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REVIEW

# Plasmid evolution in carbapenemase-producing *Enterobacteriaceae*: a review

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**Carbapenem-resistant *Enterobacteriaceae* (CRE) have been listed by the WHO as high-priority pathogens owing to their high association with mortalities and morbidities. Resistance to multiple β-lactams complicates effective clinical management of CRE infections. Using plasmid typing methods, a wide distribution of plasmid replicon groups has been reported in CREs around the world, including IncF, N, X, A/C, L/M, R, P, H, I, and W. We performed a literature search for English research papers, published between 2013 and 2018, reporting on plasmid-mediated carbapenem resistance. A rise in both carbapenemase types and associated plasmid replicon groups was seen, with China, Canada, and the United States recording a higher increase than other countries. *bla*$_{KPC}$ was the most prevalent, except in Angola and the Czech Republic, where OXA-181 ($n = 50$, 88%) and OXA-48–like ($n = 24$, 44%) carbapenemases were most prevalent, respectively; *bla*$_{KPC-2/3}$ accounted for 70% ($n = 956$) of all reported carbapenemases. IncF plasmids were found to be responsible for disseminating different antibiotic resistance genes worldwide, accounting for almost 40% ($n = 254$) of plasmid-borne carbapenemases. *bla*$_{CTX-M}$, *bla*$_{TEM}$, *bla*$_{SHV}$, *bla*$_{OXA-1/9}$, *qnr*, and *aac-(6′)-Ib* were mostly detected concurrently with carbapenemases. Most reported plasmids were conjugative but not present in multiple countries or species, suggesting limited interspecies and interboundary transmission of a common plasmid. A major limitation to effective characterization of plasmid evolution was the use of PCR-based instead of whole-plasmid sequencing–based plasmid typing.**

**Keywords:** CRE; carbapenem resistance; plasmid typing; replicon types; incompatibility groups

## Introduction

Prescription of carbapenems is increasing extensively worldwide owing to their relative safety and efficacy in resolving most otherwise fatal multidrug-resistant (MDR) bacterial infections. Subsequently, this is triggering and leading to the selection of resistance to carbapenems among an increasing number of Gram-negative bacterial pathogens, including *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*.[1] The increasing worldwide incidence and prevalence of carbapenem-resistant *Enterobacteriaceae* (CRE), *P. aeruginosa*, and *A. baumannii*, with their very high attributable mortalities ranging from 6.6% to 20%, are considered global threats to human and animal health.[2–5] Subsequently, they have been listed as priority 1 critical pathogens by the World Health Organization.[6] Owing to the importance of carbapenems in the clinical management of MDR infections, the emergence and rapid dissemination of CREs that are also resistant to fluoroquinolones, aminoglycosides, and colistin reduce therapeutic options.[7,8] Although CREs have been mostly isolated from healthcare-associated infections, *Enterobacteriaceae* also cause community-acquired infections, which helps explain the spread of CREs in the community.[9]

Carbapenem resistance is mainly driven by carbapenemases found on mobile genetic elements

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(MGEs), such as integrons, insertion sequences, transposons, and mobile plasmids, that can shuttle carbapenemase-expressing genes within and across bacterial cells of the same or different species.[10–12] The ability of plasmids to carry multiple antibiotic resistance genes (ARGs) and be mobilized across same and different species via conjugation make them very important in the molecular epidemiology of CREs.[12,13] This is further complicated by the ability of multiple plasmids, depending on their incompatibility (Inc), to be harbored in a single CRE cell. Coupled with their extrachromosomal and self-replicative characteristics, plasmids are crucial for bacterial adaptation and survival in unsuitable environments.[13,14]

The centrality of plasmids in the epidemiology of antibiotic resistance necessitates an in-depth study into their structural and genetic characteristics. Plasmid replicon typing is the main technique used in identifying and classifying plasmids carrying virulence and/or ARGs.[15] These typing schemes, which include the PCR-based replicon typing (PBRT) and plasmid mobility (MOB) typing, can determine whether antibiotic resistance is driven by a dominant or diverse plasmid type(s).[16]

### *Literature search strategy*

PubMed was searched for all English research papers using the following search words: "carbapenems," "carbapenemase," "*Enterobacteriaceae,*" and "plasmids." This search yielded a total of 2098 articles after duplications were removed. A search period of 6 years, from January 1, 2013 to August 30, 2019, was applied, which decreased the number of papers to a total of 862. The title and abstracts of these papers were screened for eligibility according to our hypothesis and research questions, which resulted in 102 research papers being included in the analysis. The inclusion criteria included all papers retrieved using the keywords "carbapenem," "carbapenemase," "*Enterobacteriaceae*," and "plasmid," and reporting plasmid replicon groups associated with carbapenemases in *Enterobacteriaceae* species. We excluded all papers that reported plasmid replicon groups in noncarbapenemase-producing *Enterobacteriaceae* (Fig. 1). Plasmid sequences of unpublished articles but deposited in Genbank were also included in this review (Supplementary Materials, online only), and accession numbers are shown in Table S1 (online only).

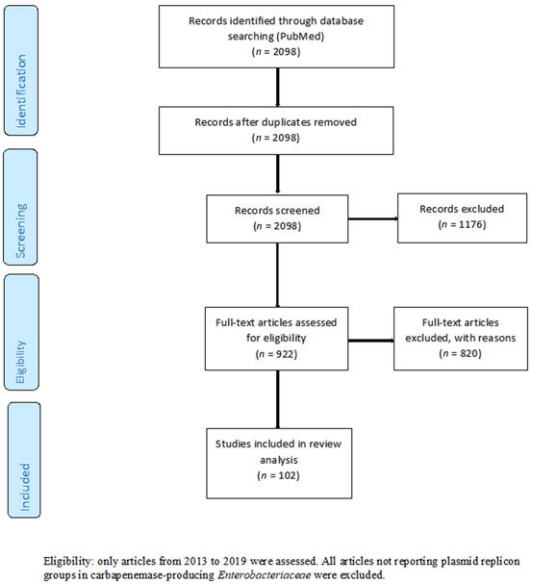


**Figure 1.** PRISMA-adapted flow diagram of included and excluded studies. Adapted from the PRISMA website (http://prisma-statement.org/PRISMAStatement/CitingAndUsingPRISMA.aspx).

### *Statistical analysis*

All pie and bar charts in this review were constructed after analysis and calculation of the results using Microsoft Excel 365®. All charts were also designed using Microsoft Excel 365.

### *Evidence before this review*

To our knowledge, two previous articles have been published on this topic, a mini review published by Carattoli[17] focused on plasmid families in *Enterobacteriaceae*; a second review, published by Mathers *et al.*,[18] focused on high-risk clones in the spread of MDR *Enterobacteriaceae* and associated resistance plasmids. In contrast to the former minireview, our review provides an update on plasmid families associated with carbapenemases; in contrast to the latter review, which did not report the frequency of carbapenemase genes and their associated plasmid groups, our review aims to provide such data, in addition to looking at all *Enterobacteriaceae* species instead of specific clones.

### *Purpose of this review*

Our systematic review aims to provide insights into plasmids mediating the dissemination of carbapenem resistance in *Enterobacteriaceae*. It focuses on the following aspects: classification of

carbapenemases, methods used in plasmid classification, plasmid biology and incompatibility plasmid groups, plasmid epidemiology, and MGEs associated with Inc groups. Thus, our review aims to highlight the frequency and evolution of plasmids carrying carbapenemase genes over the last 5 years. Information that we provide also shows the evolution of the genetic structures in different incompatibility groups, which helps to explain the spread of carbapenemases and plasmids worldwide.

## Carbapenems used as last resort antibiotics

Carbapenems are β-lactam antibiotics that differ from other β-lactams by the presence of a carbon instead of a sulfone at the fourth position of the lactam ring.[19] Carbapenems have broad-spectrum activity against both Gram-negative and Gram-positive bacteria, and are usually reserved for serious infections caused by Gram-negative bacteria (GNB).[20] However, each carbapenem differs in stability, ability to inhibit or induce β-lactamases, and resistance to β-lactamases.[21] These characteristics have been used to classify carbapenems into three groups. Group 1 carbapenems, such as ertapenem and panipenem, have limited activity against nonfermentative GNB and are suitable for community-acquired infections. Group 2 carbapenems include biapenem, doripenem, imipenem, and meropenem and are active against nonfermentative GNB and suitable for hospital-acquired infections. Group 3 carbapenems, such as PZ-601 (not licensed), comprise the cationic and dithiocarbamate carbapenems and have extended spectrum of activity; they are also active against methicillin-resistant *Staphylococcus aureus*.[22,23] Carbapenems are usually saved for β-lactamase–producers that are resistant to almost all classes of β-lactams, except carbapenems. However, some *Enterobacteriaceae* and other nonfermenters may produce carbapenem-hydrolyzing enzymes that enable them to resist even carbapenem activity.[23] Carbapenemase production is thus the major mechanism of carbapenem resistance in *Enterobacteriaceae*.

## Classification of carbapenemases

Carbapenemases hydrolyze carbapenems and all other β-lactams[24] by breaking the β-lactam ring structure of β-lactam antibiotics, thus disrupting their function. β-Lactamases are classified into different classes according to either their amino acid sequence or their functionality, that is, substrate specificity.

In the 1980s, Ambler grouped β-lactamases into four classes, that is, classes A–D, based on their amino acid sequence homology.[25] These classes function by different mechanisms based on the molecules at their active sites. Classes A, C, and D have serine at their active sites and use a serine ester hydrolysis mechanism, while class B members have a zinc ion(s) at their active sites, which facilitates substrate catalysis.[26,27] Among these four classes, carbapenemases are placed in only three: classes A, B, and D.

The functionality classification scheme consists of three major groups: groups 1–3. Group 1 consists of cephalosporinases; group 2 are the penicillinases, cephalosporinases, and broad-spectrum β-lactamases inhibitors; and group 3 comprises the metallo-β-lactamases (MBLs).[28,29] In this scheme, carbapenemases are placed in Group 2 (class A and D) and Group 3 (class B), with the former being serine carbapenemases (SBLs).[10,28,29]

### *Class A carbapenemases*

The first class A carbapenemase to be described was chromosomally located and reported in both clinical and environmental GNB.[30] It was only in the 1990s that plasmid-mediated class A carbapenemases were commonly described in clinical GNB, including in *Enterobacteriaceae*, *P. aeruginosa*, and *Acinetobacter* species.[31] Both chromosomally and plasmid-mediated carbapenemases are capable of hydrolyzing almost all β-lactams, including carbapenems, while SBLs are inhibited by commercially available β-lactamase inhibitors, such as clavulanic acid and tazobactam.[30,32] The most commonly described plasmid-mediated class A carbapenemases are the *Klebsiella pneumoniae* carbapenemase (KPC) and Guiana extended-spectrum β-lactamase (GES).

The GES family has more than 20 variants, with GES-1 showing activity toward other β-lactams but not carbapenems.[33,34] Most GES variants have activity toward broad-spectrum cephalosporins, but amino acid substitution in other variants extends their activity toward carbapenems.[34] Such variants with carbapenemase activity include GES-2, GES-4, GES-5, GES-6, GES-14, GES-16, and GES-18.[33,35–39] GES-2 is commonly detected in *Pseudomonas* spp.,

and it was first identified in a clonal outbreak of *P. aeruginosa* in South Africa.[40] Additionally, GES-5 has been described in *Pseudomonas* spp. and *Enterobacteriaceae*, and has been widely reported in South America, with a few reports in Canada, the Czech Republic, Turkey, Portugal, South Africa, and South Korea.[12,34,41–44] Other GES variants are also reported, although rarely.[45,46]

KPCs have broad-spectrum activity against almost all β-lactams, including carbapenems, and they are mostly reported in *K. pneumoniae* clinical isolates.[47,48] However, in the last decade, KPC has also been reported in other species of *Enterobacteriaceae*, including *Escherichia coli*, *Enterobacter* spp., *Klebsiella oxytoca*, *Proteus mirabilis*, *Serratia marcescens*, *Morganella morganii*, and *Citrobacter freundii*, among others.[48–51] KPC carbapenemases are widely distributed worldwide, but they are mostly reported in the United States, where they cause majority of reported cases of infection.[52,53] In the United States, KPC producers are usually associated with hospital outbreaks caused by patient-to-patient transmission of clonally related resistant organisms.[54] More than 20 KPC variants have been described, but KPC-2 and KPC-3 are most reported and widely distributed.[48,55] KPCs have been reported in several *K. pneumoniae* sequence types (ST), although ST258, ST11, and, more recently, ST101, are the major players associated with pandemic spread.[12,54,56–58]

### *Class B metallo-β-lactamases*

Class B carbapenemases, or MBLs, are broad-spectrum β-lactamases capable of hydrolyzing all clinically available β-lactams except monobactams and are not inhibited by the commercially available β-lactamase inhibitors clavulanic acid, tazobactam, or sulbactam.[34,59] However, MBLs are inhibited by metal ion chelators, such as ethylene diamine tetra-acetic acid (EDTA) and dipicolinic acid,[59–62] as their hydrolytic activity is dependent on the interaction between the active site zinc ion ($Zn^{2+}$) and the β-lactam.[61] The most common MBLs reported in *Enterobacteriaceae* include Verona integron-encoded metallo-β-lactamase (VIM), imipenemase (IMP), and New Delhi metallo-β-lactamase (NDM).[56,60,61,63,64]

