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REVIEW

Epidemiology of β-Lactamase-Producing Pathogens

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SUMMARY β-Lactam antibiotics have been widely used as therapeutic agents for the past 70 years, resulting in emergence of an abundance of β-lactam-inactivating β-lactamases. Although penicillinases in *Staphylococcus aureus* challenged the initial uses of penicillin, β-lactamases are most important in Gram-negative bacteria, particularly in enteric and nonfermentative pathogens, where collectively they confer re-

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sistance to all β-lactam-containing antibiotics. Critical β-lactamases are those enzymes whose genes are encoded on mobile elements that are transferable among species. Major β-lactamase families include plasmid-mediated extended-spectrum β-lactamases (ESBLs), AmpC cephalosporinases, and carbapenemases now appearing globally, with geographic preferences for specific variants. CTX-M enzymes include the most common ESBLs that are prevalent in all areas of the world. In contrast, KPC serine carbapenemases are present more frequently in the Americas, the Mediterranean countries, and China, whereas NDM metallo-β-lactamases are more prevalent in the Indian subcontinent and Eastern Europe. As selective pressure from β-lactam use continues, multiple β-lactamases per organism are increasingly common, including pathogens carrying three different carbapenemase genes. These organisms may be spread throughout health care facilities as well as in the community, warranting close attention to increased infection control measures and stewardship of the β-lactam-containing drugs in an effort to control selection of even more deleterious pathogens.

KEYWORDS ESBL, beta-lactamase, carbapenemase, epidemiology, resistance

INTRODUCTION

Antibiotics, specifically those in the β-lactam class, are essential to the practice of medicine in the 21st century, where almost two-thirds of recent hospital prescriptions include these agents (1). The most common β-lactam-containing agents belong to four major chemical classes, penicillins, cephalosporins, carbapenems, and monobactams (Fig. 1). Because these agents are so valuable, the medical community is quite alarmed that resistance to these drugs continues to increase in all parts of the world (1–4). Although resistance patterns may be geographically distinct, the threat remains that any new resistance mechanism may spread rapidly to other areas. For example, the gene encoding the New Delhi metallo-β-lactamase-1 (bla_{NDM-1}), leading to resistance to most β-lactam antibiotics (5), was identified as early as 2006, with its occurrence initially confined to the Indian subcontinent (5–7). However, the gene became globally disseminated in fewer than 5 years of the first known occurrence, due in part to the travel of infected or colonized individuals to Europe, the Middle East, and North America (8). Thus, it is important to monitor resistance as a function of time and location, with the goal of containment of emerging resistance determinants to restricted geographical settings.

Much of the resistance to β-lactams is due to the enzymes that inactivate these molecules, i.e., the β-lactamases, which are discussed in greater detail in this review (9). Both the Centers for Disease Control and Prevention, or CDC (10), and the World Health Organization, or WHO (11), have designated β-lactamase-producing Gram-negative bacteria some of the world's most serious or critical threats. Pharmaceutical efforts to contain or subvert these enzymes by designing new molecules with expanded clinical applications have resulted in scientific, and some clinical, success. In the past decade, six new β-lactam-containing agents have been approved by the FDA: ceftaroline, ceftolozane-tazobactam, ceftazidime-avibactam, meropenem-vaborbactam, imipenem-cilastatin-relebactam, and cefiderocol (12, 13) (https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-complicated-urinary-tract-and-complicated-intra-abdominal-infections); four of these are β-lactam antibiotics paired with a β-lactamase-inhibitor to deter a β-lactamase from inactivating the antibiotic (13).

Although several recent reviews have described the almost 3,000 unique, naturally occurring β-lactamases in various epidemiological contexts (9, 13–20), this review contains updated information about the global prevalence of the most prominent of these enzymes. The kinds of organisms that produce β-lactamases include environmental bacteria, such as the *Bacillus* spp., but the role of these enzymes in clinical medicine is more relevant and far-reaching. Once thought to be primarily a concern in hospital-acquired infections, β-lactamases are now found in many community settings in patients of all ages. Colonization with β-lactamase-producing pathogens is found not only in hospitals but also in health care centers, as well as in the general population.

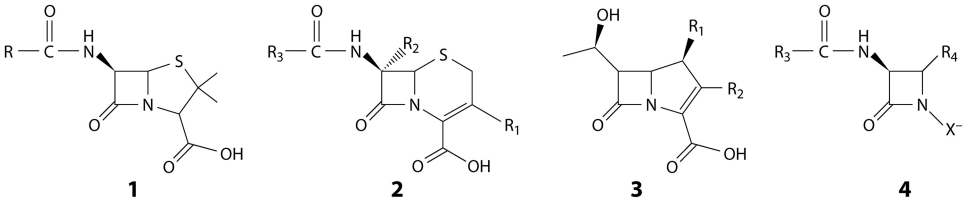

FIG 1 Generic structures of β-lactams most important in clinical medicine. Structures include penicillin (1), cephalosporin (2), carbapenem (3), and monobactam (4).

Some specific β-lactamases, such as the plasmid-encoded TEM-, SHV-, and OXA-type enzymes, are ubiquitous, even in contemporary isolates (21). However, other enzymes have been identified only in one specific niche with little or no dissemination, such as the SPM-1 metallo-β-lactamase (MBL), which has not been identified outside Brazil, with the exception of a Swiss patient hospitalized initially in Brazil (22). It is important to note the sources and dissemination of the most prominent, and the most deleterious, β-lactamases in order to guide the most effective use of the β-lactam antibiotics in various geographical locations. In this review, the epidemiology of clinically relevant and widely dispersed β-lactamases is presented concerning present and past geographical and temporal differences of β-lactamase-producing human pathogens. Because of the breadth of the topic, only selected references have been cited, with an attempt to include more recent surveillance data when possible. Important trends and suggestions for the future are noted.

β-LACTAM RESISTANCE

Resistance to the β-lactams can be manifest via multiple mechanisms related to the mechanism of action of these agents (23). β-Lactams serve as surrogate substrates for critical bacterial cell wall-synthesizing proteins, known as penicillin-binding proteins, or PBPs, that are responsible for the cross-linking of cell wall fragments before cell division can occur (24). Although PBPs differ structurally among various species of bacteria, the mechanism of killing is identical, with acylation of an active-site serine in the transpeptidase domain of the PBP as the definitive characteristic of the inhibitory activity (25). As penicillins became an essential component of the hospital armamentarium, Gram-positive pathogens were the first bacteria to exhibit resistance in outbreak proportions. After the introduction of cephalosporins and penicillinase-resistant penicillins, Gram-negative bacteria with their more complex cell wall structure were more likely to develop novel resistance mechanisms. In both sets of organisms, PBP modifications, as well as production of the hydrolytic β-lactamases, especially those that rely on an active serine for catalysis, have played critical roles in the emergence of resistant pathogens. The relationship between mechanism of action and the β-lactamase-associated mechanism of resistance is exemplified in the representation of a Gram-negative bacterial cell in Fig. 2. In this illustration, the β-lactam can bind to a PBP anchored on the inner membrane of the cell to prevent cell growth and division, unless it is intercepted and inactivated by a β-lactamase in the periplasmic space. In both cases, the β-lactam reacts to form a reactive intermediate that may be hydrolyzed rapidly, as in the case of the β-lactamases, with half-lives measured in fractions of a second (26), or slowly, as for PBPs that remain catalytically nonfunctional for sufficient periods to facilitate bacterial cell death; e.g., the half-life for a penicillin-transpeptidase complex in *Streptomyces* spp. has been recorded as high as 900 min (27). As discussed below, other mechanisms may also be operative.

β-Lactamases

Several recent reviews have appeared describing the role of β-lactamases as the predominant β-lactam resistance determinant in Gram-negative bacteria (9, 13, 28, 29). Briefly, these enzymes eliminate the killing activity of β-lactams by binding the drug, breaking the amide bond of the four-membered azetidinone ring present in every

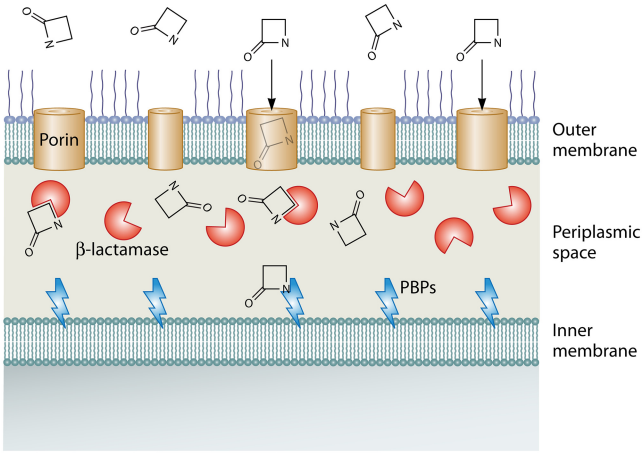

FIG 2 Schematic showing the interaction of β-lactam antibiotics with β-lactam interactive proteins in Gram-negative bacteria.

β-lactam (Fig. 1), and adding a water molecule to the ring-opened molecule. Distinct mechanisms exist for β-lactamases that utilize an active-site serine for hydrolysis and enzymes that require at least one divalent Zn atom for hydrolysis. The serine β-lactamases function by initially forming a covalent acylated enzyme, whereas in MBLs, formation of a noncovalent reactive complex with the β-lactam is facilitated by Zn^{2+}. Notably, the resulting product from both reactions is the identical microbiologically inactive molecule that is incapable of forming an enzymatically productive complex with a PBP. The result is continued survival of the bacterial cell. More detailed descriptions of the hydrolysis mechanisms for the two groups of enzymes have recently been reviewed (13, 30–32).

Nomenclature for β-lactamases is based on two major attributes of the physiologically important enzymes, i.e., structure and function. Structural classes were first defined by Ambler in 1980 (33), using the four β-lactamase amino acid sequences known at the time to describe class A enzymes, with a serine in the active site, and class B MBLs (33). Since then, class C and class D serine-based β-lactamases have been defined, based on molecular size and distinctive homologous motifs (34, 35). Modifications to the Ambler scheme were recently proposed by Philippon et al., who have suggested subclasses of class A β-lactamases (36). Functional classification schemes have been described for over 50 years based on biochemical attributes, such as substrate profiles, relative hydrolysis rates compared to that of reference β-lactams, and interactions with inhibitors (37). Updated functional nomenclature based on a combination of biochemical attributes and structural class assignments was proposed in 1995 by Bush et al. (38), with additional subgroups added in 2010 by Bush and Jacoby (39). Other functional names are widely used to describe β-lactamases that span more than one group or class. For example, carbapenemases, β-lactamases that are capable of hydrolyzing carbapenems at a rate that is clinically relevant, may belong to structural class A, B, or D, or they may belong to functional group 2df or 2f or group 3 (39). Extended-spectrum β-lactamases, or ESBLs, may include class A, C, or D enzymes, or they may be categorized as groups 1e, 2be, 2de, and 2e (39). A listing of the most important β-lactamases described in this review is shown in Table 1 together with the nomenclature used to describe these enzymes.

