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Plasmids carrying antimicrobial resistance genes in Enterobacteriaceae

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Bacterial antimicrobial resistance (AMR) is constantly evolving and horizontal gene transfer through plasmids plays a major role. The identification of plasmid characteristics and their association with different bacterial hosts provides crucial knowledge that is essential to understand the contribution of plasmids to the transmission of AMR determinants. Molecular identification of plasmid and strain genotypes elicits a distinction between spread of AMR genes by plasmids and dissemination of these genes by spread of bacterial clones. For this reason several methods are used to type the plasmids, e.g. PCR-based replicon typing (PBRT) or relaxase typing. Currently, there are 28 known plasmid types in Enterobacteriaceae distinguished by PBRT. Frequently reported plasmids [IncF, IncI, IncA/C, IncL (previously designated IncL/M), IncN and IncH] are the ones that bear the greatest variety of resistance genes. The purpose of this review is to provide an overview of all known AMR-related plasmid families in Enterobacteriaceae, the resistance genes they carry and their geographical distribution.

Introduction

Even before the widespread therapeutic use of antibiotics, bacteria with penicillinase activity were discovered that could actively destroy penicillin in order to survive in penicillin-containing environments.[1] In the first reports on the spread of genetic material between bacterial cells, fertility factors were noted, which were not only capable of spreading antimicrobial resistance (AMR) but also of curing auxotrophic mutations through R-factors.[2–4] Later, it was recognized that these factors, designated plamids, were autonomous DNA molecules capable of self-transmission between cells, and that they were also capable of mobilizing part of the chromosome through a process termed high-frequency recombination (Hfr).[5] The acquisition of novel genes by plasmids through mobile genetic elements such as transposons or insertion sequences, and their ability to replicate in a wide range of hosts, made them perfect vectors for the spread of AMR. Therefore, the identification of plasmid characteristics and behaviour in different bacterial hosts provides fundamental knowledge regarding the transmission of AMR. Molecular identification of plasmid and strain genotypes can distinguish whether the spread of AMR genes is driven by epidemic plasmids to different hosts or by clonal spread of bacterial organisms harbouring these plasmids with AMR genes.

In her review, Carattoli[6] focused mainly on resistance genes carried by 'epidemic plasmid types', which are defined as plasmids that have been detected in different countries, in bacteria of different origins and sources. The purpose of this review is to describe the characteristics of all currently known AMR-related plasmid families in Enterobacteriaceae, the resistance genes they carry and their geographical distribution.

Plasmid typing

The first plasmid typing scheme was developed by Datta and Hedges in 1971.[7,8] Transfer frequencies of plasmids belonging to different groups and their stable coexistence in bacterial cells were determined. Five incompatibility groups were defined based on conjugation experiments: W (based on a reference strain received from Tsutomu Watanabe, who discovered the phenomenon of incompatibility),[4] F (fi^+), I (produce I-type pili), N and P. Later, this scheme was updated and 23 plasmid incompatibility groups were recognized: B, C, D, E, FI, FII, FIII, FIV, H, Iα, I_2, Iγ, Iδ, Iζ, J, K, M, N, P, T, V, W and X.[9] Some additional annotations were made: plasmids incompatible with both IncA and IncC were designated IncA/C. Those previously named IncL were renamed IncM and former IncS were renamed IncH.[9]

Nowadays, the most frequently used plasmid typing scheme is called Inc/rep typing. The classification by Inc/rep typing is mostly consistent with the conjugation-based scheme. The first replicon typing method was based on Southern hybridization with 19

different replicons,[10] which were screened for their ability to express incompatibility towards the parental plasmids or miniplasmids used in their construction. Whenever possible, loci involved in plasmid copy number control were chosen rather than partition loci as these are present in all plasmids. Inc types have been independently identified in three different genera. Currently, there are 28 Inc types in Enterobacteriaceae, 14 in *Pseudomonas* and approximately 18 in *Staphylococcus*.[11]

Subsequently, PCR-based replicon typing (PBRT) was developed by Carattoli *et al.*[12] This scheme is based on a set of primers targeting different regions (such as *rep* genes, iterons, RNAI) specific for each plasmid group. Targets for identification of additional plasmid groups were added to the typing method by Garcia-Fernandez *et al.*[13] and Villa *et al.*[14] The method was adapted by Boot *et al.*[15] with the aim to speed up the procedure and to make it more sensitive using real-time PCR, which may increase sensitivity of detection of low-copy plasmid replicons.

Bousquet *et al.*[16] proposed a scheme which may be used in addition to PBRT. Different partition systems located on multidrug resistance (MDR) plasmids were identified which led to the design of a multiplex PCR method called plasmid partition gene typing (PAR-T). This method can be used for the classification of plasmids in *Klebsiella pneumoniae*, *Escherichia coli* and *Salmonella enterica*.

An alternative scheme for plasmid typing takes into account the differences in *mob* genes encoding for relaxases, which are important relaxosome components in both conjugative and mobilizable plasmids.[17] All known plasmid relaxases were divided into six groups and each family is specific in the details of its DNA-processing mechanism.[17,18] This relaxase or MOB classification does not detect IncR plasmids, as these do not contain a relaxase gene.[19] There is a high correlation with the PBRT scheme, which means that plasmids of each Inc type have relaxases of a single MOB subfamily (Figure 1). Therefore, high abundance of specific MOB families such as MOB_F and MOB_P correlates with abundant PBRT types such as the IncF complex, the IncI1 complex and the ColE-like plasmids. Some exceptions were explained by plasmid co-integration and secondary deletions.[20]

Another relaxase screening method, also called degenerate primer MOB typing (DPMT), was developed by Alvarado *et al.*[20] This scheme allows both typing of known plasmid groups and detection of plasmids not previously assigned to any Inc type.

Another typing scheme aimed at *mob* genes encoding for relaxases was developed by Compain *et al.*[21] and is called plasmid relaxase gene typing (PRaseT). This protocol distinguishes five relaxase clades arbitrarily designated HIα, HIβ, HIγ, HIδ and HIε among IncHI1 and IncHI2 plasmids. It also identifies IncX1–4 and ColE plasmids, which were initially untypeable with the PBRT method. In contrast to most other methods, PRaseT excludes a relatively large number of plasmid types such as IncFIV, IncFVI, IncFVII, IncY, IncR, IncI2, IncT, IncFIII-VII, IncJ and IncQ3 although these last three can also not be detected using the PBRT scheme.

Within other plasmid groups, different lineages can be identified by RFLP. This method, first introduced by Kiko *et al.*[22] in 1979, relies on digestion of plasmid DNA with restriction enzymes and comparison of obtained profiles.

An additional tool called plasmid multilocus sequence typing (pMLST) was developed to further differentiate plasmids within incompatibility groups. pMLST schemes were developed for IncA/C, IncI and IncN plasmids to increase the discriminatory power in the characterization of plasmids and to confirm epidemiological and evolutionary relatedness.[23–25] The IncHI2 subtyping is done by double locus sequence typing (DLST), as it includes only two targets.[26] The subtyping of F-plasmids is increasingly difficult due to their potential multireplicon status. The replicon sequence typing scheme (RST) was developed for this purpose, leading to the FAB formula of a plasmid.[14] The FIA replicon is typed based on the sequence encoding the iterons and the replication protein RepA, for which 20 different alleles currently have been reported. The FIB replicon is typed based on the sequence of the *repB* gene for which 69 alleles were reported. The FII replicon is determined by the sequence of the *copA* gene for which 105 alleles were reported. Some additional species-specific FII replicons were also described including 5 alleles of *repA3* for *Salmonella* spp., 12 sequence variants for the region upstream of *repA* in *Klebsiella* spp. and 6 variants for the region downstream of *repA* in *Yersinia* spp., respectively referred to as FIIS, FIIK and FIIY. Finally, the FII replicon can also be replaced by the non-functional FIC for which five variants have currently been reported. Based on that, the FAB formula was created to type IncF plasmids.[14] Unfortunately, comparison of IncF plasmids with a defined FAB formula to those without is impossible and only general conclusions can be drawn.

