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MINIREVIEW

Resistance Plasmid Families in *Enterobacteriaceae*[▽]

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Bacteria carry extrachromosomal, self-replicating genetic elements called plasmids. A plasmid is defined as a double-stranded, circular DNA molecule capable of autonomous replication. By definition, plasmids do not carry genes essential for the growth of host cells under nonstressed conditions (109). Plasmids have systems which guarantee their autonomous replication but also have mechanisms controlling their copy number and ensuring stable inheritance during cell division. They can promote lateral transfer among bacteria of different genera and kingdoms through the conjugation process. Many plasmids encode addiction systems generally based on toxin-antitoxin factors, which are able to kill daughter cells that do not inherit the plasmid during cell division (46). These systems efficiently promote plasmid maintenance in the bacterial population, regardless of other selective pressure, and do not provide any apparent benefit to the bacterium hosting the plasmid. However, most of the plasmids confer positively selectable phenotypes with the presence of antimicrobial resistance genes. We consider plasmids to be living organisms in spite of their simple structure, since they are unit elements of a continuous lineage with individual evolutionary history. Conjugative plasmids resemble lambdoid phages, which are capable of theta replication during vegetative growth and rolling-circle replication during "packaging" of the DNA into a recipient cell (62).

The ability to recognize and categorize plasmids in homogeneous groups on the basis of their phylogenetic relatedness is helpful to analyze their distribution in nature and their relationship to host cells and to discover their evolutionary origins (34).

Identification and classification of plasmids should be based on genetic traits that are present and constant. These criteria are best met by traits concerned with plasmid maintenance, especially replication controls (28). In 1971, Hedges and Datta proposed a plasmid classification scheme based on the stability of plasmids during conjugation, a phenomenon called plasmid incompatibility (27, 47). Incompatibility is a manifestation of the relatedness of plasmids that share common replication controls (27, 78). Incompatibility was defined as the inability of two related plasmids to be propagated stably in the same cell line; thus, only compatible plasmids can be rescued in transconjugants. The first incompatibility (Inc) groups were defined as follows: IncI, plasmids producing type I pili susceptible to phage Ifl; IncN, N3-related plasmids susceptible to phage IKe; IncF, plasmids producing type F pili susceptible to phage Ff; and IncP, RP4-related plasmids susceptible to the PRR1 phage (27, 47). Currently, 27 Inc groups are recognized in *Enterobacteriaceae* by the Plasmid Section of the National Collection of Type Cultures (London, United Kingdom), including six IncF (FII to VII) and three IncI (I1, Iγ, I2) variants. In 1988, Couturier and colleagues proposed a genetic plasmid typing scheme based on Southern blot hybridization, using cloned replication regions (replicons) as probes (26). This approach successfully provided classification for both conjugative and nonconjugative plasmids, but the low specificity of the hybridization method underestimated plasmid diversity because of the cross-hybridization reaction among highly related replicons (repI, repB/O, repFII, repFIC). Since 2005, a PCR-based replicon typing (PBRT) scheme has been available, targeting the replicons of the major plasmid families occurring in *Enterobacteriaceae* (HI2, HI1, I1-γ, X, L/M, N, FIA, FIB, FIC, W, Y, P, A/C, T, K, B/O) and also including PCR assays (FrepB and FIIAs PCRs), detecting the FII, FIII, FIV, and FIV variants and the FII replicon of the *Salmonella* virulence plasmids, respectively (12). However, the PBRT scheme still has several limitations, since the classification is currently based on plasmids belonging to the classic Inc groups and can fail to identify divergent or novel replicons. The most accurate method to characterize a plasmid is based on the determination of the full-length DNA sequence, and to date, more than 800 plasmids from *Gammaproteobacteria* have been fully sequenced (http://www.ncbi.nlm.nih.gov/genome/), contributing to the identification of novel plasmid families. Furthermore, more than 1,000 resistance plasmids have been typed and assigned to specific plasmid families by PBRT and hybridization/conjugation methods. This review aims to provide an overview of the major plasmid families that are currently emerging in multidrug-resistant *Enterobacteriaceae* strains isolated worldwide among those conferring resistance to clinically relevant antibiotics, such as extended-spectrum cephalosporins, fluoroquinolones, and aminoglycosides (Table 1).

PLASMIDS CARRYING ESBLs IN *ENTEROBACTERIACEAE* OF HUMAN AND ANIMAL ORIGIN

Enterobacteriaceae producing expanded-spectrum β-lactamases (ESBLs), those of the CTX-M type in particular, are a major problem worldwide, causing outbreaks as well as sporadic infections (85).

The emergence and wide spread of the CTX-M-15 enzyme is

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TABLE 1. Overview of plasmid families associated with AmpC, ESBLs, 16S rRNA methylases, Qnr, and MBLs in *Enterobacteriaceae*