Non-β-Lactamase-Mediated Resistance

Although β-lactam resistance is most commonly associated with β-lactamase production in Gram-negative bacteria, other resistance mechanisms may also be operative in both Gram-negative and Gram-positive organisms. The most obvious mechanism is due to production of low-affinity PBPs, which require large inhibitory amounts of β-lactams for bacterial killing. In Gram-positive bacteria, mosaic low-affinity PBPs may

TABLE 1 Nomenclature of clinically important enzymes named in this review[d]

Molecular class or subclass	Functional group or subgroup	Common name[a]	Clinically relevant enzyme(s) or enzyme family(ies)	Characteristic substrate profile[b]	Characteristic inhibitor profile[c]
A	2a	Penicillinase	PC1/*blaZ*	Narrow-spectrum PENs	CA, TZB
A	2b	Penicillinase	TEM-1, SHV-1	Narrow-spectrum PENs, early CEPHs	CA, TZB
A	2be	ESBL	TEM-10, SHV-2, CTX-M-15	Narrow-spectrum PENs, early CEPHs, ES-CEPHs, monobactams	CA, TZB, AVI
A	2br	IRT	TEM-30 (IRT-2)	PENs, early CEPHs	TZB, AVI
A	2e	ESBL cephalosporinase	CepA	ES-CEPHs	CA but not ATM
A	2f	Carbapenemase	KPC	All FDA-approved β-lactams	AVI, REL, VAB
A	2f	Carbapenemase	SME	PENs, early CEPHs, carbapenems, monobactams; not ES-CEPHS	CA, AVI, VAB
B1, B3	3a	MBL, carbapenemase	IMP, NDM, VIM, SPM	All PENs, CEPHs, carbapenems; not monobactams	EDTA; no clinically approved inhibitor
B2	3b	MBL, carbapenemase	L1, CphA	Carbapenems preferred	EDTA; no clinically approved inhibitor
C	1	Cephalosporinase	AmpC	CEPHs	ATM, AVI, VAB
D	2d	Oxacillinase	OXA-1	PENs, especially oxacillin/cloxacillin	Variable
D	2df	Carbapenemase	OXA-23, OXA-48, OXA-181, OXA-232	PENs, especially oxacillin/cloxacillin, carbapenems	AVI (OXA-48)

[a]ESBL, extended-spectrum β-lactamase; IRT, inhibitor-resistant TEM; MBL, metallo-β-lactamase.
[b]CEPH, cephalosporin; ES-CEPHS, expanded-spectrum cephalosporins; PEN, penicillin.
[c]ATM, aztreonam; AVI, avibactam; CA, clavulanic acid; REL, relebactam; TZB, tazobactam; VAB, vaborbactam.
[d]Nomenclature is based on the Bush and Jacoby scheme (39).

occur, as in *Streptococcus pneumoniae* (40), or there may be acquisition of a rogue PBP, such as PBP2a (or PBP2′), encoded by the *mecA* gene in *Staphylococcus aureus* and resulting in methicillin-resistant *S. aureus*, or MRSA (41, 42). Mutations in essential PBPs in Gram-negative bacteria occur less frequently than other resistance mechanisms but have been reported in *Haemophilus influenzae*, *Pseudomonas aeruginosa*, and *E. coli* clinical isolates (43–46).

In Gram-negative bacteria, non-β-lactamase-associated resistance mechanisms that limit intracellular drug concentrations are common. Decreased penetration into the cell can be caused by mutations in the genes encoding outer membrane proteins (OMPs) that serve as porins, the water-filled channels through which β-lactams can traverse the outer membrane (Fig. 2). These mutations may involve changes in the regulatory mechanisms affecting OMP production, or they may result in nonfunctional or deleted porins, as reported for OMPs in the *Enterobacteriaceae* and for OprD production in *P. aeruginosa* (47–50). Concurrent with defective porins, resistance may also occur due to the upregulation of efflux pumps, such as AcrAB-TolC in the enteric bacteria or the multidrug efflux (Mex) pumps in *P. aeruginosa*, and is exacerbated by the presence or hyperproduction of β-lactamases (51–54).

Resistance Emergence

Treatment with β-lactam antibiotics disrupts the microbial flora of the patient being treated, sometimes resulting in the development of resistance in not only the infection-causing pathogen but also in the organisms comprising the normal flora. This subsequently affects the environment and people surrounding the patient. This means that not only the hospital unit but also health care workers and, subsequently, their immediate contacts are affected by the development of resistance. Furthermore, groups of people in close proximity, such as in day care centers or in long-term care facilities, are affected by the use of antibiotics that select for transmissible β-lactam-resistant organisms, either as colonizing bacteria or as infecting pathogens that can freely move between the community and the hospital (55, 56).

Resistance to β-lactams can develop in previously susceptible organisms through mutations in genes encoding naturally occurring chromosomally encoded β-lactamases or by acquisition of foreign DNA encoding new β-lactamases (17, 23). As bacterial pathogens grow, chromosomal and plasmid DNA replicates through a process that is highly prone to

errors concerning base incorporation, leading to nucleotide substitutions that occur randomly at a frequency of approximately 10^{-9} per gene (57). Exposure to the β-lactam antibiotic does not cause the mutations but rather selects for strains that mutate during normal replication cycles, thereby allowing the mutated bacterial cell to survive in the presence of the antibiotic. In β-lactamases, a single-nucleotide mutation leading to one amino acid change can greatly alter the functionality of an enzyme. Examples include the emergence of the first extended-spectrum β-lactamase (ESBL), in which glycine was substituted for Ser238 in the SHV-1 β-lactamase, resulting in SHV-2, which was resistant to expanded-spectrum cephalosporins (58, 59). A more recent example is the discovery of *K. pneumoniae* carbapenemase 35 (KPC-35), which contains a single leucine-to-proline substitution from KPC-2, resulting in reduced susceptibility to ceftazidime-avibactam (60).

In addition to random point mutations, replication errors may lead to deletions of a few base pairs of a gene, leading to inactive protein. Furthermore, mobile elements can insert DNA into genes or regulatory elements, thereby affecting the interaction of antibacterial agents with the bacterial target or altering the level of gene expression. Maintenance of a mutation causing antibiotic resistance in a bacterial pathogen is solely dependent upon how that mutation affects the fitness or virulence of that organism. When resistant mutants emerge that are still able to replicate and cause disease, they can gain a foothold in the population that is maintained by continued use of that antibiotic (61).

The most common way that bacteria become resistant to β-lactam antibiotics is through the acquisition of genes expressing β-lactamases (62). DNA transfer among bacteria primarily occurs through the acquisition of plasmids, some of which are self-transmissible, in that they carry genes to initiate the direct transfer to another bacterial cell. These large transferrable plasmids can accommodate multiple resistance genes and are the ideal vector for the dissemination of resistance genes. Within plasmids, resistance genes are often carried by transposons, which can transfer determinants between plasmids or transport them into and out of the chromosome (63). These genes are often a part of an integron that can acquire and express resistance determinants behind a single promoter. Many β-lactamase genes, particularly metallo-carbapenemases, can exist as gene cassettes inserted into integrons (63–65).

Among bacterial pathogens, dissemination of resistance genes contained in plasmids, transposons, and integrons has resulted in so-called gene epidemics (61). TEM-1, the first plasmid-encoded β-lactamase described in the literature, in 1965, originated in an *E. coli* isolate from a patient in Greece but has spread globally to multiple bacterial species (66, 67). It has been found in up to 70% of clinical isolates of *Enterobacteriaceae*, in a few *Pseudomonas aeruginosa* isolates, and in 30% of *Neisseria gonorrhoeae* isolates (67–69). In Japan and France, the prevalence of TEM-1 in *H. influenzae* declined after the adoption of the type B vaccine (70, 71), but the occurrence of TEM-1-producing strains in Sweden remained relatively constant between 2002 and 2010 (72). In all the reports, numbers of β-lactamase-negative, ampicillin-resistant isolates increased over time. In addition, multiple TEM-bearing plasmids in *H. influenzae* have been shown to affect fitness differently, also contributing to the loss of the TEM-1 enzyme (73).

Many of the β-lactamases now found on mobile elements are believed to have originated in the chromosomes of other bacterial species. A few examples include SHV-type β-lactamases, which are derived from a chromosomal SHV-1 β-lactamase of *K. pneumoniae*; the plasmid-encoded AmpC enzymes expressed in *K. pneumoniae* and *E. coli*, which are nearly identical to chromosomal AmpC genes found in *Enterobacter cloacae* complex (ACT-1 and MIR-1), *Citrobacter freundii* (CMY type), *Hafnia alvei* (ACC-1), and *Morganella morganii* (DHA-1); and the most common contemporary ESBL, the cefotaxime-hydrolyzing β-lactamase CTX-M type, which appears to have originated from *Kluyvera* spp. (59, 74–76).

Bacterial resistance to β-lactam antibiotics primarily results from modification of the target penicillin-binding proteins, decreased intracellular concentrations due to reduced permeability or efflux, or inactivation of the antibiotic from β-lactamases, which

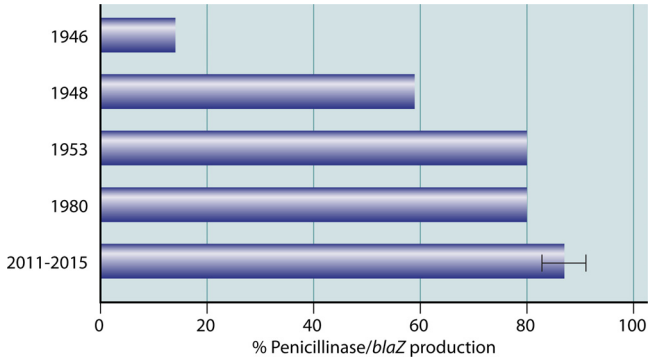

FIG 3 Prevalence of penicillinase (*blaZ*)-producing staphylococci from global sources. Data for the years 1946 to 1980 were from references 84 and 85. Data for the years 2011 to 2017 include studies from Trinidad and Tobago (88), Kuwait (89), China (90), and the United States (91), with the range of percentages shown by the error bars.

is the most common mechanism. Innate resistance to β-lactams occurs in certain pathogens. As a consequence, entire species of bacterial pathogens have been selected following repeated exposure to antibiotics due to this innate resistance. In addition, the introduction of new therapies has sometimes led to the unexpected consequence of shifting the etiology of some of the common hospital-based infections to species that are naturally more resistant than the pathogens they replaced. For example, carbapenemase-producing *Acinetobacter baumannii* and *Stenotrophomonas maltophilia* have become increasingly prevalent in many intensive care units (ICUs) following the increased use of carbapenems, especially among patients with mechanical ventilation (77–80).

EPIDEMIOLOGY OF β-LACTAMASE-PRODUCING PATHOGENS

Bacteria Producing Species-Specific β-Lactamases

Gram-positive bacteria. Penicillin was first utilized clinically to treat infections caused by streptococci, followed by its use against staphylococcal infections in the early 1940s. "Penicillinase" activity was first reported in 1940 in a "*Bacillus*" (*Escherichia*) *coli* strain but was not clinically relevant at the time (81). However, shortly thereafter, penicillin resistance was reported in the staphylococci due to a structurally different "penicillin inactivator" (82, 83). Resistant strains increased rapidly thereafter. In the late 1940s, penicillin resistance in *S. aureus* was monitored in St. Thomas's Hospital in London over a 5-year period, with an increase from 14% in 1946 to 59% in 1948 (84). By 1953, 80% of hospital staphylococci were reported to be penicillin resistant, presumably due to penicillinase production (85). As shown in Fig. 3, penicillinase production in methicillin-susceptible *S. aureus* (MSSA) plateaued at approximately 80 to 85% by 1980 (86, 87). The most recent studies report between 83.8% and 91% of MSSA isolates producing the penicillinase gene *blaZ* from locations as diverse as Trinidad, Kuwait, China, and the United States (88–91). An exception to this trend is in Sweden, where only 43% of MSSA isolates in 2008 to 2009 were penicillinase producers, increasing to 71% in 2014 to 2015 (92). Note that essentially all MRSA isolates are penicillinase positive due to the close relationship between regulators of the defining MRSA *mecA* and the staphylococcal *blaZ* genes (93, 94). At least four different functional types of staphylococcal penicillinases have been described (95), but there has been only limited interest in the past 20 years in pursuing the molecular characteristics or additional epidemiology associated with these enzymes (96). Although the staphylococcal *blaZ* appeared briefly in rare *Enterococcus faecalis* isolates beginning in the 1980s (97, 98), the gene appears to have been lost from the enterococcal clonal complex responsible for multiple small outbreaks worldwide (99). There have been no recent reports of its presence (100). Likewise, no β-lactamases have been identified among the streptococci.

Gram-negative fermentative bacteria. AmpC β-lactamases belong to Ambler class C and Bush-Jacoby-Medeiros functional group 1. In addition to penicillins and early cephalosporins, they also confer resistance to the oxyimino-cephalosporins, such as ceftazidime, cefotaxime, and ceftriaxone, the monobactams, and cephamycins, such as cefoxitin (39, 101). Most class C enzymes are not inhibited by classical inhibitors clavulanate, sulbactam, and tazobactam; however, they are efficiently inhibited by the newer inhibitors avibactam, relebactam, and vaborbactam (102). In addition, class C enzymes are inhibited by aztreonam (38, 103). Class C β-lactamases tend to have a larger active site than do class A enzymes, which may allow them to bind the bulky side chains of the expanded-spectrum oxyiminocephalosporins (104).

