Plasmid-Mediated Quinolone Resistance

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ABSTRACT 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 protect 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 was added as an additional resistance mechanism. The search for transferable nalidixic acid resistance in over 500 Gram-negative strains in the 1970s was unrevealing (4). In the 1980s 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be present in a nalidixic acid-resistant isolate of Shigella dysenteriae from Bangladesh (7), but this claim was later withdrawn (8).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 nonsusceptibility 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 1,000 members) pentapeptide repeat family of proteins (21). Knowledge of the sequence allowed the 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 Mycobacterium 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 hydrophilic residue (i-2) point inward, while the remaining amino acids (i-1, i+1, i+2) 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. Figure 2 shows that for DNA gyrase inhibited by 6 μM (2 μg/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 IC₅₀ of 1.75 to 3 μM and lacks any protective effect against ciprofloxacin. EfsQnr is intermediate. It partially protects E. coli gyrase against ciprofloxacin inhibition but also inhibits ATP-dependent supercoiling activity of gyrase with an IC₅₀ 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 quinolone 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 *Clostridium 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 alga* (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 younghae* of both clinical (61) and environmental origin. The small, nonconjugative plasmids that carry *qnrD* can be found in other *Enterobacteriaceae* but are especially likely to be found in *Proteae*, such as *Proteus mirabilis*, *Proteus 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 CoIE1-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 *psfP*, implying that the putative mobilization pathways may be related. In plasmid pLM24 *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.

![Fig. 2](https://www.asmscience.org/MicrobiolSpectrum) QnrB1 protection of DNA gyrase from ciprofloxacin inhibition of supercoiling. Reaction mixtures of 30 μl were analyzed by agarose gel electrophoresis. Reaction mixtures contained 0.2 μg relaxed pBR322 DNA (lanes 1 to 14), 6.7 nM gyrase (lanes 2 to 14), 2 μg/ml ciprofloxacin (lanes 3 to 14), and QnrB-His6 fusion protein at 25 μM (lane 4), 5 μM (lane 5), 2.5 μM (lane 6), 0.5 μM (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 reference 27. doi:10.1128/microbiolspec.PLAS-0006-2013.f2
but lacking a transposase (90). The \textit{qnrC} gene is found downstream from IS\textit{Pmi1}, an insertion sequence also belonging to the IS3 family (28). \textit{qnrD} has typically been found on small, nonconjugative plasmids and is also located inside a mobile insertion cassette (29, 62–64, 91). \textit{qnrVC} is so far the only \textit{qnr} gene located in a cassette with a linked \textit{attC} site (92). \textit{qnrVC} genes have been found on plasmids in \textit{A. punctata} (30) and \textit{Vibrio fluvialis} (32), within integrons in \textit{Acinetobacter baumannii} (93) and \textit{Pseudomonas aeruginosa} (94), and within the transmissible SXT integrating element of \textit{V. cholerae} (34, 95).

### TABLE 1 Representative plasmids and transmissible PMQR genes

<table>
<thead>
<tr>
<th>Plasmid</th>
<th>PMQR gene</th>
<th>Host</th>
<th>Year of isolation</th>
<th>Size (kb)</th>
<th>Inc group</th>
<th>Country</th>
<th>Linked \textit{bla} genes</th>
<th>Reference</th>
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<td>France</td>
<td>VEB-1</td>
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<td>\textit{S. enterica}</td>
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<td>\textit{K. pneumoniae}</td>
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<td>X1</td>
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*a Only unusual \textit{bla} genes are shown.

*b Not specified.

"CTX-M-9 group. See reference for details.

*c Unidentified bacteria in activated sludge.

*d Transmitted as part of an integrating conjugative element.

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### TABLE 2 Distribution of PMQR genes

