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Review

Plasmid-mediated quinolone resistance: Mechanisms, detection, and epidemiology in the Arab countries

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ABSTRACT

Quinolones are an important antimicrobial class used widely in the treatment of enterobacterial infections. Although there are multiple mechanisms of quinolone resistance, attention should be paid to plasmid-mediated genes due to their ability to facilitate the spread of quinolone resistance, the selection of mutants with a higher-level of quinolone resistance, and the promotion of treatment failure. Since their discovery in 1998, plasmid-mediated quinolone resistance (PMQR) mechanisms have been reported more frequently worldwide especially with the extensive use of quinolones in humans and animals. Nevertheless, data from the Arab countries are rare and often scattered. Understanding the prevalence and distribution of PMQR is essential to stop the irrational use of quinolone in these countries. This manuscript describes the quinolone resistance mechanisms and particularly PMQR among *Enterobacteriaceae* as well as their methods of detection. Then the available data on the epidemiology of PMQR in clinical and environmental isolates from the Arab countries are extensively reviewed along with the other associated resistance genes. These data shows a wide dissemination of PMQR genes among *Enterobacteriaceae* isolates from humans, animals, and environments in these countries with increasing rates over the years and a common association with other antibiotic resistance genes as $bla_{CTX\text{-}M\text{-}15}$. The incontrovertible emergence of PMQR in the Arab countries highlights the pressing need for effective stewardship efforts to prevent the selection of a higher rate of quinolone resistance and to preserve these crucial antibiotics.

1. Introduction

Quinolones, a class of synthetic antimicrobial agents, are one of the most commonly prescribed antibiotics in the world. The development of quinolones began with the accidental discovery of nalidixic acid as a byproduct of the synthesis of chloroquine (an antimalarial compound) (Aldred et al., 2014). They were introduced into clinical use earlier in the 1960s to treat uncomplicated urinary tract infections (UTIs) due to Gram-negative bacteria. Subsequently, newer generations of quinolones were developed with several structural modifications, improved activity against both Gram-positive and Gram-negative bacteria, and enhanced pharmacokinetics and pharmacodynamics properties (Aldred et al., 2014; Correia et al., 2017; Fàbrega et al., 2009; Gutierrez et al., 2018; Redgrave et al., 2014). Quinolones inhibit DNA synthesis by converting their targets, gyrase and topoisomerase IV, into toxic enzymes that fragment the bacterial chromosome (Aldred et al., 2014). Quinolone resistance has emerged due to the increased usage of these drugs in both human and veterinary medicines and become a prevalent clinical issue that is threatening their use (Correia et al., 2017). For many years, quinolones resistance was thought to arise only by chromosomal mutations but during the last decade a series of Plasmid-Mediated Quinolone Resistance mechanisms (PMQR) was discovered and was more frequently reported worldwide among *Enterobacteriaceae* as well as in Arab countries (Cattoir and Nordmann, 2009; Yanat et al., 2017b). These countries mostly suffer from poor or absence of surveillance on antimicrobial use (Alhomoud et al., 2017; Almohammed and Bird, 2018; Khalifeh et al., 2017). From 2000 to 2015, rates of quinolone use have increased by 10% - 40% in Arab countries reaching up to > 1000 Defined Daily Dose[2] (DDD) per 1000 population in certain countries such as Lebanon, Egypt, and United Arab Emirates (The Center for Disease Dynamics, Economics, and Policy, 2017). Understanding the prevalence and distribution of PMQR is essential to stop the irrational use of quinolone in these countries. This review provides an overview of the mode of action of quinolones, their resistance mechanisms, PMQR detection methods, and describes the epidemiology of PMQR in the Arab countries.

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2. Quinolones: mode of action

Quinolones are potent inhibitors of two essential bacterial type II topoisomerases: DNA gyrase and topoisomerase IV, both of which play an important role in DNA synthesis, transcription, and cell division (Aldred et al., 2014; Correia et al., 2017; Fàbrega et al., 2009; Gutierrez et al., 2018; Redgrave et al., 2014). These enzymes modulate DNA topology by promoting the following processes: (i) the cleavage of both strands of one DNA duplex and formation of the "cleavage complex", which consists of a transient covalent phosphotyrosine link between the 5′ end of cleaved DNA and a conserved tyrosine residue on the protein (enzyme); (ii) the passage of second double-stranded deoxyribonucleic acid (dsDNA) molecule through the break; (iii) and the religation of the original strands and restoration of the phosphodiester bond (Gutierrez et al., 2018).