AmpC enzymes are most often found as chromosomal β-lactamases that are produced by many species of Gram-negative bacteria (101). In clinical isolates of *C. freundii*, *Enterobacter aerogenes*, *E. cloacae* complex, and *Serratia marcescens*, AmpC enzymes are particularly important because they are inducible in these species. There is usually low-level basal expression of AmpC, which becomes high level upon exposure to certain β-lactams. In its natural state, the expression of AmpC is under the control of the repressor gene *ampR*, encoding a member of the LysR transcriptional regulator family. Repression and activation are closely linked to the processes of cell wall peptidoglycan synthesis and breakdown and involve a complex system with several additional genes, including *ampD* and *ampG* (105, 106). A mutation in any of the regulatory genes can result in constitutive upregulation of the AmpC β-lactamase. One or more mutations in *ampD* is the most common cause of constitutive high-level expression of AmpC hyperexpression in clinical isolates (107). Several species, including *E. coli* and *Shigella* spp., possess a chromosomally encoded AmpC but lack the repressor *ampR* gene, rendering the gene noninducible (101). The AmpC β-lactamase is usually produced at low levels in these organisms and rarely contributes to β-lactam resistance.

The genes encoding AmpC β-lactamases have been mobilized and are now widely found in plasmids. The first plasmid-encoded AmpC variant was identified in 1989 from *K. pneumoniae* isolated in South Korea from a patient with a wound infection. The isolate was notable because of its high degree of resistance to cefoxitin; the enzyme responsible for this resistance was named CMY-1, because phenotypically it was a cephamycinase (108). Within the next decade, several families of plasmid-encoded AmpC variants were reported, especially in clinical isolates, of *K. pneumoniae* and *E. coli*. Based on DNA sequence homology, the source of plasmid-based *ampC* genes has been attributed to several genera of bacteria, with a number of AmpC families reported (101). The following AmpC families have been described: two families of CMY β-lactamases (CMY-1 and CMY-2) originated from *Aeromonas hydrophila* and *C. freundii*, respectively; FOX- and MOX-type enzymes are derived from *Aeromonas* spp.; the ACC family originated from *H. alvei*; the LAT family of cephalosporinases arose from *C. freundii*; the MIR and ACT families originated from *Enterobacter* spp.; and the DHA family stemmed from *M. morganii* (74, 101, 109). These plasmid-mediated enzymes are often expressed constitutively at high levels due to strong promoters and high gene copy numbers. Plasmid-mediated class C β-lactamases have been detected in numerous genera of *Enterobacteriaceae*, including *K. pneumoniae*, *E. aerogenes*, *Salmonella enterica* serotype Senftenberg, *E. coli*, *Proteus mirabilis*, *M. morganii*, and *Klebsiella oxytoca*. Strains expressing plasmid-encoded AmpC enzymes can also become resistant to carbapenems with the loss of outer membrane porin proteins in clinical isolates of *K. pneumoniae* and *S. enterica* (75, 110–112).

Nonfermentative bacteria. (i) *Aeromonas* spp. The various species of *Aeromonas* produce multiple chromosomally mediated β-lactamases from molecular classes B, C, and D and can be uniquely species specific (113). A variety of class C AmpC-type β-lactamases have been characterized from *Aeromonas* spp., including CepS from *A. hydrophila* (originally misidentified as *Aeromonas veronii* bv. *sobria*), AsbA1 from *Aeromonas jandaei*, CepH from *A. hydrophila*, CAV-1 from *Aeromonas caviae*, MOX-4 from *A. caviae*, and TRU-1 from *Aeromonas enteropelogenes* (113). As with most other chromosomally encoded AmpC enzymes, these β-lactamases are under regulatory control that

allows for induction of the enzyme and the selection of derepressed mutants that express high levels of enzyme (114). Many species of *Aeromonas* carry the metallo-β-lactamase CphA, which has a unique substrate profile, in that it inactivates penems and carbapenems but not penicillins and cephalosporins (115). CphA is discussed in more detail in the carbapenemase section.

(ii) *Acinetobacter* spp. *Acinetobacter* spp., especially the *Acinetobacter calcoaceticus-A. baumannii* complex, also carries an intrinsic gene encoding AmpC, which is called bla_{ADC}, for *Acinetobacter*-derived cephalosporinase (116). The *ampC* gene of *A. baumannii* was first described and sequenced in 2000 (117). Increased resistance to expanded-spectrum cephalosporins can occur when ADC becomes overexpressed due to the acquisition of a strong promoter located on the insertion element IS*Aba1*, which targets a specific position upstream of the intrinsic *ampC* gene of *A. baumannii* (118). The gene encoding ADC is highly variable, and the majority of the variations in the amino acid sequence do not alter the spectrum of resistance (119). A database has been established to track the various alleles of ADC (120).

Chromosomally encoded class D OXA-type β-lactamases are intrinsic to several species of *Acinetobacter*, including *A. baumannii*, *A. calcoaceticus*, *Acinetobacter pittii*, and *Acinetobacter lwoffii* (116). Virtually all *A. baumannii* isolates possess the gene encoding OXA-51 or one of its related variants that confer very low carbapenem resistance (121, 122). The expression of this β-lactamase becomes increased when mobile elements like the insertion sequence IS*Aba1* are positioned upstream of this gene in an opposite orientation and act as promoter sequences (121). OXA-23, the first OXA-type enzyme with higher carbapenemase activity discovered in *A. baumannii*, was described in 1985 and was originally named ARI-1 (123). Other OXA carbapenemases have been reported in *A. baumannii*, such as OXA-58, OXA-24/-40, and OXA-143, but other than OXA-51, OXA-23 remains the most common (121, 124). Sequencing and phylogenetic comparisons have revealed that these enzymes fall into 18 groups and that the acquisition of bla_{OXA} genes by *Acinetobacter* spp. was ancient (116). A survey of clonality in 2013 reported that the predominant clonal type shifted from clonal cluster 3 to clonal cluster 2, a cluster highly associated with carbapenem resistance mediated by OXA-23 (125). A case-controlled study in Pittsburgh, where CC2 is prevalent, found that the mortality rate of patients with cancer and these multidrug-resistant *A. baumannii* infections was 41.9%, compared to 29.0% for the control group (126). Other localized health care sites have reported a greater diversity of infection-causing *Acinetobacter* clones depending on the source of the index cases, with as many as four different clonal types isolated from a single patient (127, 128).

(iii) *Burkholderia* spp. The majority of clinical isolates of *Burkholderia pseudomallei* complex possess a chromosomally encoded class A β-lactamase called PenA, an enzyme that confers resistance to penicillins and early-generation cephalosporins (129). Although ceftazidime is the treatment of choice for this organism, mutations in PenA have led to resistance in both ceftazidime and clavulanate (130). PenA has also been described in the *Burkholderia cepacia* complex. In a study of clinical isolates of *Burkholderia multivorans* from cystic fibrosis patients, 90% of the strains were susceptible to ceftazidime-avibactam, suggesting that this combination is useful in treating strains expressing PenA (131).

(iv) *Pseudomonas aeruginosa*. Chromosomally encoded inducible AmpC β-lactamases are also found in nonfermentative Gram-negative pathogens. In *P. aeruginosa*, the chromosomally encoded AmpC, called PDC, contributes to the natural resistance to aminopenicillins as well as early cephalosporins (132). Similar to what is seen in the *Enterobacteriaceae*, mutations in the regulatory genes involving peptidoglycan recycling can lead to the hyperproduction of AmpC, resulting in resistance to antipseudomonal penicillins, such ticarcillin, piperacillin, and aztreonam, and late-generation cephalosporins, such as ceftazidime and cefepime (133). Mutations in the genes encoding AmpC as well as changes in OMPs and efflux pumps can also contribute to resistance to cefepime (133). PDC enzymes are highly variable in sequence, which translates into variations in spectrum of activity. Some of the variants have been noted

to provide resistance to imipenem and newer β-lactam–β-lactamase inhibitor combinations, such as ceftolozane-tazobactam (134). The chromosome of *P. aeruginosa* may also contain genes for OXA-type β-lactamases, including OXA-50 (135, 136).

(v) *Stenotrophomonas maltophilia*. *S. maltophilia* produces two chromosomally encoded β-lactamases, L1, a metallo-β-lactamase, and L2, a class A cephalosporinase inhibited by clavulanate (137, 138). Both enzymes are inducible and utilize some of the same regulatory genes that control AmpC-type β-lactamases; however, the response to induction is different for the two enzymes (139, 140). The L1 and L2 β-lactamases confer resistance to virtually all β-lactams, although newer β-lactam–β-lactamase combinations, such as aztreonam-avibactam, may be useful in the future due to the stability of aztreonam to hydrolysis by L1 and the inhibition of L2 cephalosporinase by avibactam (141). There is an increased incidence of infections caused by *S. maltophilia* in the hospital setting, especially among immunocompromised patients, resulting in increased mortality attributed to this organism (142). A recent genetic study of 130 *S. maltophilia* clinical isolates from the United States revealed 90 different sequence types with 34 and 43 novel variants of the L1 and L2 β-lactamases, respectively (80). Unfortunately, functional information was not provided to describe the effects of the mostly conservative amino acid substitutions found in the variants.

Anaerobic bacteria. Anaerobic bacteria produce several species-specific β-lactamases that confer resistance to many noncarbapenem β-lactams. A chromosomal class A β-lactamase, designated DES-1, has been identified in some, but not all, *Desulfovibrio desulfuricans* strains, an organism phylogenetically related to *Bacteroides* spp. (143). This enzyme is most closely related to PenA from *Burkholderia pseudomallei* and provides resistance to ureidopenicillins and expanded-spectrum cephalosporins. A class D β-lactamase named FUS-1 (OXA-85) has been characterized from *Fusobacterium nucleatum* subsp. *polymorphum* strains resistant to penicillin and amoxicillin (144). The bla_{FUS-1} gene is located on the chromosome and shares the closest ancestral relationship with OXA-63 from *Brachyspira pilosicoli* (53% identity). β-Lactamases have also been described for the anaerobic Gram-positive organism *Clostridium difficile* (145). Whole-genome sequencing revealed an open reading frame annotated as a putative β-lactamase gene with conserved amino acid sequence motifs characteristic of class D β-lactamases, which was subsequently named bla_{CDD}. This β-lactamase is inducible and provides broad-spectrum activity against various β-lactam antibiotics, including penicillins and expanded-spectrum cephalosporins.

Gram-Negative Bacteria Producing Plasmid-Encoded ESBLs

Nomenclature. In 1989, Bush defined group 2b′, subsequently called group 2be, enzymes as "β-lactamases that are capable of hydrolyzing aminothiazoleoxime β-lactam antibiotics, or the 'extended-broad-spectrum' antibiotics, at rates at least 10% that of benzylpenicillin and that are strongly inhibited by clavulanic acid" (38, 146). This definition originally included enzymes such as the chromosomal K1 β-lactamase from *K. oxytoca*; in 2010, the designation was expanded by Bush and Jacoby to include subgroups of class A, class C, and class D enzymes (39). However, other investigators believe the designation should refer to those plasmid-encoded β-lactamases that have emerged only from molecular class A enzymes belonging to functional group 2b, capable of hydrolyzing penicillins as well as narrow- and expanded-spectrum cephalosporins (38, 39). Traditional ESBLs are inhibited by the older β-lactamase inhibitors clavulanate, sulbactam, and tazobactam, as well as by more recently FDA-approved inhibitors, such as avibactam, relebactam, and vaborbactam. In the early ESBL definition, inhibition by clavulanate was a requirement for inclusion in this group, but in recent years, this prerequisite has been challenged by the diversity of the enzymes characterized that meet one or more of the attributes of the ESBL group (147). A recent literature survey of United States hospital infections caused by ESBL-producing *E. coli* and *K. pneumoniae* concluded that the rates of these infections were increasing, although specific data were difficult to assess due to differing definitions of ESBL (148).