<table>
<thead>
<tr>
<th>PMQR gene</th>
<th>Source country</th>
<th>Organism</th>
<th>Mobilizing element</th>
<th>Reference</th>
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<tr>
<td>qnrA1</td>
<td>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</td>
<td>Acinetobacter baumannii, C. freundii, E. aerogenes, Enterobacter cloacae, Enterobacter sakazakii, E. coli, Haemophilus parasuis, K. oxytoca, K. pneumoniae, P. mirabilis, P. aeruginosa, Pseudomonas oryzihabitans, Pseudomonas putida, S. enterica, Serratia marcescens, Shigella sonnei, S. maltophilia, V. fluvialis</td>
<td>ISCR1</td>
<td>25, 153, 156, 236, 291</td>
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<td>qnrA3</td>
<td>China, France, Hong Kong</td>
<td>K. pneumoniae, Klyuyvera ascorbata, Klyuyvera spp., S. enterica, S. algea</td>
<td>ISCR1, IS26</td>
<td>25, 153, 156, 236, 291</td>
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<td>qnrA6</td>
<td>France, Tunisia</td>
<td>C. freundii, K. pneumoniae, P. mirabilis, P. stuartii</td>
<td>ISCR1</td>
<td>237, 292, 293</td>
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<td>qnrB1</td>
<td>Algeria, Argentina, Brazil, China, Czech Republic, Denmark, France, Egypt, Italy, Ivory Coast, Malaysia, Mexico, Morocco, Netherlands, Nigeria, Norway, Saudi Arabia, Scotland, Singapore, South Korea, Spain, Sweden, Thailand, Tunisia, Turkey, UK, USA</td>
<td>C. freundii, Citrobacter koseri, E. cloacae, Enterobacter gergoviae, E. coli, Klebsiella ornithinolytica, K. pneumoniae, S. enterica, S. marcescens</td>
<td>Orf1005, IS26</td>
<td>27, 67, 72, 73, 98, 102, 105, 109, 110, 113, 120, 125, 132, 139, 145, 155, 157, 161, 227, 238, 250, 256, 263, 268, 269, 271, 279, 281, 284, 285, 287, 288, 292, 294, 296, 301, 302</td>
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<td>C. freundii, E. cloacae, E. coli, K. oxytoca, K. pneumoniae, S. enterica, S. typhi</td>
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<td>27, 61, 67, 73, 75, 96, 98, 108, 115, 116, 120, 125, 132, 139, 145, 155, 157, 161, 227, 238, 250, 256, 263, 268, 269, 271, 279, 281, 284, 285, 287, 289, 292, 299, 301, 303, 316</td>
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<td>E. coli</td>
<td>ISCR1</td>
<td>238</td>
</tr>
<tr>
<td>qnrB5</td>
<td>Denmark, France, Mexico, South Korea, UK, USA</td>
<td>E. coli, K. pneumoniae, S. enterica</td>
<td>ISCR1</td>
<td>96, 97, 145, 259, 265, 279, 288, 295, 299, 303, 305, 320</td>
</tr>
<tr>
<td>qnrB7</td>
<td>Kuwait, Netherlands, Norway, South Korea</td>
<td>C. freundii, E. cloacae, K. pneumoniae, S. enterica</td>
<td>ISCR1</td>
<td>98, 155, 296, 313</td>
</tr>
<tr>
<td>qnrB8</td>
<td>Brazil, China, France, Kuwait, South Korea, UK</td>
<td>C. freundii, E. aerogenes</td>
<td>ISCR1</td>
<td>98, 104, 269, 299, 306, 313</td>
</tr>
<tr>
<td>qnrB9</td>
<td>China, South Korea</td>
<td>C. freundii</td>
<td>ISCR1</td>
<td>98, 290, 323</td>
</tr>
<tr>
<td>qnrB10</td>
<td>Argentina, Bolivia, China, Malaysia, Nigeria, Peru, South Korea</td>
<td>C. freundii, E. aerogenes, Enterobacter amnigenus, E. cloacae, E. coli, K. pneumoniae, Salmonella choleraesuis, S. marcescens</td>
<td>ISCR1</td>
<td>73, 127, 145, 153, 281, 302, 314, 324</td>
</tr>
<tr>
<td>qnrB12</td>
<td>Netherlands, South Korea</td>
<td>C. freundii, S. enterica</td>
<td>ISCR1</td>
<td>98, 155, 281</td>
</tr>
<tr>
<td>qnrB16</td>
<td>South Korea</td>
<td>K. pneumoniae</td>
<td>ISCR1</td>
<td>281</td>
</tr>
<tr>
<td>qnrB19</td>
<td>Argentina, Bolivia, Brazil, Columbia, Czech Republic, Finland, Denmark, Germany, Italy, Mexico, Netherlands, Nigeria, Peru, Poland, South Korea, UK, USA, Venezuela</td>
<td>E. aerogenes, Escherichia fergusonii, E. coli, K. oxytoca, K. pneumoniae, K. ascorbata, S. enterica, S. sonnei</td>
<td>ISEp1, IS26</td>
<td>73, 78, 83, 86, 120, 148, 155, 158, 166, 169, 288, 289, 301, 314, 315, 322, 324–329</td>
</tr>
</tbody>
</table>
### TABLE 2 Distribution of PMQR genes (continued)