Enzyme[a]	Replicon(s)[b]	Species[c]	No. of plasmids	Country(ies)[e]	Source(s)	Reference(s) or GenBank accession no.
CMY-2	A/C	*Escherichia coli*, *S. enterica* [Agona, Anatum, Bredeney, Heidelberg, Newport, Typhimurium]	155	Canada, France, Honduras, Iraq, Ireland, UK, USA	Humans, cattle, pigs, poultry	1, 14, 32, 48, 73, 113
	I1	*E. coli*, *S. enterica* [4,5,12:I:−, Ajiobo, Heidelberg, Thompson, Typhimurium]	30	Canada, France, Gambia, Italy, UK, USA	Humans, cattle, horses, dogs, pigs, poultry	1, 14, 32, 38, 48
	FIA-FIB	*E. coli*	1	UK	Humans	48
	NT	*E. coli*, *S. enterica* [Heidelberg]	6	Canada, UK	Cattle, poultry, pigs	1, 73
CMY-4	A/C	*S. enterica* [Senftenberg]	1	UK	Humans	48
CMY-7	I1	*E. coli*	11	Pakistan, UK	Humans	48
CMY-8 (CTX-M-3)	HI2	*Klebsiella pneumoniae*	1	Taiwan	Humans	19
CMY-21	I1	*E. coli*	1	UK	Humans	48
CMY-31	ColE	*S. enterica* [Newport]	1	USA	Humans	118
CMY-36	ColE	*K. pneumoniae*	1	Greece	Humans	118
CTX-M-1	N	*E. coli*, *Klebsiella pneumoniae*	29	Denmark, France, Spain	Humans, pigs	30, 69, 72, 76
	I1	*E. coli*	16	France, Italy	Humans, poultry, dogs	38, 42, 69
	FII	*K. pneumoniae*	2	Spain	Humans	30
	L/M	*E. coli*	2	Spain	Humans	76
	NT	*E. coli*	1	France	Poultry	42
CTX-M-2	A/C	*E. coli*	14	Bolivia, France, Peru, UK	Humans	48, 69, 81
	HI2	*E. coli*	5	France, Belgium	Humans, poultry	37, 69
	P	*E. coli*	2	France, Ireland	Humans	48, 69
	I1	*E. coli*	1	France	Humans	69
	FVII	*E. coli*	1	Bolivia, Peru	Humans	81
	NT	*E. coli*	3	Bolivia, Peru	Humans	81
CTX-M-3 (ArmA)	L/M	*E. coli*, *Enterobacter cloacae*, *Citrobacter freundii*, *K. pneumoniae*, *Klebsiella oxytoca*, *Proteus mirabilis*, *Salmonella enterica*, *Shigella flexneri*, *Serratia marcescens*	73	Bulgaria, Croatia, France, Korea, Poland, Russia	Humans	4, 5, 35, 43, 54, 66, 69, 100, 104
	N	*E. coli*, *S. enterica* [Virchow]	5	Australia, Spain, UK	Humans	30, 48, 119
	A/C	*E. coli*	2	Spain	Humans	29, 76
	I1	*S. enterica* [Anatum, Potsdam]	2	Taiwan	Humans	67
	FII	*E. coli*	3	Australia, Croatia	Humans	66, 119
	NT	*E. coli*	3	Croatia, France	Humans	43, 66, 69
CTX-M-9	HI2	*E. coli*, *E. cloacae*, *K. pneumoniae*, *S. enterica* [Virchow]	68	France, Honduras, Pakistan, Spain, UK	Humans, poultry	30, 36, 37, 48, 77
	P	*E. coli*, *K. pneumoniae*	10	Spain	Humans	77
	FII, FIB	*E. coli*	12	Australia, France, Spain	Humans	30, 36, 69, 77, 119
	I1	*E. coli*, *K. pneumoniae*	8	Spain	Humans	30, 77
	Y	*E. coli*	2	Spain	Humans	77
	B/O	*E. coli*	1	Spain	Humans	77
	K	*E. coli*	1	Spain	Humans	30
	NT	*E. coli*	2	France, Spain	Humans	69, 77
CTX-M-10	K	*E. coli*	1	Spain	Humans	30
	NT	*E. coli*	1	Spain	Humans	30
CTX-M-14	K	*E. coli*	28	Australia, France, Spain, UK	Cattle, humans	30, 48, 64, 69, 74, 119
	FII, FIB	*E. coli*, *K. pneumoniae*	13	Australia, France	Humans	69, 118
	I1	*E. coli*	8	Australia, Bolivia, France, Peru, Spain, UK	Humans	4, 48,74, 81, 119
	HI2	*E. coli*	2	Spain	Humans	74
	B	*E. coli*	2	Australia	Humans	119
	A/C	*E. coli*	1	France	Humans	69
	NT	*E. coli*, *S. enterica* [Stanley]	9	Australia, France, Spain, Thailand, UK	Humans, cattle	4, 30, 48, 64, 69, 119
CTX-M-15 [TEM-1, AAC(6′)-IB-CR]	FII, FIA, FIB	*E. coli*, *K. pneumoniae*, *S. sonnei*, *S. enterica* [Enteritidis]	152	Australia, Bolivia, Canada, Central African Republic, Croatia, Czech Republic, France, Kuwait, India, Italy, Portugal, Spain, Switzerland, Tunisia, Turkey, Peru, UK	Humans	8, 13, 25, 30, 44, 48, 50, 55, 61, 66, 69, 76, 81, 90, 119
	I1	*E. coli*, *S. enterica* [Anatum, Ohio, Infantis, Typhimurium]	14	Australia, France, UK	Humans	48, 69, 119
	A/C	*E. coli*	1	France	Humans	69
	L/M	*E. coli*	1	France	Humans	69
	N	*E. coli*	1	France	Humans	69
	NT	*E. coli*, *K. pneumoniae*	22	Australia, Bolivia, Canada, France, Peru, Turkey	Humans	8, 44, 48, 69, 81, 119
CTX-M-17	ColE	*K. pneumoniae*	1	Vietnam	Humans	10
CTX-M-24	FII	*E. coli*	2	Australia	Humans	119
	I1	*E. coli*	2	Bolivia, Peru	Humans	81