ESBL variants. Originally, ESBL enzymes were TEM and SHV variants displaying amino acid substitutions that changed their substrate profile to include the expanded-spectrum cephalosporins. The first ESBL (SHV-2) was described in 1985 and was found in a single strain of *Klebsiella ozaenae* isolated in Germany (149). Given the ease of whole-genome sequencing available today, multiple variants of the common TEM and SHV enzymes have been identified. There are now 183 nonduplicative variants of TEM and 178 variants of SHV, although not all of these possess the ESBL phenotype (https://www.ncbi.nlm.nih.gov/pathogens/isolates#/refgene/TEM; https://www.ncbi.nlm.nih.gov/pathogens/isolates#/refgene/SHV; https://externalwebapps.lahey.org/studies/). Changes at a limited number of amino acids are responsible for conferring the ESBL phenotype (59). Both TEM- and SHV-type ESBLs were described throughout the United States and Europe in the late 1980s and 1990s, with specific variants noted to be regional in distribution (150–152). For example, TEM-10 was responsible for several unrelated outbreaks of ESBL-producing organisms in the United States but was rarely seen in Europe (55). The prevalence of these enzymes has now diminished at the same time as the worldwide dissemination of isolates producing CTX-M-type β-lactamases (15).

CTX-M-type β-lactamases were also first reported in the 1980s. At first they were a curious addition to the list of ESBLs, but since the year 2000 they have spread worldwide and are now the most common type of ESBL (153). The CTX-M-type enzymes can be phylogenetically divided into five distinct clusters in which the group members share >94% identity (in contrast, ≤90% identity is observed between the members belonging to the other groups) (154). In general, CTX-M β-lactamases hydrolyze cefotaxime and ceftriaxone better than ceftazidime, although the spectrum varies by enzyme. CTX-M-15 can hydrolyze ceftazidime at higher rates than CTX-M-3, which may be a contributing factor for the successful spread of this enzyme (155). CTX-M-type enzymes are readily inhibited by all of the commercially available β-lactamase inhibitors, including the newest additions of avibactam and vaborbactam (102). The origin of the CTX-M-type enzymes is thought to be in *Kluyvera* spp., a rarely encountered environmental member of the *Enterobacteriaceae* (156). Genes presumed to be precursors of CTX-M-type enzymes have been identified among the chromosomes of *Kluyvera cryocrescens* (CTX-M-1 group), *Kluyvera ascorbata* (CTX-M-2 group), and *Kluyvera georgiana* (CTX-M-8, CTX-M-25, and CTX-M-9) (157). Plasmids and conjugative genetic elements such as IS*Ecp1*-like, IS*CR1*, and class 1 integrons house the $bla_{\text{CTX-M}}$ genes and contribute to its mobilization (158). CTX-M β-lactamases are quite commonly found in *E. coli* and *K. pneumoniae* but are also found in other species of *Enterobacteriaceae*, including typhoidal and nontyphoidal *Salmonella* spp., *Shigella* spp., *C. freundii*, *Enterobacter* spp., and *S. marcescens*, as well as several species of nonfermenters (153, 157).

Although not classical ESBLs as defined by inhibition by clavulanate, a number of OXA-type β-lactamase variants, such as OXA-11 and OXA-14 to OXA-20, are associated with an ESBL phenotype in that they confer resistance to some of the late-generation cephalosporins (159). Many of these are derived from OXA-10 and OXA-2 and are commonly found in *P. aeruginosa*. OXA-163 is an interesting variant of OXA-48 in that it has an ESBL phenotype but is not a carbapenemase (160). In addition, OXA-1 (identical to OXA-30) hydrolyzes cefepime well and is prevalent among *Enterobacteriaceae* that also contain $bla_{\text{CTX-M-15}}$ (161).

In recent years, multilocus sequence typing (MLST) has been used extensively to track and monitor the spread of resistance. As a result of these studies, several widely disseminated sequence types (ST) have been found in epidemics and outbreaks due to resistant organisms that are highly associated with certain resistance mechanisms. *E. coli* sequence type 131 (ST131, clade C) has been identified as the predominant lineage for *E. coli* causing extraintestinal infections, and the dissemination of CTX-M-15 has been driven in part by the spread of this successful clone (162). Isolates belonging to this lineage and phylogenetic group B2 have several virulence markers that contribute to its spread and can cause severe infections (163). The global dissemination of ST131, clade C, has led to an increase of fluoroquinolone-resistant and CTX-M-

type β-lactamase-producing *E. coli* worldwide (153, 162–164). Prevalence studies showed that ST131 comprises up to 30% of all clinical isolates of extraintestinal *E. coli* clinical isolates and 40 to 80% of ESBL-producing isolates (153, 165).

Additional, less common ESBLs, other than TEM, SHV, and CTX-M, that have been found in clinically relevant settings include GES, PER, VEB, BES, BEL, SFO, and TLA β-lactamases (59). Once limited to the hospital setting, ESBL-producing isolates quickly expanded into nursing homes and community settings as well (55, 166). The impact of *Enterobacteriaceae* possessing ESBLs has had a significant impact on the choice of empirical antimicrobial therapy, driving the use of carbapenems in many institutions and resulting in increased resistance to carbapenems (167, 168).

Nonfermentative bacteria. OXA-type extended-spectrum β-lactamases were originally found more commonly among *P. aeruginosa* isolates than in *Enterobacteriaceae*. Many of these were derived from OXA-2 or OXA-10 (169). In a recent study of *P. aeruginosa* isolated from patients in Tehran, 27.5% of the strains possessed a plasmid-mediated ESBL and were isolates found to contain genes for $bla_{\text{OXA-4}}$, $bla_{\text{GES-1}}$, and $bla_{\text{VEB-1}}$ (170). VEB, GES, and OXA-type enzymes are also commonly found in Poland (171). In Saudi Arabia, VEB-1 and OXA-10 were found to be the most prevalent plasmid-mediated β-lactamases in *P. aeruginosa* (169).

ESBLs have been described among both environmental and clinical isolates of *Aeromonas* spp. There have been case reports of infections caused by *A. hydrophila* that carried $bla_{\text{TEM-24}}$ and *A. caviae* with $bla_{\text{CTX-M-3}}$ or $bla_{\text{PER-3}}$ (172–174). Recently, CTX-M-3-producing *A. salmonicida* was isolated from the surgical site wound of a patient following leech therapy to restore blood flow to an amputated digit (175). It is likely that the presence of ESBLs in *Aeromonas* spp. is underreported, because the phenotypic testing would be masked by the presence of intrinsic AmpC and metallo-β-lactamases in this species (113).

Carbapenemase-Producing Bacteria

Species-specific serine carbapenemases. (i) SME carbapenemases. SME serine carbapenemases have been reported only in isolates of *Serratia marcescens* in which the relatively rare bla_{SME} gene is located in the chromosome (176). An identifying characteristic of isolates expressing SME is that they are resistant to carbapenems but susceptible to expanded-spectrum cephalosporins like ceftazidime (177). To date, four variants of the original SME-1 enzyme have been reported (178–180). The first two SME-producing isolates were reported from England (177) but have not appeared to spread to the rest of Europe. Sporadic reports of these enzymes in the United States have occurred since 2004, with a relatively large outbreak of 19 SME-2-producing *S. marcescens* isolates appearing in Boston from 1994 to 1999 (176). Although most reported incidences of SME enzymes have been in the United States, these carbapenemases have also been reported in Argentina, Australia, Brazil, Canada, and Switzerland (176, 180–182). It is likely that SME enzymes are present in many other locations but have gone undetected because many laboratories do not test for a bla_{SME} gene in their routine diagnostic testing for carbapenemases (176, 183).

Increasing numbers of SME enzymes have recently been reported from the Americas and the United Kingdom. In the United Kingdom, seven carbapenemase-producing *S. marcescens* isolates were identified in 2015 to 2016 after many years of no reported SME enzymes (183). Even greater numbers of these isolates were reported from Canada; the number of carbapenem-resistant *S. marcescens* isolates submitted to the National Microbiology Laboratory increased from 13 isolates in 2010 to 33 and 29 in 2012 and 2013, respectively. Among these 75 Canadian isolates, 30 of them (40%) carried a bla_{SME} gene encoding either SME-1 ($n = 24$) or SME-2 ($n = 6$) enzymes (184). Genomic analyses of three native Canadian isolates, the UK isolates, and a United States isolate selected during antibiotic therapy revealed that the bla_{SME} gene resided in a cryptic prophage genomic island, SmarGI1-1 (*S. marcescens* genomic island 1-1), inserted in the chromosome (183–185). In the U.S. isolate, both the SME and AmpC enzymes were inducible

in the initial isolate and hyperproduced after several months of antibiotic treatment in the affected patient, due in part to missense and nonsense mutations in *ampD* (185).

(ii) IMI/NMC carbapenemases. Other chromosomal serine carbapenemases include those in the IMI and NMC families identified to date only in isolates of the *E. cloacae* complex of organisms. Imipenem-resistant *E. cloacae* isolates from two California patients in 1984 were the original sources for the chromosomal IMI-1 enzyme (186). Like SME, the IMI β-lactamase confers resistance to carbapenems but not expanded-spectrum cephalosporins (186). Recently, IMI-type enzymes have been identified from China, Japan, and the French island of Mayotte (Indian Ocean) (187–189). In the latter two areas, the producing isolates were both carbapenem and colistin resistant. The NMC-A serine carbapenemase was first identified from a 1990 French isolate of *E. cloacae* (190) and shares 97% sequence identity with IMI-1 (186). At this time, the accepted nomenclature uses IMI as the family name for any new members of this set of related carbapenemases (https://ftp.ncbi.nlm.nih.gov/pathogen/betalactamases/Allele.tab, accessed 31 August 2019). NMC-A also has been reported occasionally in isolates of *Enterobacter* spp. from North America and in a Japanese tourist treated in Italy (191–194). Antonelli et al. have described an integrative mobile element that encoded an Xer tyrosine recombinase that was likely responsible for integration of the $bla_{\text{NMC-A}}$ carbapenemase gene into the chromosome of *Enterobacter* spp. (194). Recent genomic analyses of Canadian isolates have shown that both NMC-A and IMI genes were found on EludIMEX-1-like integrative mobile elements, most of which were integrated into the chromosome (193). The genes encoding IMI-5 and IMI-6 were found on IncFII-type plasmids, indicating that these currently *Enterobacter*-specific enzymes have the potential to spread to other genera (193).

Acquired serine carbapenemases. (i) KPC carbapenemases. In the late 1990s, the *K. pneumoniae* carbapenemase (KPC) family of β-lactamases began to emerge on the east coast of the United States and has become the most common carbapenemase detected globally (195–197). Characteristics of this family of acquired serine carbapenemases includes a molecular structure similar to that of other class A enzymes but with only 50%, 39%, and 35% amino acid sequence identity to the more common CTX-M-1, SHV-1, and TEM-1 enzymes, respectively (198). The KPC enzymes exist as one of at least 40 variants differing in most cases by less than five amino acids from the original KPC-2 and KPC-3 enzymes (https://www.ncbi.nlm.nih.gov/pathogens/isolates#/refgene/KPC, accessed 24 August 2019) and are found among many different genera of *Enterobacteriaceae* and *P. aeruginosa* (199, 200). KPC carbapenemases possess a large and shallow active site, allowing these enzymes to accommodate a wide range of β-lactam molecules, including cephalosporins, monobactams, and carbapenems (198). Isolates producing KPC-type enzymes not only are resistant to most β-lactams but also are often multidrug resistant, because they additionally encode a multitude of other resistance genes, rendering them virtually panresistant to many of the currently available first-line options for therapy (201–203). KPC-type β-lactamases are not inhibited by clavulanate or tazobactam; however, they are inhibited well by the newer β-lactamase inhibitors, such as avibactam, relebactam, and vaborbactam (199, 204, 205). However, strains harboring mutants of bla_{KPC} can become resistant to ceftazidime-avibactam via increased catalytic activity for ceftazidime (206, 207).