IMP types were among the acquired MBLs first identified in *Enterobacteriaceae*, the most common variant being IMP-1.[61] In 1991, IMP-1 was isolated for the first time in *S. marcescens* in Japan, and was located on a class 1 integron.[34] Since then, more than 40 variants have been reported in Japan, Taiwan, and around the whole world.[30]

The first occurrence of VIM-type (VIM-1) β-lactamase was in 1997 in Verona, Italy in a *P. aeruginosa* isolate; VIM-2 was reported in France.[60,65–67] So far, more than 40 variants of VIM have been described, albeit VIM-2 is the most common worldwide[34,68] VIM-2 is usually common in *Pseudomonas* spp., while VIM-1 is common in *Enterobacteriaceae*.[17,69] VIM-type carbapenemases have been reported in more than 17 countries but are most prevalent in Africa and Europe.[70] *K. pneumoniae* species are mostly associated with VIM variants, followed by *Enterobacter cloacae*, *Citrobacter* spp., and *E. coli* in Greece, Spain, and, rarely, in Germany and the Czech Republic.[70–72] Since 2014, sporadic reports of VIM-4–producing *K. pneumoniae* and *E. cloacae* were identified in Mediterranean countries.[72]

First emergence of NDM was described in *K. pneumoniae* and *E. coli* clinical isolates in 2009 from a Swedish patient in New Delhi, India.[73] Since August 2010, NDM has spread worldwide to Canada, China, Europe, Japan, South Asia, Africa, Australia, and the United States.[74–76] Epidemiological analysis of the NDM-1 gene shows that it originated from the Indian subcontinent. NDM-1 is the most common variant described worldwide, but NDM-1 to NDM-9 have been published and 12 variants have been assigned.[77,78] NDM-4, NDM-5, and NDM-7 were reported to have increased carbapenemase activity compared with NDM-1.[61,79–81]

### *Class D carbapenemases*

Class D β-lactamases are referred to as oxacillin-hydrolyzing enzymes and comprise more than 200 enzymes, a few of which have carbapenemase activity.[61] The most prevalent variants are OXA-48 and OXA-181, which weakly hydrolyze carbapenems.[82] Most OXA variants are commonly reported in *A. baumannii* and rarely in *Enterobacteriaceae*.[66,83] This class of β-lactamases is not inhibited by commercially available β-lactamase inhibitors and/or EDTA.[82]

Since the emergence of OXA-48, it has been increasingly reported in *Enterobacteriaceae* species, including *E. coli*, *Enterobacter* spp., *C. freundii*,

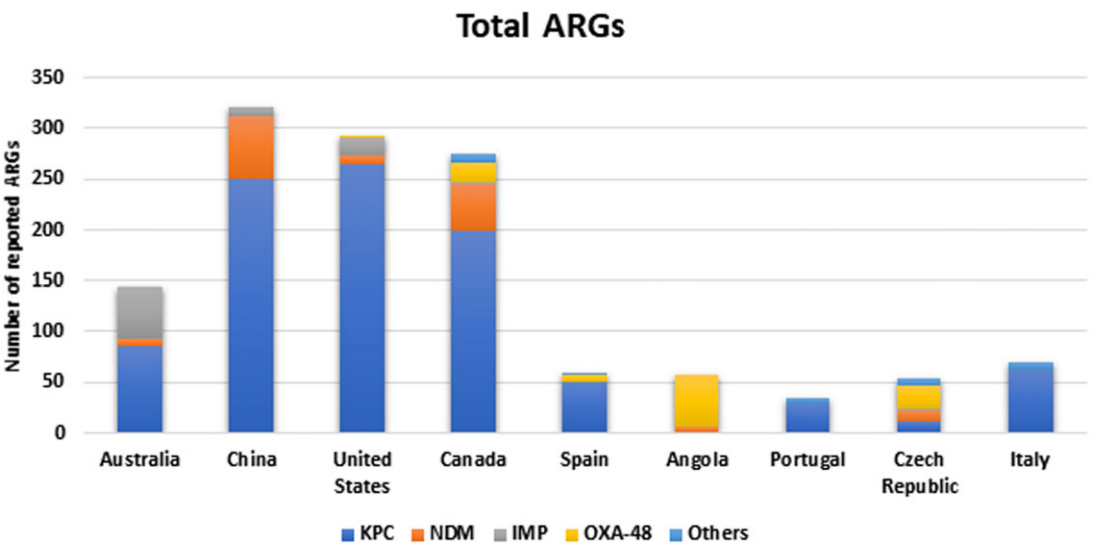


**Figure 2.** **Frequency distribution of carbapenemase genes reported in countries represented by the included articles. KPC (blue bars) were the commonest per country except in Angola and the Czech Republic. China, the United States, and Canada had more included studies and hence, higher carbapenemase incidence. ARGs, antibiotic resistant genes.**

*K. oxytoca*, *Providencia rettgeri*, and *Salmonella marcescens*.[40,84] Although OXA-48 hydrolyzes carbapenems to a lesser extent, their co-occurrence with other resistance mechanisms, such as membrane impermeability, may result in high-level resistance.[40] OXA-48 is widespread in *Enterobacteriaceae* worldwide and has been reported in countries in the Middle East (Saudi Arabia and Israel), Africa (Libya, Egypt, Algeria, Morocco, and South Africa), Asia (Russia, India, China, and Taiwan), and South America (Argentina, Brazil, and Colombia).[76,85–90] The geographical distribution frequency of carbapenemase genes reported per country in the articles included in this review is shown in Figure 2.

## Methods used in plasmid classification

The identification and classification of plasmids form the foundation of research looking at different plasmid groups in bacteria. Scientists gave much attention to this topic after discovering the role of plasmids in the acquisition and dissemination of virulence and resistance genes by horizontal gene transfer.[14] Classification of plasmids is very important in studying the biology, adaptation, and evolution of microbial populations. Size and number of plasmids in a bacterial cell are usually determined using gel electrophoresis and/or pulsed field gel electrophoresis.[91] Plasmids are classified according to their incompatibility (Inc) or replicon group, which is based on the replication factors expressed by the plasmid in the bacteria. Incompatibility was determined by introducing a plasmid of unknown replicon group in a recipient with a plasmid of known replicon group. The two plasmids are assigned to the same replicon group if the resident plasmid is eliminated. If this plasmid is not eliminated, the two plasmids are assigned to different incompatibility groups.[92] This method was used for several years to trace the dissemination of antibiotic resistance plasmids and the evolution of new plasmids. Couturier *et al.* proposed a new method based on hybridization of the major plasmid replicon groups in *Enterobacteriaceae*.[93] This method was labor-intensive and almost impossible on large sample sizes. To overcome these limitations, new typing schemes were introduced to facilitate the characterization and epidemiological analysis of resistance plasmids.[94]

Numerous plasmid classification schemes, including replicon and degenerate primer MOB typing (DPMT), which, respectively, targets loci encoding replicons and mobility functions, are now widely used in research.[15,95,96] Carattoli *et al.* developed a PBRT method that uses five multiplex PCRs and three simplex PCRs with 18 sets

of primers that target the major plasmid replicon groups in *Enterobacteriaceae*.[97] Subsequently, this method was updated to incorporate emerging plasmid replicon groups, such as IncR and IncU. Until recently, this method has been useful in the identification and classification of major antibiotic resistance plasmids circulating among *Enterobacteriaceae*. The PBRT scheme increased knowledge of plasmid diversity and revealed that conjugative plasmids belonging to a few widespread replicon groups carry clinically relevant ARGs.[98] Real-time PCR has also been used with the same principle as the PBRT method, which speeds up the detection and classification of plasmids and reduces human error and contamination.[99]

In 2011, a commercially available PCR-based typing kit was introduced, which includes all the modifications that have been incorporated since 2005–2010.[100] This kit contains all reagents and primers needed to perform the PCR, but still uses the same principle as the original PBRT method. The PBRT kit detects 28 replicons and is composed of eight multiplex PCRs and positive control plasmids for all the PCRs.[100] Even though this method is still labor-intensive and time-consuming, it may detect more plasmid replicons than the 2005 PBRT scheme.[100]

A technique based on plasmid mobility, called DPMT, was introduced by Francia and colleagues in 2006.[101,102] This technique uses degenerate primers to target relaxase sequences for separating plasmids into MOB types identified by *in silico* MOB typing.[95,103] The MOB typing overcomes replicon typing limitations in that it targets relaxases, of which only one can be encoded in a plasmid. Unlike the PBRT, which detects plasmids at higher resolution, the MOB typing uses lower resolution to classify plasmids.[94,98] However, PBRT and DPMT have been combined to successfully classify plasmids in clinically relevant pathogens.[104]

However, these typing schemes have a relatively lower discriminatory power than recent techniques, such as plasmid multilocus sequence typing (pMLST), whole-plasmid sequencing (WPS), and whole-genome sequencing (WGS).[94] The PBRT methods have drawbacks, including (1) the presence of multiple replicons in a single plasmid, which complicates plasmid classification; (2) rapid evolution of plasmid replicons; and (3) the presence of hybrid replication regions that make plasmid classification complicated.[94,98] Nevertheless, PCR-based typing methods may be used preliminarily for screening plasmids prior to using higher resolution techniques. All typing techniques discussed above have played a major role in plasmid evolution and epidemiology research in different countries worldwide.

pMLST is a tool used to further subtype already known plasmid Inc groups that occur very frequently in bacterial cells.[105] This technique has been used to successfully subtype IncF, IncHI1, IncHI2, IncI1, and IncN plasmids (www.pubmlst.org/plasmid/). A/C subtyping was also developed to increase the discriminatory power for plasmid epidemiology studies. Hancock *et al.* recommended the use of pMLST and other PCR methods to further subtype A/C plasmids.[106] García-Fernández and colleagues suggested that pMLST be used as a second-line plasmid typing technique after PCR-based methods to identify plasmids.[107] pMLST has been used for epidemiological description of virulence and resistance plasmids in both human and animal reservoirs; and more plasmid groups can be classified by pMLST.[107] In cases where pMLST is not available and plasmid subtyping is needed, the conventional technique restriction fragment length polymorphism (RFLP) can be used. However, the results produced by RFLP method can be difficult to interpret and subjective.[94]

WGS overcomes the defined limitations of typing methods, and many plasmids can be typed in a reasonable timeframe.[108] According to Carloni and colleagues, plasmid sequencing was able to detect novel plasmids previously not identified by the PBRT scheme.[100] One major advantage of WGS is its ability to provide researchers with sequences of new/unknown plasmids.[100] Short read sequencers, such as Illumina and Ion Torrent, as well as long read sequencers, such as PacBio and Oxford Nanopore, are used for WGS or WPS, albeit PacBio is preferred for complete plasmid sequencing and gapless assembly.[100] Long-read sequencers are able to sequence repetitive sequences and/or multiple copies of the same mobile elements, which are usually longer than the read length covered by short-read sequencers; assembly programs will collapse such reads, identifying them as a single contig.[11] Long-read sequencing therefore provides a comprehensive insight into the epidemiology and

evolution of plasmids, although it is more expensive and error prone because of lower throughput or coverage.[109] Subsequently, hybrid (short- and long-read) sequencing and assembly has been proposed and proven to override the deficiencies of both long- and short-read sequencers.[43,110] For instance, Li and colleagues used Illumina and PacBio to yield high-quality sequence reads; PacBio's proovread pipeline was used to correct the long read errors.[51]

Plasmid prediction database servers, such as Plasmidfinder, pMLST, PLACNET, and plasmidSPAdes, enable easy identification and annotation of relevant plasmid sequences from large WGS datasets,[43,96,111] as well as assemble plasmids from WGS data.[43,96,112,113] PlasmidFinder is a web-based tool that allows the submission of raw or assembled reads, which are searched for through a plasmid replicon database to identify replicons and assign the plasmid to an Inc group.[96] The plasmid constellation network (PLACNET) is a graph-based tool that reconstructs plasmids from short-read WGS raw data and is applied in plasmid diversity and adaptation.[114] The PLACNET tool uses three types of data for reconstruction of plasmids: (1) scaffold links and coverage; (2) comparison to a reference plasmid; and (3) sequences, such as replication initiator proteins.[112] Although this tool assembles plasmid contigs automatically, it relies on manual trimming of the graph.[113]

Furthermore, in 2017, PLACNETw (https://castillo.dicom.unican.es/) was developed based on the PLACNET database, automating all BLAST searches. PLACNETw extracts only the needed plasmid information, and graph-based presentation is automated.[115] In 2016, Antipov and colleagues developed a novel plasmid prediction database (PlasmidSPAdes) that also allows *de novo* plasmid contig assembly by manipulating differences in coverage in raw sequence reads.[113] PLACNET and PlasmidSPAdes are Linux-based applications that do not run on Windows and use raw sequence reads instead of assembled fasta files. A more recent Linux-based application for identifying known plasmid sequences from WGS data is PlasmidSeeker,[116] which also uses raw reads and *k-mer* abundance to identify plasmid sequences. PlasmidSeeker is unable to assemble plasmid sequences from raw reads *de novo*.

