Is plasmid-mediated quinolone resistance a clinically significant problem?

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ABSTRACT

Although resistance to quinolones is commonly chromosomally-encoded in Enterobacteriaceae, the emergence of plasmid-mediated quinolone resistance (PMQR) has also been reported, with at least three known resistance mechanisms to date, i.e., Qnr, aminoglycoside acetyltransferase AAC(6\(^{-}\))Ib-cr and QepA. Qnr proteins protect target enzymes (DNA gyrase and type IV topoisomerase) from quinolone inhibition, the AAC(6\(^{-}\))Ib-cr enzyme acetylates norfloxacin and ciprofloxacin, and the QepA efflux pump extrudes hydrophilic fluoroquinolones. Although these PMQR determinants confer only low-level resistance to quinolones and/or fluoroquinolones, they may provide a favourable background in which the selection of additional chromosomally-encoded quinolone resistance mechanisms can occur.

Keywords AAC(6\(^{-}\))Ib-cr, plasmid-mediated, QepA, QnrA, quinolones, resistance

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Resistance to quinolones and fluoroquinolones has been studied extensively among human and veterinary isolates of bacteria during the last three decades, with an increasing trend towards resistance being related to heavy usage [1]. The mechanisms of resistance to this antibiotic class were considered originally to be only chromosomally-encoded, i.e., mostly involving impaired drug targets (DNA gyrase and topoisomerase IV), decreased outer-membrane permeability (porin defects) and over-expression of naturally occurring efflux systems [2]. Although thought to be impossible because of the plasmid curing effect of quinolones, plasmid-mediated quinolone resistance (PMQR) was first reported in 1998 in a \textit{Klebsiella pneumoniae} isolate from the USA [3].

The first PMQR determinant (Qnr, lately termed QnrA) is a protein with 218 amino-acids that belongs to the family of pentapeptide repeat proteins [3]. Two other Qnr-type determinants have subsequently been discovered in Enterobacteriaceae, namely QnrB and QnrS, that share 40\% and 59\% amino-acid identity, respectively, with QnrA [4,5]. Qnr determinants may act by binding directly to both DNA gyrase and topoisomerase IV, thereby resulting in an absence of inhibition by quinolones [6–8]. Qnr determinants confer resistance to nalidixic acid, but only slightly reduced susceptibility to fluoroquinolones (a 16–32-fold increase in MICs) [4,5]. From a clinical point of view, Qnr determinants may increase the mutant prevention concentration of ciprofloxacin by more than ten-fold (from 0.2 to 3.2 mg/L), thus facilitating the recovery of mutants with higher levels of resistance to quinolones [5]. Qnr-positive isolates may therefore provide a favourable background in which in-vivo selection of additional chromosome-borne mechanisms of resistance to quinolones can occur during or after treatment with fluoroquinolones [9]. However, the expression of QnrA does not modify the bactericidal activity of fluoroquinolones [10].

The three types of Qnr determinants have now been identified worldwide on all five continents in many different enterobacterial species, but mostly in both community and nosocomial isolates of \textit{Escherichia coli}, \textit{Enterobacter} spp., \textit{Salmonella} spp. and \textit{K. pneumoniae} [4,5]. Their overall prevalence may range from 0.2\% to 50\%, depending on the criteria used to select the strains investigated (e.g., resistance to
genes, to nalidixic acid or to fluoroquinolones) [5]. Interestingly, the QnrA and QnrB determinants have often been associated with plasmid-encoded expanded-spectrum β-lactamases (SHV, CTX-M, or VEB-1 types) or AmpC (FOX-5 and DHA-1 types), whereas QnrS has not [4,5,11]. It has been shown that the Qnr determinants probably originate in aquatic species of bacteria, with *Shewanella algae* and *Vibrio splendidus* being the progenitors of *qnrA* and *qnrS*-like genes [12,13]. The *qnrS* gene has also been demonstrated recently in isolates of *Aeromonas* spp. from the River Seine in Paris, which emphasises the role of the aquatic environment as a reservoir of PMQR [14].

Another type of PMQR determinant has been discovered in *qnrA*-positive *E. coli* [15]. The *aac(6′)-Ib-cr* (for ciprofloxacin resistance) gene encodes an aminoglycoside acetyltransferase responsible for resistance to kanamycin, tobramycin, and amikacin. This variant possesses two substitutions at codons 102 (Trp → Arg) and 179 (Asp → Tyr) as compared with the wild-type AAC(6′)-Ib enzyme [15]. Consequently, the variant enzyme acetylates ciprofloxacin and norfloxacin, conferring slightly higher MICs (a two- to four-fold increase) [15]. The expression of AAC(6′)-Ib-cr may facilitate the survival of DNA gyrase and topoisomerase IV mutants, with an increase in their mutant prevention concentration from 0.2 to 3.2 mg/L [5,15]. According to the few surveys performed in Enterobacteriaceae, this enzyme may be more widespread than Qnr determinants, and is frequently associated with the increasing problem of expanded-spectrum β-lactamases, e.g., CTX-M-15, among community-acquired enterobacterial isolates [16,17].

Very recently, a third type of PMQR determinant has been identified in two *E. coli* clinical isolates from Japan and Belgium [18,19]. The *qepA* gene (for quinolones efflux pump) encodes a protein that resembles a 14-transmembrane-segment putative efflux pump belonging to the major facilitator superfamily of proton-dependent transporters [18,19]. This protein confers resistance to the hydrophilic quinolones, e.g., norfloxacin, ciprofloxacin and enrofloxacin, with a 32–64-fold increase in MIC [18]. To date, the only provisional epidemiological data for QepA have indicated that it has a low prevalence (0.3%) (47th Interscience Conference on Antimicrobial Agents and Chemotherapy, Chicago, 2007; C2-158). A genetic linkage between the *qepA* gene and the *rmtB* (an aminoglycoside ribosylmethytransferase) gene has been demonstrated, and it seems likely that these two genes are part of a transposable element flanked by two copies of IS26 [19]. This suggests that there is potential for selection of the QepA determinant by the use of aminoglycosides, and of aminoglycoside resistance by the use of quinolones.

The discovery of three major mechanisms of PMQR within the last 10 years is peculiar. These discoveries may reflect the emergence of novel mechanisms of resistance, or simply a deeper investigation of resistance mechanisms in clinical isolates worldwide. Further studies may provide the answers to several outstanding questions, including the following: (i) what is the relationship between quinolones in the environment that are poorly biodegraded and the prevalence of these resistance mechanisms? (ii) are other PMQR mechanisms waiting to be discovered, e.g., is the quinolone hydroxylation resistance mechanism demonstrated in some fungi capable of being transferred to bacteria [20]? (iii) are these resistance mechanisms really new and emerging (retrospective prevalence studies will be needed to answer this question)? (iv) what is the extent of the spread of these resistance mechanisms in the environment? and (v) of most importance, to what extent will the presence of these resistance mechanisms lead to clinical failure of quinolone- and/or fluoroquinolone-containing treatment regimens?

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**REFERENCES**