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TABLE 1—*Continued*

Enzyme[a]	Replicon(s)[b]	Species[c]	No. of plasmids	Country(ies)[e]	Source(s)	Reference(s) or GenBank accession no.
CTX-M-27	FII	*E. coli*	1	Australia	Humans	119
CTX-M-32	N	*E. coli*	8	Spain	Humans	30, 76
CTX-M-40	N	*E. coli*	1	UK	Humans	48
CTX-M-42	L/M	*E. coli*	2	Russia	Humans	104
CTX-M-53	Q	*S. enterica* [Westhampton]	1	France		DQ268764
CTX-M-56	A/C	*E. coli*	2	Bolivia, Peru	Humans	81
CTX-M-62	NT	*K. pneumoniae*	1	Australia	Humans	119
DHA-1	FII, FIA	*S. enterica* [Senftenberg]	2	UK	Humans	48
SHV-2	A/C	*E. coli*	1	France	Humans	69
	FII, FIB	*E. coli*	2	France	Humans	69
	NT	*E. coli*	3	France	Humans	69
SHV-4	NT	*E. coli*	2	France	Humans	69
SHV-5	L/M	*K. oxytoca*, *K. pneumoniae*, *E. coli*, *E. cloacae*	118	Albania, USA	Humans	98, 110
	FII, FIB	*E. coli*, *K. pneumoniae*	2	Spain, Poland	Humans	30, 117
	A/C	*E. coli*	1	France	Humans	69
	NT	*E. coli*	1	France	Humans	69
SHV-12	I1	*E. coli*, *K. pneumoniae*	12	Italy, Spain	Humans, poultry	14, 30, 38, 69
	K	*E. coli*, *K. pneumoniae*	5	Spain	Humans	30
	FII, FIB	*E. coli*, *K. pneumoniae* *Enterobacter aerogenes*, *S. marcescens*	9	Australia, France, Italy, Spain	Humans	14, 30, 69, 119
	A/C	*E. coli*, *K. oxytoca*	3	Australia, France, Italy	Humans	14, 69, 119
	HI2	*E. coli*	1	Spain	Humans	30
	FIIK[d]	*K. pneumoniae*	1	USA		CP000649
	NT	*E. coli*	4	France, Spain	Humans	30, 69
TEM-1	FII, FIA, FIB	*E. coli*	31	France	Humans	69
	I1	*E. coli*, *S. enterica*	7	Czech Republic, France	Humans	51, 69
	HI1	*S. enterica*	2	Czech Republic	Humans	51
	K	*E. coli*	1	France	Humans	69
	ColE	*K. pneumoniae*, *S. enterica* [Typhimurium]	2	Italy, USA	Humans, rabbits	83, 101
	NT	*E. coli*	10	France	Humans	69
Inhibitor-resistant TEM	FII, FIA, FIB	*E. coli*	35	France	Humans	69
	I1	*E. coli*	3	France	Humans	69
	NT	*E. coli*	4	France	Humans	69
TEM-3	A/C	*E. coli*	2	France	Humans	69
	L/M	*E. coli*	1	France	Humans	69
	NT	*E. coli*	1	France	Humans	69
TEM-10	L/M	*E. coli*	1	France	Humans	69
TEM-21	A/C	*E. coli*	7	France	Humans	69
	NT	*E. coli*	1	France	Humans	69
TEM-24	A/C	*E. coli*	27	France	Humans	69
	Y	*E. coli*	1	France	Humans	69
	NT	*E. coli*	3	France	Humans	69
TEM-52	I1	*E. coli*, *S. enterica* [Agona, Derby, Infantis, Paratyphi B, Typhimurium]	20	France, Belgium	Humans, poultry	22, 69
	NT	*E. coli*	3	France	Humans	69
VEB-1 (QnrA1)	A/C	*E. coli*, *E. cloacae*, *C. freundii* *Providencia stuartii*, *P. mirabilis*	13	Algeria, Canada, France, Thailand, Turkey	Humans	96
GES-5	Q	*E. cloacae*	1	France	Humans	EU266532
KPC-2	N	*K. pneumoniae*	1	USA	Humans	FJ223607
	ColE	*K. pneumoniae*	1	Colombia	Humans	EU176012
IMP-4 (QnrB2, QnrB-4, ArmA)	L/M	*E. coli*, *K. pneumoniae*, *K. oxytoca*, *C. freundii*, *E. cloacae*, *Citrobacter amalonaticus*, *S. marcescens*, *Morganella morganii*	22	Australia	Humans	33
	A/C	*E. coli*, *K. pneumoniae*, *S. marcescens*, *Citrobacter koseri*, *E. cloacae*, *K. oxytoca*	15	Australia	Humans	33
	HI2	*Citrobacter youngae*	1	Australia	Humans	33
	NT	*K. pneumoniae*	1	Australia	Humans	33
IMP-8 (QnrB2, SHV-12)	HI2	*E. cloacae*	2	Taiwan	Humans	20
IMP-13	A/C, P	*S. enterica* [Anatum, Typhimurium]	2	Colombia	Chicken, cheese	79
VIM-1	N	*E. coli*, *K. pneumoniae*	17	Greece	Humans	14, 99
	HI2	*E. cloacae*	4	Spain	Humans	108
	I1	*E. coli*, *K. pneumoniae*,	15	Spain	Humans	108
	W	*Serratia liquefaciens*, *K. oxytoca*	2	Greece	Humans	71
	NT	*K. pneumoniae*	1	Greece	Humans	99
VIM-4 (CMY-4)	A/C	*E. cloacae*, *K. pneumoniae*	2	Italy	Humans	14

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TABLE 1—*Continued*

Enzyme[a]	Replicon(s)[b]	Species[c]	No. of plasmids	Country(ies)[e]	Source(s)	Reference(s) or GenBank accession no.
ArmA	L/M	*C. amalonaticus*, *C. freundii*, *E. coli*, *K. pneumoniae*, *M. morganii*, *S. marcescens*	38	France, Korea	Humans	35, 53
	FII, FIIAs[d]	*E. coli*, *K. pneumoniae*, *E. cloacae*, *S. marcescens*	28	Korea	Humans	4, 53
	A/C	*E. coli*, *K. pneumoniae*, *C. freundii*	9	Korea	Humans	53
	HI2	*E. cloacae*	4	Korea	Humans	53
	N	*E. coli*	1	Spain	Pigs	45
	NT	*E. coli*, *K. pneumoniae*, *Enterobacter* spp.	79	Belgium, Korea	Humans	5, 53
RmtB (CTX-M-14)	A/C	*E. coli*, *K. pneumoniae*, *C. freundii*	53	Korea	Humans	53, 54
	FII	*E. coli*, *K. pneumoniae*	9	Belgium, France, Korea	Humans	4, 5, 53
	I1	*E. coli*	1	Korea	Humans	53
MphA	I1	*S. sonnei*	1	France	Humans	7
QepA (QnrS1, RmtB, LAP-1)	FII-FIA-FIB	*E. aerogenes*, *E. coli*	3	France, Korea	Humans	82, 86
QepA-2	FII-FIA	*E. coli*	1	France	Humans	16
QnrA1 [SHV-12, CTX-M-3, CTX-M-9, AAC(6′)-IB-CR]	L/M	*E. cloacae*, *S. marcescens*	6	Korea	Humans	59
	HI2	*K. pneumoniae*, *E. cloacae*	2	Australia, France	Humans	96
	FII	*E. aerogenes*	1	France	Humans	96
	I1	*K. pneumoniae*	1	France	Humans	96
QnrA3	N	*K. pneumoniae*, *K. ascorbata*	2	France	Humans	60
QnrB1 [AAC(6′)-IB-CR]	L/M	*C. freundii*, *S. marcescens*	2	Korea	Humans	59
QnrB2 [CTX-M-3, AAC(6′)-IB-CR]	FII, FIA	*E. coli*	1	Portugal	Dog	97
	L/M	*E. cloacae*	1	Korea	Humans	59
	N	*S. enterica* [Bredeney]	1	The Netherlands	Poultry	39
QnrB4 [ArmA, CTX-M-14, DHA-1, SHV-12, AAC(6′)-IB-CR]	FIIAs,[d] FIA	*E. coli*, *K. pneumoniae*, *E. cloacae*	34	Korea	Humans	107
	L/M	*C. freundii*	1	Korea	Humans	59
QnrB6 (ArmA, DHA-1)	FIIAs[d]	*K. pneumoniae*	1	Korea	Humans	107
QnrB19 (SHV-12)	N	*S. enterica* [Typhimurium]	1	The Netherlands	Poultry	39
	L/M	*S. enterica* [Typhimurium]	1	Italy	Humans	FJ790886
QnrS1 [LAP-2, AAC(6′)-IB-CR]	ColE	*S. enterica* [Typhimurium, Virginia, Corvallis, Anatum]	29	The Netherlands, Taiwan, UK	Humans	39, 49, 56, 116
	N	*S. enterica* [Virchow, Kentucky, Saintpaul]	5	The Netherlands, UK	Humans	39, 49
	L/M	*E. cloacae*, *K. pneumoniae*	2	Korea	Humans	59, 107
	R	*K. pneumoniae*, *S. enterica* [Montevideo]	2	Taiwan, The Netherlands	Humans	21, 39
	HI2	*S. enterica* [Stanley]	1	The Netherlands	Humans	39
	NT	*S. enterica* [Stanley, Virginia, Virchow]	6	Turkey, UK	Humans, poultry	2, 49
QnrS2	U	*Aeromonas punctata*, *Aeromonas allosaccharophila*, *Aeromonas media*	3	France, Switzerland	Environment	15, 89
	Q	Not identified	ND[f]	Germany	Environment	6