## Plasmid biology and incompatibility groups

Plasmids are usually double-stranded (ds) extrachromosomal material or DNA that can replicate independently from the chromosome. These dsDNA molecules occur naturally in bacterial cells and are essential for bacterial adaptability and persistence.[117] Thus, bacterial fitness may also be gained under some ecological conditions via the accessory genes carried on these plasmids.[118] For example, increased survival and competitive fitness is seen in bacteria carrying plasmids with heavy-metal resistance genes and ARGs.[119] Plasmids that occur naturally vary in size (1–100s kilobases) and in copy number (1–100s in a cell).

Plasmids mediate the acquisition and dissemination of ARGs, including carbapenemases, through conjugation,[120] which is only achievable by mobile/conjugative plasmids. The conjugative machinery shares the same relaxase, a key protein that recognizes the origin of transfer (*ori*T) in conjugation.[121] Conjugative plasmids carry all the genes that are responsible for self-transfer, including the type IV coupling protein and all the components needed for mating channels that assemble a type IV protein secretion systems (T4SS).[121] These systems are responsible for transporting proteins, such as virulence factors and toxins extracellularly. The conjugative T4SS also exports DNA substrates.[122]

Hedges and Datta defined plasmids based on their stability (Inc) and defined four Inc types including: (1) the type F pili-producing plasmids, which are susceptible to phage Ff (IncF); (2) the type I pili-producing plasmids, susceptible to phage Ifl (IncI); (3) plasmids related to N3, susceptible to phage Ike (IncN); and (4) plasmids related to RP4, susceptible to phage PRR1 (IncP).[92] Numerous plasmid incompatibility (Inc) replicon groups have been associated with carriage of ARGs, thereby facilitating intra- and interspecies transfer.

### *Plasmid types and incompatibility groups associated with carbapenemases*

To date, 27 major plasmid incompatibility groups are associated with ARGs in *Enterobacteriaceae*.[17,93,123] A wide distribution of plasmid replicon groups has been reported in CREs, including IncF, N, X, A/C, L/M, R, P, H, I, and W. These replicon groups are associated with

different carbapenemases, with IncF, A/C, and X being the most prevalent in carbapenemase production compared with the other Inc groups. The most prevalent incompatibility types in *Enterobacteriaceae* are the IncF plasmids, which have been reported in different sources around the world.[17,18]

Plasmid host range is usually a term used to describe the range of hosts in which a plasmid can replicate. This host range varies among plasmids, and the terms "narrow host range" and "broad host range" are used for the plasmid host range differentiation.[124,125] Narrow-host-range self-transmissible plasmids are mainly of IncF, IncH, and IncI types, while L/M, IncN, IncP, and IncW can replicate in broad host ranges.[124,126] Table 1 and Figures 2–4 show the different ARGs reported in each country and their associated plasmid replicon groups mediating the spread of these genes.

**IncF plasmids.** IncF plasmids are narrow-host-range plasmids that rely on both host-encoded and self-encoded factors for replication.[123] They are usually large in size (>100 kb), but with low copy number and often carry an additional replicon type to initiate replication.[127] This a strategy used by narrow-host-range plasmids to obtain broad-host-range replication. An example of this was seen in plasmid pKPX-1, from NDM-producing *K. pneumoniae* clinical isolates, which contains a narrow-host-range (IncFIB) and a broad-host-range (IncR) replicon to assist with broad-host-range replication.[128] This is an important characteristic of IncF plasmids, but these plasmids still encode regions essential for conjugative transfer, replication, and segregational stability.[117] Moreover, the plasmid's multireplicon state can allow for acquisition of a plasmid carrying an incompatible replicon when replication is controlled by a compatible replicon, allowing the replicon not responsible for replication to undergo genetic alteration.[123,129]

IncF plasmids are mostly associated with extended-spectrum β-lactamases (ESBLs), particularly $bla_{\text{CTX-M-15}}$. A major IncF plasmid carrying $bla_{\text{CTX-M-15}}$ was reported by Coque *et al.* to contain an MDR region containing $bla_{\text{TEM-1}}$, $bla_{\text{OXA-1}}$, and *aac(6′)-Ib-Cr*, and other determinants of aminoglycoside and tetracycline resistance.[130] Moreover, these plasmids have been recently associated with carbapenemases in *Enterobacteriaceae*. Their great intracellular versatility and rapid evolution of their replicons' regulatory sequences allow them to succeed in spreading among *Enterobacteriaceae*.[123] This has been shown in most studies focusing on KPC- and NDM-producing *E. coli* and *K. pneumoniae* in different countries.[128,131–134]

The first occurrence of an IncF plasmid (pKpQIL) in *K. pneumoniae* ST258 was reported by Villa and colleagues, which was a 113-kb plasmid belonging to the IncFII replicon group.[123] Since then, IncF plasmids have been reported in other countries where they mediate the spread of $bla_{\text{KPC}}$. Examples of IncF plasmids in *K. pneumoniae* carrying KPC include pBK30683 (140-kb) and pBK30661 (73.6-kb) plasmids, which were reported in U.S. hospitals from patients with urinary tract infections.[135] pBK30661 was identified as an IncFIA plasmid harboring nine ARGs for β-lactam resistance ($bla_{\text{KPC-3}}$, $bla_{\text{TEM-1}}$, $bla_{\text{OXA-9}}$), aminoglycoside resistance (*aacA4*, *aadA1*, *strA*, *strB*), sulfonamide resistance (*sul2*), and trimethoprim resistance (*dfrA14*).[135] Other IncF types, such as pKP1504-KPC and pGR-1780, have also been reported to spread $bla_{\text{KPC-2}}$ in *K. pneumoniae* clinical isolates, specifically isolates ST258 and ST147.[136]

These narrow-host range (IncF) plasmids are not only responsible for disseminating KPC, but also NDM in *E. coli* and *K. pneumoniae*.[137–139] Multiple plasmids have been reported, since 2012 and until recently, to carry NDM variants, particularly on IncFIB and IncFII plasmid types in *K. pneumoniae* and *E. coli*, respectively (Table 1 and Fig. 3).[128,131–133,140] Larger plasmids, such as pPMK1-NDM (304.5 kb) and pNDM-EcoGN568 (166.7 kb), are examples of NDM-1–containing plasmids that contain other resistance determinants, including β-lactamases, with pPMK1-NDM containing a large conjugative transfer module.[132,141] Other IncF plasmids, including pEh1A, pNDM-Ec1GN574, pKOX-NDM-1, and pCRCB-101_1, are also responsible for the dissemination of $bla_{\text{NDM-1}}$ in other species, such as *C. freundii*, *Enterobacter hormaechei*, and *Klebsiella michiganensis*.[128,134,141,142] pNDM-Ec1GN574 and pKOX-NDM1 plasmids are similar in size (110.8 kb), with the NDM region being flanked by 256 bp direct repeats that are suggested to be responsible for the acquisition of $bla_{\text{NDM-1}}$.[141] An IncFII plasmid was also reported in an isolate in China carrying NDM-5 and MCR-1 genes.[143]

**Table 1. Major plasmids mediating carbapenem resistance in *Enterobacteriaceae***

| Country | Year | Species | Clone | Plasmid type (Inc) | Size (kb) | Plasmid conjugation/ mobility | Carbapenemase gene | Other resistance | Genetic elements | References |
|---|---|---|---|---|---|---|---|---|---|---|
| Australia | 2018 | *K. pneumoniae* | ST258 | FIB, FII | _ | _ | *bla*$_{KPC-2}$ | _ | Tn*4401* | 169 |
| | | *K. oxytoca* | _ | FII | _ | _ | *bla*$_{KPC-2}$ | _ | _ | |
| | | *C. farmeri* | _ | FII, R | _ | _ | *bla*$_{KPC-2}$ | _ | Tn*4401* | |
| | | *C. freundii* | _ | R | _ | _ | *bla*$_{KPC-2}$ | _ | Tn*4401* | |
| | 2016 | *S. enterica* | ST19 | HI2 | 339 | Conjugative | *bla*$_{IMP-4}$ | TEM-1, *sul1*, OXA-1, *aacA4*, *qnrB2* | Class 1 integron | 185 |
| | 2015 | *E. cloacae* | ST127 | FII | _ | Conjugative | *bla*$_{NDM-1}$ | _ | _ | 131 |
| | | | ST265 | X3 | _ | Conjugative | *bla*$_{NDM-1}$ | _ | _ | |
| | | | ST45 | L/M | _ | Conjugative | *bla*$_{IMP-4}$ | TEM-1, SHV, CTX-M, *qnr*, *aac (6')-Ib* | Class 1 integron | |
| | | | ST1 | HI2 | _ | Non-conjugative | *bla*$_{IMP-4}$ | TEM-4, *qnrB2*, *aaCA4* | Class 1 integron | |
| | | *E. hermannii* | ST1 | HI2 | _ | Non-conjugative | *bla*$_{IMP-4}$ | *qnrB*, TEM-1, SHV, *aac(6')-Ib* | Class 1 integron | |
| | | *E. aerogenes* | ST45 | L/M | _ | Conjugative | *bla*$_{IMP-4}$ | *qnrB*, TEM-1, *aac(6')-Ib* | Class 1 integron | |
| | | *E. asburiae* | ST1 | HI2 | _ | Non-conjugative | *bla*$_{IMP-4}$ | TEM-1, *aac(6')-Ib* | Class 1 integron | |
| | | *E. coli* | _ | HI2 | _ | Non-conjugative | *bla*$_{IMP-4}$ | *qnrB*, TEM-1, *aac(6')-Ib* | Class 1 integron | |
| | | *K. pneumoniae* | _ | HI2, L/M | _ | Conjugative | *bla*$_{IMP-4}$ | *qnr*, TEM-1, SHV, *aac(6')-Ib* | Class 1 integron | |
| | | *C. freundii* | _ | HI2 | _ | Non-conjugative | *bla*$_{IMP-4}$ | TEM-1, SHV, CTX-M, *qnr*, *aac (6')-Ib* | Class 1 integron | |
| | | *C. koseri* | _ | HI2 | _ | Non-conjugative | *bla*$_{IMP-4}$ | *qnrB*, TEM-1, *aac(6')-Ib* | Class 1 integron | |
| | | *P. mirabilis* | _ | HI2 | _ | Non-conjugative | *bla*$_{IMP-4}$ | *qnrB*, TEM-1, SHV, *aac(6')-Ib* | Class 1 integron | |
| China | 2018 | *K. pneumoniae* | ST11 | FII | _ | _ | *bla*$_{KPC-2}$ | CTX-M-65, SHV-12, TEM-1 | Tn*1721*-Tn*3*-IS*26* | 146 |
| | | | ST11 | FII, I1 | _ | _ | *bla*$_{KPC-2}$ | CTX-M-55, SHV-12, DHA-1 | Tn*1721*-Tn*3*-IS*26* | |
| | 2018 | *K. pneumoniae* | ST11 | FII, N | _ | _ | *bla*$_{KPC-2}$ | CTX-M-65, SHV-12, TEM-1 | Tn*1721*-Tn*3*-IS*26* | 146 |
| | | | ST571 | A/C | _ | _ | *bla*$_{NDM-1}$ | CMY-2, TEM-1 | _ | |
| | | | ST1723 | P, FII | _ | _ | *bla*$_{IMP-4}$ | CTX-M, SHV-12, TEM-1 | _ | |
| | | *K. aerogenes* | _ | X6 | | Conjugative | *bla*$_{KPC-2}$ | TEM-1 | Tn6296 & ISkpn19 | 104 |
| | | *P. mirabilis* | _ | X6 | | Conjugative | *bla*$_{KPC-2}$ | TEM-1 | Tn6296 & ISkpn19 | |