One of the big challenges for plasmid replicon typing is multireplicon plasmids. The best known multireplicon plasmid is the earlier-mentioned IncF which can carry an FII, FIA and/or FIB replicon. Additionally, some plasmids can cointegrate, creating another type of multireplicon plasmid.[27–31] These pose a difficulty for typing and further understanding of plasmid and antimicrobial resistance epidemiology, as additional tests are required to distinguish between multiple plasmids present in the cell and a cointegrate.

The first plasmid incompatibility groups were defined and confirmed by conjugation. Nowadays, with more plasmid sequences publically available, it has become easier to study the genetic relationship between plasmids. We believe that in order to define new incompatibility (sub)groups it is necessary to confirm the data obtained through sequencing with conjugation-based incompatibility tests. For that reason, readers should be cautious when interpreting data from papers, not to mistake new replicon types for new plasmid incompatibility groups, without confirmation of the results by conjugation experiments.

Additionally, given the increasing availability of whole genome sequence data, the challenge is to trace back the typing schemes mentioned above to plasmid DNA sequences. This transition has recently been addressed by Orlek *et al.*,[32] who compared a curated dataset of publicly available plasmid sequences to replicon and MOB typing schemes.

Publication inclusion criteria

Publications chosen for this review were found on PubMed using the key words 'resistance plasmid' or 'Inc plasmid' as search criteria. Resistance determinants, described in the cited publications, were taken into account only if there was a clear linkage between plasmid Inc type and the resistance gene. The authors are aware of possible bias in the created database as many publications focus on ESBLs or carbapenemases. Additionally, the prevalence of plasmid types that are not included in the PBRT scheme may be

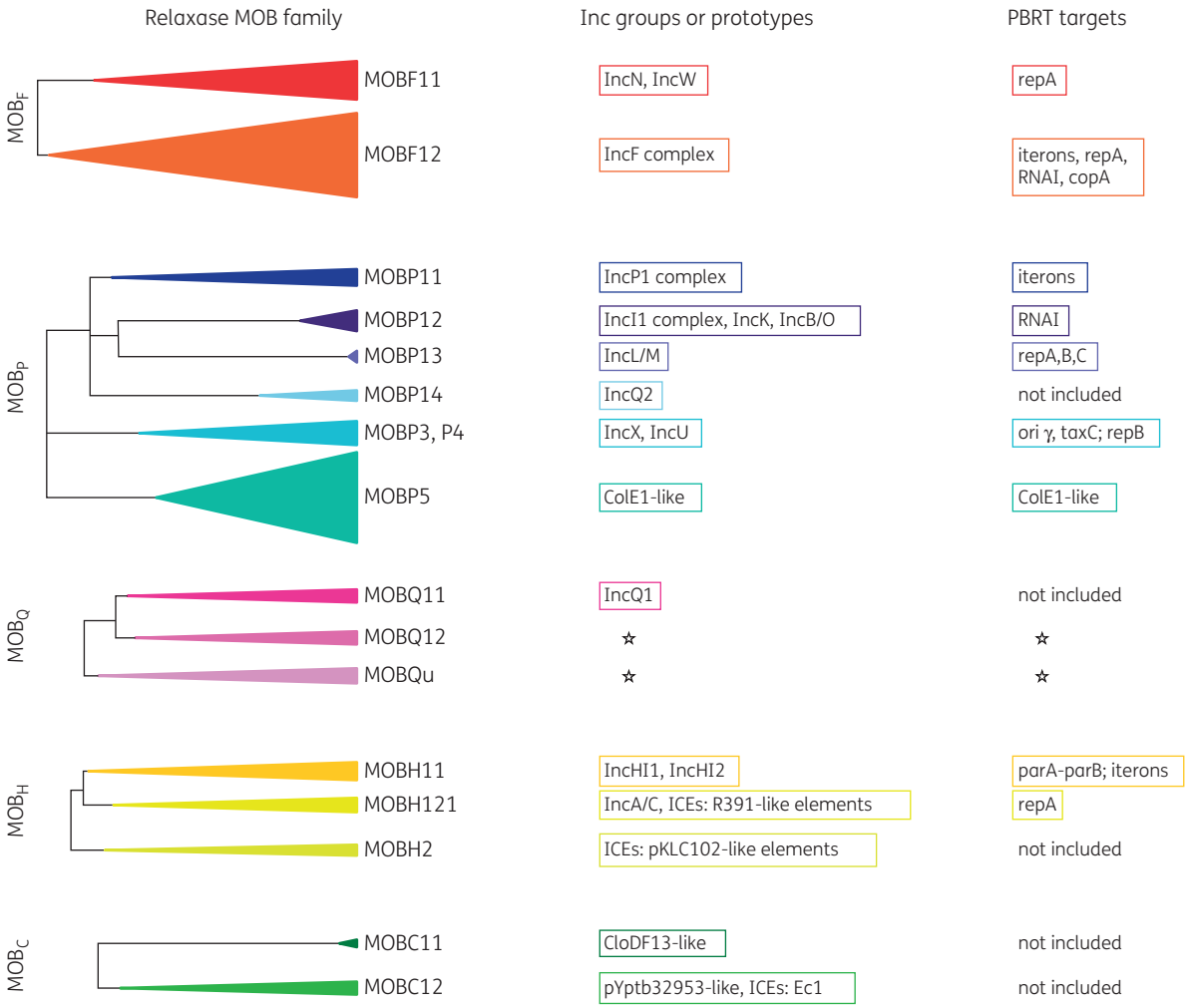

Figure 1. Inc/REP family distribution of gammaproteobacterial plasmids according to relaxase type. Adapted from Alvarado *et al.*[20] This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

underestimated. A description of plasmids associated with AMR is given below. A summary of prevalent plasmids is given in Table 1.

IncF plasmids

Plasmids belonging to the IncF group, or MOB$_F$ according to relaxase typing,[19] are low-copy number, conjugative plasmids with size ranging from 45 to 200 kb. In the PBRT scheme, the target gene for these plasmids is the *repA* gene.[12] The host range is limited to the family of Enterobacteriaceae. In contrast to most other plasmid groups, IncF plasmids can encode several replicons; typical multireplicon IncF plasmids carry the FII replicon together with FIA and FIB. Additionally, it was shown that IncF plasmids with different F alleles are compatible.[14] In addition to this multireplicon status, IncF plasmids were reported to form cointegrates with IncI1, where the two replicon genes were separated by IS*100*, and an IncN replicon.[31,29]

IncF is the most frequently described plasmid type from human and animal sources (Figure 2) and it is mainly found in *E. coli*. The most frequently described resistance genes on IncF plasmids are ESBL genes, genes encoding carbapenemases, genes encoding aminoglycoside-modifying enzymes and plasmid-mediated quinolone resistance (PMQR) genes (Figure 3). As many research projects have focused on ESBLs, the collection of plasmids reported is likely to be biased towards those plasmids that encode ESBLs.

