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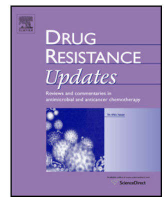

Invited review

# Plasmid-mediated quinolone resistance: Two decades on

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ABSTRACT

After two decades of the discovery of plasmid-mediated quinolone resistance (PMQR), three different mechanisms have been associated to this phenomenon: target protection (Qnr proteins, including several families with multiple alleles), active efflux pumps (mainly QepA and OqxAB pumps) and drug modification [AAC(6′)-Ib-cr acetyltransferase]. PMQR genes are usually associated with mobile or transposable elements on plasmids, and, in the case of *qnr* genes, are often incorporated into *sul1*-type integrons. PMQR has been found in clinical and environmental isolates around the world and appears to be spreading. Although the three PMQR mechanisms alone cause only low-level resistance to quinolones, they can complement other mechanisms of chromosomal resistance to reach clinical resistance level and facilitate the selection of higher-level resistance, raising a threat to the treatment of infections by microorganisms that host these mechanisms.

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## 1. Introduction: the discovery of plasmid-mediated quinolone resistance

Resistance to quinolones in gram-negative bacteria, including enterobacteria and non-fermenters in particular, has reached worldwide worrying dimensions. This forms a contrast to the situation when fluoroquinolones were introduced into clinical practice in the final two decades of the last century, since it was only after several years of (presumably inadequate) use that resistant isolates started to emerge.

Resistance was initially related to chromosomal mechanisms and was most frequently the result of alterations in the targets of quinolones (type II topoisomerases: DNA gyrase or topoisomerase IV), usually associated with non-specific low-level resistance mechanisms, such as decreased permeability (due to the loss or structural modification of porins or altered lipopolysaccharide) or basal or increased energy-dependent efflux (Hooper, 2000) (Table 1). Mutations in the regulatory genes (indirectly related to permeability and/or efflux) were also commonly involved. It has recently been observed that some fungi (basidiomycetes) are able to degrade fluoroquinolones, although this has not been proved among clinical isolates (Wetzstein et al., 1997, 1998, 1999; Čvančarová et al., 2015). Multiple chromosomal genes were also later shown to be involved in low-level quinolone resistance, and a recent study has indicated that the actual cause of resistance to quinolones in laboratory mutants has still not been completely defined (Vinué et al., 2015).

For many years, it was thought that it is (almost) impossible that plasmid-mediated mechanisms of (fluoro)quinolone resistance exist, which was explained by the facts that fluoroquinolones are synthetic drugs, that they were able to cure plasmids in many bacteria, and that in gram-negative bacteria it was observed a dominance of the quinolone sensitive (determined by a wild-type DNA-gyrase) over the quinolone-resistant (caused by a mutant DNA-gyrase) phenotype. In 1987, plasmid-mediated resistance to quinolones was described in *Shigella dysenteriae* (Munshi et al., 1987), although it was later demonstrated that this observation was not correct and that chromosomal mutations had actually been selected due to an indirect plasmid effect that affected the mutation rate in the corresponding host. An interesting observation was also made that organisms producing microcin B17 (a protein that interferes with DNA replication and supercoiling) also produce an inhibitor (McbG), which protects a microcin B17-producing strain from self-inhibition; it was reported that a plasmid containing *mcbG* was capable of determining a moderate increase in the level of quinolone resistance in host bacteria (Lomovskaya et al., 1996). Again, at the end of the 1990s, another group presented convincing evidence that a plasmid they constructed coding for an abnormal topoisomerase II also determined low-level resistance to quinolones, although such a mechanism is not currently known to occur in bacteria cultured from clinical samples or other natural sources (Gómez-Gómez et al., 1997).