[a] Plasmids carrying more than one resistance gene are listed only one time with the most relevant resistant mechanism encoded, and additional resistance colocalizing on the same plasmid is reported in parentheses.
[b] NT, plasmids that were not typeable.
[c] *Salmonella enterica* serovars are listed in brackets.
[d] FIIAs and FIIK indicates replicons homologous to those of the *Salmonella* virulence plasmids (13) and the pKPN4 plasmid of *K. pneumoniae* (GenBank accession no. CP000649), respectively.
[e] UK, United Kingdom, USA, United States.
[f] ND, not determined.

one of the most relevant findings associated with the current epidemiology of ESBLs worldwide (68, 85). Recent studies have demonstrated that the highly virulent *Escherichia coli* O25:H4-ST131 is responsible for the pandemic dissemination of the CTX-M-15 enzyme (63, 115).

The $bla_{\text{CTX-M-15}}$ gene, often associated with the $bla_{\text{TEM-1}}$, $bla_{\text{OXA-1}}$, and *aac(6′)-Ib-cr* resistance genes, has been located mainly on plasmids belonging to the IncF group (Table 1). IncF plasmids are low-copy-number plasmids, often carrying more than one replicon. It has been proposed that in multireplicon plasmids, one replicon is strongly conserved due to the selective pressure imposed by the necessity of duplicating the plasmid, while the other is free to diverge (105). It was also demonstrated that mutations occurring in the antisense RNA regulating the expression of the replicase gene (*repA*) of repFII can change the compatibility of this replicon (75). Interestingly, IncF plasmids carrying the $bla_{\text{CTX-M-15}}$ gene are not a homogeneous group of plasmids; they vary in size (50 to 200 kb), carry the repFII replicon alone or in combination with repFIA or/and repFIB, and show different antisense RNA sequence variants in the repFII replicon (13, 48). These observations suggest that these plasmids are evolving through

replicon sequence divergence, mosaicism, and replicon cointegration and resolution processes (80).

IncF plasmids carrying the $bla_{CTX\text{-}M\text{-}15}$ gene are not exclusive to clone ST131, since they were identified in other *E. coli* sequence types (ST405, ST354, ST28, and ST695), in a *Shigella sonnei* strain isolated from a Czech patient, in *Salmonella enterica* serovar Enteritidis in the United Kingdom, and in a *Klebsiella pneumoniae* strain in Spain (25, 30, 50). The $bla_{CTX\text{-}M\text{-}15}$ gene expression is driven by the IS*Ecp1* insertion sequence, which is also implicated by its mobilization from the *Kluyvera* genome (93). The $bla_{TEM\text{-}1}$ gene, mobilized by the Tn*3* transposon, often coexists with the $bla_{CTX\text{-}M\text{-}15}$ gene on the same plasmid, and the Tn*3* transposase is the target site for the integration of the IS*Ecp1*–$bla_{CTX\text{-}M\text{-}15}$ element into the IncF scaffold (8). Tn*3*-type transposons are known to confer transposition immunity (a plasmid containing a copy of Tn*3* is resistant to further insertion of Tn*3* elements); thus, Tn*3*-mediated acquisition of resistance genes onto IncF plasmids already carrying Tn*3* is not possible. Marcadé and colleagues suggested that $bla_{CTX\text{-}M\text{-}15}$ or $bla_{CTX\text{-}M\text{-}14}$ genes (both mobilized by the IS*Ecp1* elements from the *Kluyvera* genome) can be acquired on an IncF plasmid carrying a resident Tn*3*::$bla_{TEM\text{-}1}$ gene, while other resistance genes mobilized by Tn*3*-related transposons cannot (69). This hypothesis was supported by the fact that ESBL genes located on Tn*3* transposons such as $bla_{TEM\text{-}3}$, $bla_{TEM\text{-}21}$, and $bla_{TEM\text{-}24}$ were located mostly on IncA/C and not on IncF plasmids, while IncF plasmids were largely prevalent in *E. coli* producing TEM-1 or inhibitor-resistant TEM, and none of these isolates carried IncA/C plasmids. These authors suggested that the differential distribution of the resistance gene variants is caused by the Tn*3* transposition immunity (69). This hypothesis raises interesting questions about the role played by the assortment of plasmid and transposon types in the mechanisms of acquisition and diffusion of resistance genes within a bacterial cell.

Other CTX-M variants are amplified locally, such as CTX-M-9 and CTX-M-14 in both Portugal and Spain and CTX-M-3 in Eastern European countries (24, 74, 77). Plasmids belonging to the IncL/M family were responsible for the spread of CTX-M-3 in Poland, since common plasmid scaffolds were identified in eight species in 15 hospitals (3, 69). The representative plasmid of that family was pCTX-M-3, first observed in 1996 in *Citrobacter freundii* isolates in which CTX-M-3 had been originally identified (43). IncL/M plasmids carrying the $bla_{CTX\text{-}M\text{-}3}$ gene were also reported in other Eastern European countries and in France, Belgium, and Korea, and very often, the aminoglycoside resistance gene *armA* has been colocalized on the same IncL/M plasmid as the $bla_{CTX\text{-}M\text{-}3}$ gene (Table 1).

The spread of $bla_{CTX\text{-}M\text{-}9}$ in clinical *E. coli* and *S. enterica* serovar Virchow was largely due to the dissemination of plasmids in the IncHI2 group, although this gene has been found sporadically with other plasmid families (Table 1). Plasmids of the IncHI2 group were also associated with the $bla_{CTX\text{-}M\text{-}2}$ gene in France and Spain (Table 1). Interestingly, both $bla_{CTX\text{-}M\text{-}9}$, deriving from *Kluyvera georgiana*, and $bla_{CTX\text{-}M\text{-}2}$, deriving from *Kluyvera ascorbata*, were identified while embedded in class 1 integrons bearing IS*CR1* (112). The IncHI2 prototypic plasmid was first identified in *Serratia marcescens* in the United States in 1969, but at that time, this plasmid did not contain any $bla_{CTX\text{-}M}$ genes or integrons; thus, these resistance determinants probably represent a recent acquisition into novel IncHI2 plasmid derivatives (41).

