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Plasmid-mediated quinolone resistance

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Summary

Three mechanisms for plasmid-mediated quinolone resistance (PMQR) have been discovered since 1998. Plasmid genes *qnrA*, *qnrB*, *qnrC*, *qnrD*, *qnrS*, and *qnrVC* code for proteins of the pentapeptide repeat family that protects DNA gyrase and topoisomerase IV from quinolone inhibition. The *qnr* genes appear to have been acquired from chromosomal genes in aquatic bacteria, are usually associated with mobilizing or transposable elements on plasmids, and are often incorporated into *sul1*-type integrons. The second plasmid-mediated mechanism involves acetylation of quinolones with an appropriate amino nitrogen target by a variant of the common aminoglycoside acetyltransferase AAC(6′)-Ib. The third mechanism is enhanced efflux produced by plasmid genes for pumps QepAB and OqxAB. PMQR has been found in clinical and environmental isolates around the world and appears to be spreading. The plasmid-mediated mechanisms provide only low-level resistance that by itself does not exceed the clinical breakpoint for susceptibility but nonetheless facilitates selection of higher-level resistance and makes infection by pathogens containing PMQR harder to treat.

Introduction

Plasmid-mediated quinolone resistance (PMQR) was late in being discovered. Nalidixic acid, the first quinolone to be used clinically, was introduced in 1967 for urinary tract infections. Resistance was soon observed and could also be readily selected in the laboratory. It was produced by amino acid substitutions in the cellular targets of quinolone action: DNA gyrase and topoisomerase IV (1–3). Later, decreased quinolone accumulation due to pump activation and porin loss were added as additional resistance mechanisms. Search for transferable nalidixic acid resistance in over 500 gram-negative strains in the 1970s was unrevealing (4). In the 1980’s fluoroquinolones became available that were more potent and broader in spectrum. Quinolone usage increased with subsequent parallel increases in quinolone resistance (5, 6). In 1987 PMQR was reported to be present in a nalidixic acid resistant isolate of *Shigella dysenteriae* from Bangladesh (7), but this claim was later withdrawn (8). True PMQR was reported in 1998 in a multiresistant urinary *Klebsiella pneumoniae* isolate at the University of Alabama that could transfer low level resistance to nalidixic acid, ciprofloxacin, and other quinolones to a variety of gram-negative recipients (9). The responsible gene was termed *qnr*, later amended to *qnrA*, as additional *qnr* alleles were discovered. Investigation of a *qnrA* plasmid from Shanghai that provided more than the expected level of ciprofloxacin resistance led to the discovery in

2006 of a second mechanism for PMQR: modification of certain quinolones by a particular aminoglycoside acetyltransferase, AAC(6′)-Ib-cr (10). A third mechanism for PMQR was added in 2007 with the discovery of plasmid-mediated quinolone efflux pumps QepA (11, 12) and OqxAB (13). A multiplex PCR assay for eight PMQR genes (lacking only *qnrVC*) has recently been perfected (14). In the past decade these genes have been found in bacterial isolates from around the world. They reduce the susceptibility of bacteria to quinolones, usually not to the level of non-susceptibility, but facilitating the selection of more quinolone resistant mutants and treatment failure. PMQR has been frequently reviewed (15–20).

Qnr Structure and Function

Cloning and sequencing *qnrA* revealed that it encoded a 218 residue protein with a tandemly repeating unit of five amino acids that indicated membership in the large (more than 1000 members) pentapeptide repeat family of proteins (21). Knowledge of the sequence allowed search for *qnrA* by PCR, and it was soon discovered in a growing number of organisms, including other *K. pneumoniae* strains in the United States (22, 23), *Escherichia coli* isolates in Shanghai (24), and *Salmonella enterica* strains in Hong Kong (25). *qnrA* was subsequently followed by discovery of plasmid-mediated *qnrS* (26), *qnrB* (27), *qnrC* (28), and *qnrD* (29). The *qnrVC* gene from *Vibrio cholerae* can also be located in a plasmid (30–33) or in transmissible form as part of an integrating conjugative element (34). These *qnr* genes generally differ in sequence by 35 % or more from *qnrA* and each other. Allelic variants have also been described in each family differing by 10% or less: 5 alleles for *qnrVC*, 7 alleles for *qnrA*, 9 for *qnrS*, and 71 for *qnrB* (35)(<http://www.lahey.org/qnrstudies/>, accessed 12/09/13). *qnr* genes are also found on the chromosome of both gram negative and gram positive bacteria from both clinical and environmental sources (36–38).

The sequence of pentapeptide repeat proteins can be represented as [S,T,A,V][D,N][L,F][S,T,R][G] (39). The first such protein to have its structure determined by x-ray crystallography was MfpA, encoded on the chromosome of mycobacterial species including *M. smegmatis* where its deletion increased fluoroquinolone susceptibility (40). MfpA is a dimer linked C-terminus to C-terminus and folded into a right-handed quadrilateral β helix with size, shape, and charge mimicking the β form of DNA (41). The middle, usually hydrophobic, amino acid (i) of the pentapeptide repeat and the first polar or hydrophobic residue (i–2) point inward while the remaining (i–1, i+1, i+2) amino acids are oriented outward presenting a generally anionic surface. Extensive hydrogen bonding between backbone atoms of neighboring coils stabilizes the helix. The structures of three Qnr proteins are known: EfsQnr from *Enterococcus faecalis* (42), AhQnr from *Aeromonas hydrophila* (43), and plasmid-mediated QnrB1 (44). All are rod-like dimers (Fig. 1). The monomers of QnrB1 and AhQnr have projecting loops of 8 and 12 amino acids that are important for their activity (Fig. 1). Deletion of the smaller A loop reduces quinolone protection while deletion of the larger B loop or both loops destroys protective activity (43, 44). Deletion of even a single amino acid in the larger loop compromises protective activity (45). MfpA and EfsQnr lack loops, but EfsQnr differs from MfpA in having an additional β -helical rung, a capping peptide, and a 25-amino acid flexible extension required for full protective activity.

Topoisomerases twist and untwist the DNA helix by binding to it and introducing a pair of staggered, single-strand breaks in one segment through which a second DNA segment is passed (46). Quinolones bind to the complex of enzyme and DNA stabilizing the cleavage or cleaved complex, blocking religation, and leading ultimately to lethal double stranded breaks (47). In cell-free systems QnrA (21, 48), QnrB (27, 45, 49), QnrS (50), AhQnr (43), and EfsQnr (42) have been shown to protect *E. coli* DNA gyrase from quinolone inhibition (Fig. 2). Protection of topoisomerase IV by QnrA has been demonstrated as well (51). Protection occurs at low concentrations of Qnr relative to quinolone. Fig. 2 shows that for DNA gyrase inhibited by 6 μM (2 $\mu\text{g}/\text{ml}$) ciprofloxacin, half protection required only 0.5 nM QnrB1 and some protective effect was seen with as little as 5 pM (27). At high QnrB concentrations (25–30 μM in the same system) gyrase inhibition occurs (27, 49). In contrast MfpA inhibits *M. tuberculosis* or *E. coli* gyrase with an IC_{50} of 1.75 to 3 μM and lacks any protective effect against ciprofloxacin. EfsQnr is intermediate. It partially protect *E. coli* gyrase against ciprofloxacin inhibition but also inhibits ATP-dependent supercoiling activity of gyrase with an IC_{50} of 1.2 μM (42). In a gel displacement assay QnrA binds to DNA gyrase and its GyrA and GyrB subunits and also to topoisomerase IV and its ParC and ParE subunits (48, 51). Competition between MfpA and substrate DNA for binding to gyrase has been proposed as the mechanism for its inhibitory effect (41). Qnr proteins with their additional structural features (loops, N-terminal extension) are proposed to bind to gyrase and topoisomerase IV targets in such a way as to destabilize the cleavage complex between enzyme, DNA, and quinolone causing its release, religation of DNA, and regeneration of active topoisomerase (43, 44).