The gene expressing KPC is usually found within a form of the composite transposon Tn*4401* that may vary with length while retaining similar gene content (208). The successful spread of KPC has been due primarily to the spread of *K. pneumoniae* isolates belonging to the successful clonal complex 258 (CC258) or ST258 (clades I and II), found in both hospital and community isolates (202, 203, 209–212). In a survey of KPC-producing *K. pneumoniae* collected globally in 2012, Peirano et al. found that 290 of 522 (55.6%) isolates from 19 different countries belonged to CC258 (210). These isolates were divided between two clades, with both $bla_{\text{KPC-2}}$ and $bla_{\text{KPC-3}}$ located on $\text{IncFII}_{\text{K2-like}}$ plasmids; ST258 clade I was more frequently associated with $bla_{\text{KPC-2,}}$ whereas clade II was more frequently associated with $bla_{\text{KPC-3}}$ (210). Large outbreaks of KPC-producing *K. pneumoniae* in Poland and Colombia have also been attributed to strains belonging

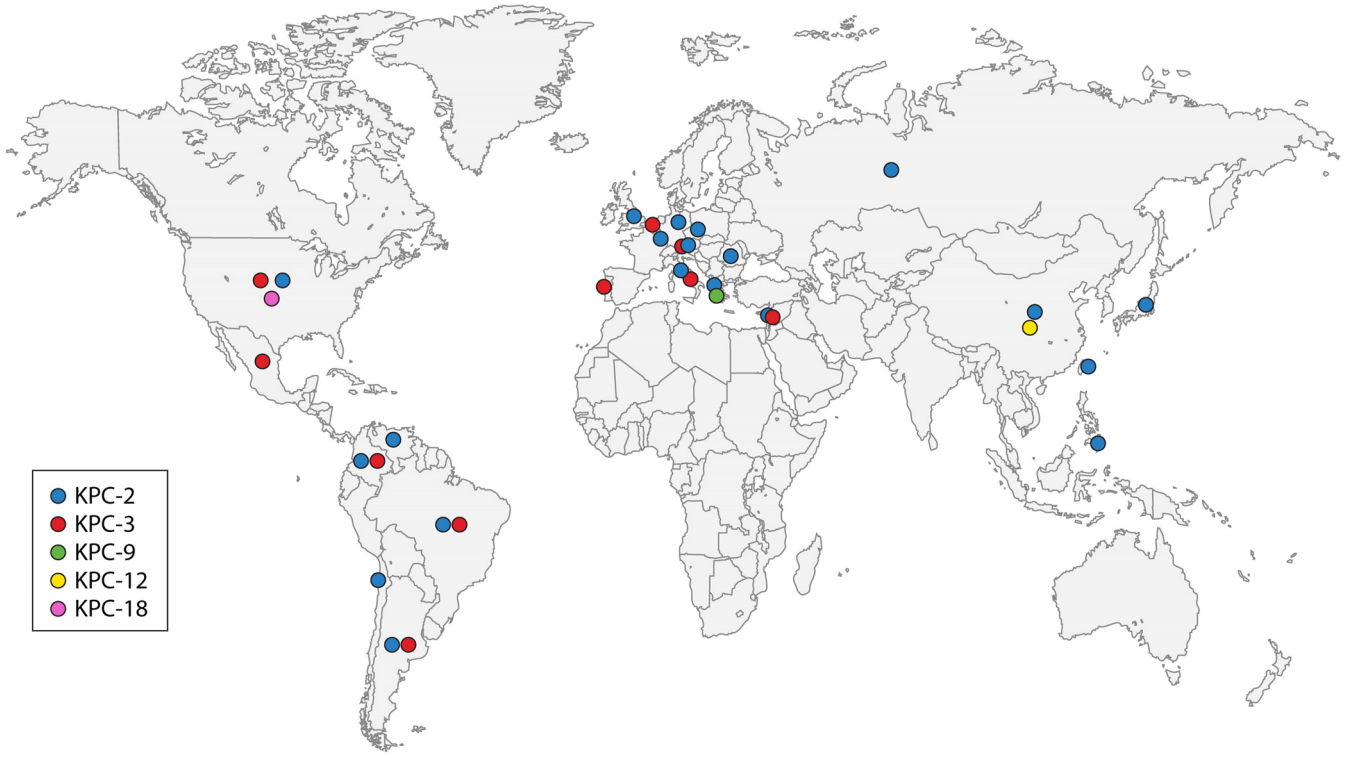

FIG 4 Distribution of KPC-positive *Enterobacteriaceae* and *P. aeruginosa* collected in 2012 to 2014 from surveillance data. (Republished from reference 199.)

to ST258, with bla_{KPC} often found inside the Tn*4401* transposon (213, 214). In an extensive European genomic study of carbapenem-resistant *K. pneumoniae* from 244 hospitals in 32 countries, ST258/512 *K. pneumoniae*, originating in the United States, was identified as the likely progenitor of the large majority of European carbapenemase-producing isolates (215). Rojas et al. have proposed that the emergence of an epidemic KPC-producing *K. pneumoniae* ST258 clone in Colombia was due to the convergence of two different evolutionary pathways; one involved the horizontal transfer of bla_{KPC-2} mobile elements, and the other was due to the establishment of the highly virulent clonal group 258 (ST258) strain that carried bla_{KPC-3} (214). *K. pneumoniae* ST258 isolates containing bla_{KPC} in the bacterial chromosome now have been reported by several different groups and may be more common than originally expected (216, 217). Sequence types other than ST258 have also been reported, with major representatives including ST11, the predominant type in China and Taiwan, and ST25, ST147, and ST512 in the Americas and Europe (210, 213, 217–220).

KPC was first identified in 1996 in North Carolina from an isolate of *K. pneumoniae* from a single patient (195). Although the next steps in dissemination were never identified, in the following decade, *K. pneumoniae* expressing KPC-2 gained a foothold and became endemic in New York City (221). Subsequently, the epidemiology of KPC-producing pathogens has expanded far beyond the northeast United States such that KPC enzymes have become the most common carbapenemases detected globally (222, 223). During the mid-2000s, several outbreaks of *K. pneumoniae* type ST258 were documented in hospitals in Israel caused by strains that were nearly identical to the KPC-producing strains detected in New York (224). This was attributed to the frequent travel back and forth of citizens of both countries. In a survey of Gram-negative pathogens collected from 2012 to 2014, KPC-producing isolates were found in 22 countries on four continents, as seen in Fig. 4 (199). In addition to *K. pneumoniae*, KPC-type β-lactamases were also found in *E. aerogenes*, *E. coli*, *K. oxytoca*, *C. freundii*, and several other species (199). Outside the United States, recent outbreaks of KPC-producing *K. pneumoniae* have been reported in Brazil, China, Ecuador, Germany,

Greece, South Korea, Poland, Portugal, Switzerland, and Taiwan (213, 218–220, 225–232). A widely publicized outbreak of KPC-producing *K. pneumoniae* in the United States was documented in a clinical trial unit at the National Institutes of Health, resulting in the death of 11 of 18 infected patients as a result of infection-associated causes (233). Whole-genome sequencing was used to trace the infection to a single index case who left the unit 3 weeks prior to the next apparent case. The implementation of strict infection control practices subsequently halted the outbreak; however, sporadic cases still occur (233). The prevalence of KPC in *K. pneumoniae* isolates in New York City and Israel declined after the initial peak outbreaks, most likely due to strategic efforts to reduce the use of indwelling catheters plus increased infection control measures (234, 235). Carbapenem-resistant *Enterobacteriaceae* (CRE) bacteremia caused by KPC-producing *K. pneumoniae* is associated with high mortality rates and remains a problem in the New York-New Jersey area, which is the epicenter of CRE in the United States (211). However, the overall prevalence of clinical isolates expressing KPC has declined across New York City through massive infection control efforts (234). It is important to note that the promiscuous plasmids harboring bla_{KPC} also commonly carry genes encoding resistance to aminoglycosides and additional β-lactamases, including ESBLs and metallo-β-lactamases (199, 200).

(ii) OXA carbapenemases. Within the class D OXA family of β-lactamases, only a small fraction has a functional role as a carbapenemase. Among these are OXA-23, OXA-40, and the increasingly prevalent OXA-48, with its related variants, OXA-162, OXA-181, and OXA-232 (236). The OXA carbapenemases generally have hydrolytic activity against penicillins and broad-spectrum carbapenems and are poorly inhibited by β-lactamase inhibitors, except for avibactam (52, 237, 238). OXA-48 in particular hydrolyzes a narrower spectrum of β-lactams, with clinically relevant hydrolysis of penicillins and imipenem and lower hydrolysis of meropenem (239). The bla_{OXA-48} gene is often found in Tn*1999* composite transposons that harbor copies of IS*1999* flanking both sides of this β-lactamase gene (240). Isolates that express OXA-48 may be susceptible to cephalosporins and have only modestly elevated carbapenem MIC values, with many imipenem MICs of ≤ 2 μg/ml (241, 242). High-level resistance to carbapenems is usually due to a secondary nonenzymatic resistance mechanism in these isolates (239). The low levels of carbapenem resistance provided by this enzyme can make detection of strains harboring this resistance mechanism difficult.

OXA-48 was first described among clinical isolates of *K. pneumoniae* from Turkey and has subsequently disseminated in Europe and the Mediterranean region, but it is found less frequently in the Americas (236, 239). In Spain, 72% of the 121 carbapenemase-producing *E. coli* isolates encoded OXA-48 in 2012 to 2014 (243); in a second Spanish study, 816 *Enterobacteriaceae* isolates producing OXA-48 were identified from 2013 to 2014, most frequently in *K. pneumoniae* (242). In a set of Spanish carbapenemase-producing *Citrobacter* species isolates collected between 2013 and 2015, 32% produced an OXA-48-type enzyme (244). A recent 2015 global survey of 11,559 *Enterobacteriaceae* isolates from 30 countries on five continents identified 40 OXA-48-producing strains; 95% were *K. pneumoniae* and all were from Europe, with 55% from Turkey (245). Another recent global surveillance study reported bla_{OXA-48} and bla_{OXA-48}-like genes in 0.7% of 14 different species of *Enterobacteriaceae* collected from 2012 to 2015 in 20 countries (246). In addition, 8.7% of these isolates also coexpressed a metallo-β-lactamase. The incidence of OXA-48-type enzymes has been lower in Canada than in much of Europe but began to increase beginning in 2015. Throughout Canada, 67 OXA-48-like-producing isolates were collected in the 3-year period between 2011 and 2014, with many of these associated with international travel; in 2018, 21% (261/1,219) of the Canadian carbapenemase-producing enteric isolates were reported to produce OXA-48-like enzymes (247 and personal communication with M. Mulvey, Public Health Agency of Canada). The frequency of OXA-48 production in the United States has been low, with occasional localized isolates reported (248–250). Interestingly, OXA-23 is often found in *P. mirabilis* and was the causative pathogen in a cluster of community-onset

infections in France (251). However, this provided only low-level resistance to carbapenems in this organism and may go undetected.

Species-specific metallo-β-lactamases. (i) *Aeromonas* spp. CphA, the metallo-β-lactamase found in many waterborne *Aeromonas* spp., selectively hydrolyzes penems and carbapenems but no other β-lactams (115). CphA has been found in *A. bestiarum*, *A. caviae*, *A. hydrophila*, *A. sobria*, *A. veronii*, and *A. jandaei* but has not been identified in *A. trota* or *A. schubertii* (252, 253). The production of the MBL CphA is not readily detected by conventional *in vitro* susceptibility tests unless a large inoculum is used; only about 30% of *Aeromonas* spp. tested resistant to imipenem with the standard inoculum (254, 255). In contrast, the presence of CphA can be detected with the modified Hodge test (254). Sources for CphA-producing *Aeromonas* species isolates include Italian rivers and sewage from an urban wastewater treatment plant (256, 257). *Aeromonas* spp. are most often associated with isolates from aquatic animals, including fish, shrimp, and pet turtles, but increasing numbers of CphA-producing patient isolates are being described (253, 255, 258, 259). As a partial explanation, a genetic relationship between *Aeromonas* species fish isolates and CphA-producing patient isolates was recently demonstrated in Taiwan (255). The emergence of imipenem-resistant CphA-producing isolates of *Aeromonas* spp. following therapy with carbapenems has also been reported (260).