The $bla_{VEB\text{-}1}$ gene has been identified in a large variety of gram-negative bacteria, including *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*. The $bla_{VEB\text{-}1}$ gene in *Enterobacteriaceae* isolated from Canada, France, Thailand, and Turkey was located on one single plasmid type in the IncA/C group (96). This IncA/C plasmid often carried the *qnrA1* gene, conferring reduced susceptibility to fluoroquinolones. The $bla_{VEB\text{-}1}$ plasmids, negative for the *qnrA1* gene, were identified in *Providencia stuartii* and *Proteus mirabilis* from Algeria (96). Interestingly, $bla_{VEB\text{-}1}$-positive *P. aeruginosa* isolates from the four countries mentioned above were negative for the IncA/C plasmid type, ruling out the hypothesis that these plasmids were also at the origin of $bla_{VEB\text{-}1}$ acquisition in *P. aeruginosa* (96). The $bla_{VEB\text{-}1}$ gene example clearly indicates that plasmid typing is useful to investigate the routes of dissemination for a peculiar resistance gene among different bacterial species.

Klebsiella producers of SHV-5 largely prevailed in the United States during the 1993–2000 period, carrying the $bla_{SHV\text{-}5}$ gene located on IncL/M plasmids that were also reported in *Salmonella* isolated from children in Albania (98, 110). The $bla_{SHV\text{-}12}$ gene variant largely prevailed in *K. pneumoniae* isolates from Europe, and it was located on plasmids from different families (Table 1). Recently, the pKPN4 plasmid carrying the $bla_{SHV\text{-}12}$ gene was completely sequenced (GenBank accession no. CP000649). This plasmid carries a novel replicase gene (*repA*), showing 74% nucleotide identity with the currently known *repA* genes of the IncFII family, suggesting that this novel IncFII-related family could contribute to the diffusion of the $bla_{SHV\text{-}12}$ gene.

TEM-52, first identified in *Salmonella* sp. isolates of animal origin, is currently found in different enterobacterial species. In particular, the $bla_{TEM\text{-}52}$ gene disseminates on IncI1 plasmids from *S. enterica* serovars Agona, Derby, Infantis, Paratyphi B, and Typhimurium as well as in *S. enterica* serovar Infantis isolates from poultry (22).

IncI1 plasmids were associated with the spread of several other ESBL genes (Tables 1 and 2). *E. coli* producing CTX-M-1 was identified in 10.7% of poultry fecal samples collected in 2005 from 10 slaughterhouses located in seven districts in France, and the $bla_{CTX\text{-}M\text{-}1}$ gene was located on IncI1 plasmids in all the isolates (42). Recently, the $bla_{CTX\text{-}M\text{-}1}$ gene was associated with IncI1 in *E. coli* isolated from human patients in different parts of France, suggesting a potential link between animals and humans for the dissemination of this gene variant in this country (69). However, the IncI1 plasmids are so recurrent in *Enterobacteriaceae* that a further typing scheme has been proposed by using plasmid multilocus sequence typing (http://pubmlst.org/plasmid/) (38), and to date, 15 sequence types have been described, indicating great variability among the members of the IncI1 family. However, all IncI1 plasmids are characterized by the presence of a cluster encoding the type IV pili, contributing to adhesion and invasion of shigatoxigenic *E. coli* (58). These peculiar pili are considered a virulence factor, and the association of epidemic ability and resistance determinants may have favored the dissemination of plasmids belonging to this plasmid family.

Besides the IncI1 plasmids, the $bla_{CTX\text{-}M\text{-}1}$ gene was also

TABLE 2. Major plasmid families and associated resistance genes in drug-resistant *Enterobacteriaceae* isolated worldwide from human and animal sources

Replicon	No. of plasmids	Resistance genes	Species	HFEC (%)[a]	AFEC (%)[a]
F	331	*aac(6′)-Ib-cr*, bla_{CMY-2}, $bla_{CTX-M-1-2-3-9-14-15-24-27}$, bla_{DHA-1}, $bla_{SHV-2-5-12}$, bla_{TEM-1}, *armA*, *rmtB*, *qepA*, *qepA2*, *qnrA1*, *qnrB2*, *qnrB4*, *qnrB6*, *qnrB19*, *qnrS1*	*E. aerogenes*, *E. cloacae*, *E. coli*, *K. pneumoniae*, *S. enterica*, *S. marcescens*, *S. sonnei*	53.5	67.0
A/C	317	$bla_{CMY-2-4}$, $bla_{CTX-M-2-3-14-15-56}$, $bla_{SHV-2-5-12}$, $bla_{TEM-3-21-24}$, $bla_{IMP-4-8-13}$, bla_{VIM-4}, bla_{VEB-1}, *armA*, *rmtB*, *qnrA1*	*C. freundii*, *C. koseri*, *E. cloacae*, *E. coli*, *K. oxytoca*, *K. pneumoniae*, *P. mirabilis*, *P. stuartii*, *S. enterica*, *S. marcescens*	1.0	0.0
L/M	270	*aac(6′)-Ib-cr*, $bla_{CTX-M-1-3-15-42}$, $bla_{TEM-3-10}$, bla_{SHV-5}, $bla_{IMP-4-8}$, *armA*, *qnrA1*, *qnrB1*, *qnrB2*, *qnrB4*, *qnrS1*	*C. amalonaticus*, *C. freundii*, *E. aerogenes*, *E. cloacae*, *E. coli*, *K. oxytoca*, *K. pneumoniae*, *M. morganii*, *P. mirabilis*, *S. enterica*, *S. flexneri*, *S. marcescens*	0.0	0.0
I1	146	$bla_{CMY-2-7-21}$, $bla_{CTX-M-1-2-3-9-14-15-24}$, bla_{SHV-12}, $bla_{TEM-1-3-52}$, bla_{VIM-1}, *armA*, *rmtB*, *mphA*, *qnrA1*	*E. coli*, *K. pneumoniae*, *S. enterica*, *S. sonnei*	6.9	17.4
HI2	90	$bla_{CTX-M-2-3-9-14}$, bla_{SHV-12}, bla_{IMP-4}, bla_{VIM-1}, *armA*, *qnrA1*, *qnrS1*	*C. youngae*, *E. cloacae*, *E. coli*, *K. pneumoniae*, *S. enterica*	0.0	3.3
N	70	bla_{KPC-2}, $bla_{CTX-M-1-3-15-32-40}$, bla_{VIM-1}, *qnrA3*, *qnrB2*, *qnrB19*, *qnrS1*, *armA*	*E. coli*, *K. ascorbata*, *K. pneumoniae*, *S. enterica*	0.0	10.9

[a] Occurrence of replicon types among 101 *E. coli* strains isolated from the feces of healthy, antibiotic-free humans (HFEC) and among 92 avian fecal *E. coli* strains (AFEC), detected by PBRT (52).

identified on plasmids belonging to the IncN group in human clinical strains of *E. coli* and *K. pneumoniae* from France and Spain and in pigs and farm personnel from Denmark (30, 69, 72, 76). Interestingly, Moodley and Guardabassi demonstrated that IncN plasmids were transmitted within the farm between pigs and the farm workers, across multiple *E. coli* lineages (72). The finding that IncI1 and IncN are both involved in the transmission of the $bla_{CTX-M-1}$ gene strongly suggests an animal reservoir for this ESBL gene variant, since either IncN or IncI1 plasmid type has been demonstrated to be highly prevalent in *E. coli* of the avian fecal flora and in *Salmonella* spp. from retail meat and food-producing animals (52, 87). The spread of $bla_{CTX-M-1}$-carrying plasmids in animals could be sustained by the use of expanded-spectrum cephalosporins in veterinary medicine. In vivo experiments demonstrated the selection and proliferation of indigenous CTX-M-1-producing *E. coli* in the intestinal flora of pigs treated with amoxicillin, ceftiofur, or cefquinome, and such effects persisted for a period longer than the withdrawal time required for these antimicrobials (17).