*Continued*

**Table 1.** ***Continued***

| Country | Year | Species | Clone | Plasmid type (Inc) | Size (kb) | Plasmid conjugation/ mobility | Carbapenemase gene | Other resistance | Genetic elements | References |
|---|---|---|---|---|---|---|---|---|---|---|
| | | *S. marcescens* | _ | X6 | | Conjugative | *bla*$_{KPC-2}$ | TEM-1, *qnr*S1 | Tn6296 & ISkpn19 (Tn6292) | |
| | | *M. morganii* | _ | X6 | | Conjugative | *bla*$_{KPC-2}$ | _ | Tn6296 & ISkpn19 | |
| | | *E. hormaechei* | ST177 | FII | 109 | Conjugative | *bla*$_{NDM-1}$ | – | – | 192 |
| | | *E. coli* | ST167 | FII/FIA | 144 | Conjugative | *bla*$_{NDM-5}$ | *aadA2, aadA5*, TEM-1, *Sul*1, *drfA12*, *drfA15* | IS*26* | 193 |
| | | | ST167 | X3 | 80 | – | *bla*$_{NDM-1}$ | – | IS*Aba 125* | 194 |
| | | | ST1114 | X3 | 46 | Conjugative | *bla*$_{NDM-20}$ | – | IS*Aba125* | 195 |
| | | | ST405 | FII | – | – | *bla*$_{NDM-1}$ | – | – | 196 |
| | | | – | X3 | 46 | – | *bla*$_{NDM-1}$ | – | IS*Aba125* | |
| | | *C. freundii* | – | X3 | 80 | – | *bla*$_{NDM-1}$ | CTX-M-15 | IS*Aba125* | |
| | 2017 | *K. pneumoniae* | _ | _ | _ | _ | *bla*$_{KPC-2}$ | *rmtB*, CTX-M-65, TEM-1, SHV-11, *catA2*, *fosA*, *oqxA* | _ | 184 |
| | | | ST14 | X3 | 46.161 | Conjugative | *bla*$_{NDM-5}$ | CTX-M-15 | _ | 175 |
| | | *E. coli* | ST48 | X3 | 47 | Conjugative | *bla*$_{NDM-1}$ | CTX-M-64, TEM-1b, *sul2*, *aadA5*, *rmtB* | IS | 144 |
| | | | ST10 | X3 | 102.512 | Conjugative | *bla*$_{NDM-5}$ | mcr-1, *aadA2*, *sul1*, *dfrA12*, *aac(3)-IId* | IS*3000* | 137 |
| | | | ST4981 | FII | 92 | Conjugative | *bla*$_{NDM-5}$ | mcr-1, TEM-1B, erm | IS*30* | |
| | 2016 | *K. pneumoniae* | ST105 | FI | 50 | Conjugative | *bla*$_{NDM-1}$, *bla*$_{IMP-4}$ | *qnrS1*, *qnrB4*, *aacA4*, CTX-M-15, SHV-1 | IS*3000* | 197 |
| | | | ST2250 | FII | 30 | Conjugative | *bla*$_{NDM-5}$ | – | IS*3000* | 174 |
| | | | ST3835 | X3 | 54 | Conjugative | *bla*$_{NDM-1}$ | CTX-M-15, SHV-12, CMY-42, OXA-1 | | 52 |
| | | *C. sakazakii* | _ | B/O | 80 | Conjugative | *bla*$_{NDM-9}$ | mcr-1, *fosA3*, CTX-M-55, *qnrS* | IS26 | 198 |
| | | *P. mirabilis* | _ | X3 | 40 | Conjugative | *bla*$_{NDM-5}$ | _ | IS*3000* | 174 |
| | | *E. cloacae* | ST231 | A/C | 130.573 | Non-conjugative | *bla*$_{NDM-1}$ | MBL, strA, strB, aadA2, armAmph2, mel, sul1 and sul2, dfrA12, qacE1 | Class 1 integron | 148 |
| | | | | X6 | 10.756 | Conjugative | *bla*$_{KPC-3}$ | TEM-1 | Tn3-Tn1722 | |
| | 2015 | *E. cloacae* | ST120 | HI2 | 340 | Conjugative | *bla*$_{NDM-1}$ | *armA*, *fosA3* | IS*Aba*125 | 183 |
| | | | ST93 | A/C | 55 | Conjugative | *bla*$_{NDM-1}$ | *armA* | IS*Aba*125 | |

*Continued*

**Table 1.** ***Continued***

| Country | Year | Species | Clone | Plasmid type (Inc) | Size (kb) | Plasmid conjugation/ mobility | Carbapenemase gene | Other resistance | Genetic elements | References |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | ST88 | N | 65 | Conjugative | *bla*$_{NDM-1}$ | TEM-1, CTX-M-3 | IS*Aba125* | |
| | | | _ | X3 | 54.035 | Conjugative | *bla*$_{NDM-1}$ | | IS*5* | 179 |
| | | *K. pneumoniae* | ST11 | FII-FIB | 110.786 | Conjugative | *bla*$_{NDM-1}$ | *sul1*, *rmtC* | IS*CR3*, IS*Ehe3* | 199 |
| | | | Clone B, A | X3 | 7.8 | Conjugative | *bla*$_{NDM-1}$ | _ | _ | 179 |
| | | *C. sakazakii* | _ | B/O | 80 | Conjugative | *bla*$_{NDM-9}$ | MCR-1, CTX-M-9, CTX-M-1, | IS | 198 |
| | | *R. planticola* | _ | X3 | 53.134 | Conjugative | *bla*$_{NDM-1}$ | SHV-12 | IS*26*, IS*Aba 125*, IS*5* | 199 |
| | 2014 | *K. pneumoniae* | ST889 /966 | A/C | 245 | Conjugative | *bla*$_{NDM-1}$ | TEM-1, CTX-M-15 | _ | 176 |
| | | | ST113 | N | 55 | Conjugative | *bla*$_{NDM-1}$ | _ | _ | |
| | | *E. cloacae* | ST40 | FIB | 310 | Conjugative | *bla*$_{NDM-1}$ | TEM-1, CMY-30, FosA3 | – | |
| | 2014 | *E. cloacae* | ST410 | I1 | 60 | Conjugative | *bla*$_{NDM-1}$ | TEM-1, CTX-M-15, CMY-30 | _ | 176 |
| | | *C. freundii* | _ | A/C | 170 | Conjugative | *bla*$_{NDM-1}$ | FosA3, CMY-73 | _ | |
| United States | 2018 | *E. cloacae* | ST171 | HI2 | 315 | – | *bla*$_{KPC-4}$ | – | Tn*4401b* | 200 |
| | | | ST171 | FIA | 141 | – | *bla*$_{KPC-3}$ | – | Tn*4401d* | |
| | 2017 | *K. pneumoniae* | ST111 | N | 69.888 | Conjugative | *bla*$_{KPC-2}$ | *aac(6')-Ib*, *aadA1*, OXA -9, TEM-1, *strB*, *strA*, *sull2* | Tn*4401b* | 49 |
| | | *K. michiganensis* | _ | N | 68.763 | Conjugative | *bla*$_{KPC-2}$ | aac(6')-Ib, aadA1, OXA -9, TEM-1, strB, strA, sull2 | Tn*4401b* | |
| | | *E. coli* | ST218 | Q1 | 10 | Non-conjugative | *bla*$_{IMP-27}$ | CMY-2 | _ | 177 |
| | | *P. mirabilis* | _ | Q1 | 10 | Non-conjugative | *bla*$_{IMP-27}$ | _ | _ | |
| | | *P. vulgaris* | _ | Q1 | 10 | Non-conjugative | *bla*$_{IMP-27}$ | _ | _ | |
| | | *E. cloacae* | _ | Q1 | 10 | Non-conjugative | *bla*$_{IMP-27}$ | _ | _ | |
| | | *C. farmeri* | _ | Q1 | 10 | Non-conjugative | *bla*$_{IMP-27}$ | _ | _ | |
| | 2016 | *E. coli* | ST617 | N | 108 | Conjugative | *bla*$_{KPC-3}$ | TEM-1 | Tn*4401b* | 84 |
| | | | ST131 | FII | 116 | Conjugative | *bla*$_{KPC-2}$ | TEM-1 | Tn*4401a* | |
| | | | ST2289 | FIA, A/C | 99 | Conjugative | *bla*$_{KPC-2}$ | TEM-1, OXA-9, FOX-5, PSE-1 | Tn*4401d* | |
| | | | ST405 | X3 | 39.520 | Conjugative | *bla*$_{NDM-5}$ | *strA*, *strB*, *aac(6')-Ibcr*, OXA-1, *sul1* | _ | 147 |

*Continued*

**Table 1.** ***Continued***

| Country | Year | Species | Clone | Plasmid type (Inc) | Size (kb) | Plasmid conjugation/ mobility | Carbapenemase gene | Other resistance | Genetic elements | References |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | ST595 | _ | 44 | | $bla_{KPC-3}$ | OXA-9, TEM-1A, *aac(6')-Ib*, *aadA1*, *qnrB19* | Tn*4401b* | 50 |
| | | *E. xiangfangensis* | ST114 | F | _ | | $bla_{KPC-3}$ | *qnrS1*, TEM-1A | Tn*4401b* | |
| | 2016 | *E. hormaechei* | ST594 | Col | _ | | $bla_{KPC-2}$ | TEM-1B, SHV-12, *strB*, *strA*, *aadA2*, *aac(6')-Iic*, *qnrB2*, *sul1*, *sul2*, *dfrA18* | Tn*4401* | 50 |
| | | | ST269 | _ | 44 | | $bla_{KPC-2}$ | TEM-1B, *qnrB2*, *sul1*, *dfrB3* | Tn*4401* | |
| | | | ST113 | A/C | 66 | | $bla_{KPC-4}$ | TEM-1A, OXA-1, *aadA1*, *aac(3)-via*, *aph*, *mph* (A), *catB3*, *arr-3*, *qnrS1*, *sul1*, *dfrA14*, TEM-1B, *sul2*, *strA*, *strB* | Tn*4401* | |
| | 2015 | *E. cloacae* | ST171 | FIA | 63.481 | _ | $bla_{KPC-3}$ | TEM-1, OXA-9 | Tn*1331*/Tn*4401* | 201 |
| | | | ST171 | HI2 | _ | _ | $bla_{KPC-4}$ | TEM-1, OXA-1 | Tn*4401b* | 168 |
| | | | ST78 | N | _ | _ | $bla_{KPC-4}$ | _ | Tn*4401b* | |
| | | *K. pneumoniae* | ST101 | L/M | | | $bla_{OXA-48}$ | _ | Tn*1991* | |
| | | | ST258 | R | | | $bla_{KPC-2}$ | _ | Tn*4401a* | |
| | | | ST113 | N | | | $bla_{KPC-4}$ | _ | Tn*4401b* | |
| | | | ST258 | I2 | | | $bla_{KPC-3}$ | _ | Tn*4401b* | |
| | | | ST258 | A/C2 | | | $bla_{KPC-2}$ | _ | Tn*4401e* | |
| | | | ST16 | X3 | | | $bla_{KPC-3}$ | _ | Tn*4401b* | |
| | | *E. coli* | ST131 | X3 | 116.803 | _ | $bla_{KPC-3}$ | TEM-1, OXA-9, *sul2*, *strAB* | Tn*4401* | 201 |
| | 2014 | *K. pneumoniae* | ST258 | FIA | 73.635 | Non-conjugative | $bla_{KPC-3}$ | TEM-1, OXA-9, *aacA4*, *aadA1*, *strB*, *sul1*, *dfrA14* | Tn*4401* /Tn*1331* | 129 |
| | | | ST963 | FII | 139.941 | Conjugative | $bla_{KPC-3}$ | _ | Tn*1331* /Tn*4401d* | |
| | | *E. cloacae* | ST93 /253 /171 | N | 90 | | $bla_{KPC-3}$ | SHV-5 | _ | 48 |
| | | | | N | 90 | _ | $bla_{KPC-2}$ | CTX-M-15, SXT | _ | |
| | | | | FIB | 30 | | $bla_{KPC-2}$ | _ | _ | |

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**Table 1.** ***Continued***

| Country | Year | Species | Clone | Plasmid type (Inc) | Size (kb) | Plasmid conjugation/ mobility | Carbapenemase gene | Other resistance | Genetic elements | References |
|---|---|---|---|---|---|---|---|---|---|---|
| Japan | 2018 | *K. pneumoniae* | ST1471 | L | – | – | *bla*$_{IMP-1}$ | – | – | 202 |
| | 2015 | *K. pneumoniae* | ST5 | N | 47.236 | Conjugative | *bla*$_{IMP-6}$ | CTX-M-2, *aacA4'*, *aadA2*, *tetR-tetA* | Class 1 integron (In*722*) | 164 |
| | | *K. oxytoca* | ST37 | N | _ | Conjugative | *bla*$_{IMP-6}$ | CTX-M-2 | Class 1 integron (In*722*) | |
| | | *E. coli* | ST37 | N | _ | Conjugative | *bla*$_{IMP-6}$ | CTX-M-2 | Class 1 integron (In*722*) | |
| Mexico | 2017 | *K. pneumoniae* | ST392 | IIIk | 130 | Conjugation | *bla*$_{NDM-1}$ | _ | _ | 182 |
| | | | ST309 | FII | 130 | Conjugation | *bla*$_{NDM-1}$ | _ | _ | |
| | | *E. cloacae* | ST182 | FII | 150 | Conjugation | *bla*$_{NDM-1}$ | _ | _ | |
| | | *E. coli* | ST10 | FII | 13 | Conjugation | *bla*$_{NDM-1}$ | _ | _ | |
| | 2015 | *K. pneumoniae* | ST22 | FII | _ | Conjugation | *bla*$_{NDM-1}$ | CTX-M-15 | _ | 178 |
| | | *E. coli* | ST617 | FII | _ | Conjugation | *bla*$_{NDM-1}$ | CTX-M-15 | _ | |
| | | *E. cloacae* | ST182 | FII | _ | Conjugation | *bla*$_{NDM-1}$ | CTX-M-15 | _ | |
| Spain | 2017 | *E. coli* | ST1434 | N | 70 | Conjugation | *bla*$_{KPC-2}$ | OXA-1, *aac(6')-Ib-cr*, *qnrB6* | _ | 173 |
| | | | ST5001 | R | 48 | _ | *bla*$_{KPC-2}$ | _ | _ | |
| | | | ST216 | R | 48 | Non-conjugative | *bla*$_{KPC-2}$ | *aac(6')-Ib* | _ | |
| | | | ST131 | L/M | 61.395 | Conjugative | *bla*$_{OXA-48}$ | _ | Tn*1991.2* | |
| | | *E. cloacae* | ST822 | FIB | 170 | _ | *bla*$_{IMI-2}$ | _ | _ | |
| | | | ST823 | N | 70 | Conjugative | *bla*$_{KPC-2}$ | *aac(6')-Ib*, *qnrB6* | _ | |
| | | *K. oxytoca* | _ | N | 60 | _ | *bla*$_{KPC-2}$, *bla*$_{VIM-1}$ | OXA-1, *aac(6')-Ib* | _ | 173 |
| | | *R. ornithinolytica* | _ | R | 70 | _ | *bla*$_{VIM-1}$ | OXA-1, *aac(6')-Ib*, *qnrB5* | _ | |
| Spain | 2017 | *R. ornithinolytica* | _ | P6 | _ | _ | *bla*$_{KPC-2}$ | TEM-1 | IS*Kpn6*-IS*pn27* | 184 |
| | | *C. freundii* | _ | P6 | 40 | Conjugative | *bla*$_{KPC-2}$ | TEM-1 | IS*Kpn6*-IS*pn27* | |
| | | *E. cloacae* | _ | P6 | _ | _ | *bla*$_{KPC-2}$ | TEM-1 | IS*Kpn6*-IS*pn27* | |
| | | *K. pneumoniae* | _ | N | _ | _ | *bla*$_{KPC-2}$ | TEM-1 | IS*Kpn6*-IS*pn27* | |
| | | *Kluyveraa sp.* | _ | U | _ | _ | *bla*$_{KPC-2}$ | TEM-1 | IS*Kpn6*-IS*pn27* | |
| Poland | 2016 | *K. pneumoniae* | ST11 | R | 90 | Non-conjugative | *bla*$_{NDM-1}$ | CTX-M-15, TEM-1, OXA-1 | Tn*125* | 54 |
| | | | ST11 | FII | 100 | Conjugative | *bla*$_{NDM-1}$ | TEM-1 | Tn*125* | |
| | | | ST11 | R+FII | 80 | Non-conjugative | *bla*$_{NDM-1}$ | TEM-1, OXA-1 | Tn*125* | |
| Italy | 2015 | *K. pneumoniae* | ST101 | FII | _ | Conjugative | *bla*$_{KPC-2}$ | CTX-M-1 | _ | 203 |
| | | | ST1789 | FII | _ | Conjugative | *bla*$_{KPC-2}$ | CTX-M-1 | _ | |
| | | | ST512 | FII | _ | Conjugative | *bla*$_{KPC-3}$ | _ | _ | |
| | | | ST405 | FII | _ | Conjugative | *bla*$_{KPC-3}$ | _ | _ | |