<table>
<thead>
<tr>
<th>PMQR gene</th>
<th>Source country</th>
<th>Organism</th>
<th>Mobilizing element</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>qnrB20</td>
<td>Mexico, Singapore</td>
<td>K. pneumoniae</td>
<td>Orf1005, IS26</td>
<td>72, 288</td>
</tr>
<tr>
<td>qnrB22</td>
<td>South Korea</td>
<td>C. freundii</td>
<td>330</td>
<td></td>
</tr>
<tr>
<td>qnrB23</td>
<td>South Korea</td>
<td>C. freundii</td>
<td>330</td>
<td></td>
</tr>
<tr>
<td>qnrB26</td>
<td>China</td>
<td>P. vulgaris</td>
<td>290</td>
<td></td>
</tr>
<tr>
<td>qnrB31</td>
<td>China</td>
<td>K. pneumoniae</td>
<td>331</td>
<td></td>
</tr>
<tr>
<td>qnrB32</td>
<td>China</td>
<td>K. pneumoniae</td>
<td>331, 332</td>
<td></td>
</tr>
<tr>
<td>qnrS3</td>
<td>China</td>
<td>E. coli</td>
<td>162</td>
<td></td>
</tr>
<tr>
<td>qnrS4</td>
<td>Denmark</td>
<td>S. enterica</td>
<td>295</td>
<td></td>
</tr>
<tr>
<td>qnrS5</td>
<td>South Korea</td>
<td>Aeromonas spp.</td>
<td>345</td>
<td></td>
</tr>
<tr>
<td>qnrC</td>
<td>China</td>
<td>P. mirabilis</td>
<td>ISPm1</td>
<td>28</td>
</tr>
<tr>
<td>qnrD1</td>
<td>China, Czech Republic, France, India, Italy, Netherlands, Nigeria, Poland, Spain</td>
<td>E. coli, C. freundii, K. pneumoniae, M. morgani, P. mirabilis, P. vulgaris, P. rettgeri, P. aeruginosa, S. enterica</td>
<td>29, 62, 63, 91, 138, 143, 155, 204, 323, 340, 346, 347</td>
<td></td>
</tr>
<tr>
<td>qnrVC1</td>
<td>Bangladesh, Brazil, India, Tunisia</td>
<td>P. aeruginosa, V. cholerae</td>
<td>33, 54, 92, 94, 95</td>
<td></td>
</tr>
<tr>
<td>qnrVC3</td>
<td>India</td>
<td>V. cholerae</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>qnrVC4</td>
<td>China, Haiti, Portugal</td>
<td>A. hydrophila, A. punctata, Aeromonas spp., Pseudomonas spp., V. cholerae</td>
<td>ISCR1</td>
<td></td>
</tr>
<tr>
<td>qnrVC5</td>
<td>China, Haiti, India</td>
<td>Vibrio parahaemolyticus, V. cholerae, V. fluvialis</td>
<td>31–33</td>
<td></td>
</tr>
<tr>
<td>qnrVC6</td>
<td>China</td>
<td>A. baumannii</td>
<td>93</td>
<td></td>
</tr>
<tr>
<td>oqxAB</td>
<td>Argentina, Czech Republic, China, Denmark, Hong Kong, Italy, Japan, Poland, South Korea, Spain</td>
<td>E. coli, K. oxytoca, K. pneumoniae, S. enterica</td>
<td>IS26</td>
<td></td>
</tr>
<tr>
<td>qepA2</td>
<td>France</td>
<td>E. coli</td>
<td>ISCR3C</td>
<td></td>
</tr>
</tbody>
</table>

*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.*
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 blaDHA-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 coacquisition 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 E. coli and species of Enterobacter, Klebsiella, and Salmonella (Table 2). They have been conspicuously rare in nonfermenters but have occasionally been reported in P. aeruginosa, other Pseudomonas spp. (138, 139), A. baumannii (139, 140), and S. 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 and 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...
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 the greatest prevalence in Enterobacter cloacae, less in K. pneumoniae, and the least in E. coli (127, 143–146). Higher frequencies result if samples are preselected for extended-spectrum β-lactamase 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 Serratia 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 an 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 acetytransferase active on such aminoglycosides as amikacin, kanamycin, and tobramycin but is 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-cr enzyme with consequent Trp128Arg and Asp205Tyr substitutions (182) and nonfunctional 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 extended-spectrum β-lactamase 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 in other Enterobacteriaceae (145, 184, 194, 195) and has often been more common than qnr alleles (14, 73, 184, 192, 194, 196).