Further evidence supporting the hypothesis that the animal reservoir of ESBL may be linked to the spread of a particular plasmid family comes from a 1-year longitudinal study of a farm in the United Kingdom (64). This study demonstrated the rapid dissemination of genetically unrelated *E. coli* producing CTX-M-14, and the diffusion of the $bla_{CTX-M-14}$ gene was related to the spread of a common plasmid in the IncK group. The association IncK–$bla_{CTX-M-14}$ was then observed in human clinical *E. coli* isolates from Spain and in two recent isolates from France, thus suggesting an epidemic diffusion of IncK plasmids carrying the $bla_{CTX-M-14}$ gene in Europe (30, 69, 74).

PLASMIDS CARRYING AmpC β-LACTAMASES IN *ENTEROBACTERIACEAE*

The family of AmpC β-lactamases includes the chromosomal enzymes of *E. coli*, *Enterobacter* spp., *Citrobacter* spp., *Morganella* spp., *Proteus* spp., *P. aeruginosa*, and other species, in addition to a growing number of plasmid-mediated β-lactamases related to the above-mentioned enzymes. Since AmpC β-lactamase production is frequently accompanied by multiresistance to antibiotics, therapeutic options become limited. In addition, failure to identify AmpC β-lactamase producers may lead to inappropriate antimicrobial treatment and may result in increased mortality (88). Dissemination of organisms that produce CMY, an AmpC that originated from the chromosome of *Citrobacter freundii*, has been linked to specific plasmid families that are recurrent in isolates from animal sources (1, 73, 113).

The majority of the bla_{CMY-2} plasmids identified in *E. coli* and *Salmonella* spp. in the United States were categorized in the IncA/C group (Table 1). Whole-plasmid DNA sequencing of the IncA/C plasmid from *S. enterica* serovar Newport indicated a high degree of sequence identity and gene synteny with the *Yersinia pestis* pIP1202 and fish pathogen *Yersinia ruckeri* YR71 plasmid backbones, suggesting recent acquisition of these plasmids from a common ancestor. In addition, the *Y. pestis* pIP1202-like plasmid backbone was detected in numerous multidrug-resistant enterobacterial pathogens isolated from retail meat samples collected between 2002 and 2005 in the United States (113). IncA/C-positive strains were isolated from beef, chicken, turkey, and pork and were found in samples from different regions of the United States, revealing that this common plasmid backbone is broadly disseminated among resistant zoonotic pathogens associated with agriculture in this country (73, 114). Interestingly, repA/C replicons occurred in only 1.0% of *E. coli* obtained from healthy humans not exposed to antimicrobials and were absent in fecal flora from healthy birds (Table 2) (52). Therefore, the occurrence of IncA/C plasmids seems advantageous in bacterial populations that are under antimicrobial selective pressure, likely related to the use of ceftiofur in veterinary medicine (114). Singer and colleagues (103) have recently demonstrated that the effect of therapeutic ceftiofur administration on dairy cattle resulted in a significant drop in the gram-negative enteric bacterial population, which allowed for the detection of CMY-2-producing *E. coli* in the

fecal flora of the treated animals. At the conclusion of the treatment regimen, the selection pressure of ceftiofur declined, and fecal *E. coli* counts rapidly returned to pretreatment levels, with a low prevalence of CMY-2 producers. Interestingly, horizontal transfer of the bla_{CMY-2}-carrying plasmid was not observed among the different *E. coli* populations colonizing the intestinal tract of the animals, thus not demonstrating a real link between antibiotic use and the emergence or amplification of this resistance gene (103).

Several bla_{CMY} gene variants were also associated with the IncI1 plasmid family (Table 1). As previously mentioned, IncI1 plasmids are widespread in *E. coli* animal strains (17.4% and 41% in avian commensal and pathogenic *E. coli* strains, respectively), again suggesting that the dissemination of this gene could occur in the intestinal tract of animals (52).

PLASMID-MEDIATED CARBAPENEM RESISTANCE IN *ENTEROBACTERIACEAE*

Carbapenemases that hydrolyze most β-lactams, including carbapenems, are classified in four molecular classes, and most of the class A carbapenemases are chromosomally encoded (IMI, NMC-A, and SME) with the exception of KPC enzymes identified in *Enterobacteriaceae* (and rarely in *Pseudomonas aeruginosa*) and the GES-type enzymes identified in *Enterobacteriaceae* and *P. aeruginosa*. The class B enzymes are the most clinically significant carbapenemases; they are metallo-β-lactamases (MBLs), mostly of the IMP and the VIM series. They have been reported worldwide, and their genes are carried by plasmids and integrons, hydrolyzing all β-lactams with the exception of aztreonam (95). The 1998–2004 global SENTRY survey found only rare examples of MBL genes (bla_{IMP-1}, bla_{IMP-11}, and bla_{VIM-1}) among *Enterobacteriaceae* isolates (29).The bla_{IMP-4} gene was recognized in Australian *Enterobacteriaceae* from Sydney in 2003 to 2006 and caused outbreaks in Melbourne in 2004 and 2005. IncL/M plasmids were identified in 22 of 23 Sydney isolates over 3 years, while IncA/C plasmids were detected in all Melbourne isolates. Thus, in Australia, distinct broad-host-range plasmids carrying identical cassette arrays in different contexts simultaneously emerged in two cities, with no apparent mixing over several years (33).

VIM enzymes have been found mainly in nonfermenting gram-negative bacteria, but their numbers are increasing in *Enterobacteriaceae* (108). Most VIM-producing isolates are sporadic and clonally unrelated, although clonal epidemics have also been described, and some countries such as Greece are close to having an endemic situation (14, 99). *K. pneumoniae* isolates carrying the bla_{VIM-1} gene and *E. coli* isolates carrying bla_{VIM-1} and bla_{CMY-13} genes, randomly collected from five different hospitals in Athens and Piraeus from 2001 to 2003 and representative of the VIM-1-producing isolates circulating in Greece, were all assigned to the IncN group, indicating the spread of an epidemic plasmid associated with the emergence of the bla_{VIM-1} gene in that country (14). Moreover, recent identification of bla_{VIM-1}, often associated with bla_{SHV-5} within the same cell but located on a different plasmid, confirmed the transfer via self-transmissible IncN plasmids in *K. pneumoniae* (99). The bla_{VIM-1} gene was also recently identified on IncW broad-host-range plasmids in *Serratia liquefaciens* and *Klebsiella oxytoca* from Greece, suggesting a novel vehicle for a larger dissemination of this resistance threat in this country (71).