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**Table 1.** ***Continued***

| Country | Year | Species | Clone | Plasmid type (Inc) | Size (kb) | Plasmid conjugation/ mobility | Carbapenemase gene | Other resistance | Genetic elements | References |
|---|---|---|---|---|---|---|---|---|---|---|
| | | *E. coli* | ST131 | N | _ | Conjugative | $bla_{VIM-1}$ | _ | _ | |
| | | | ST5 | X3, FIB, colE | | | $bla_{KPC-3}$ | SHV-11 | Tn*4401a* | 91 |
| | | *C. freundii* | ST91 | X3 | _ | | $bla_{KPC-3}$ | SHV-11 | Tn*4401a* | |
| | | | ST96 | X3 | | | $bla_{KPC-3}$, $bla_{VIM-2}$ | SHV-11, TEM-1, CTX-M-9 | Tn*4401a* | |
| | | | | X3, N, HI1 | | | $bla_{KPC-3}$, $bla_{VIM-2}$ | SHV-11, TEM-1, CTX-M-9 | Tn*4401a* | |
| Canada | 2016 | *K. pneumoniae* | ST258 | FIA | _ | _ | $bla_{KPC-3}$ | SHV, TEM | _ | 42 |
| | | | ST512 | FIA, FII | _ | _ | $bla_{KPC-3}$ | SHV, TEM | _ | |
| | | | ST15 | N | – | – | $bla_{KPC-3}$ | SHV, TEM, CTX-M, OXA-1, CMY-2 | – | |
| Canada | 2016 | *K. pneumoniae* | ST15 | N | _ | _ | $bla_{KPC-3}$ | SHV, TEM, CTX-M, OXA-1, CMY-2 | _ | 42 |
| | | | ST437 | R | _ | _ | $bla_{NDM-1}$ | SHV, CTX-M | _ | |
| | | | ST11 | A/C | _ | _ | $bla_{NDM-1}$ | SHV, OXA-1 | _ | |
| | | | ST147 | R | _ | _ | $bla_{NDM-1}$ | SHV, CTX-M, OXA-1 | _ | |
| | | | ST15 | R | _ | _ | $bla_{NDM-1}$ | SHV, TEM, CTX-M | _ | |
| | | | ST16 | A/C | _ | _ | $bla_{NDM-1}$ | SHV-1, CTX-15, OXA-1, CMY-6 | _ | |
| | | | ST101 | N | _ | _ | $bla_{OXA-48}$ | SHV, OXA-1 | _ | |
| | | *E. coli* | Cluster II | FIIA | | | $bla_{KPC-3}$ | _ | _ | |
| | | | Cluster VI | N | | | $bla_{KPC-3}$ | _ | _ | |
| | | *E. cloacae* | Cluster IV | P, L/M | _ | _ | $bla_{KPC-3}$ | _ | _ | |
| | | | _ | L/M | | | $bla_{KPC-3}$ | _ | _ | |
| | | | _ | FIIA | _ | _ | $bla_{KPC-3}$ | _ | _ | |
| | | | Cluster VI | N | | | $bla_{KPC-3}$ | _ | _ | |
| | | | _ | Y | _ | _ | $bla_{VIM-1}$ | _ | _ | |
| | | | _ | R | _ | _ | $bla_{VIM-1}$ | _ | _ | |
| | | *E. aerogenes* | Cluster VI | N | | | $bla_{KPC-3}$ | _ | _ | |
| | | *C. freundii* | Cluster IV | P, L/M | _ | _ | $bla_{KPC-3}$ | _ | _ | |
| | | *C. koseri* | Cluster IV | P, L/M | _ | _ | $bla_{KPC-3}$ | _ | _ | |
| | | *C. youngae* | Cluster IV | P, L/M | | | $bla_{KPC-3}$ | _ | _ | |
| | | *R. planticola* | _ | N | _ | _ | $bla_{KPC-3}$ | _ | _ | |
| | | | Cluster VI | N | _ | _ | $bla_{KPC-3}$ | _ | _ | |
| | | | Cluster IV | P, L/M | _ | _ | $bla_{KPC-3}$ | _ | _ | |

*Continued*

**Table 1.** ***Continued***

| Country | Year | Species | Clone | Plasmid type (Inc) | Size (kb) | Plasmid conjugation/ mobility | Carbapenemase gene | Other resistance | Genetic elements | References |
|---|---|---|---|---|---|---|---|---|---|---|
| Canada | 2014 | *K. pneumoniae* | ST258 | F, I2 | 120, 80 | _ | *bla*$_{KPC-3}$ | TEM-1, SHV-11 | Tn*4401b* | 47 |
| | | | ST258 | I2 | 70 | _ | *bla*$_{KPC-3}$ | TEM-1, SHV-11 | Tn*4401b* | |
| | | | ST258 | A/C, FII | 100 | _ | *bla*$_{KPC-2}$ | TEM-1, SHV-11 | Tn*4401a* | |
| | | | ST258 | FII, I2 | 80 | _ | *bla*$_{KPC-2}$ | TEM-1, SHV-11 | Tn*4401a* | |
| | | | ST258 | N, FII | 50 | _ | *bla*$_{KPC-2}$ | OXA-1, SHV-11 | Tn*4401b* | |
| | | *E. cloacae* | ST258 | HI2 | 120 | _ | *bla*$_{KPC-3}$ | TEM-1 | Tn*4401b* | |
| | | *C. freundii* | _ | A/C | 180 | _ | *bla*$_{KPC-2}$ | TEM-1 | Tn*4401b* | |
| | | *R. ornithinolytica* | _ | F | 70 | _ | *bla*$_{KPC-2}$ | _ | Tn*4401b* | |
| Myanmar | 2019 | *E. coli* | ST167 /101 /410 | FII | – | – | *bla*$_{NDM-5}$ | CTX-M-15 | IS*Sba14* | 204 |
| | | | ST410 | X3 | 50 | – | *bla*$_{NDM-4/7}$ | – | IS*sba14* | |
| | 2017 | *E. coli* | - | A/C | | Conjugative | *bla*$_{NDM-1}$ | CTY-4 | Tn*125*, Tn*1548* | 134 |
| | | | _ | X3 | 47 | Conjugative | *bla*$_{NDM-4}$ | _ | Tn*3* | |
| | | | _ | X3 | | Conjugative | *bla*$_{NDM-7}$ | _ | Tn*3* | |
| | | | _ | X3 | | Conjugative | *bla*$_{NDM-5}$ | _ | Tn*3* | |
| | | | _ | FII | | Conjugative | *bla*$_{NDM-4}$ | _ | IS*26* | |
| | | | _ | FII | | Conjugative | *bla*$_{NDM-5}$ | _ | IS*26* | |
| Germany | 2018 | *E. coli* | ST131 | HI2 | 300 | – | *bla*$_{VIM-1}$ | *aac(6')-Ib-cr*, *aacA4*, *aadA1*, ACC-1, CMY-2, *catA1*, *strA/B*, *Sul*1 | Tn21 | 205 |
| | | *S. infantis* | ST32 | HI2 | 300 | – | *bla*$_{VIM-1}$ | *aac(6')-Ib-cr*, *aacA4*, *aadA1*, ACC-1, CMY-2, *catA1*, *strA/B*, *Sul*1 | Tn21 | |
| Portugal | 2018 | *E. coli* | ST131 | Q2 | 13 | Non-conjugative | *bla*$_{KPC-21}$ | – | IS*kp6* | 206 |
| Denmark | 2018 | *E. coli* | ST410 | F | – | – | *bla*$_{OXA-181}$ | CTX-M-15, TEM-30 | – | 207 |
| Denmark | 2018 | *E. coli* | – | X3 | – | – | *bla*$_{NDM-5}$ | CMY-2 | – | 207 |
| | | *K. pneumoniae* | ST35 | HI2 | 314 | Conjugative | *bla*$_{OXA-436}$ | – | IS*91* /IS*CR1* | 208 |
| | | *C. freundii* | ST22/65 | HI2 | 314 | Conjugative | *bla*$_{OXA-436}$ | – | IS*91*/IS *CR1* | |
| | | *E. asburiae* | – | HI2 | 314 | Conjugative | *bla*$_{OXA-436}$ | – | IS*91*/IS *CR1* | |
| Romania | 2015 | *K. pneumoniae* | ST258 | FII | | Conjugative | *bla*$_{KPC-2}$ | CTX-M-15, TEM-1, OXA-1, OXA-9, AAC-6′-1b | Tn*4401* | 53 |

*Continued*

**Table 1.** ***Continued***

| Country | Year | Species | Clone | Plasmid type (Inc) | Size (kb) | Plasmid conjugation/ mobility | Carbapenemase gene | Other resistance | Genetic elements | References |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | ST101 | L/M | | Conjugative | *bla*$_{OXA-48}$ | CTX-M-15, TEM-1, OXA-9, AAC-6′-1b-cr | Tn*1999.2* | |
| | | *E. cloacae* | ST93 | FII | | Conjugative | *bla*$_{VIM-4}$ | CTX-M-15, TEM-1, OXA-1, AAC-6′-1b | Class 1 integron | |
| Kuwait | 2017 | *K. pneumoniae* | ST1399 | A/C | 165 | Conjugative | *bla*$_{VIM-4}$ | TEM-1, SHV-12, CTX-M-15, CMY-4, aac(6')-Ib-cr | In416 | 209 |
| | | *E. aerogenes* | _ | FII | | Conjugative | *bla*$_{KPC-3}$ | TEM-1, OXA-30, CTX-M-15 | Tn*4401b* | |
| | | *E. coli* | ST58 | FII | | _ | *bla*$_{KPC-3}$ | TEM-1 | Tn*4401b* | |
| | | *K. pneumoniae* | ST11 | FII | | Conjugative | *bla*$_{KPC-3}$ | TEM-1, SHV-11, OXA-30, CTX-M-15 | Tn*4401b* | |
| | | | ST147 | FII | | Conjugative | *bla*$_{KPC-3}$ | TEM-1, SHV-11 | Tn*4401b* | |
| | | | ST1138 | FII | | Conjugative | *bla*$_{KPC-3}$ | TEM-1, SHV-36 | Tn*4401b* | |
| Lebanon | 2018 | *E. coli* | ST354 | L/M | – | – | *bla*$_{OXA-48}$ | CTX-M-15, CMY-42, TEM-1b, OXA-1 | IS*1999* | 210 |
| | | | ST410 | X3 | – | – | *bla*$_{OXA-181}$ | CMY-2/4, CTX-M-15, TEM-1B, OXA-1 | – | |
| Thailand | 2018 | *K. pneumoniae* | – | H1B | 297 | – | *bla*$_{NDM-1}$ | *aadA2*, *armA*, *aph(3')*-Vla, *Sul*1, CTX-M-15, *qnrB1* | – | 211 |
| Pakistan | 2018 | *K. pneumoniae* | ST101 | L/M | – | – | *bla*$_{OXA-48}$ | CTX-M-15, SHV-28, TEM-1, OXA-10 | – | 212 |
| Czech Republic | 2017 | *E. coli* | ST4956 /ST216 | L | 64 | _ | *bla*$_{OXA-48}$ | _ | – | 153 |
| | | *E. cloacae* | ST109 | L | 64 | _ | *bla*$_{OXA-48}$ | CTX-M-15, OXA-1, TEM-1 | Tn*1999.2* | |
| | | *K. pneumoniae* | ST101 | L | 64 | _ | *bla*$_{OXA-48}$ | CTX-M-15, TEM-1 | Tn*1999.2* | |
| Czech Republic | 2017 | *K. pneumoniae* | ST18 | X3 | 51 | _ | *bla*$_{OXA-181}$ | CTX-M-15, OXA-1, TEM-1 | IS*26* | 153 |
| | | | ST15 | colE2 | 13 | _ | *bla*$_{OXA-232}$, *bla*$_{NDM-1}$ | CTX-M-15, OXA-1 | Tn*1000* | |