(ii) *Bacteroides fragilis*. Carbapenem resistance in *B. fragilis* was first reported in 1983 in Japan (261), followed by a description of carbapenemase activity in similar isolates in the United States in 1986 (262). Conflicting nomenclature is used to describe this carbapenemase as either CfiA or CcrA, an enzyme also recognized for its ability to confer resistance to cefoxitin (263, 264). The *cfiA-ccrA* gene is usually silent and is expressed only if an insertion sequence has inserted upstream of this structural gene, and it has been reported to occur only in *B. fragilis* (265–267). Although the *cfiA-ccrA* gene occurs in $<$10% of *B. fragilis* isolates, it has been reported worldwide, including in Japan, Argentina, China, Slovenia, and the United States, where the incidence of carbapenem-resistant *B. fragilis* remained $\leq$2.5% during 2008 through 2012 (266–269).

(iii) *Bacillus* spp. The Gram-positive bacilli *Bacillus anthracis* and *Bacillus cereus* are generally regarded as environmental bacteria but are responsible for occasional human infections in patients, including animal caretakers/herders, immunocompromised individuals, or neonates (270, 271). Each species produces both a chromosomal serine penicillinase and an MBL, both of which are species specific. However, the frequency of clinical resistance to penicillin and other β-lactam antibiotics in *B. anthracis* is low and has been reported to range from 2 to 16% in isolates from the United States, South Africa, or France (272). The *bla2* MBL from *B. anthracis* has 92% sequence identity with the 569H MBL from *B. cereus* and has low affinity for β-lactams in multiple classes, including the carbapenem imipenem (273, 274). Gene expression of both the chromosomal *bla1* penicillinase and the *bla2* MBL may be either silent or constitutive and is controlled by the genes *sigP*, an extracytoplasmic function sigma factor, and *rsiP* (BA2503), an anti-sigma factor (275).

(iv) *Elizabethkingia* spp. *Elizabethkingia meningoseptica* (formerly *Chryseobacterium menigosepticum* and *Flavobacterium menigosepticum*) is a Gram-negative bacterial pathogen that is increasingly reported in hospital-acquired outbreaks and is known to survive and thrive in the hospital environment (276). Although most commonly associated with immunocompromised patients, *E. meningoseptica* has been associated with pediatric infections with increased frequency (277). *E. meningoseptica* and the related species *Elizabethkingia anophelis* are intrinsically resistant to most β-lactams due to the presence of two metallo-β-lactamases, BlaB and GOB-type variants (278, 279).

(v) *Stenotrophomonas maltophilia*. As described above, *S. maltophilia* produces the chromosomally encoded inducible metallo-β-lactamase L1 and the class A cephalosporinase L2 (137, 138). Production of the tetrameric L1 enzyme, inducible by imipenem, is associated with resistance to β-lactams, including the carbapenems (280). At least 34 novel variants of the L1 β-lactamase have been reported, distributed into four clades according to amino acid identities (80). Although patient isolates of *S. maltophilia* are

highly heterogeneous concerning sequence type, genotypic associations between specific genomic groups and L1 clades have been reported (80). As antibiotic resistance in the pathogen has increased over the past 20 years, future therapeutic options may include the investigational siderophore cephalosporin cefiderocol, with *in vitro* inhibitory concentrations of ≤0.5 μg/ml (281).

Acquired metallo-β-lactamases. (i) IMP carbapenemases. In 1990, Japanese scientists identified the first IMP (active on imipenem) MBL in *P. aeruginosa* on a conjugative plasmid that soon appeared in *S. marcescens* and other *Enterobacteriaceae* in Japan (282–284). Both broad-host-range and narrow-host-range plasmids are associated with bla_{IMP} genes, contributing to their continued dissemination (285). The IMP enzymes confer resistance to penicillins and cephalosporins as well as to carbapenems, but, like other MBLs, they do not hydrolyze aztreonam. In many isolates, only low-level carbapenem resistance is observed, with as many as 20% of IMP-producing *Enterobacteriaceae* testing susceptible to imipenem (286). IMP carbapenemases have remained continuing contributors to carbapenem resistance in Japan as well as in other regions of Southeast Asia (285–288). A recent global surveillance study showed a further spread of IMP-4-producing strains into Australia (289). In addition, a country-wide outbreak of *P. aeruginosa* expressing IMP-13 was detected in Italy (290, 291). Although they have not spread extensively throughout the rest of the world, they are being reported more frequently in Middle Eastern countries (292, 293).

(ii) VIM carbapenemases. Two novel VIM (Verona integron-encoded metallo-β-lactamase) metallo-carbapenemases were first identified in Italy and France in 1997 and 1996, both from *P. aeruginosa* isolates containing bla_{VIM} gene cassettes inserted into a class 1 integron (64, 294). Today, VIM MBLs are found globally, mainly in *K. pneumoniae* and *E. cloacae* complex (287, 295, 296). Although they are identified more frequently than IMP MBLs, they represent a minority of all carbapenemases in carbapenem-resistant pathogens (222, 223, 297). The enzymes were not closely related to other MBLs based on amino acid sequences, with only 28 to 31% sequence identity between the VIM-1/VIM-2 carbapenemases and IMP-1 (64, 294). Biochemically, VIM-2 has a broad substrate hydrolysis profile, which includes penicillins, carbapenems, and most cephalosporins but not aztreonam (294). Worldwide, VIM-2 is the most prevalent VIM-type metalloenzyme in *P. aeruginosa* (287).

Epidemiologically, the VIM carbapenemases initially spread rapidly throughout southern Europe, with major outbreaks of VIM-producing *P. aeruginosa* reported in Italy and Greece by 2006, followed by outbreaks of VIM-producing *K. pneumoniae* (298–301). Until 2008, carbapenemase production in Greece was primarily due to VIM MBLs, until a hyperepidemic KPC-encoding *K. pneumoniae* clone invaded their hospitals (302). By 2014, up to 80% of the carbapenemase-producing *K. pneumoniae* isolates from Greek hospitals produced KPC carbapenemases, with only 12 to 20% of the isolates producing VIM enzymes (303, 304). However, resurgence in the prevalence of VIM enzymes in a Greek university hospital was recently reported. Physicians began prescribing ceftazidime-avibactam in the intensive care unit for patients with KPC-producing bloodstream infections because of the activity of avibactam against the KPC β-lactamase and the reported clinical superiority and low resistance of the combination compared to that of colistin (305). From 2015 to 2017, 88% of carbapenem-resistant *K. pneumoniae* isolates harbored bla_{KPC}; none produced bla_{VIM}. At the end of 2018, the first year after ceftazidime-avibactam had been introduced, 51% of the carbapenem-resistant *K. pneumoniae* isolates tested positive for MBLs: 38% were bla_{VIM} positive, and 11% were positive for both bla_{VIM} and bla_{KPC}. Of the 49% (22/45) of the isolates producing KPC enzymes, four isolates were resistant to ceftazidime-avibactam due to production of an MBL that is not inhibited by avibactam (199, 305). With the introduction of other serine β-lactamase inhibitor combinations into clinical practice, similar scenarios can be expected in the future.

(iii) NDM carbapenemases. The New Delhi metallo-β-lactamase (NDM) was first described in 2009 in an isolate of *K. pneumoniae* from a patient in Sweden that had previously been admitted to two different hospitals in India (5). NDM-1 shares very little

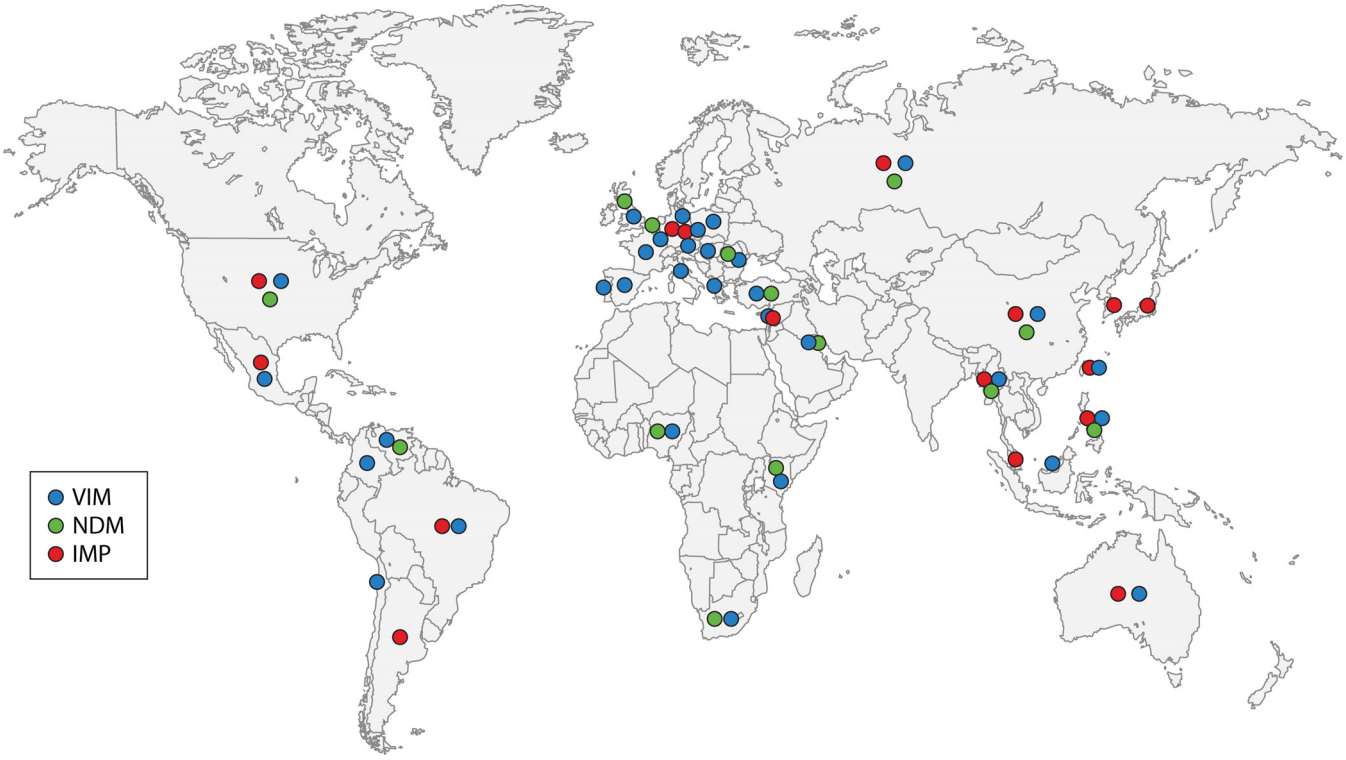

FIG 5 Global distribution of metallo-β-lactamase-positive *Enterobacteriaceae* and *P. aeruginosa*, including NDM-type enzymes collected from 2012 to 2014 from surveillance. (Republished from reference 287).

sequence homology with the other MBLs commonly found in *Enterobacteriaceae*. The closest relative is VIM-1, with only 32.4% amino acid identity (306). A recent surveillance study of isolates collected from 40 countries in 2012 to 2014 showed that NDM-type enzymes accounted for 44.2% of all MBL-producing *Enterobacteriaceae* collected (287). Over 80% of recent *E. coli* isolates with NDM enzymes originated from Asia, predominantly from India, followed by China (307). Retrospective analyses of clinical isolates from India identified bla_{NDM-1} as early as 2006 (6). Within a few years, the gene had become endemic to all parts of India and Pakistan and had begun to spread into northern Europe (7). In less than a decade since those initial few reports, NDM-1 has spread across the globe (Fig. 5) and has been detected in many species of pathogenic enteric bacteria, foodborne *Shigella* spp. and *Vibrio cholerae*, and the nonfermenters *A. baumannii* and *P. aeruginosa* (287, 308). Isolates expressing NDM-1 are often multidrug resistant due to the movement of bla_{NDM} genes with other resistance determinants. For example, there has been strong correlation with the presence of NDM-1 and the prevalent ArmA, RmtB, or RmtC 16S rRNA methylases that cause resistance to aminoglycosides, including the recently approved plazomicin (309, 310).