Indeed, quinolones benefit from the strand cleavage generated by type II topoisomerases when carrying out their sensitive physiological functions. They bind to the DNA-enzyme cleavage complex, stabilizing it, preventing the ligation step, inhibiting the overall catalytic activity of these enzymes, leading to chromosomal breaks, and thus promoting lethal bacterial damage. Therefore, quinolones transform these enzymes into cellular toxins and act as "topoisomerase poisons" (Aldred et al., 2014). As a response to these DNA breaks associated with the inhibition of DNA synthesis, two secondary processes of quinolone-mediated cell death were described and differed among quinolone-class derivatives. In the first process, quinolone lethality needs protein synthesis and the accumulation of toxic reactive oxygen species (ROS); the bacteria trigger the SOS pathway and the expression of many DNA repair pathways, which promote the accumulation of highly toxic ROS that are harmful and lead to bacterial death (Aldred et al., 2014; Rodríguez-Martínez et al., 2011; Wang et al., 2010). Recently, it was evidenced that paradoxical bacterial survival at high quinolone concentrations was mainly due to a drop in ROS levels, emphasizing thus the key role of ROS in cell death (Luan et al., 2018). In the second process of quinolone lethality, quinolones destabilize the cleavage complex by dissociating gyrase subunits leading to a direct fragmentation of chromosome and cell death that is insensitive to protein synthesis and putative ROS effects (Drlica et al., 2008; Luan et al., 2018; Wang et al., 2010).

3. Quinolone resistance

Quinolones have been widely used to treat Gram-negative and Gram-positive bacteria in human and veterinary medicines despite the recommendations to limited use of these drugs (World Health Organization (WHO), 2017). Consequently, the misuse and abuse of quinolones have led to the emergence of quinolone-resistant bacteria (Hooper and Jacoby, 2015). Quinolone resistance can be classified into 2 categories: Chromosomal-mediated resistance and plasmid-mediated resistance.

3.1. Chromosomal-mediated resistance

3.1.1. Mutations altering the target enzymes and their drug-binding affinity

One of the bacteria's strategies to disrupt quinolones action is to alter their target's susceptibility. Quinolone resistance mutations occur most often in the quinolone-resistance determining regions (QRDRs), within the subunits constituting DNA gyrase (GyrA and GyrB) and topoisomerase IV (ParC and ParE). Therefore, a single amino acid mutation in these regions can modify the target protein structure. This has the effect of reducing the quinolone binding affinity and the lethal DNA breaks, thus leading to quinolone resistance (Correia et al., 2017; Yoshida et al., 1990). Generally, the mutations in GyrA and ParC are more frequent than those in GyrB and ParE. A single amino acid mutation in one target confers a low-level of resistance while a high-level of resistance demands a combination of mutations in one target or both GyrA and ParC in Gram-negative organisms (Aldred et al., 2014; Barnard and Maxwell, 2001; Correia et al., 2017; Nakamura et al., 1989; Ouabdesselam et al., 1995; Sáenz et al., 2003; Vila et al., 1994).

3.1.2. Mutations altering the permeability

Quinolones can diffuse through the outer membrane of Gram-negative organisms using porin pathway. Hence, the second mechanism of quinolone resistance is to reduce or block antibiotics influx into the cell, which occurs due to porin loss, porin downregulation, modulation of the size or conductance of the porin channel. Moreover, multiple studies have shown that alteration of OmpF, OmpC, OmpD, OmpA, and OmpX porins expression, increased the MIC of quinolones and other drugs, thus correlating with quinolones resistance (Chapman and Georgopapadakou, 1988; Chenia et al., 2006; Dupont et al., 2007; Hirai et al., 1986a; Kishii and Takei, 2009; Rushdy et al., 2013).

Efflux pumps are membrane proteins that allow microorganisms to get rid of toxic substances such as antimicrobial agents, by an active transport mechanism. Therefore, efflux pumps play a key role in drug resistance. In *Enterobacteriaceae*, the overexpression of AcrAB-TolC efflux pump is implied in quinolone resistance (Piddock, 2006; Viveiros et al., 2007). Different regulatory genes such as *acrR*, *marA*, *rob*, and *soxS* control the overexpression of this pump. Thus, mutations in these genes can reduce the uptake and increase the extrusion of quinolones (Alekshun and Levy, 1997; Fàbrega et al., 2009; Poole, 2000). Interestingly, the modification in quinolone influx and efflux without any other resistance mechanism, can lead to a low-level of resistance but also creates an advantageous environment for other forms of resistance to develop and disseminate (Aldred et al., 2014; Correia et al., 2017; Hirai et al., 1986b).