*Continued*

**Table 1.** ***Continued***

| Country | Year | Species | Clone | Plasmid type (Inc) | Size (kb) | Plasmid conjugation/ mobility | Carbapenemase gene | Other resistance | Genetic elements | References |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | ST11 | L | 65 | _ | *bla*$_{OXA-48}$ | CTX-M-15 | Tn*1999.5* | |
| | | *P. stuartii* | _ | A/C | 100 | Conjugative | *bla*$_{NDM-1}$ | CTX-M-15 | _ | |
| | | | ST1301 | X3 | >150 | Nonconjugative | *bla*$_{OXA-181}$ | CTX-M-15, *qnrS* | IS*Esp1-IS3000-*IS*Kpn19* | |
| | | | ST15 | X3 | 120 | Conjugative | *bla*$_{NDM-1}$ | CTX-M-15 | _ | |
| Taiwan | 2018 | *K. pneumoniae* | ST11 | – | 86 | – | *bla*$_{KPC-2}$ | CTX-M, SHV, TEM | IS*1* | 213 |
| Egypt | 2016 | *K. pneumoniae* | ST147 | colE, R | 60–97 | Conjugative | *bla*$_{NDM-1}$ | CTX-M-15, SHV-11, *aac(3)-IIa*, *aph(30)-Ia*, *aac(60)-Ib-cr*, *rmtF*, *qnrB* | IS*Aba125* | 214 |
| | | | ST11 | colE, R, F | 55 | Conjugative | *bla*$_{NDM-1}$ | CTX-M-15, SHV-11, *aac(3)-IIa*, *aph(30)-Ia*, *aac(6')-Ib-cr*, *rmtF*, *qnrB* | IS*Aba125* | |
| Gabon | 2017 | *K. pneumoniae* | ST307 | X3 | _ | Conjugative | *bla*$_{NDM-7}$ | CTX-M-15, SHV-28, OXA-9, *aac(6')-Ib*, *sul*, *fosA* | Transposon | 215 |
| | | *E. cloacae* | _ | X3 | _ | Conjugative | *bla*$_{NDM-7}$ | OXA-9, ampR, SHV-12, TEM-104 | Transposon | |
| India | 2019 | *K. pneumoniae* | ST347 | FII | 153 | Conjugative | *bla*$_{NDM-1}$ | CTX-M-15, *qnr*S1, *qnr*B1, *oqxAB*, *aac(6')-Ib-cr* | IS*Aba125* | 216 |
| | | | ST29 | FII | 115 | Conjugative | *bla*$_{NDM-1}$ | CTX-M-15, *qnr*S1, *oqxAB* | IS*Ec33* | |
| | | | ST1224 | FII | 270 | Conjugative | *bla*$_{NDM-1}$ | CTX-M-15, *qnr*S1, *qnr*B1, *oqxAB*, *aac(6')-Ib-cr* | IS*Aba125* | |
| | | | ST2558 | FII | 173 | Conjuagtive | *bla*$_{NDM-1}$ | CTX-M-15, *qnr*S1, *aac(6')-Ib* | IS*Ec33* | |
| | 2016 | *S. enterica* | _ | A/C | 146 | Conjugative | *bla*$_{NDM-1}$ | CMY -4 | IS*26*, IS*4321* | 186 |
| Vietnam | 2015 | *K. pneumoniae* | | FII, A/C | _ | _ | *bla*$_{NDM-1}$ | TEM, CTX-M | _ | 173 |
| | | *E. cloacae* | | FII, A/C | _ | _ | *bla*$_{NDM-1}$ | TEM, CTX-M, SHV | _ | |
| Vietnam | 2015 | *E. coli* | | FII | _ | _ | *bla*$_{NDM-1}$ | TEM, CTX-M, SHV | _ | 172 |
| | | *C. freundii* | | FII, A/C | _ | _ | *bla*$_{NDM-1}$ | TEM, CTX-M | _ | |
| | | *K. oxytoca* | | FII | _ | _ | *bla*$_{NDM-1}$ | TEM, CTX-M | _ | |
| Brazil | 2015 | *E. hormaechei* | | F | 96.124 | Conjugative | *bla*$_{NDM-1}$ | _ | Tn*3000* | 136 |
| Korea | 2018 | *K. pneumoniae* | ST340 | X3 | – | – | *bla*$_{NDM-1}$ | – | IS | 217 |
| | | *E. coli* | ST1642 | X3 | 69.409 | Conjugative | *bla*$_{KPC-2}$ | SHV-11 | Tn*4401* | 145 |

*Continued*

**Table 1.** ***Continued***

| Country | Year | Species | Clone | Plasmid type (Inc) | Size (kb) | Plasmid conjugation/ mobility | Carbapenemase gene | Other resistance | Genetic elements | References |
|---|---|---|---|---|---|---|---|---|---|---|
| France | 2018 | *K. pneumoniae* | ST395 | L | 62 | – | *bla*$_{OXA-48}$ | CTX-M-15, *aac(6')-Ib-cr*, *qnr*S | – | 218 |
| | | | – | L/M | 63 | Conjugative | *bla*$_{OXA-48}$ | CTX-M-1 | IS*9999* | |
| | | | – | L/M | 167 | Conjugative | *bla*$_{OXA-48}$ | – | IS*9999* | |
| Belgium | 2016 | *E. cloacae* | ST346 | L/M | 78.907 | Conjugative | *bla*$_{GES6/7}$ | _ | Class 1 integron | 191 |
| Ireland | 2014 | *K. pneumoniae* | _ | L/M | 63.578 | Conjugative | *bla*$_{OXA-48}$ | _ | Tn*1999* | 152 |
| | | | _ | FIB | 63 | Conjugative | *bla*$_{OXA-48}$ | _ | Tn*1999* | |
| | | | _ | FII | 63 | Conjugative | *bla*$_{OXA-48}$ | _ | Tn*1999* | |
| | | | _ | Y | _ | _ | *bla*$_{OXA-48}$ | _ | _ | |
| Tunisia | 2018 | *P. mirabilis* | – | P & A/C | – | – | *bla*$_{NDM-1}$ | CMY-4, *qnr*A6, *aph*3 Vla, *aph*3 la | – | 219 |
| Saudi Arabia | 2018 | *K. pneumoniae* | ST152 | F, N | – | Conjugative | *bla*$_{NDM-1}$ | – | IS*Aba125* | 220 |
| | | | ST37 /974 | L/M | – | Conjugative | *bla*$_{OXA-48}$ | CTX-M-15, TEM-1, SHV-11 | – | |
| South Africa | 2018 | *E. coli* | ST167 | X3 | 46.253 | _ | *bla*$_{NDM-5}$ | _ | _ | 12 |
| | | *K. pneumoniae* | ST101 | Col | 6.141 | _ | *bla*$_{OXA-232}$ | _ | _ | |
| South Africa | 2018 | *K. pneumoniae* | ST101 | FIB | 223.434 | Conjugative | *bla*$_{NDM-1}$ | qac/sul1, DHA-1 | Tn*1548*-like | 12 |
| | | | ST2017 | R, FIB, FII | 212.326 | Conjugative | *bla*$_{NDM-1}$ | qac/sul1, DHA-1 | Tn*1548*-like | |
| | | | ST101 | Q | 8.201 | _ | *bla*$_{GES-5}$ | aacA4 | Class 1 integron | |
| Sao Tome and Principe | 2018 | *E. coli* | ST1163 | X3 | 66 | Conjugative | *bla*$_{OXA-181}$ | TEM-1 | IS*kpn19* | 221 |
| | | | ST410 | X3 | 60 | Conjugative | *bla*$_{OXA-181}$ | CTX-M-15, TEM-1 | IS*kpn19* | |
| | | *K. pneumoniae* | – | X3 | 64 | Conjugative | *bla*$_{OXA-181}$ | TEM-1 | IS*kpn19* | |
| Croatia | 2018 | *K. pneumoniae* | – | L/M | 70 | Conjugative | *bla*$_{OXA-48}$ | CTX-M-15, TEM-1, OXA-1, *qnr*A/B | IS*1999* /IS*1R* | 222 |
| | | *E. coli* | – | L/M | 70 | Conjugative | *bla*$_{OXA-48}$ | TEM-1 | IS*1999* | |
| | | *E. cloacae* | – | L/M | 70 | Conjugative | *bla*$_{OXA-48}$ | CTX-M, TEM-1 | IS*1999* | |

Although IncF plasmids are the most prevalent, other narrow-host-range incompatibility types, such as IncI, L/M, and IncX, are widely distributed and are associated with multiple carbapenemases, ESBLs, and MBLs. Only in a few instances have they been associated with the class D carbapenemases, specifically OXA-181 (Table 1).

**IncX plasmids.** IncX plasmids were previously described as less predominant in *Enterobacteriaceae* because of underestimations by PBRT. The first plasmids in this group, for example, R6K, were discovered by Kontomichalou and colleagues in 1970, during the preantibiotic era in a *Salmonella* spp. isolate. This was a 39.8-kb self-transmissible low copy number (10–15 replicons) plasmid, containing ampicillin and streptomycin resistance determinants.[144] Comparison studies looking at plasmid R6K and modern plasmids revealed that this plasmid is different from other plasmids in the IncX group, suggesting that subdivisions are required in the IncX group.[145] Only two

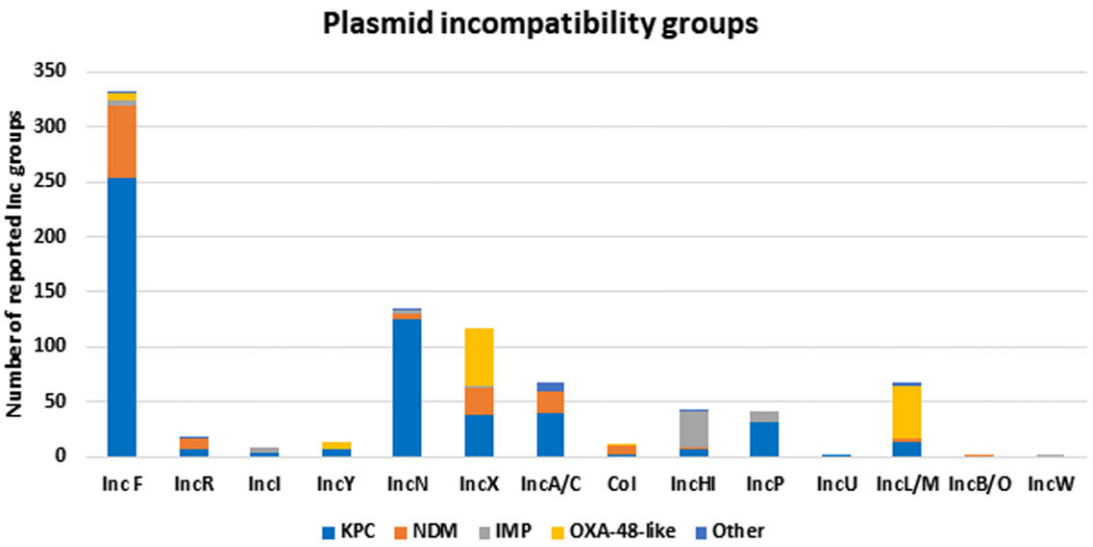


**Figure 3.** **Frequency of plasmid incompatibility groups associated with different carbapenemase genes reported in *Enterobacteriaceae* in 23 countries. The commonest of these is the IncF types, followed by IncN, IncX, IncL/M, IncA/C, IncHI, and IncP, which are mostly associated with KPC, NDM, and OXA-48-like carbapenemases.**

subgroups (IncX1 and IncX2) were initially characterized based on restriction analysis.[145] The expansion of this plasmid family to include IncX3 and IncX4 was proposed by Johnson *et al.* based on a phylogeny deduced from polymorphisms of all conserved regions of sequenced IncX plasmids.[146] Another subgroup, IncX5, was added shortly after this expansion; IncX5 was found in a KPC-5–producing *K. pneumoniae* isolate.[147] Since these expansions, IncX plasmids have been found to play a major role in the dissemination of β-lactamases, including carbapenemases. IncX1 was previously described as more predominant than IncX2 in environmental isolates.[145] However, Dobiasova and Dolejska reported a high prevalence of IncX1 and IncX4 in environmental isolates and none in human isolates in Africa.[148]