Four MBL-producing species (*K. pneumoniae*, *K. oxytoca*, *Enterobacter cloacae*, and *E. coli*) have been described in Spain. The strains showed different bla_{VIM-1} genetic environments, and the gene was located on different plasmid scaffolds. A 60-kb conjugative plasmid belonging to the IncI1 group was observed in the *K. pneumoniae* clone and in *E. coli*, while plasmids belonging to the IncH12 group were found among *E. cloacae* isolates. IncA/C plasmids carrying both the bla_{VIM-4} and bla_{CMY-4} genes were identified in Italy in clinical isolates of *K. pneumoniae* and *E. cloacae.* The scaffolds of these plasmids were similar to those of the IncA/C plasmids carrying bla_{CMY-2} or bla_{CMY-4} from *S. enterica* isolated in the United States and the United Kingdom, but the carbapenemase gene was not present on these *Salmonella* plasmids and likely represents a novel acquisition for the IncA/C plasmids (23, 48). IncA/C-IncP multireplicon plasmids carrying the bla_{IMP-13} gene were also identified in *Salmonella* found in food sources in Colombia (79).

KPC-producing *K. pneumoniae* have recently been reported in the United States and Israel and rapidly emerged in these two countries (9). PBRT applied to representative strains from the major outbreaks indicated that bla_{KPC-2}-carrying plasmids are negative for all the replicons (9). Very recently, one plasmid identified in *K. pneumoniae* in the United States, carrying two copies of the bla_{KPC-2} gene, has been fully sequenced. The plasmid scaffold belongs to the IncN group (GenBank accession no. FJ223607), but the *repA* gene of its replicon is slightly different (98% nucleotide identity with the IncN-R46 *repA* gene). In addition, a ColE-like replication origin can be recognized in the DNA sequence of a bla_{KPC-2}-positive plasmid identified in *K. pneumoniae* from Colombia (GenBank accession no. EU176012), suggesting that both IncN-like and ColE-like plasmids could be the vehicles for the spread of the bla_{KPC-2} gene.

Plasmids carrying the expanded-spectrum oxacillinase bla_{OXA-48} gene have not yet been identified (92).

PLASMIDS CONFERRING QUINOLONE AND/OR AMINOGLYCOSIDE RESISTANCE BY *qnr* AND 16S rRNA METHYLASE GENES

Quinolone resistance in *Enterobacteriaceae* is usually the result of chromosomal mutations, leading to alterations in target enzymes or drug accumulation. More recently, plasmid-mediated quinolone resistance (PMQR) has been reported by the acquisition of the *qnr*, *qepA*, and *aac(6′)-Ib-cr* genes (91). Very often, PMQR is associated with ESBLs and/or aminoglycoside resistance genes on the same plasmid, and the spread of such multidrug resistance plasmids among *Enterobacteriaceae* strains has a potential impact on the empirical management of complicated urinary tract infections (84). High-level resistance to aminoglycosides mediated by the production of 16S rRNA methylase has been increasingly reported among various gram-negative pathogens. Six plasmid-encoded 16S rRNA methylases have been identified, as follows: *rmtA* to *rmtD*, *armA*, and *npmA* (31).

As previously mentioned, the dissemination of *armA* in clinical isolates from Europe has been associated with IncL/M

plasmids colocalizing with the $bla_{CTX\text{-}M\text{-}3}$ gene (4, 5, 35, 100), while *armA* was identified on an IncN plasmid in animals from Spain (45). In a recent study performed on amikacin-resistant *Enterobacteriaceae* collected from 1995 to 1998 and from 2001 to 2006 in South Korea, an increase in the proportion of amikacin-resistant *K. pneumoniae* isolates was observed starting in 2001. The *rmtB* gene was prevalently associated with IncA/C plasmids, which colocalized with the $bla_{CTX\text{-}M\text{-}14}$ gene (53, 54). The prevalent plasmid families carrying *armA* were IncA/C and IncHI2 until 1998, but after 2001, they were replaced by plasmids of the IncF, IncL/M (also carrying the $bla_{CTX\text{-}M\text{-}3}$ gene), and untypeable groups, and plasmid transition was hypothesized as the mechanism favoring the emergence of multidrug-resistant *K. pneumoniae* in this country (53, 54).

The fully sequenced IncF plasmid pIP1206 was identified in *E. coli* in France and carried the *rmtB* and *qepA* genes, with the latter gene conferring resistance to hydrophilic fluoroquinolones by efflux. pIP1206 carried two copies of the repFII replicon and two additional replicons of the repFIA and repFIB types. This interesting multireplicon plasmid also carried addiction systems and clusters encoding virulence factors (86). The *qepA-rmtB* genes and the *qepA2* gene variant were recently identified on IncF plasmids in *Enterobacter aerogenes* from Korea and also in *E. coli* from France (16, 82).

The *qnrA1* gene was located within a *sul1*-type integron often associated with the $bla_{VEB\text{-}1}$ gene. As previously mentioned, these two genes disseminated in *Enterobacteriaceae* located on IncA/C plasmids (96), but the *qnrA1* gene alone or in association with other ESBL genes was also identified with other plasmid families (Table 1).

The *qnrB4* and *qnrB6* genes associated with *armA* and ESBL genes were identified in *E. coli*, *K. pneumoniae*, and *E. cloacae* in Korea, located on particular IncF plasmids, carrying the replicon FIIAs, similar to *Salmonella* virulence plasmids (107).

The *qnrS1* gene is frequently located on small, mobilizable plasmids that are derivatives of the ColE plasmid (39, 49, 57, 116). One of them, named pTPqnrS-1a, obtained from a multiresistant *S. enterica* serovar Typhimurium DT193 strain in the United Kingdom, has been fully sequenced (57). Plasmid pTPqnrS-1a exhibited 89% nucleotide sequence identity to the ColE plasmid pEC278, identified in a pathogenic *E. coli* strain (GenBank accession no. AY589571), and the region adjacent to the origin of replication (*oriV*) showed 99% identity to plasmid pINF5 from *S. enterica* serotype Infantis isolated from chicken carcasses in Germany (56). Small ColE-like plasmids carrying the *qnrS1* gene were also identified in strains of *S. enterica* serovars Corvallis and Anatum from The Netherlands (39).