Qnr Origin

Qnr homologs can be found on the chromosome of many γ -*Proteobacteria*, *Firmicutes*, and *Actinomycetales*, including species of *Bacillus*, *Enterococcus*, *Listeria*, and *Mycobacteria*, as well as anaerobes such as *Clostridium difficile* and *C. perfringens* (36, 38, 52, 53). Nearly 50 allelic variants have been found on the chromosome of *Stenotrophomonas maltophilia* (36, 54–57). Aquatic bacteria are especially well represented including species of *Aeromonas*, *Photobacterium*, *Shewanella*, and *Vibrio* (17, 58, 59). QnrA1 is 98% identical to the chromosomally determined Qnr of *Shewanella algae* (58), QnrS1 is 83% identical to Qnr from *Vibrio splendidus* (60), and QnrC is 72% identical to chromosomal Qnr in *Vibrio orientalis* or *V. cholerae*. (28). QnrB homologs, on the other hand, are found on the chromosome of members of the *Citrobacter freundii* complex, including *Citrobacter braakii*, *Citrobacter werkmanii* and *Citrobacter youngae* of both clinical (61) and environmental origin. The small, non-conjugative plasmids that carry *qnrD* can be found in other Enterobacteriaceae but are especially likely to be found in *Proteeae*, such as *Proteus mirabilis*, *P. vulgaris*, and *Providencia rettgeri* (62) and may have originated there (63, 64)

The wide distribution of *qnr* suggests an origin well before quinolones were discovered. Indeed, *qnrB* genes and pseudogenes have been discovered on the chromosome of *Citrobacter freundii* strains collected in the 1930s (65)

Qnr Plasmids

Genes for PMQR have been found on plasmids varying in size and incompatibility specificity (Table 1), indicating that the spread of multiple plasmids has been responsible for the dissemination of this resistance around the world. Such plasmid heterogeneity may also have contributed to the variety of bacterial hosts for PMQR and indicates that plasmid acquisition of *qnr* and other quinolone resistance determinants occurred independently multiple times.

A mobile or transposable element is almost invariably associated with *qnr* genes, (Table 2 and Fig. 3). *qnrA1* has usually been associated with *ISCR1* (66), although 63% of *qnrA1*-positive *K. pneumoniae* strains in a study from South Korea were negative for *ISCR1* by PCR (67). The *ISCR1* element is not only involved in gene mobilization. It also provides an active promoter for resistance gene expression (68). Often a single copy of *ISCR1* is found upstream from *qnrA1*, but in pMG252 and related plasmids, the *qnrA1* gene is bracketed by two copies of *ISCR1* (69, 70). The *qnrA1* *ISCR1* complex is inserted in turn into a *sul1*-type integron containing several other resistance gene cassettes (24). In pSZ50 from Mexico the integron containing *ISCR1* and *qnrA1* is duplicated in tandem (71). The *qnrA3* and *qnrA6* alleles are also linked to *ISCR1*. The gene for *qnrB1*, however, is often associated not with *ISCR1* but with *orf1005*, encoding a putative transposase (27). *qnrB1* has also been found linked to an upstream truncated *orf1005* and a downstream IS26 (72, 73), while the *qnrB20* allele is sandwiched between an upstream IS26 and a downstream *orf1005* (72). Alleles *qnrB2*, *qnrB4*, *qnrB6*, and *qnrB10* are associated with *ISCR1*, usually as a single copy (73–75), but in some plasmids two copies of *ISCR1* surround *qnrB2* (76, 77). *qnrB19* has been found in three genetic environments: within large plasmids associated with *ISEcp1C*-based transposons, in large plasmids bracketed by IS26, and in small ColE1-type plasmids (~3-kb) lacking insertion sequences in which a flanking *oriT* locus and Xer recombination site have been proposed to be involved in site-specific recombination (73, 78–82). In all three settings *qnrB19* is linked to a fragment of *pspF* implying that the putative mobilization pathways may be related. In plasmid pLRM24 *qnrB19* linked to *ISEcp1* has inserted into a Tn3-like element also containing a mobile element encoding KPC-3 carbapenemase (83). The *qnrS1* gene is not linked to *ISCR1* but is associated with an upstream Tn3-like transposon, in several plasmids containing an active TEM-1 gene (26, 73, 84–86). In other plasmids *qnrS1* is associated with IS26 (87), IS2 (88), or *ISEcl2*, a novel insertion element belonging to the IS3 family (89). On the other hand *qnrS2* has been found as part of a mobile insertion cassette, an element with bracketing inverted repeats but lacking a transposase (90). The *qnrC* gene is found downstream from *ISPmi1*, an insertion sequence also belonging to the IS3 family (28). *qnrD* has typically been found on small, nonconjugative plasmids and is also located inside a mobile insertion cassette (29, 62–64, 91). *qnrVC* is so far the only *qnr* gene located in a cassette with a linked *attC* site (92). *qnrVC* genes have been found on plasmids in *A. punctata* (30), and *V. fluvialis* (32), within integrons in *A. baumannii* (93) and *P. aeruginosa* (94), and within the transmissible SXT integrating element of *V. cholerae* (34, 95).

qnr genes are usually found in multiresistance plasmids linked to other resistance determinants. β -lactamase genes have been conspicuously common, including genes for

AmpC β -lactamases (22, 96–101), CTX-M enzymes (96, 97, 99, 100, 102–114), IMP enzymes (74, 115), KPC enzymes (116–118), LAP-1 or LAP-2 (88, 89, 119–121), SHV-12 (96, 99, 104, 105, 107, 109, 115, 119, 121–127), VEB-1 (126, 128–130), and VIM-1 (111, 131). *qnrB4* and *bla*_{DHA-1} have been found near each other on similar plasmids from around the world (96, 108, 127, 132–135). *qnrB* alleles are also frequently found in plasmids linked to variable portions of the operons for *psp* (phage shock protein) and *sap* (peptide ABC transporter, ATP-binding protein) genes. These genes flank *qnrB* on the chromosome of several *Citrobacter* spp. and their co-acquisition with *qnrB* is one of the arguments for *Citrobacter* as the source of *qnrB* alleles (61). Molecular studies with I-CeuI and S1 nuclease followed by double hybridization for *qnr* and 23s rRNA genes have identified alleles for *qnrB6* (136), *qnrB12* (137), and *qnrB16* (136) on the chromosome of several *Citrobacter* spp. Note that these same alleles have also been reported on plasmids in species other than *Citrobacter* (Table 2).