The spread of *bla*$_{CTX\text{-}M\text{-}15}$ in human *E. coli* isolates is globally associated with IncFII plasmids in ST131 and ST405 clones.[33,34] The spread of *bla*$_{CTX\text{-}M\text{-}14}$ is associated with IncF plasmids in Korea and France,[35,36] while in Spain this gene is mainly located on IncK plasmids.[37,38] In Korea, dissemination of *bla*$_{CTX\text{-}M\text{-}14}$ was driven by horizontal transfer of the same IncF plasmid rather than clonal expansion of the host cell, since the same RST type of IncF plasmid was carried by *E. coli* strains of different sequence types.[35] *bla*$_{CTX\text{-}M\text{-}1}$ located on an IncF plasmid was isolated only from animal sources.[39–43] *bla*$_{TEM\text{-}1}$ on IncF is found only in *E. coli* strains mostly of human origin.[35,44–49] The spread of *bla*$_{NDM}$ and the *rmtB* gene (mostly reported in China) is also driven by IncF plasmids.[45,50,51]

No apparent correlations have been reported between any plasmid FAB formula and the resistance genes it encodes.

Table 1. Summary of plasmid features

Replicon type	Relaxase type	Size (kb)	Copy number	Transferability	Host range
IncF	MOB_F	45–200	low	conjugative	Enterobacteriaceae
IncI	MOBP	50–250	low	conjugative	narrow
IncK, IncB/O and IncZ	MOB_P	80–150	low	conjugative	narrow
IncA/C	MOB_H	18–230	low	conjugative	narrow
IncH	MOB_H	75–400	low	conjugative	wide host range (Enterobacteriaceae, several Gram-negative organisms such as *Aeromonas salmonicida, Vibrio anguillarum* and *Yersinia ruckeri*)
IncP	MOB_P	70–275	low	conjugative	broad
IncL/M	MOB_P	50–80	low	conjugative	broad
IncN	MOB_F	30–70	low	conjugative	broad
Col	MOB_P	6–40	1–20	mobilizable	
IncX	MOB_P	30–50			narrow
IncR	not included	40–160		mobilizable	broad
IncW	MOB_F	up to 40	low	conjugative	broad
IncQ	MOB_Q	8–14	medium (4–12 copies/ cell)	mobilizable	broad (including Alpha- Beta- Delta- and Gammaproteobacteria and Cyanobacteria)
IncT	MOB_H	∼217	low	conjugative	narrow
IncU	MOB_P	29–60	low	conjugative	broad (Alpha-, Beta- and Gammaproteobacteria)

However, trends in the prevalence of these plasmids have been reported; F2: A−: B− is the predominant F plasmid type, F2: A1: B− was isolated only from humans and type F33: A−: B− seems to be disseminated mostly in China. Finally, both types F39: A−: B− and F2: A−: B− are found in combination with the N replicon as multireplicon plasmids.[51]

IncI plasmids

The I-complex plasmids contain incompatibility groups I, K, B and Z, which share morphological and serological similarities in their pili.[52] IncI, or MOB_P according to relaxase typing, is a group of low-copy-number, narrow-host-range, conjugative plasmids, which vary in size from 50 to 250 kb.[19] A typical feature for this plasmid group is the presence of a shufflon region at the 3′ end of the *pilV* gene which enables recombination between shufflon-specific sfx sites.[53] This recombination event selects one of seven different *pilV* genes, which is responsible for determination of the recipient specificity.[54] These plasmid rearrangements can cause possible difficulties during assembly of contigs obtained by WGS reads.[55] Incompatibility of IncI plasmids is expressed by a small, counter-transcript RNA, RNAI, which is also the target in the PBRT scheme. RNAI inhibits translation of RNA (RNAII) of the essential replication protein, RepA.[52]

Several variants exist within the IncI group: I1 (also named IncIα), I-γ and I2 (also named IncIδ). IncI1 and I-γ plasmids are very similar. However, there are some significant differences between their Inc RNA sequences. IncI-γ plasmid R621a lacks a stability region, which is conserved in IncI1 plasmids.[56] These plasmids also harbour different entry exclusion proteins ExcA that recognize different segments of their cognate TraY proteins thus allowing the transfer of IncI1 into recipient cells containing IncIγ and vice versa.[57]

Lv *et al.*[58] showed in a phylogenetic analysis of IncI2 plasmids that they are divided into three lineages. Additional phylogenetic analysis performed by Wong *et al.*[59] suggests that IncI2 plasmids can migrate between different bacterial species. Furthermore, they postulate cross-species migration with *E. coli* as a potential carrier.

The currently available PBRT scheme does not distinguish IncI-γ from IncI1. All IncI plasmids typed as IncI1 by PBRT should therefore be designated as IncI1-Iγ.[60] In the past, IncI-γ plasmids were typed using alignment with previously known sequences of reference plasmids: partially sequenced R621a from *E. coli*, and pSC138, isolated from the *S. enterica* serovar Choleraesuis.[61] Recently, Hiki *et al.*[62] proposed a PCR-RFLP method using CviAII enzyme, to differentiate between IncI1 and IncI-γ plasmids.

García-Fernández *et al.*[23] developed a pMLST scheme for IncI plasmids which is based on the allelic variation of five target genes: *repI, ard, trbA, sogS, pilL*. Currently there are 239 plasmid multilocus sequence types described (http://pubmlst.org/, last accessed 21 September 2017).

