{\text{VIM-1}}$) genes [98]. As of March 2016, at least 17 countries had identified *mcr-1* in gram-negative organisms in food, animals, and/or humans; several reports have documented isolates coharboring carbapenemase and/or ESBL genes with *mcr-1*; and studies have suggested a link between this unwelcome emergence and the broad agricultural and veterinary use of polymyxins [98–100].

## CONCLUSIONS

CRE continue to evolve, posing an increasing threat to patients of all ages. Mechanisms of carbapenem resistance are variable, and the breadth of MGEs in Enterobacteriaceae—carbapenemase genes and other antibiotic resistance mechanisms and virulence determinants—continues to expand. Early recognition of this global public health threat through molecular characterization, epidemiologic studies, and surveillance may allow for timely approaches in prevention. Bundled infection control measures, education and training, and interventions aimed at healthcare-associated risk factors for colonization and/or infection, as well as proactive assessment of emerging community reservoirs, may help thwart the rapid dissemination of these truly menacing pathogens.

### Notes

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