In addition to the widespread presence of bla_{NDM} on the Indian subcontinent, NDM now appears to be endemic to the Balkan countries, Northern Africa, and the Arabian Peninsula, where these countries may serve as a secondary reservoir for the enzyme (306). Recent outbreaks caused by NDM-producing *Enterobacteriaceae* have been reported in hospitals in Greece, Mexico, and the Netherlands and in a neonatal unit in China (311–313). Unlike the dissemination of KPC, high-risk clones and epidemic plasmids have not been widely implicated in the global spread of bla_{NDM} genes (209). Although geographically localized outbreaks have been associated with a single clonal strain, little commonality has been seen, with multiple sequence types and plasmids involved, demonstrating the promiscuity of bla_{NDM} genes. Examples just in Europe include a recent outbreak of NDM-producing *K. pneumoniae* isolates of sequence type 716 in Belgium (314); an outbreak in Italy due to NDM-producing *K. pneumoniae* ST16

(315); and outbreaks among eight Greek hospitals (2013 to 2016) related to ST11, the same sequence type as that seen in the first NDM-producing Greek outbreak and in a recent outbreak in Bulgaria (316). A recent global survey of pathogenic NDM-producing *E. coli* isolates identified a prevalence of sequence types ST101 and ST167 in multiple countries (307). Another study of GenBank sequences containing bla_{NDM} genes reported more than 40 sequence types each for *E. coli* and *K. pneumoniae* in 2019 (317).

Bacteria Producing Inhibitor-Resistant β-Lactamases

Inhibitor-resistant β-lactamases belonging to functional group 2br are derivatives of TEM and SHV enzymes, with amino acid substitutions that make these enzymes refractory to inhibition by clavulanic acid and sulbactam; however, most remain susceptible to inhibition by tazobactam as well as the newer inhibitors, such as avibactam (38, 39, 221). Mutations responsible for this phenotype have been noted particularly at the following amino acid positions: Met69, Ser130, Arg244, Arg275, and Asn276 (318). Most inhibitor-resistant β-lactamases are variants of the TEM-1 enzyme. These were formerly called IRT (for inhibitor-resistant TEM) but are now given sequential TEM numbering. Only three SHV-type β-lactamases have been described as being inhibitor resistant, SHV-49, -56, and -107, all identified from European *K. pneumoniae* clinical isolates (319–321). A few TEM variants maintain the ESBL phenotype and also demonstrate inhibitor resistance and are referred to as complex TEM mutant (CMT) β-lactamases (318). The prevalence of organisms producing these inhibitor-resistant enzymes may be underestimated, because many laboratories do not identify these strains routinely (322). However, a strain of *K. pneumoniae* expressing the IRT TEM-30 was identified among KPC-producing isolates in an outbreak in New York (221).

Organisms with Multiple β-Lactamases

Production of multiple β-lactamases in a single organism has become common in contemporary nosocomial isolates, especially in Gram-negative pathogens, where mobile elements carrying a variety of resistance factors are freely transferred among species. In the Gram-positive world, penicillinase-producing staphylococci appear to produce only a single β-lactamase protein in each strain, although at least four types of penicillinases have been identified in this species (95). However, β-lactamases in *S. aureus* have not received the same molecular attention as β-lactamases in Gram-negative bacteria, so it is possible that greater heterogeneity exists than is currently realized. In Gram-negative bacteria, multiple reports of clinical isolates over the past 30 years document the production of more than one β-lactamase per strain (323–325). Of the baseline pathogens identified during the recent phase 3 pathogen-directed clinical trial of ceftazidime-avibactam, only 35/302 (11.6%) tested positive for a single β-lactamase gene; nine of those isolates (3.0% of the total) contained only a chromosomal *ampC* gene (21).

Multi-β-lactamase production can occur in all β-lactamase-producing Gram-negative species but is especially noticeable with a high frequency in carbapenemase-producing, multidrug-resistant bacteria (250, 326). In a survey of carbapenem-resistant *Enterobacteriaceae* from California (2013 to 2016), 79.2% of the carbapenemase gene-positive isolates compared to 60.5% of carbapenemase gene-negative isolates also tested positive for either an ESBL- or plasmid-encoded AmpC gene (250). Of greater concern is the coproduction of multiple carbapenemases in the same organism. A survey of 52 reports of the occurrence of multiple carbapenemases in a single organism (Table 2) showed that since 2008, KPC enzymes appeared in combination with another carbapenemase in at least 110 isolates, whereas OXA-48-related carbapenemases were named in carbapenemase combinations in over 130 isolates (Table 2 and Fig. 6). In these isolates, KPC β-lactamases were more likely to be identified in combination with VIM MBLs (75% of the isolates) than with other carbapenemases (Fig. 6). Many of these isolates originated from the Americas and Greece, although three isolates from Spain produced KPC-2/3 with VIM-1 (327, 328). Fewer isolates coproduced KPC enzymes with NDM-1 (7%), IMP (6%), or OXA-48 (6%) carbapenemases. The carbapenemases copro-

TABLE 2 Production of multiple carbapenemases in the same Gram-negative pathogen, excluding *Acinetobacter* spp.

Carbapenemase class			Producing organism	No. of isolates	Yr of isolation	Location	Reference
Class A	Class B	Class D					
KPC-2	IMP-8 or IMP-10	ND[a]	*S. marcescens*, *P. aeruginosa*	7	2009–2011	Brazil, Puerto Rico	362, 363
KPC-2 or KPC-3 or KPC-17	NDM-1	ND	*C. freundii*, *E. cloacae*, *Enterobacter hormaechei*, *K. pneumoniae*	9	2010–2016	Brazil, China, Colombia, India, USA	245, 364–370
KPC-2 or KPC-3 or KPC-18	VIM-1 or VIM-type	ND	*C. freundii*, *E. cloacae*, *K. oxytoca*, *K. pneumoniae*	36	2008–2017	Greece, Spain, USA	304, 327, 328, 368, 371, 372
KPC-type	VIM-type	ND	*K. pneumoniae*	50	2013–2018	Greece	228, 305
KPC-3, SME-1	ND	ND	*S. marcescens*	3	2015	USA	373
KPC-2 or KPC-3, NMC-1	ND	ND	*K. pneumoniae*	4	2013–2017	Malaysia, USA	369, 374, 375
KPC-2, NMC-1	ND	OXA-48	*K. pneumoniae*	1	2013	Malaysia, USA	374
KPC-type	ND	OXA-48	*K. pneumoniae*	7	2013–2014	Malaysia, Taiwan	304, 374, 376
ND	IMP-4, VIM-2	ND	*S. marcescens*	15	2015	Egypt	292
ND	IMP-4 or IMP-8, NDM-1	ND	*K. pneumoniae*	6	2013	China, Malaysia	226, 374
ND	NDM-1 or NDM-type	OXA-48 or OXA-48-like	*C. freundii*, *E. cloacae*, *Enterobacter ludwigii*, *E. coli*, *K. oxytoca*, *K. pneumoniae*, *Enterobacteriaceae*	91	2007–2018	Belgium, England, France, Romania, India, Iran, Saudi Arabia, Spain, Tunisia, Turkey, USA	215, 246, 297, 304, 377–387
ND	NDM-type, VIM-type	OXA-48	*K. pneumoniae*, *Enterobacter* spp.	2	2011, 2018	USA, Vietnam	329, 370
ND	NDM-1 or NDM-5 or NDM-7	OXA-181	*E. coli*, *K. pneumoniae*	15	2010–2017	Belgium, Canada, Egypt, India, Norway, South Korea, Sri Lanka	388–395
ND	NDM-1	OXA-232	*K. pneumoniae*	4	2012–2018	India, South Korea, USA	361, 396, 397
ND	VIM-type	OXA-48-type	*C. freundii*, *Enterobacter* spp., *E. coli*, *K. pneumoniae*, *Enterobacteriaceae*	22	2006–2016	Egypt, France, India, Kuwait, Spain, Turkey	6, 244, 246, 370, 378, 383, 398

[a]ND, not detected.

duced most frequently with OXA-48-type enzymes were MBLs; 81% of these isolates also produced NDM β-lactamases, whereas 14% of the OXA-producing isolates were associated with MBLs in the VIM family (Fig. 6). When NDM-type enzymes were coproduced with other carbapenemases, OXA-48-type enzymes were present in 90% of the isolates (Fig. 6), followed by IMP (5%) and KPC (4%). Although many of the organisms coproducing carbapenemases were *K. pneumoniae* isolates (60%), dual carbapenemase production was also reported in other enteric bacteria, including *C. freundii* (4.1%), *Enterobacter* spp. (3.7%), *K. oxytoca* (0.9%), and *S. marcescens* (11.1%) (Table 2). One of the more troublesome combinations reported recently was the triple

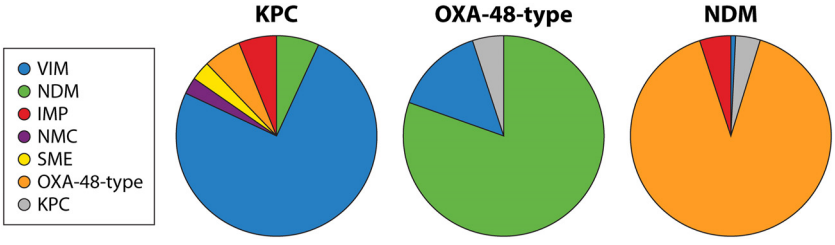

FIG 6 Coproduction of carbapenemases in the same organism. Data for production of KPC β-lactamases, OXA-48-type β-lactamases, and NDM β-lactamases with other carbapenemases were compiled from Table 2.

threat of NDM-, VIM-, and OXA-48-encoding genes in a single *K. pneumoniae* isolate; this was identified from a U.S. patient who had undergone outpatient urodynamic studies in a hospital in India (329).

Coproduction of multiple β-lactamases of different functionalities occurs frequently in Gram-negative bacteria that produce species-specific chromosomal enzymes (21). Enteric bacteria, such as *Enterobacter* spp., *Citrobacter* spp., and *S. marcescens*, and *P. aeruginosa* are affected. For example, *K. oxytoca* strains usually produce an OXY-type β-lactamase with an ESBL-like hydrolysis profile. Based on whole-genome sequencing, analysis of 12 carbapenemase-producing *K. oxytoca* isolates from Spain revealed three different bla_{OXY} genes among the strains, together with genes encoding OXA-48, VIM-1, KPC-2, or KPC-3; two isolates carried genes for VIM-1, KPC-2/3, and an OXY enzyme of the bla_{OXY-2} genotype (328). Similarly, *K. pneumoniae* usually produces at least one SHV β-lactamase (330), together with β-lactamases from other molecular classes (21). Contemporary *Enterobacter* spp., *Citrobacter* spp., and *P. mirabilis*, with their own chromosomal AmpC cephalosporinases, all have a high probability of carrying another β-lactamase from molecular class A or D (246). Frequently these are TEM-1- or OXA-1-related enzymes (21, 246). These are narrow-spectrum β-lactamases with high catalytic efficiencies for commonly prescribed penicillins (331) and are likely retained to augment the cephalosporin-specific substrate profile provided by the AmpC enzymes (38).

TRANSMISSION OF β-LACTAMASE-PRODUCING PATHOGENS

Transmission of β-lactamase-producing bacterial pathogens is dependent upon multiple factors. The human reservoir in which the resistant organism emerges is affected by various elements, including geographical location, population density, hygiene, and use of antibiotics. For example, the prevalence of ESBL-producing *E. coli* is very high in Southeast Asia, Africa, and Central America and has a much lower prevalence in Europe (332). There is even variation within Europe, as the incidence of *Enterobacteriaceae* carrying ESBLs is higher in Western European countries that border the Mediterranean but is very low in the Netherlands and Scandinavia (333). In addition, we now live in a global society that is increasingly mobile, whether it is vacationers, medical tourists, or refugees. The rapid spread of NDM-producing *Enterobacteriaceae* was attributed in part to a large volume of medical tourism from northern Europe to India (7). All of these influences contribute to outbreaks and dissemination of β-lactamase-mediated resistance.