3.2. Plasmid-mediated quinolone resistance (PMQR)

Since quinolones are fully synthetic agents, it was believed that PMQR was unlikely to exist and the resistance mechanism only arises by chromosomal mutations, until a plasmid harboring a quinolone resistance gene was accidentally discovered in 1998 by Martinez-Martinez and colleagues (Martínez-Martínez et al., 1998). Till now, three PMQR mechanisms have been identified: (i) target protection mediated by Qnr; (ii) quinolones modification through AAC (6′)-Ib-cr, an aminoglycoside acetyltransferase variant and CrpP a ciprofloxacin resistance protein enzyme; (iii) and plasmid-mediated quinolone efflux pumps (QepA and OqxAB). However, PMQR genes alone reduce quinolones susceptibility but not to the clinical level of resistance. Indeed, PMQR genes decrease the effective quinolones concentration and provide a favorable background for common mutations that affect efflux pumps and porins or alter LPS core biosynthesis to happen and even to predominate compared to *gyrA* mutations. This facilitates the selection of mutants with a higher-level of quinolone resistance and promotes treatment failure (Correia et al., 2017; Hooper and Jacoby, 2015; Strahilevitz et al., 2009; Vinué et al., 2015, 2018).

3.2.1. Target protection

The archetypal PMQR gene "*qnrA*" was first identified as a transferable gene in a multi-resistant clinical strain of *Klebsiella pneumoniae* while studying the ability of a plasmid "pMG252" to increase resistance to quinolones in a porin deficient *K. pneumoniae*, wild-type *K. pneumoniae*, and *Escherichia coli*. Unexpectedly, the plasmid pMG252 neither altered host porin expression nor reduced quinolone accumulation. Rather it facilitated the selection of higher-level of quinolone resistance, which suggests the possibility of a novel resistance mechanism (Hooper and Jacoby, 2015; Martínez-Martínez et al., 1998). Further investigations confirmed that *qnr* genes are broadly distributed especially in *Enterobacteriaceae* (Jacoby et al., 2008; Yanat et al., 2017b). These genes code for proteins belonging to the pentapeptide repeat family which are characterized by a series of 5-amino acid tandem repeats with the recurrent motif [Ser, Thr, Ala or Val] [Asp or Asn] [Leu

or Phe] [Ser, Thr or Arg] [Gly] (Vetting et al., 2006). They confer resistance to quinolones by binding to DNA gyrase and topoisomerase IV, and consequently inhibit quinolones from entering enzyme-DNA cleavage complexes (Robicsek et al., 2006a).

Up to now, 120 *qnr* variants have been identified and grouped into seven families: *qnrA* (Martínez-Martínez et al., 1998), *qnrB* (Jacoby et al., 2006), *qnrC* (Wang et al., 2009), *qnrD* (Cavaco et al., 2009), *qnrS* (Hata et al., 2005), and *qnrE* (Albornoz et al., 2017). Those variants are found in *Enterobacteriaceae*, while the seventh variant *qnrVC* (Fonseca et al., 2008), is mainly detected in *Vibrio cholerae* and other *Vibrio* spp. (Rodríguez-Martínez et al., 2011). The *qnr* families are defined by at least 30% nucleic or derived amino acid differences from each other, whereas *qnr* variants (allelic variation) are more closely related and are defined by a maximum difference of 10% between members of the same family (Jacoby et al., 2008; Strahilevitz et al., 2009).

3.2.2. Quinolone modifying enzymes

3.2.2.1. AAC (6′)-Ib-cr: Aminoglycoside 6′-N-acetyl transferase type Ib-cr. While Robicsek et al., were studying the ciprofloxacin MIC of a variety of clinical *E. coli* isolates harboring the *qnr* plasmid, they discovered that certain plasmids confer a 4-fold higher ciprofloxacin MIC than the other strains. After several experiments, they found that the level of *qnrA* expression and the number of gene copies were the same between these isolates, and there were no chromosomal mutations in the host strains, which indicates the presence of another plasmid mechanism that accounts for this increased level of resistance. A variant of an aminoglycoside acetyltransferase *aac(6′)-Ib*, causing resistance to tobramycin, kanamycin, and amikacin, was found to be responsible for this resistance and was termed *aac(6′)-Ib-cr* (cr for ciprofloxacin resistance) (Robicsek et al., 2006b).