Spread of *qnr* plasmids

PMQR genes have been found in a variety of Enterobacteriaceae, especially *Escherichia coli* and species of *Enterobacter*, *Klebsiella*, and *Salmonella* (Table 2). They have been conspicuously rare in non-fermenters but have occasionally been reported in *Pseudomonas aeruginosa*, other *Pseudomonas* spp. (138, 139), *Acinetobacter baumannii* (139, 140), and *Stenotrophomonas maltophilia* (139). Genes for *qnrA1* and *qnrB6* have also been found in *Haemophilus parasuis* from pigs in South China (141). *qnr* genes are found in a variety of gram-positive organisms but are chromosomal and not plasmid-mediated (38, 53). Of the various *qnr* varieties, *qnrB* seems somewhat more common than *qnrA* or *qnrS*, which are more common than *qnrD*. Only a single isolate of *qnrC* is known (28). The relative frequency of various alleles can be judged by the number of references in Table 2: i.e. for *qnrB* the most frequently detected alleles are *qnrB1*, *qnrB2*, *qnrB4*, *qnrB6*, *qnrB10*, and *qnrB19*. The earliest known *qnr* outside of *Citrobacter* spp, dates from 1988 (142). Studies in the last decade suggest that *qnr* detection is increasing, but is still less than 10% in unselected clinical isolates, with usually greatest prevalence in *E. cloacae*, less in *K. pneumoniae*, and least in *E. coli* (127, 143–146). Higher frequencies result if samples are preselected for ESBL or other resistance phenotypes (127, 147), but the prevalence of *qnr* genes has reached as high as 39% in an unselected sample of *E. cloacae* isolates at one hospital in China (127).

Although most prevalence studies have surveyed hospital isolates, animals have not been neglected. PMQR genes have been found in samples from domestic or wild birds (75, 86, 148, 149), cats (75, 81, 112, 150), cattle (151, 152), chickens (75, 86, 153–160), dogs (75, 81, 112, 150, 156, 161), ducks (101, 156, 160, 162), fish (163–165), geese (101, 156, 160, 162), horses (81, 86, 166), pigs (75, 101, 155, 156, 160, 162, 167), rabbits (168), reptiles (155, 169), sheep (155), turkeys (155), and zoo animals (170–172).

Regulation of *qnr*

Not surprisingly, *qnrA* expression is influenced by the strength of its promoter. A *qnrA1* plasmid from Shanghai was found to give 8-fold higher ciprofloxacin MICs than other

qnrA1 plasmids and had a 12-fold stronger promoter attributed to a 7-bp deletion between the +1 transcription initiation site and the start of the *qnrA1* gene (144). Environmental conditions have also been found to affect expression of *qnr* genes and may offer clues concerning the native function of these genes. Expression of the *qnrA* gene of *S. algae*, an organism adapted to growth at low temperature, is stimulated up to 8-fold by cold shock but not by other conditions such as DNA damage, oxidative or osmotic stress, starvation, or heat shock (173). Expression of *qnrB* alleles, on the other hand, is augmented up to 9-fold by exposure to DNA damaging agents such as ciprofloxacin or mitomycin C via an upstream LexA binding site and the classical SOS system (174, 175). *qnrD* and the chromosomal *qnr* of *S. marcescens* are similarly regulated (176). Expression of plasmid-mediated *qnrS1* or the related chromosomal *qnrVS1* of *V. splendidus* is also stimulated by ciprofloxacin up to 30-fold, but by a mechanism independent of the SOS system. No LexA binding site is found upstream from these *qnr* genes, but upstream sequence is required for quinolone stimulation to occur (177). Some naturally occurring quinolone-like compounds such as quinine, 2-hydroxyquinoline, 4-hydroxyquinoline, or the *Pseudomonas* quinolone signal for quorum sensing also induce *qnrS1*, but not *qnrVS1* (178).

AAC(6′)-Ib-cr

AAC(6′)-Ib-cr is a bifunctional variant of a common acetyltransferase active on such aminoglycosides as amikacin, kanamycin, and tobramycin but also able to acetylate those fluoroquinolones with an amino nitrogen on the piperazinyl ring, such as ciprofloxacin and norfloxacin (10). Compared to other AAC(6′)-Ib enzymes, the -cr variant has two unique amino acid substitutions: Trp102Arg and Asp179Tyr, both of which are required for quinolone acetylating activity. Models of enzyme action suggest that the Asp179Tyr replacement is particularly important in permitting π -stacking interactions with the quinolone ring to facilitate quinolone binding. The role of Trp102Arg is to position the Tyr face for optimal interaction (179) or to hydrogen bond to keto or carboxyl groups of the quinolone to fix it in place (180). Both AGG and CGG have been found as the Arg codon at 102 allowing variants of the *aac(6′)-Ib-cr* gene to be distinguished (73). A lower level of *aac(6′)-Ib-cr* expression has been found in a strain with an upstream 12-bp deletion displacing the promoter -10 box (181). A 26 amino acid larger AAC(6′)-Ib-cr4 enzyme with consequent Trp128Arg and Asp205Tyr substitutions (182) and non-functional truncated *aac(6′)-Ib-cr* genes (183) have also been reported.

The *aac(6′)-Ib-cr* gene is usually found in a cassette as part of an integron in a multiresistance plasmid, which may contain other PMQR genes. Association with ESBL CTX-M-15 is particularly common (110, 184–190). A mobile genetic element, especially IS26, is often associated (191). *aac(6′)-Ib-cr* may also be chromosomal (192, 193). The gene has been found world-wide (Table 2) in a variety of Enterobacteriaceae and even in *P. aeruginosa* (138). It is more prevalent in *E. coli* than other Enterobacteriaceae (145, 184, 194, 195), and has often been more common than *qnr* alleles (14, 75, 184, 192, 194, 196).

QepA and OqxAB

QepA is a plasmid-mediated efflux pump in the major facilitator (MFS) family that decreases susceptibility to hydrophilic fluoroquinolones, especially ciprofloxacin and norfloxacin (11, 197). *qepA* has often been found on plasmids also encoding aminoglycoside ribosomal methylase *rmtB* (12, 167, 198). Substantial differences in quinolone resistance produced by different *qepA* transconjugants suggest variability in the level of *qepA* expression, by mechanisms as yet to be defined (167). IS26 elements and ISCR3C have been implicated in mobilizing the *qepA* gene to plasmids (199). A variant differing in two amino acids (QepA2) has also been described (199).

OqxAB is an efflux pump in the resistance-nodulation-division (RND) family that was initially recognized on transmissible plasmids responsible for resistance to olaquinox used for growth enhancement in pigs (200, 201). It has a wide substrate specificity including chloramphenicol, trimethoprim, and quinolones such as ciprofloxacin, flumequin, norfloxacin, and nalidixic acid (13). *oqxAB* has been found on plasmids in clinical isolates of *E. coli* and *K. pneumoniae* and in the chromosome and on plasmids of *S. enteritidis* flanked in both locations by IS26-like elements (202–207). In *E. coli* isolates from farms in China where olaquinox was in use, *oqxAB* was found on transmissible plasmids in 39% of isolates from animals and 30% of isolates from farm workers (204). Linkage of *oqxAB* with genes for CTX-M-14 and other plasmid-mediated CTX-M alleles has been noted (160). It is common (usually 75% or more) on the chromosome of *K. pneumoniae* isolates, where up to 20-fold variation in expression implies the presence of regulatory control (73, 203, 206, 208, 209). In *K. pneumoniae* overexpression of the nearby *rarA* gene is associated with increased *oqxAB* expression, while increased expression of adjacent *oqxR* gene downregulates OqxAB production (210, 211). Sequence variants *oqxA2*, *oqxB2* and *oqxB3* have been described (208).