The epidemiology of β-lactamase-mediated resistance first and foremost follows the pathology of the bacterial pathogen in which the enzymes are found. Where you find the pathogen in a patient who requires heavy usage of β-lactam antibiotics, there too will you find various β-lactamases. For *Enterobacteriaceae*, the main reservoir of β-lactamase-producing pathogens is the digestive tract of colonized patients, with the majority of the infections caused by pathogens identical, or highly genetically related, to the colonizing organisms (334). Transmission of resistant *Enterobacteriaceae* occurs between patients with or without prior transmission to a health care worker. The rate of transmission of β-lactamase-producing pathogens can vary with species, likely according to differences in virulence factors. One study reported that the transmission rate of ESBL-producing organisms was 2-fold higher from patients colonized with *K. pneumoniae* than from those colonized with *E. coli* (335). Large-scale nosocomial outbreaks have been caused by highly virulent and transmissible isolates of ESBL- and carbapenemase-producing strains, such as *E. coli* ST131 and *K. pneumoniae* ST258 (209, 336). Although most outbreaks of β-lactamase producing *Enterobacteriaceae* occur in the ICU or in immunocompromised patients, neonates can also be affected. A recent report from Japan characterized an outbreak of ESBL-producing *E. coli* that was traced to shared breast milk from donor mothers (337).

The epidemiology of β-lactamase-producing *Enterobacteriaceae* has also changed over time. This is exemplified by the series of outbreak and endemic isolates of *E. coli* and *K. pneumoniae* expressing various β-lactamases that have been detected in the past 25 years in a single New York hospital. Ceftazidime was approved in 1984, and just

a few years later, the ESBL era was born. An outbreak of ceftazidime-resistant *K. pneumoniae* that involved 155 patients during a 19-month period, from October 1988 to March 1990, was detected in The New York Hospital Medical Center of Queens (338, 339). Characterization of these isolates showed that they contained TEM-26 together with TEM-10, two of the first ESBLs to become endemic in the United States. Infection control measures resulted in the cessation of this outbreak; however, a low level of resistance to ceftazidime persisted. In 1993, several isolates of *K. pneumoniae* were noted that were not only ceftazidime resistant but also resistant to cefotaxime. These isolates produced the SHV-7 β-lactamase and were likely selected following increased prescribing of cefotaxime as a part of the effort to control the spread of TEM-26 (340). In response to the outbreak of ESBL-producing organisms, cephamycins, especially cefotetan, became the empirical treatment of choice. Subsequently, in 1995 there was an outbreak of *E. coli* and *K. pneumoniae* isolates that were resistant to cefoxitin and cefotetan by the acquisition of a novel plasmid-mediated AmpC-type β-lactamase, designated ACT-1 (75). As a result of this new wave of resistant organisms, the use of imipenem increased dramatically in the hospital. Immediately, *K. pneumoniae* isolates producing ACT-1 also became resistant to imipenem because of the loss of an outer membrane protein (75). However, the use of imipenem during these outbreaks also helped to select for the next wave of resistance. In the early 2000s, *K. pneumoniae* expressing KPC-2 became endemic across New York City, including in this hospital (221). In a 2009 study, *K. pneumoniae* isolates coproducing both KPC and CTX-M enzymes were isolated from nonhospitalized patients with urinary tract infections who presented at the emergency room or associated clinic of this hospital (341). Through massive infection control efforts across the city, the prevalence of KPC-producing *K. pneumoniae* has declined over the last decade, but the pathogen has not completely disappeared (211, 234).

P. aeruginosa is an opportunistic pathogen that causes a variety of infections, including sepsis, pneumonia, urinary tract infections, and soft-tissue infections (342). It is a leading cause of nosocomial infections, especially in the ICU, and is associated with immunocompromised patients due to solid-organ transplantation, invasive procedures, and immunosuppressive therapy (343). *P. aeruginosa* can survive well in the environment, particularly in water sources. Several outbreaks of carbapenem-resistant *P. aeruginosa* have been traced to an environmental reservoir within the hospital (344). Until very recently, most of the β-lactam resistance in *P. aeruginosa* was attributed to the loss of the OprD porin protein combined with high-level production of the naturally occurring AmpC β-lactamase, often in isolates that had upregulated efflux systems (345). However, in recent years, acquired β-lactamases have been responsible for outbreaks with increasing frequency. ESBLs such as PER-1 and OXA-10 are commonly found in *P. aeruginosa* (346). The increase in acquired β-lactamases has been especially noteworthy, as MBLs have moved into *P. aeruginosa* and have been the cause of outbreaks in many countries worldwide (347–350).

A. baumannii can cause a variety of acute hospital infections, including pneumonia (especially ventilator-associated pneumonia), bloodstream infections, urinary tract infections, skin and soft-tissue infections, burn and surgical wound infections, endocarditis, meningitis, and osteomyelitis (351). The majority of these are nosocomial infections, because the risk factors that make patients prone to the colonization and infection with *A. baumannii* include surgical procedures, major trauma, elderly patients, and prior antibacterial therapy. In addition, infections caused by *A. baumannii* are often associated with medical treatments that rely on some kind of indwelling hardware, including mechanical ventilators, intravascular catheters, urinary catheters, and drainage tubes (352). It has been reported that *A. baumannii* is the causative pathogen in 2 to 10% of all Gram-negative hospital infections, mainly affecting critically ill patients, especially in ICUs (351). Although β-lactamases of all classes contribute to resistance in *Acinetobacter* spp., *A. baumannii* is of particular concern when it becomes resistant to carbapenems. In these cases, health care-associated infections may increase the risk of mortality from 8% to 40% (353).

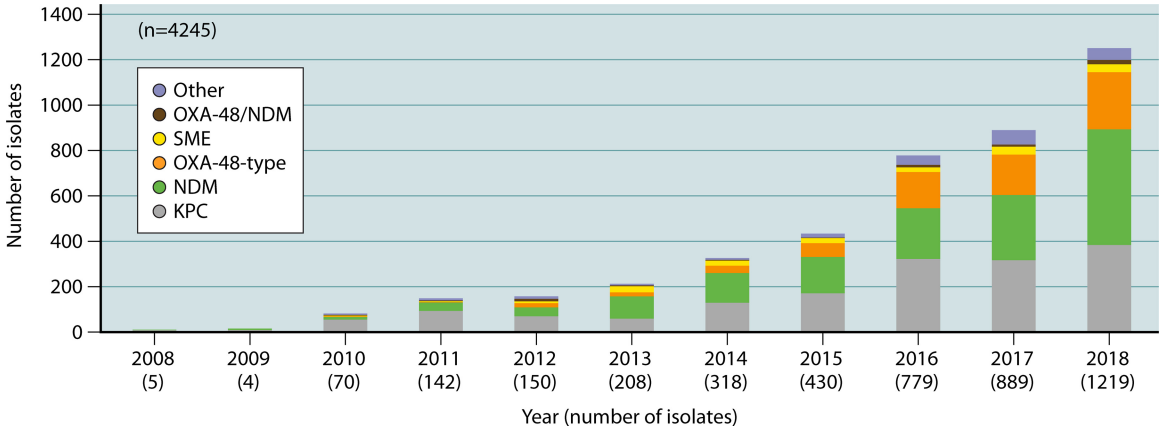

FIG 7 Surveillance of carbapenem-producing *Enterobacteriaceae* in Canada. Data were provided with the permission of Michael Mulvey, Public Health Agency of Canada.

Nosocomial infections caused by β-lactamase-producing pathogens are associated with serious health and economic adverse outcomes, such as clinical failure with increased in-hospital mortality, prolonged length of stay, and increased direct and indirect costs (354). A meta-analysis showed that bacteremia caused by ESBL-producing *Enterobacteriaceae* was associated with a higher mortality than those caused by ESBL-negative isolates (355). Furthermore, infections caused by ESBL-producing *E. coli* and *Klebsiella* spp. were associated with increased health care costs due to prolonged infection-related length of stay and indirect care costs for enhanced infection control measures (356). An evaluation associated with an outbreak of carbapenemase-producing *Enterobacteriaceae* in London concluded that the overall economic costs were due not only to the expenses of treating infections but also to lost opportunities to treat other patients (357).

FUTURE DIRECTIONS

β-Lactamase-producing pathogens will never disappear and can be expected to continue to increase with greater variety in the future. As an example, surveillance data from the Canadian Public Health Laboratory Network show the continuing increase in carbapenemase-producing nonduplicated pathogens since 2011 (Fig. 7), with greater numbers of enzymes and greater diversity among the kinds of carbapenemases over the past 9 years of surveillance (data used with permission from Michael Mulvey, Public Health Agency of Canada). Part of the reported increase may be due to better reporting of molecular data. However, it is also likely that increases in β-lactamase production are due to the ease with which these enzymes can travel between carriers and infected patients from all parts of the world. These pathogens have become well-established in both the community and in health care settings and will continue to exist as long as β-lactam antibiotics continue to be used. Although agents such as the newer β-lactamase inhibitor combinations, i.e., ceftazidime-avibactam, meropenem-vaborbactam, and imipenem-relebactam, have provided opportunities for safe and effective therapies to treat some of the most threatening carbapenemase-producing pathogens, they do not address the problems associated with metallo-β-lactamases. Even if some of the newer investigational agents are successful in treating MBL-producing pathogens, resistance to these new drugs also can be expected to emerge, as has been seen with ceftazidime-avibactam (45, 51). This resistance may be due to more than the known mechanisms of resistance, which include enzyme variants with decreased affinity for the inhibitors, altered PBPs, or decreased entry into the cell as a result of upregulated efflux pumps or changes in outer membrane proteins. Production of multiple β-lactamases from different classes, as exemplified in Table 2, will continue, so that cocktails of class-specific β-lactamase inhibitors may be required for effective treatment of serious infections.

Efforts to promote stewardship of these valuable agents are necessary and have been somewhat successful in localized areas. For example, Scandinavian countries exhibit lower resistance rates than much of the rest of Europe (2), due in part to increased use of narrow-spectrum penicillins and a reluctance to use the most advanced antibiotics in their health care centers (358, 359). As noted above, some hospitals have contained the spread of carbapenemases within their facilities as a result of stricter infection control measures (234, 235). In Israel, the reduction in the number of carbapenemase-producing *Enterobacteriaceae* required a successful effort to institute country-wide infection control measures that greatly diminished the number of new cases, but that did not entirely eradicate the causative pathogens (235). Notably, the model used to monitor and control resistance was extended to include other multidrug-resistant organisms and hospital-acquired infections (360). Thus, resistance may be confined on a national level with programs such as enhanced surveillance networks and promotion of good stewardship of the current antimicrobial agents.

Advances in molecular diagnostics are providing clinical microbiologists with the ability to define specific resistance mechanisms in clinical specimens at an early stage. Diagnostic kits that can test for multiple β-lactamases in a single assay mean that ESBL producers can be differentiated from carbapenemase- or metallo-β-lactamase-producing pathogens within hours of collecting a specimen. This allows a clinician to prescribe an appropriate antibiotic much sooner than previously possible. Another tool that is becoming more prominent is whole-genome sequencing, which provides in-depth knowledge of multiple resistance factors carried by pathogenic bacteria, thereby giving us greater insight into how therapies can be guided at an early stage (361). However, none of these approaches will eliminate the ubiquitous β-lactamase-producing bacteria that will continue to remain intimately associated with their human hosts.

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Patricia A. Bradford is the owner of Antimicrobial Development Specialists, LLC, a consulting company focusing on the late-stage development of antibiotics. During tenures at AstraZeneca, Novartis, Wyeth Pharmaceuticals, and Lederle Laboratories, she worked on antibiotic projects that included development of piperacillin-tazobactam, tigecycline, and ceftazidime-avibactam. She is a Fellow of the American Academy of Microbiology, has over 100 publications in peer-reviewed journals, and has written several review articles and book chapters. She served as an editor for *Antimicrobial Agents and Chemotherapy* (2001 to 2011) and is currently a Senior Editor for ASM's newest journal, *mSphere*. She is an active member of the Antimicrobial Susceptibility Testing subcommittee of the Clinical and Laboratory Standards Institute. Prior to working in industry, she was a clinical microbiologist at Nebraska Methodist Hospital in Omaha. She received a B.S. in Medical Technology from the University of Nebraska Medical School, Ph.D. in Medical Microbiology from Creighton University, and completed a postdoctoral fellowship with Karen Bush in β-lactamase research.