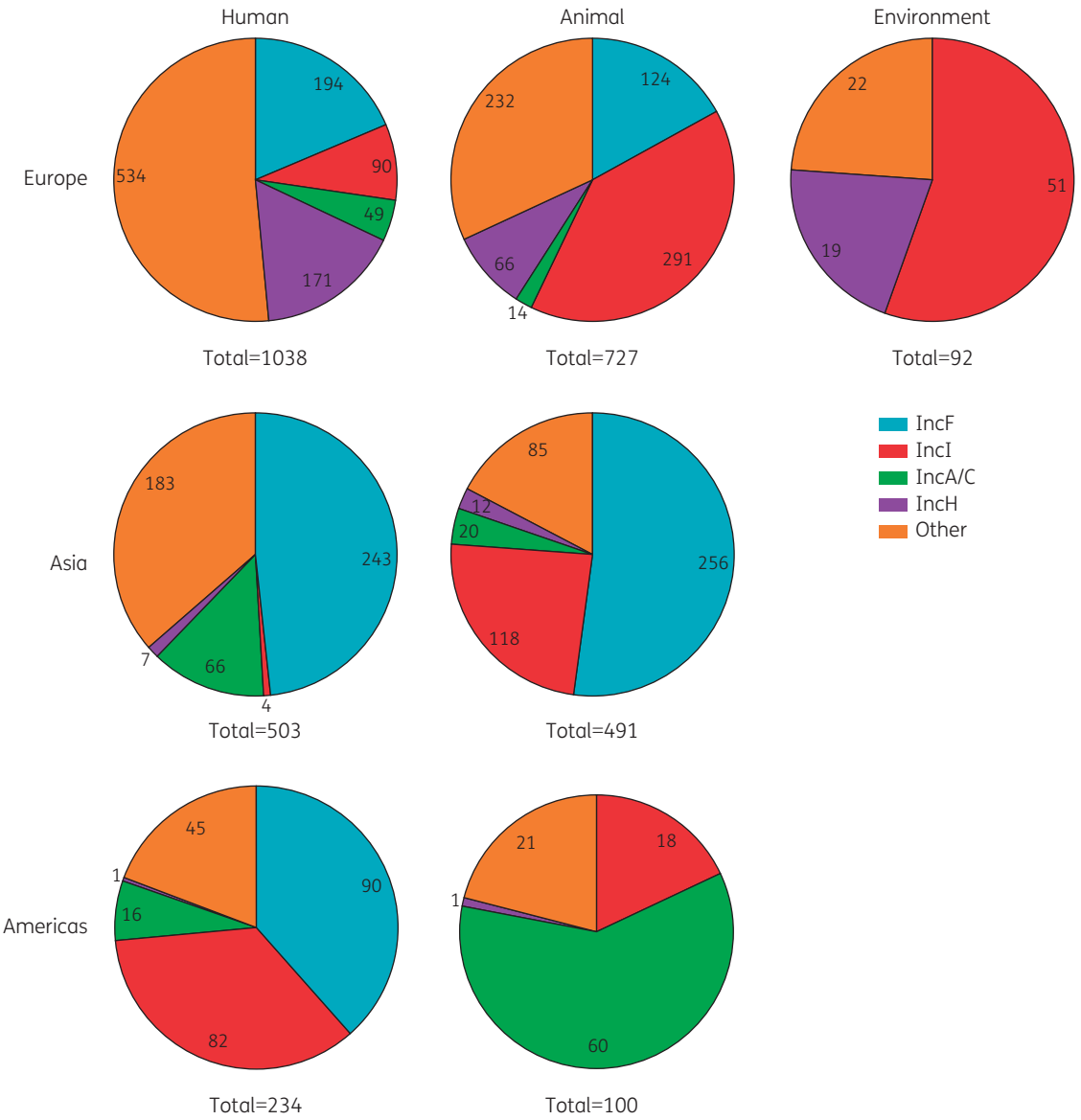

Figure 2. Distribution of different plasmid Inc types isolated from human, animal and environment across Europe, Asia and Americas (data from Table S1). Group 'other' includes: ColE, IncB/O, IncK, IncL/M, IncN, IncP, IncR, IncT, IncU, IncW, IncX, IncY and IncZ. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

IncI2 plasmids can be distinguished from IncI1-Iγ by a set of PCR primers designed by Lv *et al.*[58] that target the *repA, rci, pilO, nikB* and *finO* genes.

IncI plasmids are described predominantly in Europe (Figure 2) in *E. coli* and *S. enterica* isolated from poultry sources. ESBL and plasmid-mediated (p)AmpC genes have been described on IncI plasmids, mostly located in *E. coli*, yet genes encoding for resistance to aminoglycosides, tetracyclines and quinolones are frequently found in *S. enterica* (Figure 3).[13,63–66] $bla_{CTX\text{-}M\text{-}1}$ is the most often identified gene on IncI plasmid ST7 and 3 (Table S1, available as Supplementary data at *JAC* Online) and has often been associated with *E. coli* ST10, 58, 117 and 131.[67,68] IncI plasmids carrying $bla_{CTX\text{-}M\text{-}1}$ have been identified all over Europe in *E. coli* from poultry. These isolates are considered a possible source of these plasmid/gene combinations in *E. coli* from human infections.[67] IncI plasmids belonging to clonal complex 5 (ST10 and 36) carry $bla_{TEM\text{-}52}$ and are frequently associated with *E. coli* ST10 in livestock.[67] IncI2 plasmids are found carrying $bla_{CTX\text{-}M\text{-}55}$ and $bla_{KPC\text{-}3}$.[58,69,70] Recently, IncI2 plasmids were described to be associated with the colistin resistance gene named *mcr-1* and its variants *mcr-1.3* and *mcr-1.5*.[71–73] It was reported in both human and animal sources in China, Japan, Denmark and Spain.[71,74–78] IncI-γ plasmids carry mostly the $bla_{CMY\text{-}2}$ gene.[61,62]

IncK, IncB/O and IncZ plasmids

IncK, IncB/O and IncZ plasmids, as they all belong to the I-plasmid complex, are discussed together.

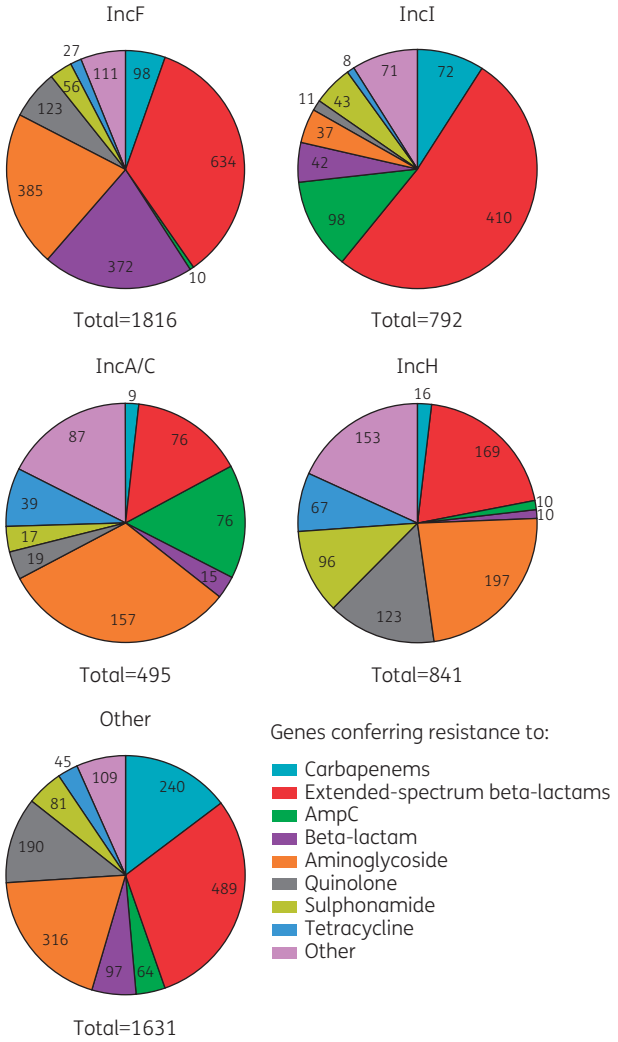

Figure 3. Distribution of genes encoding resistance to different antimicrobial classes carried by different plasmid Inc types (data from Table S1). Group 'other' includes genes encoding resistance to: trimethoprim, chloramphenicol, florfenicol, colistin, fosfomycin. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

According to relaxase typing, IncK and IncB/O belong to the MOB_P group.[19] The IncZ plasmid is not included in this typing scheme.[19] Their sizes vary between 80 and 150 kb. The presence of shufflons (widely distributed in the IncI plasmid family) was confirmed in IncK and IncZ plasmids, but not for IncB/O.[79,80] RNAI encodes antisense RNA for *repYZ* mRNA and is one of the elements responsible for plasmid incompatibility.

Recently it was shown that IncK plasmids can be divided into two compatible plasmid lineages, named IncK1 and IncK2.[81,82]

Originally, the IncB/O plasmid group was discovered and reported independently by two groups and termed IncB and IncO. However, Datta and Olarte[83] already mentioned that they may be synonymous.[84] Later, Bradley[228] referred to the IncO plasmid as IncB. In a review by Couturier,[10] IncB/O was mentioned as a plasmid group.

The fact that IncK, IncB/O and IncZ RNAI sequences, which are targets in the PBRT scheme, are very similar causes difficulties with typing. Carattoli *et al.*[12] already mentioned cross-reactivity between IncK and IncB/O replicons and aspecificity of PCR products based on primers included in the PBRT scheme was reported.[85] Considering these complications some researchers report IncK/B plasmid as a result of the inability to distinguish between IncK and IncB/O replicons.[86,87] In addition to IncK typing, as there is no pMLST scheme available, Dierikx *et al.*[88] made an RFLP scheme, using EcoRI and HindIII to differentiate plasmid variants. A recent paper by Moran *et al.*[89] showed that IncB/O-specific primers also detect the IncZ replicon.