Other plasmid-mediated efflux pumps active on quinolones have been reported but as yet little studied. Plasmid pRSB101 isolated from an uncultivated organism in activated sludge at a wastewater treatment plant contained a MDR transport system with an RND-type membrane fusion protein conferring resistance to nalidixic acid and norfloxacin (212). It differs in sequence from QepA and OqxAB. Plasmids in *S. aureus* (especially MRSA) encoding the QacBIII variant belonging to the MFS family confer decreased susceptibility to norfloxacin and ciprofloxacin (213).

Resistance produced by PMQR determinants

Table 3 shows the minimum inhibitory concentration (MIC) produced in a common *E. coli* strain by PMQR genes. *qnr* genes produce about the same resistance to ciprofloxacin and levofloxacin as single mutations in *gyrA*, but have less effect on susceptibility to nalidixic acid. *aac(6)-Ib-cr* and *qepA* give lower levels, which is confined to ciprofloxacin in the case of *aac(6)-Ib-cr* because of its substrate specificity. All provide a decrease in susceptibility that does not reach the CLSI breakpoint for even intermediate resistance. How then can PMQR genes be clinically important?

The answer is that PMQR genes facilitate the selection of higher levels of quinolone resistance. Fig. 4 shows the effect of plasmid pMG252 encoding QnrA on survival of *E. coli* J53 at increasing concentrations of ciprofloxacin. Survivors occur until a concentration of more than 1 µg/ml ciprofloxacin is reached. This limiting concentration has been termed the mutant prevention concentration (MPC), and the concentration between the MIC and MPC at which mutants are selected is the mutant selection window (214). PMQR genes exert their influence by widening the mutant selection window and elevating the MPC, as shown for both *qnr* (215, 216) and *aac(6′)-Ib-cr* (10). The same augmentation of resistance selection has been found in clinical isolates of *E. cloacae* (147). Surprisingly, in *qnr*-harboring *E. coli gyrA* resistance mutants are rarely selected (217), although resistance produced by *qnr* and *gyrA* is additive (218–220), clinical isolates with *qnr* alleles or *aac(6′)-Ib-cr* and *gyrA*, *parC*, and other resistance mutations are common (221), and *gyrA* mutants have developed in *qnr* positive isolates from patients treated with quinolone for *E. coli* (222) or *S. enterica* (223) infections.

It should be noted that higher levels of quinolone resistance are seen if a plasmid or strain carries two or more genes for quinolone resistance, such as both *qnr* and *aac(6′)-Ib-cr*, and that ciprofloxacin MICs of 2 µg/ml can be reached with *qnrA* in *E. coli* overexpressing the AcrAB multi-drug efflux pump (224). A fully resistant *E. coli* with a ciprofloxacin MIC of 4 µg/ml has been reported with plasmid-mediated *qnrS1* and *oqxAB* as well as overexpression of AcrAB and other efflux pumps (225).

While the frequency of quinolone resistance in clinical isolates has paralleled quinolone usage, the appearance of PMQR has also played a role. At Hadassah hospitals in Israel ciprofloxacin resistance was uncommon in *E. coli*, *K. pneumoniae*, and *Enterobacter* spp. until the mid-1990s, just when *qnr* and *aac(6′)-Ib-cr* genes became prevalent in these strains (143, 226). Similarly, in Korea the increasing frequency of ciprofloxacin resistance in Enterobacteriaceae since 2000 has been associated with an increasing prevalence of PMQR genes (145). In Spain also the prevalence of PMQR in clinical isolates of *E. coli* and *K. pneumoniae* increased between 2000 and 2006 (227). In Canada as well the prevalence of *aac(6′)-Ib-cr* increased in the Calgary Health Region between 2004 and 2007 (184).

Clinical importance

In animal model infections the presence of a *qnr* gene makes an infecting agent harder to treat with quinolones. This detrimental effect has been shown in mice with pneumonia produced by *K. pneumoniae* or *E. coli* (228, 229) and in *E. coli* UTI models (230, 231).

Patients treated with levofloxacin for bloodstream infections caused by gram-negative organisms with elevated quinolone MICs that were still within the susceptible category had worse outcomes than similar patients infected with more susceptible organisms (232), but a specific effect of PMQR carriage on outcome has been harder to document. Chong et al. evaluated 351 blood culture isolates of *Enterobacter* or *Klebsiella* at a health center in Korea and found 26 positive for *qnrA*, *qnrB*, or *qnrS* genes. The *qnr* positive patients were hospitalized longer, but there was no difference in in-hospital or 30-day mortality between the *qnr* positive or negative patient groups (233). Liao et al. studied 227 blood culture

isolates of *Klebsiella* from a hospital in Taiwan and found nine positive for *qnrB* or *qnrS*. 14-day mortality was similar in patients infected with or without *qnr*-containing isolates, but there was a trend for increased in-hospital mortality (234). Further studies are needed to distinguish a specific effect of *qnr* from the effect of other resistance genes so often linked to it.

Coda

The varieties of PMQR that eventually emerged exemplify the three general mechanism of bacterial resistance to any antimicrobial agents: target alteration (Qnr), drug modification (AAC(6′)-Ib-cr), and efflux pump activation (QepA and OqxAB). AAC(6′)-Ib-cr arose by mutations altering two amino acid encoded by a common aminoglycoside resistance gene. Acquisition of the other PMQR genes illustrates the variety of genetic elements now available on plasmids for resistance gene mobilization and the frequent obscurity of the ultimate gene donors. Who would have guessed that aquatic bacteria harbored *qnr* genes without evident selective advantage thus encoding a protein that blocked the action of a synthetic antimicrobial agent that they would never be expected to encounter? Unfortunately, knowledge of resistance mechanisms has not led to new therapeutic strategies. Acetylation of ciprofloxacin is inhibited competitively by aminoglycoside substrates of AAC(6′)-Ib-cr (179), but other inhibitors of the enzyme are not yet known and no efflux pump inhibitors are commercially available. Overcoming Qnr blockage of quinolone inhibition will require deeper knowledge of how this DNA mimic interacts with topoisomerase as well as the development of other bacterial topoisomerase poisons that escape the action of Qnr.

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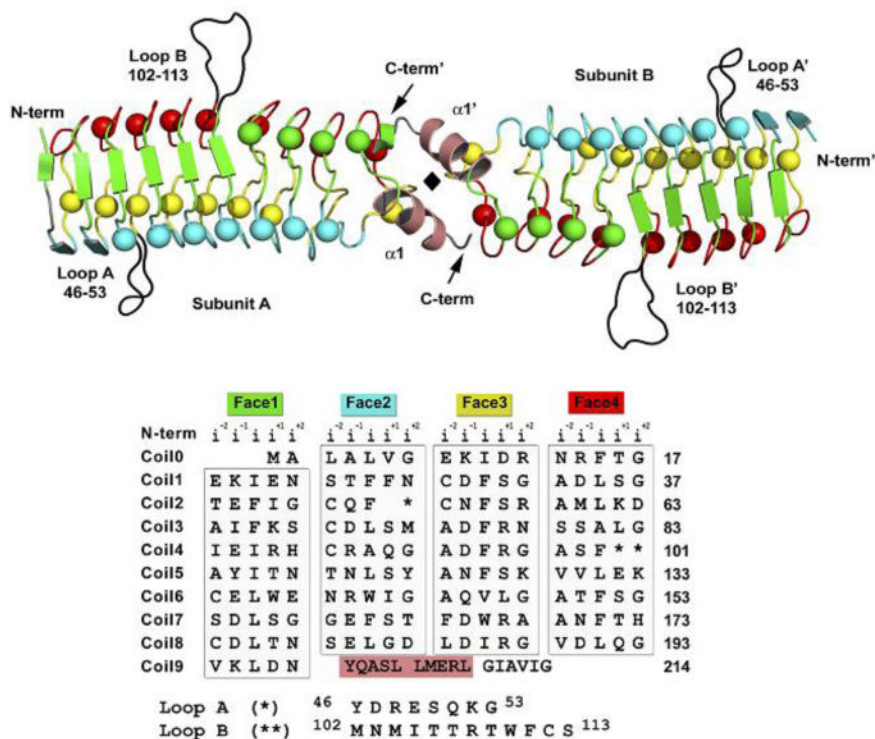