In *Salmonella* spp. from human and animal sources, the *qnrS1* gene was also located on IncN plasmids, and *qnrS1*-positive IncN plasmids were identified in *S. enterica* serotype Virchow in the United Kingdom in 2004 and 2005, causing an outbreak associated with imported cooked meat from Thailand (39, 49). As previously mentioned, IncN plasmids are common in animal fecal flora and rarer in bacteria from humans, and it could be hypothesized that IncN plasmids could have acquired the *qnrS1* gene in animals.

Plasmids of the IncU (p37) and IncQ (pGNB2) groups were associated with the *qnrS2* genes identified in the environment in *Aeromonas* spp. from France and Switzerland and in plasmid DNA obtained from a wastewater treatment plant in Germany, respectively (6, 15, 89).

Finally, the recently described PMQR variant named *qnrD* identified in *Salmonella* from China is located on a mobilizable plasmid, showing no homology with previously identified plasmids (18).

From these findings, the simultaneous and rapid increment of 16S rRNA methylases and *qnr* genes in different parts of the world seems linked to the great heterogeneity of plasmids instead of intense lateral transfer of one single plasmid type only. Such plasmid heterogeneity could have likely influenced the spread of these genes by increased bacterial host ranges. Plasmid diversity also indicates independent and multiple events of acquisition of these genes on plasmids circulating in different environments.

TARGETING PLASMIDS AMONG *ENTEROBACTERIACEAE*—CONCLUDING REMARKS

The variability of plasmids mediating antimicrobial resistance in *Enterobacteriaceae* is high but not huge. There are plasmid families that are largely prevalent and also plasmids prevalently associated with specific resistance genes (Table 2). The IncFII, IncA/C, IncL/M, and IncI1 plasmids showed the highest occurrence among typed resistance plasmids (Table 2). These plasmids can be considered "epidemic," being detected in different countries and in bacteria of different origins and sources. The occurrence of these plasmid types seems tightly linked to positive selection exerted by antimicrobial use, incrementing their prevalence compared to that observed in bacterial populations that are not preselected for antimicrobial resistance (Table 2) (52, 65, 102). However, the exception to this rule is represented by the IncF family, which is common in naturally occurring fecal flora of humans and animals, regardless of resistance genes. Johnson and colleagues detected the FII replicon in >50% of *E. coli* plasmids from feces of healthy, antibiotic-free humans and fecal flora from healthy birds (52). Additional factors are probably responsible for the spread and adaptation to the host of the IncF plasmids. The whole DNA sequences of several IncF plasmids demonstrated the presence of clusters potentially contributing to the virulence of the host cell, such as the aerobactin iron uptake system in pRSB107 (106) or the ABC transporters and raffinose and arginine deaminase operons in pIP1206 (86). Another important quality of the IncF plasmids relies in the so-called surface exclusion mediated by the plasmid-encoded TraT protein, by which a cell containing the plasmid becomes a bad recipient in additional conjugation rounds (40). Besides surface exclusion, TraT plays a role in bacterial virulence, since it was identified as being responsible for the plasmid-specified serum resistance in *E. coli* and *S. enterica* and for decreased *E. coli* sensitivity to phagocytosis by macrophages through antagonism with complement opsonization (40). Furthermore, *Salmonella*, *Shigella*, and *E. coli* O157:H7 virulence plasmids, which also belong to the IncF family, are well-known to contribute to bacterial pathogenesis by different mechanisms (toxins, serum resistance, etc.) (11). For IncF plasmids carrying virulence- and resistance-linked determinants, an infective population will be selected for antimicrobial resistance, and antimicrobial resis-

tance pressure will select the virulence traits (70). The acquisition of antimicrobial resistance genes on virulence plasmids could represent a novel tool in bacterial evolution, implementing adaptive strategies to explore and colonize novel hosts and environments (11).

Conjugative systems in gram-negative bacteria support transfer between different genera and kingdoms, regardless of their replication mechanisms. At DNA sequence level, the IncF, IncP, IncHI1, IncI1, and IncN conjugative transfer systems show highly conserved genes which have their homologs in the subset of the chromosome-located type IV secretion system, implicated in the export or uptake of DNA in different bacterial species (*Neisseria gonorrhoeae* and *Helicobacter pylori*). ColE or RSF1010 (IncQ) plasmid derivatives are not self-transmissible by conjugation and can be mobilized at a high frequency in the presence of a helper plasmid. For instance, the IncQ plasmids have been successfully mobilized to a large number of gram-negative bacterial hosts but also to *Arthrobacter* spp., *Streptomyces lividans*, *Mycobacterium smegmatis*, cyanobacteria, and even plant and animal cells, and this ability will contribute to the diffusion of resistance genes located on this plasmid type (34, 62). Moreover, it is well-known that certain plasmids can be stably maintained only in closely related bacterial hosts, while others have the ability to replicate in a broader host range (62, 111). For example, the IncF-like plasmids are limited by host range to the genera of *Enterobacteriaceae*, whereas the IncP, IncA/C, and IncQ plasmids show a wide range of hosts (62). Three strategies emerged as a means for achieving broad host range, which are the versatility of the plasmid replication, the self-sufficiency of encoding proteins necessary for the establishment of the replisome after conjugation, and the presence of two or more functioning replicons on the same plasmid, limiting the incompatibility effects (111). As extrachromosomal, independently replicating elements, plasmids rely on both self-encoded and host-encoded factors for duplication. For example, IncF plasmids need DNA gyrase, DnaB, DnaC, DnaG, SSB, and DNA polymerase III proteins for their replication, while IncQ plasmids are independent of DnaA, DnaB, DnaC, and DnaG proteins, and they provide the proteins essential for their replication (RepA, RepB, and RepC) in almost every bacterial cell (34, 111).

These observations clearly indicate that plasmid classification gives relevant information about the potential host range of a resistance gene located on a specific plasmid type. For example, $bla_{\text{CTX-M-15}}$ is not expected to disseminate to *Acinetobacter* or *Pseudomonas* spp. located on the IncFII plasmid, since the host range of this plasmid is limited to genera of *Enterobacteriaceae*, whereas genes linked to IncP, IncA/C, or IncQ plasmids are supposed to have a larger host range, including *Pseudomonas* spp. and gram-positive bacteria (111). Moreover, carbapenem-hydrolyzing oxacillinases such as $bla_{\text{OXA-58}}$ located on *A. baumannii* plasmids are not expected to disseminate in *E. coli*, since it was demonstrated that these plasmids do not replicate in this species (94).

Many questions remain unanswered about the mechanisms driving the successful dissemination of a specific plasmid type. However, the knowledge that some plasmid types are prevalent in resistant bacterial populations could be useful to explore the possibility of identifying drugs targeting these plasmid families as a medicinal strategy for the treatment of drug-resistant bacteria. An antiplasmid approach has already been proposed, based on small molecules targeting specific replication control mechanisms, inducing plasmid elimination (28). The antiplasmid approach may one day rejuvenate those antibiotics that are no longer effective due to the prevalence of specific resistance plasmid families, enabling them to be effective once again.

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