IncX plasmids are usually associated with carbapenemase genes in *Enterobacteriaceae*, particularly $bla_{KPC}$, $bla_{OXA-181}$, and $bla_{NDM}$ (Table 1). According to recent studies, IncX3 is the predominant subgroup reported to harbor both $bla_{KPC}$ and $bla_{NDM}$.[149–152] The studies reported this subgroup as predominantly associated with $bla_{NDM}$ variants, rather than $bla_{KPC}$ variants. Further, $bla_{NDM-1}$ and $bla_{NDM-5}$ were more frequently associated with IncX3 than any other $bla_{NDM}$ variant. Only in a few instances have IncX4 and IncX5 plasmids been associated with carbapenemase genes (Table 1).[150,153] In addition, an IncX5 plasmid encoding $bla_{IMP-4}$ was reported in Australia from an *E. coli* of animal origin.[154] These reports suggest that an essential role is played by IncX3 in the acquisition, emergence, and dissemination of $bla_{NDM}$. IncX3 plasmids that have been associated with the spread of $bla_{NDM}$ include pEc2A (74.8 kb), pM213_X3 (43.5 kb), pNDM-NJ-IncX3 (39.5 kb), and pKW53T-NDM (46.1 kb).[140,142,153] Other IncX3 plasmids recovered from Czech hospitals in Europe have been reported in *E. cloacae* isolates that express $bla_{NDM-4}$.[155] An IncX plasmid was reported in China in an *E. coli* isolate coexpressing both $bla_{NDM-5}$ and *mcr-1*.[143] Occurrence of IncX6 was reported in 2016 in *E. cloacae*. Moreover, the dissemination of this plasmid type has been shown in at least six *Enterobacteriaceae* species in China.[51,156] IncX6 was reported to carry both $bla_{KPC-2}$ and $bla_{KPC-3}$ in China (Table 1).[51,156] In $bla_{KPC}$-expressing *Enterobacter* spp., another subgroup, IncX7, has also been reported in the United States.[53] These findings suggest the wide dissemination of IncX subgroups in *Enterobacteriaceae* in China and the United states.

**L/M plasmids.** L/M plasmids have been considered an emerging threat owing to their increasing prevalence in MDR clinical and environmental isolates.[157] L/M plasmids are broad-host-range

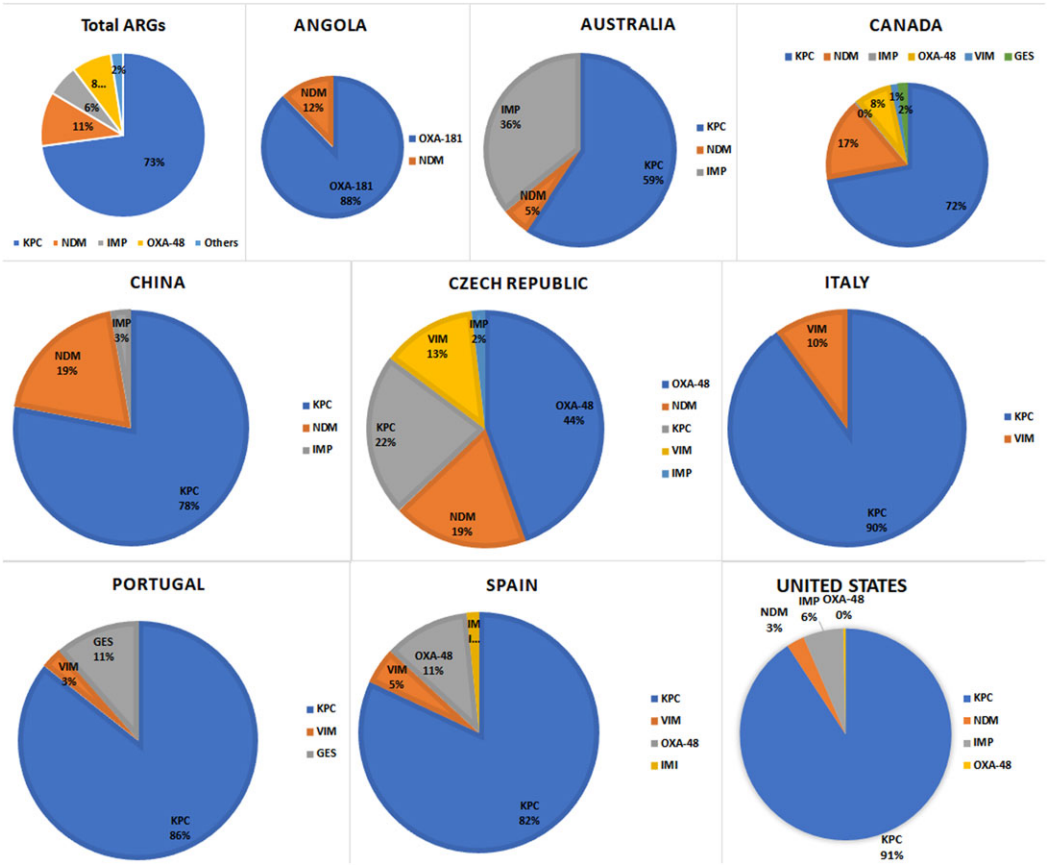


**Figure 4.** **Charts showing the frequency of carbapenemase genes per country reported in the set of papers included in this review. KPC has been reported as the most prevalent in almost all shown countries, except the Czech Republic and Angola, where OXA-48-like were the most prevalent. KPC, *Klebsiella pneumoniae* carbapenemase; VIM, Verona-Integron metallo-β-lactamase; NDM, New-Delhi metallo-β-lactamase; GES, Guiana extended-spectrum β-lactamase; IMP, imipenemase; OXA-48, oxacillinase-48.**

plasmids with an average size of 50–80 kb and a low copy number.[98] Foster *et al.* reported that the pEL60 plasmid in *Erwinia amylovora* has a basic L/M plasmid backbone but lacks genetic elements and resistance determinants.[158] Moreover, genomic analysis of L/M plasmids has shown backbone genes for replication and stability modules, a conjugative transfer system, and a *mucAB*-like mutagenic DNA repair system.[158]

Separation of this group into IncL and IncM was suggested by Carattoli *et al.* because of differences in the protein expressed, namely, ExcA, TraY, and TraX. This separation was accepted, and the PBRT scheme was updated to incorporate these separate plasmids. The IncL/IncM incompatibility group has been associated with multiple ESBLs, AmpCs, and carbapenemases, specifically class B and D genes.[157,159] Several IncL plasmids in $bla_{\text{NDM-1}}$- and $bla_{\text{OXA-48}}$-expressing clinical isolates have been widely reported, some of which include pNDM-OM (87.1 kb), pNDM-HK (88.8 kb), E71T (63.5 kb), and pOXA-48-4963 (63.5 kb).[157,160,161] Although L/M plasmids usually harbor $bla_{\text{NDM}}$ and $bla_{\text{OXA-48}}$, they are also reportedly associated with $bla_{\text{IMP}}$ in *Enterobacteriaceae* (Table 1 and Fig. 3). A few studies have identified these plasmids in $bla_{\text{IMP-4}}$-expressing isolates.[162] From isolates of animal origin, Dolejska and colleagues reported the presence of $bla_{\text{IMP-4}}$ in *E. aerogenes* on an IncM plasmid (pEa1631, 85 kb).[154] Bryant *et al.* have also reported L/M plasmids (pNE1280, 66.5 kb) in $bla_{\text{KPC}}$-expressing isolates from a female with a medical history of mitral and aortic valve stenosis,

pulmonary hypertension, restrictive lung disease, and diabetes.[163]

**A/C plasmids.** Another important broad-host-range incompatibility type is the A/C plasmid type, which harbors various carbapenemase genes. These plasmid types are different from other plasmid types in that they contain an integron with the theta replicon, three integrative hotspots, putative transcriptional regulators, and hypothetical genes.[164,165] These plasmids are large with low copy numbers. The A/C plasmid types are usually associated with cephalosporinases, for example, $bla_{CMY}$, and MBLs, for example, $bla_{NDM}$ (Table 1).[166,167] However, these plasmids have also been associated with the dissemination of carbapenemases, such as $bla_{NDM}$, $bla_{VIM}$, and $bla_{KPC}$.[155,168,169] Two A/C groups have been identified, $A/C_1$ and $A/C_2$, with $A/C_2$ being predominant.[170] However, all A/C plasmid types share most of the conserved regions, such as genes responsible for conjugative transfer (*tra*) and replication (*repA*), as well as other genes with unknown functions.[171] A/C plasmids have been thoroughly reviewed previously.[170] Only a few plasmids belong to the $A/C_1$ group, including pRA1 and pIncAC-KP4898;[172,173] the latter 156.2 kb plasmid, encoding $bla_{VIM-1}$, was recently isolated.[173] $bla_{NDM-1}$ has been associated with $A/C_2$ plasmid types in different *Enterobacteriaceae* species; and recently, $bla_{NDM-4}$ was detected on $A/C_2$ plasmids.[140] $A/C_2$ plasmids reported to carry $bla_{NDM-1}$ include pM214_AC2 (176 kb), pNDM-EcoGN568 (166.7 kb), pNDM-KN (162.7 kb), and pNDM-PstGN576 (147.8 kb).[140,141,167] pNDM-EcoGN568 is a multireplicon (IncF and A/C) circular plasmid reported to be identical to pNDM10-0505, an A/C plasmid with the same size as pNDM-EcoGN576.[141] These three plasmids share similar conserved sequences and genes, suggesting lateral transfer among different species, albeit independent acquisition of genes cannot be ruled out.[141]

**IncN plasmids.** The IncN plasmid type is also of broad host range, with high transmission efficiency. These plasmids are also important in the dissemination of carbapenemase genes, including $bla_{KPC}$, $bla_{NDM}$, $bla_{IMP}$, and $bla_{VIM}$ (Table 1).[74,147,174,175] Within this group, three subgroups with similar plasmid scaffolds but less similarity in backbone sequences have been described: IncN1 (R46), IncN2 (p271A), and IncN3 (pN-Cit);[85,176] these characteristics might be the reason for their stability and success in disseminating multiple carbapenemases. IncN plasmids are usually medium-sized conjugative plasmids documented to be associated with $bla_{VIM}$-expressing *Enterobacteriaceae* and $bla_{KPC}$-expressing *K. pneumoniae* isolates.[177] Plasmids, including p9 (70.6 kb), p12 (75.6 kb), pKPC-629 (80.1 kb), pBK31551 (83.7 kb), pKO6 (65.5 kb), and pKp58-N (69.8 kb), have been documented as carriers of $bla_{KPC}$.[52,135,178] Most of the sequences of these plasmids have been deposited in GenBank without a corresponding published article (accession numbers are given in Table S1, online only).

The pKOX105 (54.6 kb) plasmid carried regions encoding genes conferring resistance to carbapenems ($bla_{VIM-1}$), cephalosporins ($bla_{SHV-12}$), aminoglycosides (*aacA4*), trimethoprim (*dfrA14*), and quinolones (*qnrS1*).[179] This plasmid was compared with other previously reported IncN plasmid types, that is, plasmids 9 (70.6 kb) and 12 (75.6 kb), that carried $bla_{KPC}$.[178] The scaffolds between these IncN plasmids were found to be the same, but the MDR regions were different.[179] The major differences that are usually reported among IncN plasmids relate to their acquired genes.[179]

**Other plasmid groups.** Other incompatibility groups, such as IncI, ColE, IncB/O, IncH, and IncP, have also been reported to be associated with carbapenemases in *Enterobacteriaceae*, albeit they are reported in few species and are limited to a few carbapenemase genes (Table 1).