Fig. 1. The rod-like structure of the QnrB1 dimer is shown above with the sequence of the monomer below. The sequence is divided into four columns representing the four faces of the right-handed quadrilateral β -helix. Face names and color are shown at the top along with the naming convention for the five residues of the pentapeptide repeats. Loops A and B are indicated by one and two asterisks, respectively, with their sequences indicated below and the loops shown as black traces on the diagram. The N-terminal α -helix is colored salmon. The molecular 2-fold symmetry is indicated with a black diamond. Type II turn (235) containing faces are shown as spheres and type IV-containing faces as strands. Adapted from reference (44). © the American Society for Biochemistry and Molecular Biology.

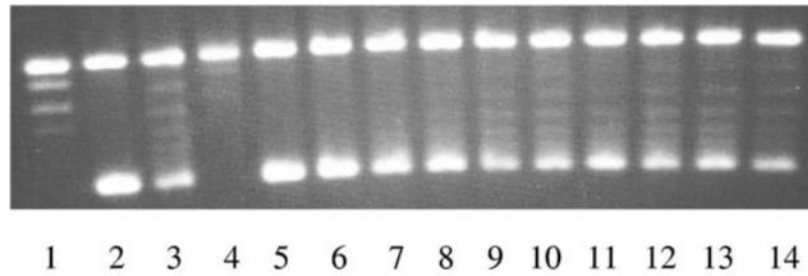


Fig. 2.

QnrB1 protection of DNA gyrase from ciprofloxacin inhibition of supercoiling. Reaction mixtures of 30 μ l were analyzed by agarose gel electrophoresis. Reaction mixtures contained 0.2 μ g relaxed pBR322 DNA (lanes 1 to 14), 6.7 nM gyrase (lanes 2 to 14), 2 μ g/ml ciprofloxacin (lanes 3 to 14), and QnrB-His6 fusion protein at 25 μ M (lane 4), 5 μ M (lane 5), 2.5 μ M (lane 6), 0.5 μ M (lane 7), 50 nM (lane 8), 5 nM (lane 9), 0.5 nM (lane 10), 50 pM (lane 11), 5 pM (lane 12), or 0.5 pM (lane 13). Reprinted from (27)

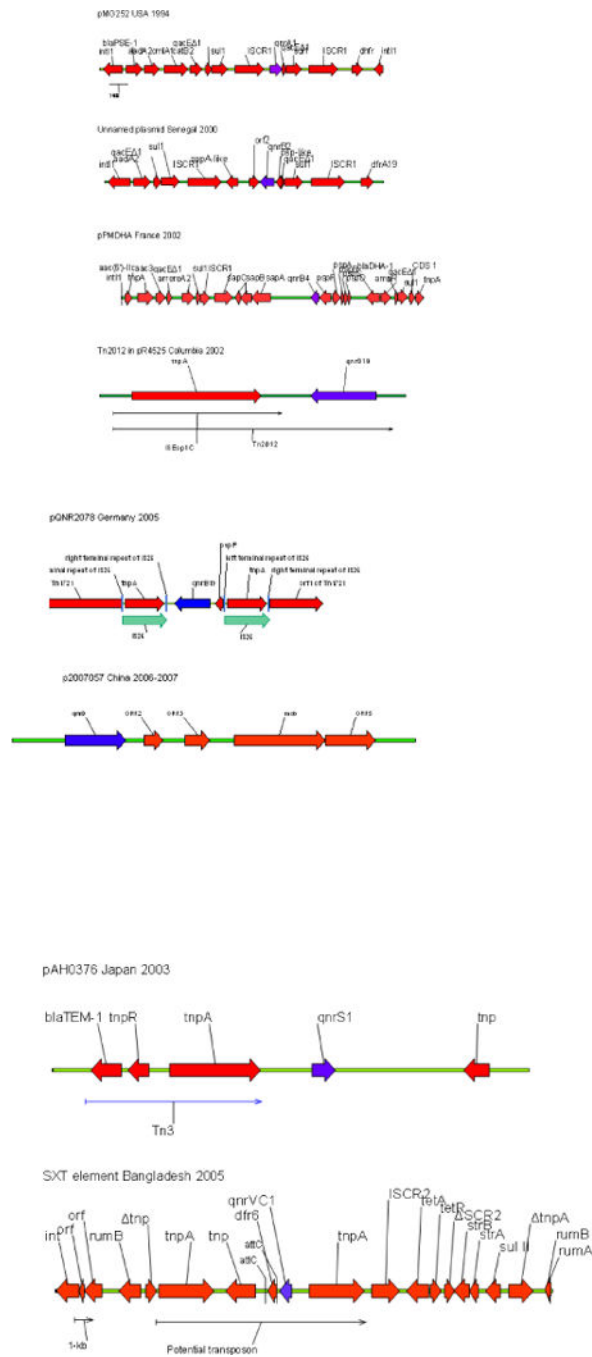


Fig. 3.
Genetic environment of *qnr* alleles.

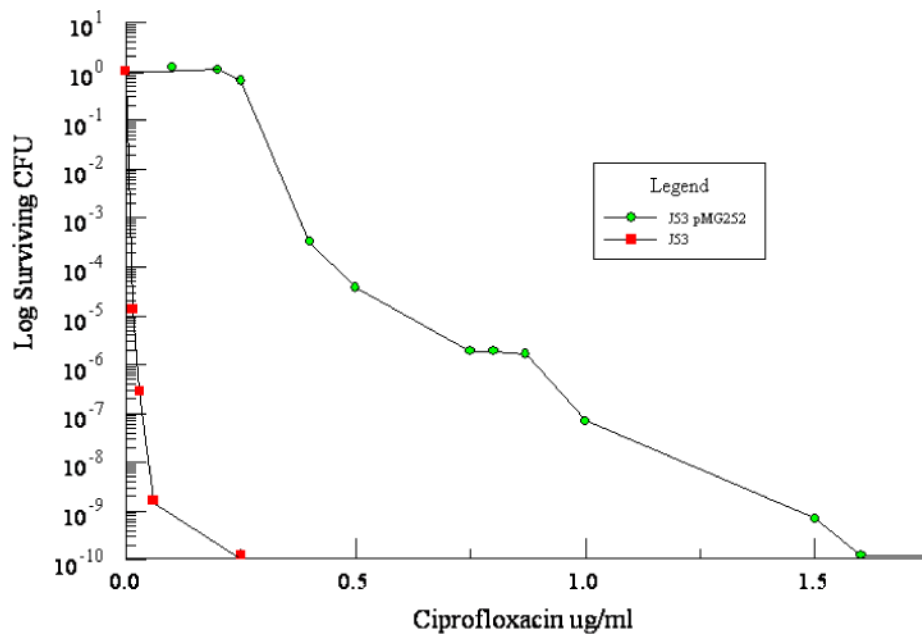


Fig. 4. Survival at increasing fluoroquinolone concentrations for *Escherichia coli* J53 and J53 pMG252. A large inoculum (10¹⁰ colony forming units) and appropriate dilutions were applied to Mueller-Hinton agar plates containing the indicated concentration of ciprofloxacin, and surviving colonies were counted after incubation for 72 h at 37°C [from (215)] with permission.

