varies depending on the efflux pump. In this regard, some efflux pumps present an expression level enough for contributing to intrinsic resistance to quinolones (Li et al. 1994; Vila and Martinez 2008), whereas for others, presenting lower level of expression, such contribution is minimal if any. In any case one important consequence of these studies is that inhibitors of efflux pumps may improve the activity of quinolones (Renau et al. 1999).

Expression of efflux pumps can be triggered in the presence of an effector or under some specific growing conditions (García-León et al. 2014b; Hernandez et al. 2011; Rosenberg et al. 2003). In addition, mutants presenting high derepressed levels of expression of efflux pumps can be selected in the presence of antibiotics, both *in vitro* and *in vivo*. These mutants can present reduced susceptibility to quinolones and to other antibiotics (acquired resistance) (Alonso and Martinez 2001; Cohen et al. 1989; Jalal et al. 2000; Ziha-Zarifi et al. 1999), although in several occasions (with some exceptions such as *Stenotrophomonas maltophilia*; see below) the observed MICs are below the breakpoint levels used for defining clinical resistance (Martinez et al. 2015) and high-level resistance is achieved just in combination with other mutations (Marcusson et al. 2009).

In occasions, high-level quinolone resistance can be achieved upon the simultaneous expression of some different MDR efflux pumps (Yang et al. 2003). However, in most studied cases, the highest level of resistance to quinolones is achieved when mutations in the target genes and increased efflux occur simultaneously (Llanes et al. 2006).

As above stated, MDR efflux pumps present a wide range of substrates, which include antibiotics belonging to different structural families (Paulsen 2003). This means that the overexpression of one single efflux pump increases the MICs for a variety of antibiotics. Consequently, efflux pumps overexpressing mutants can be selected by the selective pressure of any of the substrates of the pump. In other words, selective pressure by one antibiotic can also select for quinolone resistance (cross-selection) if both antimicrobials are substrates of the efflux pump (Cohen et al. 1989).

2.5 Transferable Quinolone Resistance

The above described mechanisms are based on the selection of mutants. For them, resistance can spread just by clonal expansion. Nevertheless, the possibility of transferrable mechanisms of resistance to quinolones was firstly proposed in the basis of *in vitro* analysis (Gomez-Gomez and Blazquez 1997; Martinez et al. 1998), and plasmids carrying quinolone resistance genes (dubbed *qnr*) were described soon afterwards (Martinez-Martinez et al. 1998). Qnr is a member of the pentapeptide repeat protein (PRP) family (Vetting et al. 2006). It binds the bacterial topoisomerases (DNA gyrase and topoisomerase IV) protecting them from the activity of quinolones. Five *qnr* families, namely,