AAC(6′)-Ib-cr is a unique variant of AAC(6′)-Ib which has two specific amino acid substitutions, Trp102Arg and Asp179Tyr. This variant is not only able to acetylate aminoglycosides but also to *N*-acetylate the amino nitrogen of the C7 piperazine ring of quinolones. This *N*-acetylation decreases the activity of quinolones that have a free piperazinyl group such as ciprofloxacin and norfloxacin. However, those having a substituted piperazinyl group like levofloxacin will not be affected. It is worthy of notice that acetylation of aminoglycosides (Kanamycin) produced by AAC(6′)-Ib-cr is less efficient than that observed by the wild-type AAC(6′)-Ib (Robicsek et al., 2006b; Strahilevitz et al., 2009). The existence of AAC(6′)-Ib-cr alone causes a low-level of ciprofloxacin resistance, lower than that conferred by Qnr proteins. Nonetheless, it is capable to raise the rate of selection of chromosomal mutants after ciprofloxacin exposure (Robicsek et al., 2006b). In addition, the coexistence of Qnr and AAC(6′)-Ib-cr in the same strain produces a higher-level of quinolone resistance than that observed with Qnr or AAC(6′)-Ib-cr alone (Fàbrega et al., 2009).

3.2.2.2. CrpP: ciprofloxacin resistance protein. Recently, a new PMQR gene was identified in a clinical *Pseudomonas aeruginosa* (*P. aeruginosa*) isolate carrying the conjugative plasmid pUM505, which confers resistance to ciprofloxacin in *P. aeruginosa* PAO1 and increases 7.5-fold the ciprofloxacin MIC in a susceptible *E. coli* strain (J53-3). Since in silico analysis of pUM505 did not show any previously known gene involved in quinolone resistance, a novel PMQR gene conferring resistance to ciprofloxacin was identified and named *crpP*. CrpP enzyme, a 65-amino acid protein, shares 40% amino acid identity with aminoglycoside phosphotransferase (APH) of *Mycobacterium smegmatis* (an enzyme that inactivates aminoglycosides through phosphorylation) and contains two conserved catalytic residues of APH enzymes. Although little activity against norfloxacin was detected, CrpP phosphorylates the ciprofloxacin through an ATP-dependant mechanism leading to possible degradation of the antibiotic and specific resistance to ciprofloxacin in *E. coli* (Chávez-Jacobo et al., 2018). Lately, *crpP*-types genes were discovered in enterobacterial isolates of nosocomial origin in Mexican hospitals, where some dated from 1994, hinting to the prior existence of such mechanisms and highlighting their potential spread in other groups of Gram-negative bacteria (Chávez-Jacobo et al., 2019).

3.2.3. Efflux pumps

3.2.3.1. OqxAB. The OqxAB is a multidrug efflux pump, belonging to the Resistance-Nodulation-Division (RND) family. It was found in a conjugative plasmid pOLA52 with two open reading frames (ORFs), *oqxA* and *oqxB* encoding, for OqxA and OqxB proteins respectively (Hansen et al., 2004; Sørensen et al., 2003). In addition to olaquindox, it confers resistance to nalidixic acid, norfloxacin, ciprofloxacin, chloramphenicol, and trimethoprim and has the ability to increase the MIC of 8-, 32- and 64-fold of nalidixic acid, ciprofloxacin, and norfloxacin, respectively (Table 1) (Hansen et al., 2007). Interestingly, after being only seen in animal infection, *oqxAB* was later reported on the plasmid of a human clinical isolate of *E. coli* and on the chromosome of *K. pneumoniae* sharing a 99% similarity with the plasmidic gene (Kim et al., 2009b). Moreover, the plasmid-mediated *oqxAB* genes were found to be flanked by IS*26*-like sequences suggesting the possibility of their mobilization from *K. pneumoniae* into composite transposons (Tn*6010*) (Kim et al., 2009b; Norman et al., 2008). Furthermore, *K. pneumoniae* was identified as a potential reservoir of *oqxAB* (Yuan et al., 2012).