Table 1

Representative plasmids and transmissible PMQR genes

Plasmid	PMQR gene	Host	Year of isolation	Size (kb)	Inc group	Country	Linked <i>bla</i> genes ^d	Reference
pMG252	<i>qnrA1</i>	<i>K. pneumoniae</i>	1994	~180		USA	FOX-5	(9)
pHSH2	<i>qnrA1</i>	<i>E. coli</i>	2000–2001	85		China		(24)
pQR1	<i>qnrA1</i>	<i>E. coli</i>	2003	180	A/C ₂	France	VEB-1	(126, 128)
<i>b</i>	<i>qnrA1</i>	<i>E. cloacae</i>	2002–2005	75	H12	France	SHV-12	(119, 126)
<i>b</i>	<i>qnrA1</i>	<i>E. aerogenes</i>	2002–2005	150	FII	France	SHV-12	(119, 126)
pSZ50	<i>qnrA1</i>	<i>E. coli</i>	2004	~50	N	Mexico		(71)
pHE96	<i>qnrA3</i>	<i>K. pneumoniae</i>	2004	70	N	France		(236)
<i>b</i>	<i>qnrA6</i>	<i>P. stuartii</i>	2011	100	A/C	Tunisia	OXA-48, PER-1, CMY-4	(237)
pMG298	<i>qnrB1</i>	<i>K. pneumoniae</i>	2002–2003	340		India	CTX-M-15	(27)
pJBE401	<i>qnrB2</i>	<i>K. pneumoniae</i>	2003	>150	L/M	Australia	IMP-4	(74)
<i>b</i>	<i>qnrB2</i>	<i>S. enterica</i>	2000			Senegal	SHV-12	(77)
pMG319	<i>qnrB4</i>	<i>E. cloacae</i>	1999–2004	200		USA	DHA-1	(238)
pPMDHA	<i>qnrB4</i>	<i>K. oxytoca</i>	2002	(Tra)		France	DHA-1	(134)
<i>b</i>	<i>qnrB4</i>	<i>E. cloacae</i>	<i>b</i>	119		China	DHA-1	(108)
pHND2	<i>qnrB6</i>	<i>K. pneumoniae</i>	2006			China	CTX-M-9G ^c	(75)
pARCF702	<i>qnrB10</i>	<i>C. freundii</i>	2005			Argentina		(239)
pR4525	<i>qnrB19</i>	<i>E. coli</i>	2002	40		Columbia	SHV-12 CTX-M-12	(78)
pLRM24	<i>qnrB19</i>	<i>K. pneumoniae</i>	2007	80		USA	KPC-3	(83, 117)
pPAB19-1	<i>qnrB19</i>	<i>S. enterica</i>	2006	2.7	ColEI	Argentina		(82)
pQAR2078	<i>qnrB19</i>	<i>E. coli</i>	2005	42.4	N	Germany		(81)
pAH0376	<i>qnrS1</i>	<i>S. flexneri</i>	2003	~50		Japan		(26)
pINF5	<i>qnrS1</i>	<i>S. enterica</i>	2004	58		Europe		(84)
TP _{qnrS-2a}	<i>qnrS1</i>	<i>S. enterica</i>	2004	44	N	UK		(240)
pK245	<i>qnrS1</i>	<i>K. pneumoniae</i>	2002	98		Taiwan	SHV-2	(87)
<i>b</i>	<i>qnrS1</i>	<i>S. enterica</i>	1999–2006	>250	H12	Netherlands	LAP-2	(120)
<i>b</i>	<i>qnrS2</i>	<i>d</i>	2004	8.5	Q	Germany		(241)
p37	<i>qnrS2</i>	<i>A. punctata</i>	2006	55	U	France		(242)
pHS10	<i>qnrC</i>	<i>P. mirabilis</i>	2006	~120		China		(28)

Plasmid	PMQR gene	Host	Year of isolation	Size (kb)	Inc group	Country	Linked <i>bla</i> genes ^a	Reference
p2007057	<i>qnrD1</i>	<i>S. enterica</i>	2006–2007	4.3		China		(29)
<i>e</i>	<i>qnrVC1</i>	<i>V. cholerae</i>	2002–2008			Bangladesh		(34)
<i>b</i>	<i>qnrVC4</i>	<i>A. punctata</i>	2008			China	PER-1	(30)
pBD146	<i>qnrVC5</i>	<i>V. fluvialis</i>	1998–2002	7.5		India		(243)
pHSH10-2	<i>aac(6′)-Ib-cr</i>	<i>E. coli</i>	2000–2001			China		(10)
pC15-1a	<i>aac(6′)-Ib-cr</i>	<i>E. coli</i>	2000–2002	92	FII	Canada	CTX-M-15	(244)
pHPA	<i>qepA1</i>	<i>E. coli</i>	2002		FII	Japan	CTX-M-12	(11)
pPI206	<i>qepA1</i>	<i>E. coli</i>	2000–2005	168	FI	Belgium		(197)
pQep	<i>qepA2</i>	<i>E. coli</i>	2007	90	FI	France		(199)
pOLA52	<i>oqxAB</i>	<i>E. coli</i>	<i>b</i>	52	X1	Denmark		(200, 202)
pHXY0908	<i>oqxAB</i>	<i>S. typhimurium</i>	2009		HI2	China		(207)

^a Only unusual *bla* genes are shown.

^b Not specified.

^c CTX-M-9 group. See reference for details.