The IncZ plasmid group was first discovered by Tschäpe and Tietze.[90] These plasmids could not be stably maintained together with an IncB plasmid. The authors suggested that it was caused by a 'dislodgement' phenomenon, which was defined as interactions leading to the elimination of the resident plasmid or recombination between the two plasmids.[91] However, Praszkier *et al.*[52] later described that IncB/O and IncZ plasmids may be incompatible with each other.

IncK plasmids are mainly associated with the spread of bla_{CMY-2} and $bla_{CTX-M-14}$ genes in Europe (especially in Spain and the UK) and are frequently found in *E. coli* from animal sources.[37,39,42,88,92–97] IncB/O plasmids are less prevalent, but carry a greater variety of resistance genes such as $bla_{CTX-M-1}$, bla_{CMY-2}, bla_{ACC-4}, bla_{SCO-1}, bla_{TEM-1}, *sul1*, *sul2*, *aad*, *strA*, *strB* and *aacA4*. (Table S1). IncZ plasmids have been reported to carry resistance to sulphonamides, ampicillin, tetracycline and chloramphenicol.[90]

IncA/C plasmids

IncA/C is a group of low-copy-number, conjugative, self-transferable plasmids with a size range of 40–230 kb, although smaller conjugative variants with sizes of 18–25 kb have also been reported.[98] According to relaxase typing, IncA/C belongs to MOB_H.[19] In the PBRT scheme *repA* is the target gene. IncA/C plasmids have a broad host range which include members of Beta-, Gamma- and Deltaproteobacteria.[99] The reference IncA/C plasmid, pRA1, was isolated from *Aeromonas liquefaciens* in 1971.[100]

Within this plasmid group, two variants have been identified: A/C_1 (corresponding to the IncA plasmid, with plasmid pRA1 as a reference) and A/C_2 (corresponding to the IncC plasmid). Although compatibility of IncA and IncC plasmids was confirmed,[101] later they were assigned to the same plasmid group called IncA/C.[102] $IncA/C_1$ and $IncA/C_2$ exhibit 26 SNPs in the *repA* gene.[103] Later analysis based on WGS data revealed that both plasmid groups carry regions that are unique to each backbone type.[104] Recently, two types were defined among the A/C_2 group, named type 1 and type 2, which diverged because of SNP accumulation and multiple insertions and deletions.[105] The two types differ in the *rhs* gene (named *rhs1* and *rhs2*) and an open reading frame between *traA* and *dsbC* (15 amino acid difference in the predicted protein). In addition, two short regions, i1 and i2, are present in type 2, but not type 1.[104]

A recent article by Hancock *et al.*[25] describes both a pMLST and a core genome pMLST (cgPMLST) for IncA/C plasmids. The pMLST includes four essential target genes for use with conventional PCR whereas the cgPMLST includes 28 conserved loci for a high resolution analysis of WGS data. Both schemes allow the distinction

between type 1 and 2 A/C_2 plasmids.[25] Currently there are 12 pMLST sequence types for IncA/C and 37 cgpMLST available (http://pubmlst.org/, last accessed 6 March 2017). An important feature of the IncA/C_2 plasmid group is the presence of AMR islands named ARI-A and ARI-B. ARI-A is only found in type 1, whereas ARI-B is found in both type 1 and type 2 A/C_2 plasmids.[104] Both islands carry a great variety of genes, encoding factors responsible for resistance to many antimicrobial classes. Recently, Harmer and Hall[106] published a set of primers to distinguish IncA/C2 type 1 and type 2 plasmids, targeting *orf1832*/*orf1847*, *rhs1*/*rhs2* and insertions i1 and i2.

Walsh *et al.*[107] reported that bla_{NDM-1}-carrying IncA/C plasmids isolated from water sources have the highest transfer rate at 25 °C or 30 °C.

IncA/C plasmids are associated with MDR (Figures 2 and 3) and are spread worldwide. They are found in isolates from both human and animal sources and involved in the global spread of bla_{CMY-2} (Table S1). IncA/C_2 are also found worldwide, in many sources and in different bacteria. IncA/C_2 can encode ESBLs (bla_{TEM}, $bla_{SHV,}$ but rarely bla_{CTX-M}), AmpC (bla_{CMY}, bla_{DHA}), carbapenemases (bla_{OXA}, bla_{NDM}, bla_{IMP}) and enzymes modifying groups of antibiotics: sulphonamides (*sul1*, *sul2*), aminoglycosides (*aphA1*, *aadA*, *aadB*, *strA*, *strB*, *aacC*), tetracyclines *tet*(A), chloramphenicol (*floR*, *catA1*) and trimethoprim (*dfrA*).[28,105,108–111]

IncH plasmids

IncHI is a group of low-copy-number plasmids with a wide host range, including the Enterobacteriaceae and several Gram-negative pathogens of fish such as *Aeromonas salmonicida*, *Vibrio anguillarum*, and *Yersinia ruckeri*.[112] The size of both plasmid subgroups varies from 75 to 400 kb.

Members of the IncHI plasmid group (MOB_H according to relaxase typing[19]) were historically named IncH1, IncH2 and IncH3 (which contains only plasmid MIP233[113]). Members of each subgroup show a high level of DNA homology within the group, but not compared with the other two. Bradley *et al.*[114] introduced the new IncHII group based on incompatibility of these plasmids with other members of the IncH group, renaming existing plasmids to IncHI1, IncHI2 and IncHI3, respectively. The relationship between IncHI and IncHII groups is thought to be similar to that of IncFI with IncFII, which are related by antigenically similar pili.[115]

The IncHI plasmid group was divided into two groups due to incompatibility of some members with IncF plasmids. Accordingly, IncHI2 are compatible with IncF plasmids, but IncHI1, which possesses *repFIA*, are incompatible.[116] These distinctions were made based on DNA–DNA hybridization.[117]

To date, only four IncHII plasmids were reported.[118] Bradley *et al.*[114] found them in *K. pneumoniae* and these were reported to be unstable in the original host and *E. coli* K-12. Additionally, they observed that IncHII seems to be incompatible with IncD plasmids. Finally, it was concluded that plasmid loss is an example of dislodgement.

In the PBRT scheme the target site for typing IncHI1 plasmids is *parA*-*parB* and the iterons for IncHI2, while IncHI3 and IncHII are not included in this typing scheme. The first tool developed to characterize IncHI plasmids was RFLP. Seven different patterns were defined and a clear difference was made between plasmids isolated in 1993 and 1996.[119] As RFLP7 was predominant after 1996, it is possible that this group may have acquired genetic features which increased its fitness or its chance of survival. IncHI pMLST, developed by Phan *et al.*,[120] includes six loci: HCM1.043, HCM1.064, HCM1.099, HCM1.116, HCM1.178ac, and HCM1.259. In addition, two plasmid clusters were made based on the presence or absence of conserved regions (named A–E) and a transposon named Ins1056. Group 1 (containing ST1–4) consists of plasmids carrying region Ins1056, but most of them lack regions C, D and E. Group 2 (containing ST6–8) involves plasmids with regions C, D and E but without Ins1056. IncHI2 DLST includes two loci: *smr0018* and *smr0199*.[26] Currently there are 14 sequence types for IncHI1 and 10 for IncHI2 available (http://pubmlst.org/, last accessed 3 June 2017).