### *Molecular epidemiology of plasmids in Enterobacteriaceae*

***K. pneumoniae.*** In the United States, KPC is the major carbapenemase associated with antibiotic resistance (Figs. 2–4).[24,49,135,180] KPC variants, such as KPC-2, KPC-3, and KPC-4, were reported in several studies in the United States and associated with multiple plasmid replicon groups, facilitating their spread. KPC-2 was commonly associated with multiple STs, but ST258 was the most prevalent in the United States. The IncF groups dominate in the spread of KPC-2 and KPC-3 in the United States and other countries, including Australia, Canada, China, Italy, Romania, and Spain[42,50,52,56,152,153,156,174] Only one study has reported on IncF groups in KPC-3 in Portugal and Romania.[56,181] Few occurrences were also

reported in other countries, including the United States, Mexico, and Spain. This plasmid replicon group is commonly reported in KPC-producing *K. pneumoniae* species.[182]

Other plasmid replicon groups, such as IncN, IncP, IncX, IncU, IncI, A/C, IncR, and L/M, are also occasionally reported in KPC-producing *K. pneumoniae*.[48,52,53,57,175,180,183,184] Moreover, these plasmid replicon groups are also associated with *K. pneumoniae* strains producing other carbapenemases. VIM has been only reported by two studies in Italy and Kuwait to be hosted by IncN and A/C.[174,177]

OXA variants in *K. pneumoniae* are usually spread by the IncF and L/M replicon groups. L/M has been reported to spread OXA-48 in different countries, including the United States, the Czech Republic, Romania, and Australia (Table 1).[56,161,162,180] OXA-181 has been reported in Angola and Australia on IncF, A/C, and IncX plasmid replicon groups (Fig. 4).[138,162]

IncX is commonly associated with the spread of NDM variants and has been mostly described in China.[185,186] Other plasmid replicon groups, including IncF, IncR, IncCol, L/M, and A/C, have also been described in NDM-producing *K. pneumoniae* in Australia, China, Mexico, and Vietnam (Fig. 3).[139,143,162,184,185,187] Furthermore, other *Klebsiella* spp., such as *K. oxytoca,* do not have a wide distribution of replicon groups, as only the IncN and IncF groups have been described in them in few countries (Table 1). IncN plasmids have been reported in *K. oxytoca* strains producing VIM-1 and IMP-6 β-lactamases.[175,177] These plasmid types were occasionally reported in VIM-1–producing *K. oxytoca* isolated from river samples.[177] Moreover, IncN plasmids have been found with $bla_{\text{IMP}}$ in Japan.[175]

***E. coli*.** Similar to *K. pneumoniae* species, *E. coli* strains have a wide distribution of plasmid replicon groups that have been reported worldwide. Most carbapenemase-producing *E. coli* usually harbor IncF plasmids, which is also dominant in *K. pneumoniae* species. IMP variants in *E. coli* are spread by multiple plasmid replicon groups, such as IncHI, IncN, IncQ, IncX, IncI, and IncW.[162,175,188] Most NDM variants in *E. coli* have been detected in China, except NDM-4, which has been mostly reported in Australia.[162] NDM-1 has been disseminated worldwide through various plasmid replicon groups, including IncF, IncI, IncX, and A/C; however, IncX is the most prevalent replicon facilitating the spread of $bla_{\text{NDM}}$.[138,141,142,189,190] Among these plasmid types, IncX-3 has been mostly associated with the dissemination of $bla_{\text{NDM-1}}$ in China, a finding different from other countries.[190–192]

***Enterobacter spp.*** In the United States, *Enterobacter* spp. are ranked eighth among all other pathogens causing healthcare-associated infections.[49] MDR *E. cloacae* isolates have been associated with bloodstream infections, resulting in bacteremia and mortality as high as 40%.[162] $bla_{\text{NDM}}$ and $bla_{\text{IMP}}$ are the predominant carbapenemases isolated from *Enterobacter* spp. in the United States, Australia, China, and Vietnam.[162,189,193] In Vietnam, $bla_{\text{NDM-1}}$ was found to be disseminated by IncF (IncFII and IncFIB) plasmids and, in a few cases, by A/C plasmids (Table 1). Similar results were reported in other countries, including the United Kingdom, Canada, and the United States (Table 1). A/C plasmids have been identified in unrelated *E. cloacae* clinical isolates in China. In addition, IncHI2 and IncN have been also implicated in the dissemination of $bla_{\text{NDM-1}}$.[194] IncHI2, L/M, and IncP are usually associated with $bla_{\text{IMP}}$ in countries such as Australia, China, and the United States in *Enterobacter* spp.[162,188,194] However, IncP plasmids have so far been identified with IMP-27-producing *Enterobacter* spp. in the United States.[188] These plasmids are also present in Spain and carry $bla_{\text{KPC-2}}$ in sewage.[195] Chavda *et al.* reported a wide distribution of plasmid Inc groups in KPC-producing *Enterobacter* spp. in New York City, which included IncN and IncX7 ($bla_{\text{KPC-2}}$), IncF and L/M ($bla_{\text{KPC-3}}$), and A/C ($bla_{\text{KPC-4}}$).[53] The complexity, diversity, and wide geographical distribution of these Inc groups disseminating major groups of classes A and B carbapenemases pose a major challenge to the control of MDR *Enterobacter* spp.

***Providencia*, *Proteus*, *Citrobacter*, and *Salmonella* spp.** Other *Enterobacteriaceae* species, including *Proteus* spp., *Providencia* spp., *Citrobacter* spp., and *Salmonella* spp., have been only reported in a relatively few cases, with few carbapenemases being identified in them (Table 1). Two major carbapenemases, $bla_{\text{IMP}}$ and $bla_{\text{NDM}}$, are predominantly detected in these species, with IncHI2, A/C, IncP, and IncX3 being the

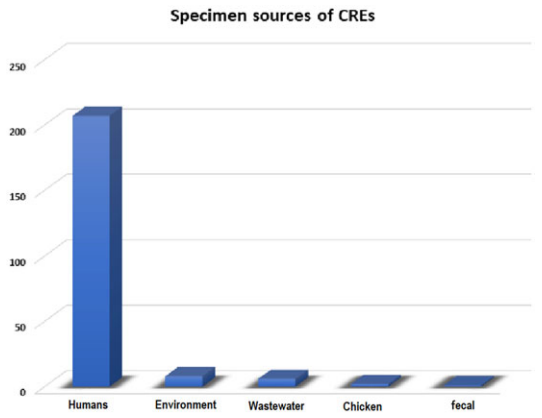


**Figure 5.** Specimen sources of CREs identified in the included articles reported in this review. Most of the specimens were obtained from humans with a small number being obtained from environmental and animal sources. Frequencies were manually calculated and graphically represented using Microsoft Excel.

plasmid types responsible for their dissemination between species.[138,141,162,185,188,196,197] The isolates in these reports were recovered from both clinical and environmental samples, including river water and domestic cats in Angola, Australia, Canada, China, India, Spain, and the United States (Table 1).[138,139,141,162,188,196,197] *Citrobacter* spp. also harbor IncX, IncR, IncHI2, IncP, and IncN plasmids, which host $bla_{NDM}$, $bla_{KPC}$, and $bla_{IMP}$ carbapenemases.[97,198,199] A hospital sewage in China was found to contain *C. freundii* that carried an IncX3 plasmid harboring $bla_{NDM-1}$.[199] Another study in China reported IncX3 plasmids in NDM-1–producing isolates collected from ready-to-eat vegetables.[200] Other countries, such as Australia, Canada, and Italy, reported other plasmid types, including IncFII, IncR, IncP, and L/M, in *Citrobacter* spp.[41,50,97,162] Recent studies have reported the increased isolation of A/C plasmids in *Enterobacteriaceae* species, including *E. coli*, *K. pneumoniae*, and *Salmonella* spp.[201] Most isolates reported in our review here were clinical isolates from humans; few studies evaluated here addressed carbapenemases and plasmid replicon groups in animal and environmental isolates (Fig. 5).

### *MGEs associated with plasmid incompatibility types*

Most MGEs are commonly found on plasmids and play an important role in disseminating antimicrobial resistance determinants. MGEs, such as integrons, transposons, and insertion sequences, may be associated with specific incompatibility groups and carbapenemases.

In most A/C plasmids, the antimicrobial resistance island is usually embedded in or upstream of the gene *rhs*1 and contains an integron, multiple transposons, a Tn*21*-tnp module, and a Tn*21*-mer module, which is interrupted by an insertion sequence IS*4321*.[202] Integrons, particularly class 1 integrons, are usually associated with A/C plasmids and gene cassettes carrying ARGs, specifically $bla_{NDM}$.[141] This was shown in multiple A/C plasmids and in one IncF (pNDM-EcoGN568) plasmid, which was identical to the A/C plasmids; the IncF plasmid only differed from the A/C plasmids by the number of ARG cassettes on the class 1 integron.[141] Other NDM-carrying plasmids, such as pM109-FII and pGUE-NDM, carry a 12-kb ARG region that surrounds $bla_{NDM}$.[140] An additional gene cassette bracketed by two IS*26* elements and carrying $bla_{TEM-1}$ was found downstream of *rmtB* (a gene expressing an aminoglycoside resistance determinant).[140]

$bla_{NDM}$ variants, such as NDM-4, -5, and -6, have been reported on IncX3 plasmids. The genetic structure of IncX3 plasmids is usually highly similar in almost all plasmids. A study performed in Myanmar found NDM-4 and NDM-7 on IncX3 plasmids that were highly similar to previously reported IncX3 plasmids; suggesting a common ancestor.[140] NDM-4 was carried on transposon Tn*3* and flanked by insertion sequences, with no other resistance gene being reported on this plasmid. The $bla_{KPC}$ regions of IncX6 plasmids are highly similar, with Tn*6296* derivatives and an IS*Kpn19* element. However, one plasmid reported by Li *et al.* contained a Tn*6296* derivative and an IS*Kpn19*-containing Tn*6292* derivative.[51,156]

The MGEs in A/C plasmids carrying other carbapenemases, such as $bla_{KPC}$, are usually different from those carrying $bla_{NDM}$. Transposons are mostly associated with the acquisition of $bla_{KPC}$. The transposon Tn*4401*, which is approximately 10 kb in size and delimited by two 39-bp inverted repeat (IR) sequences, is associated with a 5-bp target-site duplications (TSDs) on both sites adjacent to the IR sequences.[203] The 5-bp TSDs adjacent to the IR sequences are the target-site sequences for the Tn*4401* transposons. This is an important characteristic identified in plasmids p9 and p12,

which contain a functional conjugative apparatus with an ~10 kb region carrying the Tn*4401b* element with $bla_{KPC}$ and other ARGs.[178] The Tn*4401b* element in plasmid p9 shown to be inserted in an inverted orientation downstream of the EcoRII restriction/antirestriction system and the gene *uvp1* gene.[178]

Similar characteristics are seen in IncF plasmids carrying $bla_{KPC}$ with additional elements. pBK30661, an IncF plasmid whose backbone genes are separated by multiple insertion sequence elements (IS*3*, IS*26*, IS*1294*, and IS*66*), has a Tn*4401d* variant with a 68-bp deletion upstream of $bla_{KPC}$.[135] The region upstream of Tn*1331* is truncated by an 8-kb nickel resistance operon (*nic* operon), which results in a deletion of the corresponding 5-bp sequence and leaving a unique 5-bp sequence adjacent to the upstream IR sequence.[135] pNE1280, an L/M plasmid carrying $bla_{KPC}$, contained a major insertion of a 13-kb Tn*3* family transposon, Tn*4401f*, with $bla_{KPC-4}$ flanked by IS*kpn6* on the left and IS*kpn7* on the right.[163]

The genetic structure of $bla_{OXA-48}$ in L/M plasmids is different from that of other carbapenemases. This gene is usually part of Tn*1999* (Tn*1999*–Tn*1991.4*), with Tn*1991.2* being the most prevalent.[157,204] In 2016, Cuzon and colleagues reported an L/M plasmid carrying GES-5 and GES-6 on the same plasmid (Table 1). This plasmid harbored additional ARGs, including *aadA1* and *sul*1;[205] $bla_{GES-5}$ and $bla_{GES-6}$ were located on a class 1 integron, and both sides were flanked by IS*26* and IS*6100*. This pEB-1 plasmid was compared with other L/M plasmids, pEL60 and pNDM-OM, and similar characteristics were observed, except that the integration site of the ARGs array was different.[205] In South Africa, $bla_{GES-5}$ was reported on an IncQ plasmid but still within a class 1 integron, with an additional *aadA4* on an integron mobilization unit.[12]

## Conclusions

Our review showed a high frequency of $bla_{KPC}$ ($n = 956$, 73%) in almost all the countries reported, with China, Canada, Greece, and the United States having the highest percentages. The genes were associated with multiple plasmid groups, including IncF ($n = 254$, 48%), IncN ($n = 125$, 24%), IncX ($n = 38$, 7%), A/C ($n = 39$, 7%), and L/M ($n = 14$, 3%) in different *Enterobacteriaceae* species. Furthermore, specific plasmid types, such as IncF, L/M, and IncX3, have been reported to be associated with the dissemination of $bla_{KPC}$, $bla_{OXA-48}$, and $bla_{NDM}$, respectively. We also showed the frequency of carbapenemases and plasmid replicon groups in the articles used for our review. Other countries, such as the United States and China, had high frequencies due to more research being performed in these countries. Our review has also shown the important role played by MGEs, such as plasmids, transposons, and insertion sequences, in acquisition and dissemination of ARGs among *Enterobacteriaceae* species, increasing the need for new antibiotics and antibiotic stewardship strategies. We also found that a major limitation to effective characterization of plasmid evolution was the use of PCR-based instead of WPS-based plasmid typing.

WGS has proven to give enough data for plasmid characterization, albeit PBRT still forms the basis of most plasmid characterization studies, particularly in low-income countries. Obviously, long-read WPS and WGS hold the key to an efficient characterization of plasmid types, epidemiology, and evolution, and toward an efficient description of antibiotic resistance dissemination and expansion among *Enterobacteriaceae*. By overriding the deficiencies of PBRT, WPS and WGS will likely increase the effective identification and control of resistant bacteria, reducing mortalities, morbidities, and healthcare-associated expenses involved in long-term hospitalization of infected patients.

## Supporting information

Additional supporting information may be found in the online version of this article.

**Table S1.** Metadata of plasmids deposited at GenBank and included in this study.

**Supplementary dataset.** Nucleotide sequences of plasmids included in this study and obtained from Genbank.

## Competing interests

The authors declare no competing interests.

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