^d Unidentified bacteria in activated sludge

^e Transmitted as part of an integrating conjugative element

Table 2

Distribution of PMQR genes

PMQR gene	Source Country	Organism	Mobilizing element	Reference
<i>qnrA1</i>	Algeria, Australia, Belgium, Brazil, Central African Republic, China, Denmark, Egypt, France, Germany, Hungary, India, Israel, Ivory Coast, Japan, Kenya, Mexico, Morocco, Netherlands, Nigeria, Portugal, Romania, Saudi Arabia, Singapore, South Korea, Spain, Sweden, Taiwan, Thailand, Turkey, UK, Uruguay, USA, Vietnam	<i>A. baumannii</i> , <i>C. freundii</i> , <i>E. aerogenes</i> , <i>E. cloacae</i> , <i>E. sakazakii</i> , <i>E. coli</i> , <i>H. parasuis</i> , <i>K. oxytoca</i> , <i>K. pneumoniae</i> , <i>P. mirabilis</i> , <i>P. aeruginosa</i> , <i>P. oryzihabitans</i> , <i>P. putida</i> , <i>S. enterica</i> , <i>S. marcescens</i> , <i>S. sonnei</i> , <i>S. maltophilia</i> , <i>V. fluvialis</i>	ISCR1	(9, 22–24, 67, 98, 104–108, 113, 115, 119, 122–125, 127–130, 138–141, 143, 144, 147, 155, 226, 227, 238, 245–290)
<i>qnrA3</i>	China, France, Hong Kong	<i>K. pneumoniae</i> , <i>K. ascorbata</i> , <i>Kluyvera</i> spp., <i>S. enterica</i> , <i>S. algae</i>	ISCR1, IS26	(25, 153, 156, 236, 291)
<i>qnrA6</i>	France, Tunisia	<i>C. freundii</i> , <i>K. pneumoniae</i> , <i>P. mirabilis</i> , <i>P. stuartii</i>	ISCR1	(237, 292, 293)
<i>qnrB1</i>	Algeria, Argentina, Brazil, China, Czech Republic, Denmark, France, Egypt, India, Italy, Ivory Coast, Malaysia, Mexico, Morocco, Netherlands, Nigeria, Norway, Saudi Arabia, Singapore, Scotland, Singapore, South Korea, Spain, Sweden, Thailand, Tunisia, Turkey, UK	<i>C. freundii</i> , <i>C. koseri</i> , <i>E. cloacae</i> , <i>E. gergoviae</i> , <i>E. coli</i> , <i>K. ornithinolytica</i> , <i>K. pneumoniae</i> , <i>S. enterica</i> , <i>S. marcescens</i>	Orf1005, IS26	(27, 67, 72, 73, 98, 102, 105, 109, 110, 113, 162, 186, 251, 259, 263, 268, 269, 271, 279, 281, 284, 285, 287, 288, 292, 294–302)
<i>qnrB2</i>	Argentina, Australia, Bolivia, Brazil, Czech Republic, China, France, Germany, Hungary, Ireland, Israel, Kuwait, Mexico, Morocco, Netherlands, Portugal, Peru, Scotland, Senegal, South Korea, Spain, Sweden, Switzerland, Taiwan, Tunisia, UK, USA	<i>C. freundii</i> , <i>E. cloacae</i> , <i>E. coli</i> , <i>K. oxytoca</i> , <i>K. pneumoniae</i> , <i>S. enterica</i> , <i>S. typhi</i>	ISCR1	(27, 61, 67, 73, 77, 96, 98, 108, 115, 116, 120, 125, 132, 139, 145, 155, 157, 161, 227, 238, 251, 257, 259, 265, 268, 271, 273, 274, 276, 279, 281, 290, 292, 299, 301, 303–316)
<i>qnrB3</i>	USA	<i>E. coli</i>		(238)
<i>qnrB4</i>	Algeria, Australia, China, France, Germany, Ivory Coast, Japan, Morocco, Netherlands, Saudi Arabia, Singapore, South Korea, Spain, Sweden, Switzerland, Taiwan, Thailand, UK, USA	<i>C. freundii</i> , <i>C. koseri</i> , <i>E. aerogenes</i> , <i>E. cloacae</i> , <i>E. gergoviae</i> , <i>E. coli</i> , <i>K. ornithinolytica</i> , <i>K. oxytoca</i> , <i>K. pneumoniae</i> , <i>S. enterica</i> , <i>S. marcescens</i> , <i>Shigella</i> sp.	ISCR1	(61, 67, 72, 75, 96, 98, 104, 105, 108, 109, 113, 121, 127, 132, 133, 145, 155, 186, 192, 196, 220, 238, 251, 256, 257, 266, 268, 271, 276, 280, 281, 285, 287, 290, 299, 309, 310, 316–319)
<i>qnrB5</i>	Denmark, France, Mexico, South Korea, UK, USA	<i>E. coli</i> , <i>K. pneumoniae</i> , <i>S. enterica</i>		(96, 97, 145, 259, 265, 279, 288, 295, 299, 303, 305, 320)
<i>qnrB6</i>	China, France, Germany, Japan, Malaysia, Mexico, Netherlands, Poland, Singapore, South Korea, Spain, Sweden, Thailand, USA	<i>C. freundii</i> , <i>E. aerogenes</i> , <i>E. cloacae</i> , <i>E. coli</i> , <i>H. parasuis</i> , <i>K. oxytoca</i> , <i>K. pneumoniae</i> , <i>S. enterica</i> , <i>S. fonticola</i> , <i>S. marcescens</i> , <i>S. flexneri</i>	ISCR1	(67, 72, 75, 98, 100, 104, 108, 127, 139, 141, 148, 153, 155, 167, 169, 192, 196, 204, 227, 251, 257, 266–268, 273, 279, 285, 287, 288, 290, 302, 309, 321, 322)
<i>qnrB7</i>	Kuwait, Netherlands, Norway, South Korea	<i>C. freundii</i> , <i>E. cloacae</i> , <i>K. pneumoniae</i> , <i>S. enterica</i>		(98, 155, 296, 313)
<i>qnrB8</i>	Brazil, China, France, Kuwait, South Korea, UK	<i>C. freundii</i> , <i>E. aerogenes</i>		(98, 104, 269, 299, 306, 313)
<i>qnrB9</i>	China, South Korea	<i>C. freundii</i>		(98, 290, 323)