Interestingly, the transfer rate of IncHI, but not IncHII, is temperature-dependent.[112,121] The efficiency is optimal at 22–30 °C.[122] A possible explanation was suggested by Alonso *et al.*,[123] who showed that the *trhRY* genes are required for conjugation. Temperature dependency suggests that these plasmids are potential vectors for the dissemination of genes among bacterial species in aqueous and soil environments.

IncHI1and IncHI2 plasmids have been isolated in Europe from both human and animal sources (Figures 2 and 3). Many of them are reported to be associated with multidrug resistance because, besides ESBL genes, they often carry genes encoding for resistance to sulphonamides, aminoglycosides, tetracyclines and streptomycin (Figures 2 and 3). IncHI1 plasmids are considered as a main carrier of a multiple resistant phenotype in *Salmonella* Typhi.[124] IncHI2 is occasionally reported as a multireplicon plasmid, also carrying a P replicon.[96,125] In addition to $bla_{CTX-M-2}$ carried by all IncHI2/IncP multireplicon plasmids, they can also encode bla_{TEM-1}.[41,96] Recently, an IncHI2 plasmid was reported to be associated with the novel colistin resistance genes *mcr-1* and *mcr-3*.[126–128] The IncHI3 plasmid was reported to carry bla_{NDM-1} gene.[129]

IncHII plasmids were described to carry resistance to trimethoprim, streptomycin and spectinomycin, which were part of Tn*7*, and ampicillin, amikacin, chloramphenicol, gentamicin, kanamycin and tetracycline.[118]

IncP plasmids

IncP, MOB_P according to relaxase typing,[19] is a group of broad-host-range, low-copy-number plasmids ranging in size from 70 to 275 kb. The copy number is controlled by iterons which are also targeted in the PBRT scheme. IncP plasmids are classified in Enterobacteriaceae as IncP and in *Pseudomonas* spp. as IncP-1. Yakobson and Guiney[130] proposed to divide the IncP group into two subgroups named IncPα and IncPβ. Later, six subgroups of IncP plasmids were defined.[131] Classification of plasmids into subgroups is either based on the phylogeny of a single gene or multiple genes.[132] Within the Enterobacteriaceae family only plasmids from the IncPα and IncPβ groups have been reported.

IncP plasmids are often isolated from *Salmonella* Infantis from broilers in Japan. They were reported to carry genes conferring resistance to: (extended) spectrum β-lactams, sulphonamides, aminoglycosides and tetracyclines (Table S1).[87,94,109,133–138] IncP plasmids in human samples were mainly isolated from *E. coli* and *K. pneumoniae* (Table S1). Recently, an IncP plasmid was reported to be associated with the colistin resistance gene *mcr-1* and its

variant *mcr-1.6*.[139,140] This plasmid co-harboured *dfrA1*, *tet*(A) and *sul1* resistance genes.

IncL/M plasmids

IncL/M, MOB_P according to relaxase typing, is a group of broad-host-range plasmids that range in size from 50 to 80 kb and have a low copy number.[19] In IncL/M, together with IncI, IncK and IncB/O, replication is regulated by antisense RNA, which is also the determinant for plasmid incompatibility.[141] The target sites used in the PBRT scheme are *repA*, *repB* and *repC*.

Originally the plasmids IncL and IncM were separate groups. Richards and Datta[142] proposed placing IncL plasmids in the IncM group because repeated incompatibility experiments showed that IncL plasmids were incompatible with IncM plasmids. As a consequence, these groups were merged and named IncL/M. In contrast, Carattoli *et al.*[143] recently demonstrated that these plasmids should indeed be interpreted as separate incompatibility groups. This distinction was made by comparison of ExcA, TraY and TraX proteins (35%, 59% and 75% amino acid identity, respectively) and an update of the PBRT scheme has been proposed accordingly. Additionally, due to the differences in the RNAI sequence of IncM plasmids, two groups were defined and termed IncM1 and IncM2. Incompatibility tests did not confirm compatibility of IncM1 and IncM2 plasmids.

A 60 kb IncL plasmid, formerly designated IncL/M, is globally reported to be associated with bla_{OXA-48}, although this gene was also reported on IncF and IncP plasmids (Table S1). In hospitals, *K. pneumoniae* harbouring these IncL plasmids with bla_{OXA-48} is considered to be a major cause of infections.[144] It was described that Tn*1999*, which carries bla_{OXA-48}, inserts in the *tir* gene which encodes for transfer inhibition protein.[145] That may be one of the causes of such a successful dissemination of this plasmid. IncL/M plasmids (typed before the report of Carattoli) can also carry $bla_{CTX-M-1,\ -3,\ -14,\ -15}$, $bla_{TEM-1,\ -10,\ -52}$, bla_{SHV-1} and *armA* genes (Table S1).

IncN plasmids

IncN, MOB_F according to relaxase typing, is a group of broad-host-range plasmids, for which the copy number is controlled by iterons.[19] Their size ranges from 30 to 70 kb. The target site in the PBRT scheme for IncN is the *repA* gene. It was observed that plasmids belonging to the IncN group are often colocalized with IncF plasmids.[146] Yang *et al.*[147] reported a fusion of an IncN plasmid with an F33: A−: B− IncF plasmid (see the IncF section).

Recently, a new plasmid type, named IncN2, carrying a novel replicase gene (encoding Rep271) was described.[148] In contrast to IncN plasmids, IncN2 is not included in the PBRT scheme. A PCR to detect IncN2 was described by Netikul *et al.*[149]

Garcia-Fernandez *et al.*[24] developed the pMLST scheme for IncN plasmids. It involves three target genes: *repN*, *traJ* and *korA*. Currently, 16 different plasmid STs have been reported (http://pubmlst.org/; last accessed 6 March 2017).

IncN plasmids carry a great variety of resistance determinants against: extended-spectrum β-lactams, sulphonamides, quinolones, aminoglycosides, tetracyclines and streptomycin (Table S1). The $bla_{CTX-M-1}$ gene is often associated with IncN plasmid ST1. It is disseminated throughout Europe and isolated mainly from *E. coli* from animal sources. bla_{VIM-1} was found in Spain, Greece and Italy. It was mainly isolated from human *K. pneumoniae* isolates. IncN plasmids often carry Tn*1721* encoding for *tetA* and *tetR* genes and Tn*5393* carrying *strA* and *strB*.[150–153] Currently, the IncN2 plasmids have only been found in Enterobacteriaceae isolated from human samples from Thailand, Singapore and Australia.[149,154]

Colicinogenic plasmids

Colicins, which belong to the family of bacteriocins, are proteins produced by some strains of *E. coli* that are lethal for related *E. coli* strains. Colicins are encoded by genes predominantly located on plasmids.[155] One case of a chromosomally encoded colicin has been reported: colicin-like bacteriocin 28b produced by *Serratia marcescens*.[156] Two groups of colicins have so far been described based on cross-resistance: group A (TolA-dependent) containing the A, E1 to E9, K, L, N, S4, U and Y proteins. Group B is TonB-dependent and contains colicins B, D, H, Ia, Ib, M, 5 and 10.[155]

There are two groups of colicinogenic plasmids. The type I plasmids are small, mobilizable plasmids of 6–10 kb that contain approximately 20 copies per cell and mainly encode group A colicins. These plasmids have been frequently used for genetic engineering and biotechnology such as construction of vector pBR322.[157] The type II pCol plasmids are relatively large mono-copy plasmids of about 40 kb that usually encode colicins of group B.