QepA AND OqxAB

QepA is a plasmid-mediated efflux pump in the major facilitator 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 family that was initially recognized on transmissible plasmids responsible for resistance to olaquindox 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. enteritis flanked in both locations by IS26-like elements (202–207). In E. coli isolates from farms in China where olaquindox 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 the 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 multidrug resistance (MDR) transport system with a resistance-nodulation-division-type membrane fusion protein conferring resistance to nalidixic acid and norfloxacin (212). It differs in sequence from QepA and OqxAB. Plasmids in Staphylococcus aureus (especially multiresistant S. aureus) encoding the QacBIII variant belonging to the major facilitator family confer decreased susceptibility to norfloxacin and ciprofloxacin (213).

**RESISTANCE PRODUCED BY PMQR DETERMINANTS**

Table 3 shows the 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 affect 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. Figure 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 rarely selected (217) is known as the breakpoint. How then can PMQR genes be clinically important?

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

<table>
<thead>
<tr>
<th>E. coli strain</th>
<th>Ciprofloxacin</th>
<th>Levofloxacin</th>
<th>Nalidixic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>J53</td>
<td>0.008</td>
<td>0.015</td>
<td>4</td>
</tr>
<tr>
<td>J53 qnrA (S83L)</td>
<td>0.25</td>
<td>0.5</td>
<td>≥256</td>
</tr>
<tr>
<td>J53 pMG252 (qnrA)</td>
<td>0.25</td>
<td>0.5</td>
<td>16</td>
</tr>
<tr>
<td>J53 pMG298 (qnrB)</td>
<td>0.25</td>
<td>0.5</td>
<td>16</td>
</tr>
<tr>
<td>J53 pMG306 (qnrS)</td>
<td>0.25</td>
<td>0.38</td>
<td>16</td>
</tr>
<tr>
<td>J53 pMG320 (aac(6’)-Ib-cr)</td>
<td>0.06</td>
<td>0.015</td>
<td>4</td>
</tr>
<tr>
<td>J53 pAT851 (qepA)</td>
<td>0.064</td>
<td>0.032</td>
<td>4</td>
</tr>
<tr>
<td>CLSI susceptibility breakpoint</td>
<td>≤1.0</td>
<td>≤2.0</td>
<td>≤16</td>
</tr>
</tbody>
</table>

Figure 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 rarely 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 \textit{qnr} and \textit{aac(6\textprime )-Ib-cr}, and that ciprofloxacin MICs of 2 \(\mu\)g/ml can be reached with \textit{qnrA} in \textit{E. coli} overexpressing the AcrAB multidrug efflux pump (224). Fully resistant \textit{E. coli} with a ciprofloxacin MIC of 4 \(\mu\)g/ml has been reported with plasmid-mediated \textit{qnrSt} and \textit{qoxAB} 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 \textit{E. coli}, \textit{K. pneumoniae}, and \textit{Enterobacter} spp. until the mid-1990s, just when \textit{qnr} and \textit{aac(6\textprime )-Ib-cr} genes became prevalent in these strains (143, 226). Similarly, in Korea the increasing frequency of ciprofloxacin resistance in \textit{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 \textit{E. coli} and \textit{K. pneumoniae} increased between 2000 and 2006 (227). In Canada, as well, the prevalence of \textit{aac(6\textprime )-Ib-cr} increased in the Calgary Health Region between 2004 and 2007 (184).

**CLINICAL IMPORTANCE**

In animal model infections the presence of a \textit{qnr} gene makes an infecting agent harder to treat with quinolones. This detrimental effect has been shown in mice with pneumonia produced by \textit{K. pneumoniae} or \textit{E. coli} (228, 229) and in \textit{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 \textit{Enterobacter} or \textit{Klebsiella} at a health center in Korea and found 26 positive for \textit{qnrA}, \textit{qnrB}, or \textit{qnrS} genes. The \textit{qnr}-positive patients were hospitalized longer, but there was no difference in in-hospital or 30-day mortality between the \textit{qnr}-positive or -negative patient groups (233). Liao et al. studied 227 blood culture isolates of \textit{Klebsiella} from a hospital in Taiwan and found 9 positive for \textit{qnrB} or \textit{qnrS}. The 14-day mortality was similar in patients infected with or without \textit{qnr}-containing isolates, but there was a trend for increased in-hospital mortality (234). Further studies are needed to distinguish a specific effect of \textit{qnr} from the effect of other resistance genes so often linked to it.

**CODA**

The varieties of PMQR that have emerged exemplify the three general mechanisms of bacterial resistance to any antimicrobial agents: target alteration (Qnr), drug modification [AAC(6\textprime )-Ib-cr], and efflux pump activation (QepA and OqxAB). AAC(6\textprime )-Ib-cr arose by mutations altering two amino acids 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 \textit{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\textprime )-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.
Plasmid-Mediated Quinolone Resistance

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Conflict of interest: We disclose no conflicts.

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