PMQR gene	Source Country	Organism	Mobilizing element	Reference
<i>qnrB10</i>	Argentina, Bolivia, China, Malaysia, Nigeria, Peru, South Korea	<i>C. braakii</i> , <i>C. freundii</i> , <i>E. amnigenus</i> , <i>E. cloacae</i> , <i>E. coli</i> , <i>K. pneumoniae</i> , <i>S. Choleraesuis</i> , <i>S. marcescens</i>	ISCR1	(73, 127, 145, 153, 281, 302, 314, 324)
<i>qnrB12</i>	Netherlands, South Korea	<i>C. freundii</i> , <i>S. enterica</i>		(98, 155)
<i>qnrB16</i>	South Korea	<i>K. pneumoniae</i>		(281)
<i>qnrB19</i>	Argentina, Bolivia, Brazil, Columbia, Czech Republic, Finland, Denmark, Germany, Italy, Mexico, Netherlands, Nigeria, Peru, Poland, South Korea, UK, USA, Venezuela	<i>E. aerogenes</i> , <i>E. fergusonii</i> , <i>E. coli</i> , <i>K. oxytoca</i> , <i>K. pneumoniae</i> , <i>K. ascorbata</i> , <i>S. enterica</i> , <i>S. sonnei</i>	ISEcp1, IS26	(73, 78–83, 86, 120, 148, 155, 158, 166, 169, 288, 289, 301, 314, 315, 322, 324–329)
<i>qnrB20</i>	Mexico, Singapore	<i>K. pneumoniae</i>	Orf1005, IS26	(72, 288)
<i>qnrB22</i>	South Korea	<i>C. werkmanii</i> ^a		(330)
<i>qnrB23</i>	South Korea	<i>C. freundii</i> ^a		(330)
<i>qnrB26</i>	China	<i>P. vulgaris</i>		(290)
<i>qnrB31</i>	China	<i>K. pneumoniae</i>		(331)
<i>qnrB32</i>	China	<i>K. pneumoniae</i>		(331, 332)
<i>qnrS1</i>	Algeria, Argentina, Belgium, Bolivia, Brazil, Canada, China, Czech Republic, Denmark, Egypt, France, Germany, Greece, Hungary, Israel, Italy, Ivory Coast, Japan, Malaysia, Mexico, Morocco, Netherlands, Nigeria, Norway, Poland, Peru, Romania, Serbia, South Africa, South Korea, Slovakia, Spain, Sweden, Switzerland, Taiwan, Thailand, Tunisia, Turkey, UK, USA, Vietnam	<i>C. freundii</i> , <i>C. koseri</i> , <i>E. aerogenes</i> , <i>E. cloacae</i> , <i>E. coli</i> , <i>K. oxytoca</i> , <i>K. pneumoniae</i> , <i>M. morgani</i> , <i>P. mirabilis</i> , <i>S. enterica</i> , <i>S. typhi</i> , <i>S. boydii</i> , <i>S. flexneri</i> , <i>S. dysenteriae</i>		(26, 67, 73, 75, 84, 86, 98, 104, 105, 107–109, 115, 119–121, 125, 127, 131, 132, 143, 145, 148, 150, 151, 153–156, 158, 166, 167, 169, 172, 184, 186, 192, 196, 204, 220, 227, 240, 251, 255–257, 259, 261, 262, 264, 265, 268–273, 276, 279, 281, 284, 285, 287, 290, 292, 294–296, 299, 301–303, 305, 307, 308, 314–316, 318–322, 324, 333–341)
<i>qnrS2</i>	China, Czech Republic, Denmark, France, Germany, India, South Korea, Spain, Switzerland, USA	<i>A. allosaccharophila</i> , <i>A. caviae</i> , <i>A. hydrophila</i> , <i>A. media</i> , <i>A. punctata</i> , <i>A. veronii</i> , <i>E. cloacae</i> , <i>Pseudoalteromonas</i> spp., <i>Pseudomonas</i> spp., <i>S. enterica</i> , <i>S. marcescens</i> , <i>Shigella</i> sp.		(90, 100, 127, 148, 156, 167, 241, 242, 266, 272, 295, 299, 303, 319, 323, 342–345)
<i>qnrS3</i>	China	<i>E. coli</i>		(162)
<i>qnrS4</i>	Denmark	<i>S. enterica</i>		(295)
<i>qnrS5</i>	South Korea	<i>Aeromonas</i> spp.		(345)
<i>qnrC</i>	China	<i>P. mirabilis</i>	ISPmi1	(28)
<i>qnrD1</i>	China, Czech Republic, France, India, Italy, Netherlands, Nigeria, Poland, Spain	<i>E. coli</i> , <i>C. freundii</i> , <i>K. pneumoniae</i> , <i>M. morgani</i> , <i>P. mirabilis</i> , <i>P. vulgaris</i> , <i>P. rettgeri</i> , <i>P. aeruginosa</i> , <i>S. enterica</i>		(29, 62, 63, 91, 138, 148, 155, 204, 323, 340, 346, 347)
<i>qnrVC1</i>	Bangladesh, Brazil, India, Tunisia	<i>P. aeruginosa</i> , <i>V. cholerae</i>		(33, 34, 92, 94, 95)
<i>qnrVC3</i>	India	<i>V. cholerae</i>		(95)
<i>qnrVC4</i>	China, Haiti, Portugal	<i>A. hydrophila</i> , <i>A. punctata</i> , <i>Aeromonas</i> sp., <i>Pseudomonas</i> sp., <i>V. cholera</i>	ISCR1	(30, 33)
<i>qnrVC5</i>	China, Haiti, India	<i>V. parahaemolyticus</i> , <i>V. cholera</i> , <i>V. fluvialis</i>		(31–33)

PMQR gene	Source Country	Organism	Mobilizing element	Reference
<i>qnrVC6</i>	China	<i>A. baumannii</i>		(93)
<i>aac(6)-Ib-cr</i>	Algeria, Argentina, Australia, Bolivia, Brazil, Bulgaria, Canada, China, Croatia, Czech Republic, Denmark, Egypt, France, Germany, Hungary, India, Israel, Italy, Japan, Kenya, Mexico, Netherlands, Nigeria, Norway, Portugal, Peru, Saudi Arabia, Serbia, Singapore, Slovenia, South Korea, Spain, Switzerland, Taiwan, Thailand, UK, Uruguay, USA, Vietnam	<i>C. braakii</i> , <i>C. freundii</i> , <i>C. koseri</i> , <i>E. aerogenes</i> , <i>E. cloacae</i> , <i>E. coli</i> , <i>H. parasuis</i> , <i>K. pneumoniae</i> , <i>Kluyvera</i> spp., <i>L. hongkongensis</i> , <i>M. morgani</i> , <i>P. aeruginosa</i> , <i>P. luteola</i> , <i>P. oryzihabitans</i> , <i>P. mirabilis</i> , <i>Raoultella</i> spp., <i>S. enterica</i> , <i>S. marcescens</i> , <i>S. odorifera</i> , <i>S. flexneri</i> , <i>S. sonnei</i> , <i>Shigella</i> sp., <i>V. fluvialis</i>	IS26	(10, 14, 67, 73, 75, 100–102, 104, 110, 113, 116, 125, 127, 133, 138, 141, 145, 148, 150, 153, 155–157, 161, 167, 169, 172, 182, 184–187, 189, 190, 192, 194–196, 220, 226, 256, 261, 263, 266, 267, 270, 272, 275, 278, 284, 287, 288, 290, 296, 297, 301, 315, 316, 318, 319, 322, 336, 348–362)
<i>oqxAB</i>	Argentina, Czech Republic, China, Denmark, Hong Kong, Italy, Japan, Poland, Serbia, South Korea, Spain	<i>E. coli</i> , <i>K. oxytoca</i> , <i>K. pneumoniae</i> , <i>S. enterica</i>	IS26	(73, 101, 148, 156, 168, 202–206, 208, 339, 360, 363, 364)
<i>qepA1</i>	Belgium, Bolivia, Canada, China, Egypt, India, Japan, Mexico, Nigeria, South Korea, Spain, UK, USA, Vietnam	<i>E. cloacae</i> , <i>E. coli</i> , <i>K. pneumoniae</i> , <i>M. morgani</i> , <i>P. oryzihabitans</i> , <i>S. enterica</i> , <i>S. flexneri</i>	IS26, ISCR3C	(11, 12, 75, 114, 138, 145, 150, 153, 156, 167, 187, 192, 196–198, 220, 261, 270, 272, 284, 285, 290, 321, 324, 361, 365–367)
<i>qepA2</i>	France	<i>E. coli</i>	ISCR3C	(199)

^a *Citrobacter* spp. contain both plasmid-mediated and chromosomal *qnr* genes. Genes for *qnrB22* and *qnrB23* were transferred by conjugation to *E. coli* and hence proved to be plasmid determined.

Table 3Effect of different quinolone resistance mechanisms on quinolone susceptibility of *E. coli*.

<i>E. coli</i> Strain	MIC µg/ml		
	Ciprofloxacin	Levofloxacin	Nalidixic acid
J53	0.008	0.015	4
J53 <i>gyrA</i> (S83L)	0.25	0.5	256
J53 pMG252 (<i>qnrA1</i>)	0.25	0.5	16
J53 pMG298 (<i>qnrB1</i>)	0.25	0.5	16
J53 pMG306 (<i>qnrS1</i>)	0.25	0.38	16
J53 pMG320 (<i>aac(6)-Ib-cr</i>)	0.06	0.015	4
J53 pAT851 (<i>qepA</i>)	0.064	0.032	4
CLSI susceptibility breakpoint	1.0	2.0	16