Since the 1990s, some of us became interested in studying the mechanisms of resistance to cephamycins, extended-spectrum cephalosporins and carbapenems in enterobacteria (with special emphasis on *Klebsiella pneumoniae*). Our analysis of the contribution of OmpK35 and OmpK36 porins to resistance focused on the phenotypic effect of the loss of these two porins in bacteria to which plasmids coding for extended-spectrum beta-lactamases or plasmid-mediated AmpC enzymes (carbapenemases were rarely considered in clinical isolates at the time) were transferred. Following the accepted dogma that quinolone resistance was not related to plasmids, we generally tested ciprofloxacin in our phenotypic analysis of transconjugants as an indirect marker that it was not the donor strain that has grown on the selecting plates.

It is also noteworthy that earlier reports indicated that a common mechanism (mediated by chromosomal genes) was involved in tolerance to both quinolone and β-lactam antibiotics (Wolfson et al., 1990; Black et al., 1991). In the case that this or a similar mechanism would eventually be encoded by a mobilizable plasmid, we hypothesized that our analysis of ciprofloxacin susceptibility in the tested transconjugants would also allow it to be discovered. In fact, we observed that transconjugants from a porin-deficient *K. pneumoniae* containing a plasmid (pMG252, coding for FOX-5) from a clinical isolate of *K. pneumoniae* isolated in 1994 in Birmingham, Alabama, USA (G.A. Jacoby's collection) presented a moderate increase in the MIC (Minimum Inhibitory Concentration) of ciprofloxacin – and other quinolones – compared with the recipient strain (Martínez-Martínez et al., 1997, 1998). We were lucky to make this observation, although, as we pointed out, the discovery of plasmid-mediated quinolone resistance was not strictly serendipitous. Further studies on pMG252 allowed the gene responsible for quinolone resistance (initially called *qnrA* – after ***q***ui***n***olone ***r***esistance – later renamed *qnrA1*) to be identified (Tran and Jacoby, 2002). Multiple families of Qnr proteins (many involving multiple variants) were subsequently discovered (see Jacoby et al., 2008 for additional details). Qnr proteins were shown to be members of the pentapeptide repeat protein (PRP, see below) family, and to be related to MfpA, a protein cloned from *Mycobacterium smegmatis* that also causes (low-level) resistance to fluoroquinolones.

Two other mechanisms unrelated to Qnr, but also encoded by plasmid genes, have been discovered; one of these corresponds to an acetyltransferase [AAC(6′)-Ib-cr] (Robicsek et al., 2006) which is a variant of an enzyme involved in aminoglycoside modification (and resistance), the other includes active efflux pumps such as QepA and OqxAB (Hansen et al., 2004; Périchon et al., 2007; Yamane et al., 2007).

Table S1 presents a summary of available information about prevalence and epidemiology data during the years 2010–2015 for both chromosomal- and plasmid-mediated mechanisms of quinolone resistance.

Hundreds of publications have studied the phenomenon of plasmid-mediated quinolone resistance (PMQR) in greater depth. As for April 30, 2016, more than 700 (734) publications can be found in the public database PubMed under this keyword. Several reviews have been reported in recent years on plasmid-mediated quinolone resistance (Cattoir and Nordmann, 2009; Jacoby et al., 2014; Nordmann and Poirel, 2005; Poirel et al., 2012; Rodríguez-Martínez et al., 2011a,b; Strahilevitz et al., 2009). The purpose of this article is providing an update on several aspects that have emerged since.

## 2. Qnr proteins

### 2.1. Nomenclature of qnr determinants

An increasing number of *qnr* determinants (whether plasmid-located or not) have been described in the literature. In order to prevent confusion and establish a common nomenclature, a database was set up in 2008 at http://www.lahey.org/qnrStudies, using an online submission system to update new allele numbers (Jacoby et al., 2008) (Table 2). Only full-length sequences and naturally occurring alleles are assigned numbers, with priority given to numbers already published, then to those in accepted or submitted manuscripts, and finally to those with a date of submission to GenBank. Only amino acid changes are considered and new Qnr proteins should preferably be shown to be capable of interfering with *in vitro* quinolone antibacterial activity. It has been agreed that numbers for the *qnrB* family are to be defined by taking into account the second ATG initiation codon – common to all variants

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