ColE1 plasmids, MOB_P according to relaxase typing,[19] are regulated by an antisense RNA, which by binding to a pre-primer RNA alters its secondary structure and prevents its subsequent processing to form a primer for the initiation of DNA synthesis.[158] Additionally, Davison[159] confirmed that incompatibility of ColE plasmids is expressed by loop II′ of RNA I which interacts with both the loop I and loop II regions of RNA II. A single mutation in this region can give rise to two different ColE1 plasmids, with independent copy numbers, replication and resistance level.[160]

Although ColE plasmids have been found to carry different AMR genes, they are predominantly associated with spread of *qnrS1* and *qnrB19* genes.[13,63,161–163] They are most often found in *S. enterica* strains isolated from human samples. Surprisingly, *qnrB* genes carried by ColE plasmids were found frequently (27%) in a remote Amazonas population which had no previous exposure to therapeutic antibiotics.[164] Additionally, β-lactamases $bla_{CTX-M-17}$, bla_{CMY-31} and bla_{CMY-36} carried by ColE1-like plasmid were described.[165,166] Moreover, Herrera-Leon *et al.*[161] reported that ColE plasmids, in addition to *qnrS1*, also frequently harboured *sul2*, *strA/B* and *tetA* genes. ColE plasmids were reported to carry novel colistin resistance genes *mcr-4* and *mcr-5*.[167,168] ColE1 plasmids bearing different AMR genes can further coexist in the same bacterial host, providing multiresistant phenotypes.[169]

IncX

IncX, MOB_P according to relaxase typing, is a group of narrow-host-range plasmids.[19] IncX plasmids have six known subtypes (X1–X6) and their size ranges from 30 to ∼50 kb. PBRT includes primers that recognize only IncX1 and 2, for which the target site is ori γ, meaning that the prevalence of IncX3–6 may be underestimated. Johnson *et al.*[170] designed a set of primers targeting the *taxC* gene, which allows the differentiation of plasmids belonging to

groups X1–4. Recently, based on differences in the *taxC* gene, novel subgroups X5 and IncX6 were identified.[171] Acquisition of IncX plasmids has caused phage type conversion in *Salmonella* Enteritidis.[172] This is interesting from an epidemiological perspective, since phage typing was traditionally used in epidemiological studies on *Salmonella*.[173,174] IncX plasmids were shown to be able to form cointegrants with pSLT (*Salmonella* serotype-specific plasmid-carrying virulence genes) which resulted in a broadening of the host range of the new plasmid.[175]

IncX plasmids were present in *Salmonella* strains which were isolated before antibiotics were commonly used.[176] Nowadays, IncX plasmids are isolated mainly from both *Salmonella* and *E. coli* from human and animal sources (Table S1). These plasmids encode primarily AMR determinants against extended-spectrum β-lactams and quinolones. In addition, tetracycline and trimethoprim resistance determinants can be carried by IncX plasmids (Table S1). Genes encoding carbapenemases (mainly bla_{KPC} and bla_{NDM}) are reported on IncX plasmids.[177–179] Recently, an IncX4 plasmid was reported to be associated with the colistin resistance genes *mcr-1* and *mcr-2*.[75,126,180]

Rarely detected plasmids

A number of plasmids are not often reported in literature but, as most of them have a broad host range and can carry multiple AMR genes, these are involved in the continuous spread of resistance genes.

IncR

The IncR plasmids range in size from 40 to 160 kb and are not included in the MOB typing as these plasmids do not contain a relaxase gene.[19] Sequencing results indicate that these plasmids do not possess conjugational transfer genes.[181] However, because of their broad host range, Bielak *et al.*[182] postulated that IncR plasmids are mobilizable. IncR plasmids can form multireplicon cointegrates with IncA/C or IncN plasmids.[27,28] The first IncR plasmid was detected from a *Salmonella* Montevideo isolate and conferred a multidrug-resistance phenotype, including resistance to aminoglycosides, chloramphenicol and tetracycline.[13] In addition, IncR plasmids have been reported to carry genes conferring resistance to antibiotics belonging to many classes including: β-lactams, sulphonamides, quinolones, aminoglycosides, tetracyclines, chloramphenicol and trimethoprim (Table S1).

IncW

IncW, MOB_F according to relaxase typing,[19] is a group of low-copy-number, broad-host-range plasmids with sizes up to 40 kb. Host species are Alpha-, Beta-, Gamma-, Deltaproteobacteria and Bacteroidetes.[183] IncW plasmids are considered the smallest conjugative plasmids. The IncW plasmid R388 was shown to be essential for mobilization of the plasmids RSF1010 (IncQ) and ColE1.[184] In the PBRT scheme the *repA* gene is the target site.

IncW plasmids were found in many bacterial sources in the 1980s.[183] Although primers recognizing these plasmids are included in the PBRT, IncW plasmids are currently rarely detected.

The reference IncW plasmid (pSa) was shown to carry genes conferring resistance to chloramphenicol, tetracyclines, sulphonamides, gentamicin and trimethoprim.[185] Later, plasmids carrying a subset of these genes were reported.[183,186] IncW plasmids were also shown to encode the carbapenemase bla_{KPC-2} and metallo-β-lactamase bla_{VIM-1} genes.[187,188]

IncQ

The IncQ group can be subdivided into two major groups, of which IncQ1 belongs to the MOB_Q group, while IncQ2 belongs to the MOB_P group, according to relaxase typing. These groups are not detected by PBRT.[19] IncQ is a group of mobilizable plasmids with a medium-range copy number (4–12 copies/cell) and a size range from 8 to 14 kb. These plasmids have a broad host range including Alpha-, Beta-, Delta- and Gammaproteobacteria and Cyanobacteria. It was proposed that its broad host range is a result of the presence of genes required for plasmid replication.[189] The IncQ reference plasmid RSF1010 encodes RepA, -B and -C proteins,[190] but it also requires host-encoded single-strand binding proteins, DNA gyrase and the γ subunit of the DNA polymerase III.[191]

IncQ plasmid incompatibility is expressed through direct repeats at *oriV*, which was confirmed in both RSF1010 and R1162.[192,193] Becker and Mayer[229] reported that introduction of additional direct repeats into the origin of replication of R1162 resulted in a decreased copy number. This suggests that the lack of a partitioning or stability system leads to a high copy number, which prevents plasmid loss. Additionally, it was proven that members of subclasses of the IncQ family are compatible with each other due to evolution of their iteron sequences.[194]

Rawlings and Tietze[189] suggested dividing the IncQ family into two groups based on their Rep protein similarities. Plasmids RSF1010, pIE1107, pIE1115, pIE1130 and pDN1 form the first group (IncQ1), and pTF-FC2 and pTC-F14 make up the second (IncQ2).[195] Further subgroups were defined according to their iteron sequence variability and incompatibility. Plasmids which are incompatible with RSF1010 were designated IncQ-1α. Plasmids that were incompatible with pIE1107, pIE1115 or pDN1 were designated IncQ-1β. IncQ-1γ was assigned to plasmids which are incompatible with pIE1130. Furthermore, IncQ2 was subdivided into IncQ-2α for pTF-FC2 and IncQ-2β for pTC-F14.[189]

Additionally, after *in silico* alignment of *repA, repB* and *repC* genes from known IncQ plasmids,[195] Loftie-Eaton and Rawlings[195] proposed two new subclasses named IncQ3 and IncQ4, of which the latter consists of only one member, pPNAP08.[196]

IncQ plasmids were reported to carry bla_{CMY-4}, bla_{GES-1} and the *sul2-strA-strB* gene cluster.[197–199]

IncT

Rts1, a reference plasmid for the IncT group and MOB_H according to relaxase typing,[19] is a low-copy-number, narrow-host-range, 217 kb plasmid originally isolated from *Proteus vulgaris.*[200] The target site in the PBRT scheme is the *repA* gene. Most plasmids belonging to this group exhibit thermosensitive replication and conjugation, which are stable at 37 °C and 25 °C, respectively, but

inhibited at 42 °C and 37 °C.[201] Interestingly, R394 isolated from *Proteus rettgeri* did not show this thermosensitive phenotype for stability and conjugation.[202] This phenomenon was later explained by the fact that R394 is a cointegrate plasmid containing IncT and IncN replicons.[30]

Early isolated IncT plasmids were carrying kanamycin- (Rst1) or sulphonamide resistance genes (R485). Recently, a *Proteus mirabilis*-carrying $bla_{CTX-M-2}$ on an IncT plasmid was reported in Japan.[203–205] IncT plasmids were also reported to carry $bla_{OXA-181}$.[206]

IncU

IncU (MOB_P according to relaxase typing[19]) is a group of broad-host-range plasmids isolated from Alpha-, Beta- and Gammaproteobacteria.[207] These plasmids are low-copy-number with sizes ranging between 29 and 60 kb.[208] The first IncU plasmids were isolated from *Aeromonas salmonicida*.[209] The stabilization module of RA3 encodes seven homologues to IncP plasmid products and its conjugative transfer region is highly similar to the one from the PromA plasmid,[210] which is a novel family of broad-host-range plasmids, which seem to have no phenotypical effect on the host (cryptic plasmids).[211]

Plasmid Rms149 has been classified as a novel IncG plasmid; however, later studies showed that this plasmid is a member of the IncU group.[212,213]

IncU plasmids were reported to carry resistance to: trimethoprim, chloramphenicol, ampicillin, tetracyclines, sulphonamides, kanamycin and streptomycin.[208,214]

IncD

The first IncD plasmid was mentioned by Datta.[9] Later, Coetzee *et al.*[215] reaffirmed existence of this group performing compatibility experiments. However, the group is not included in the PBRT scheme.

IncD plasmids belong to the IncF-like group of plasmids based on classification by genetic relatedness and pilus structure.[216] Plasmids examined by Coetzee *et al.*[215] were conjugative and can be transferred between members of the Enterobacteriaceae family. Transfer between other families has not been determined. They can carry resistance determinants to ampicillin and kanamycin. Unfortunately, no plasmid of this incompatibility group was fully sequenced and there are no reports revealing the functional biology or prevalence of these plasmids.

IncJ

In 1972 Coetzee *et al.*[202] described a new plasmid called R391 and assigned it to the new IncJ incompatibility group. Later it was discovered that R391 rather belongs to the group of integrative and conjugative elements (ICEs). These elements are integrated in the chromosome, but after excision they circularize, replicate autonomously and are self-transmissible via conjugation.[217]

Recent work of Carraro *et al.*[218] shows that stability of R391 family members depends on replication starting at *oriT* by TraI. Additionally, these plasmids encode the toxin–antitoxin system *hipAB*, although this is not highly conserved. These results suggest that ICEs are more similar to plasmids than was previously thought but, as these are not actually plasmids, they are not detected by the PBRT scheme.

IncY

IncY is a group of prophages which replicate as autonomous plasmids. Their size range is approximately 90–100 kb and they are low-copy-number plasmids.[219] Although they contain iterons close to the *repA* gene which is also the target in the PBRT scheme, their involvement in the incompatibility reaction was not confirmed.[220]

IncY were confirmed to confer resistance to ampicillin and carry the bla_{SHV-2} gene.[219,221] Additionally they are reported to be associated within a cell with IncF and/or IncI plasmids or IncHI2.[96,134,222–227]

Untypeable plasmids

Many authors report plasmids which they designate as 'untypeable'. There are reports of untypeable plasmids with variable sizes (20–260 kb) that carry genes encoding for different antimicrobial classes: β-lactams including cephalosporins and carbapenems, sulphonamides, quinolones and aminoglycosides (Table S2).

Although the PBRT scheme is widely used, it is recognized that it cannot detect all known plasmid types. The false negative results that were described for IncL/M have been solved by a new set of primers that was described for subdividing these plasmids. For other plasmids such as IncX3–4 and the IncFIII-VII replicons, currently no PCR methods have been described that can be used in addition to the PBRT scheme. Another consideration is the continuous rearrangement and mutations that plasmids undergo, which may also occur in the regions that are used for plasmid typing. This may result in novel untypeable plasmids evolving from currently well-studied plasmid types.

Conclusions and future perspective

Since the first incompatibility experiments performed by Couturier *et al.*[10] in 1988, a lot has changed. Different typing methodologies are used in literature, which hampers a comparison of results from these studies. Nowadays, the PBRT scheme is the most commonly used technique for plasmid typing of Enterobacteriaceae, as it facilitates rapid identification of the dominant replicon types. Its use has led to a more unified way of plasmid identification, which in turn has resulted in a large expansion of our knowledge of plasmid epidemiology. The commercially available PBRT kit is kept up to date by periodic inclusion of newly described targets for plasmid identification. The main disadvantage, however, is that it can only detect plasmids included in the scheme, and that some plasmids harbour more than one replication machinery. Typing plasmids according to the relaxase gene has a higher discriminatory power, but it misses plasmids which do not contain a relaxase gene.

Carattoli[6] has provided an extensive overview of plasmids and their associated resistance genes. The work presented here provides an update about all known resistance plasmids in Enterobacteriaceae.

A great variety of plasmids can be found in human, animal and environmental isolates. The most abundant plasmids, often referred to as epidemic plasmids, are IncF, IncI, IncA/C and IncH. There are differences in prevalence of certain plasmids from different sources and on different continents. Animals in Europe are mainly colonized by *E.coli*-carrying IncI plasmids, while in Asian

animals the dominant plasmid is IncF and in animals from North and South America the dominant plasmid type is IncA/C. From human sources, IncF is the most abundant plasmid isolated in Asia and North and South America, while in Europe isolates are more diverse, including IncI and IncH. Next to IncF, IncA/C also seems to be abundant among humans in North and South America.

ESBLs are the most frequently described enzymes conferring resistance to antimicrobials encoded on plasmids. Enzymes hydrolysing aminoglycosides and genes encoding for resistance to quinolones and sulphonamides are often co-transferred through transposons located on a plasmid. We also show that various plasmids seem to be associated to a different range of antibiotic resistance gene classes, e.g. IncF carry a wide variety of gene classes, while IncI plasmids are mainly associated with ESBLs. Some plasmids even have a strong correlation with specific genes, like IncL/M with bla_{OXA-48}, or IncK plasmids with bla_{CMY-2} or $bla_{CTX-M-14}$. However, the exact nature of these specific relationships is still not fully understood.

Given the fact that the number of studies performed on all continents varies and certain resistance determinants are studied more intensively, the data presented in this article will inevitably be slightly biased. Therefore, the observed differences should be interpreted with care. Most papers describe data from Europe. Additionally, most of them focus on β-lactamases, which means that the prevalence of other antibiotic classes may be underestimated. Furthermore, most plasmids are typed using the PBRT scheme, which means that the prevalence of the plasmids not included in that scheme can be underestimated.

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Transparency declarations

None to declare.

Disclaimer

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Supplementary data

Tables S1 and S2 are available as Supplementary data at *JAC* Online.

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