3.2.3.2. QepA. In 2007, Yamane et al., identified a plasmid, pHPA, carrying a gene encoding a novel PMQR mechanism “QepA” in a clinical *E. coli* isolate demonstrating resistance to various fluoroquinolones in Japan (Yamane et al., 2007). QepA is a plasmid-mediated efflux pump conferring resistance to hydrophilic quinolones such as norfloxacin and ciprofloxacin with 32- to 64-fold increase of MICs (Table 1). On the other hand, it has little or no effect on hydrophobic quinolones such as nalidixic acid, levofloxacin, and moxifloxacin (Ruiz et al., 2012; Yamane et al., 2007). QepA shows a high similarity to members of the Major Facilitator Superfamily[3] (MFS) present in Gram-positive *Actinomycetales*, suggesting it is the source of this gene (Ruiz et al., 2012; Yamane et al., 2007).

4. Detection methods of PMQR

Due to the ability of PMQR genes to increase the risk of selection of higher-level of quinolone-resistant mutants, their molecular detection is important particularly in the absence of phenotypic tests that distinguish between chromosomal- and plasmid-mediated quinolone resistance.

Although the determination of quinolone MIC values as established by EUCAST/CLSI can detect low-level of quinolone resistance and differentiate between wild and non-wild-type isolates, it is not used as standard procedure in all the routine laboratories. Nalidixic acid disc has been used for long time as a screening tool of low-level quinolone resistance (first step mutants in QRDR). However, since it failed to detect isolates carrying PMQR, which are often susceptible to nalidixic acid, it can no longer be used as an indicator of quinolones susceptibility (Humphries et al., 2012). In order to rapidly detect a low-level of quinolone resistance, Skov et al., have developed a 5 µg pefloxacin disk method for the detection of fluoroquinolone-resistant *Salmonella enterica*. The pefloxacin test can distinguish between wild-types and resistant isolates even if they are harboring PMQR genes, but not isolates with AAC(6′)-Ib-cr. It has been approved and implemented by both CLSI and EUCAST as a surrogate agent for the detection of fluoroquinolone resistance in *S. enterica* (Deak et al., 2015; Skov et al., 2015).

So far, phenotypic tests cannot identify and unravel all the mechanisms involved in PMQR; therefore, molecular detection is necessary. Since quinolones lead to DNA breakage, a rapid and accurate method based on the detection of DNA fragmentation has been developed to evaluate the susceptibility of *E. coli* strains, including low-level

[3] MFS: Major Facilitator Superfamily.

Table 1
Summary of the different quinolone resistance mechanisms and their associated impact on the MIC of ciprofloxacin in *E. coli*.

	Resistance mechanism	Proteins	Genes	Resistance phenotype	Susceptible *E. coli* ciprofloxacin MIC (Strain name)	Resistant *E. coli* Ciprofloxacin MIC (Strain name)	Fold change in Ciprofloxacin MIC	References
Chromosomal-mediated quinolone resistance	Target alteration with reduced drug binding	DNA gyrase	*gyrA*	Quinolones	0.008 (J53)	0.25 (J53 *gyrA* mutant (S83L))	32	Hooper and Jacoby (2015); Strahilevitz et al. (2009); Yoshida et al. (1990)
			gyrB		0.0125 (KL16)	0.1 (KL16 *gyrB* mutant (D426N))	8	Yoshida et al. (1991)
		Topoisomerase IV	*parC*		0.015 (WT)	0.03 (WT-4 *ParC* mutant (S80I))	0–2	Bagel et al. (1999)
			parE		–	–	–	Hopkins et al. (2005)
	Alteration of porin expression	Porin proteins e.g.: OmpF, OmpC, OmpD, OmpA, and OmpX	Major porin genes	Multiple antibiotics including quinolones	0.013 (CS109)	0.05[a] (KE7 (ompF$^-$))	2–4	Fàbrega et al. (2009); Hirai et al. (1986a); Redgrave et al. (2014)
	Alteration of efflux system	Efflux pumps e.g.: AcrAB-TolC	Regulatory genes	Multiple antibiotics including quinolones	0.016 (Nu14)	0.064[b] (Nu93 *marR* (R77L))	4–8	Komp Lindgren et al. (2005); Redgrave et al. (2014)
Plasmid-mediated quinolone resistance	Target Protection	Qnr	*Qnr*	Quinolones	0.008 (J53)	0.25 (J53 pMG252 *_qnrA1*)	> 30	Hooper and Jacoby (2015); Strahilevitz et al. (2009)
	Enzyme inactivation	AAC(6′)-Ib-cr	*aac(6′)-Ib-cr*	Quinolones (ciprofloxacin and norfloxacin) and aminoglycosides	0.008 (J53)	0.06 (J53 pMG320_*aac (6′)-Ib-cr*)	4	Hooper and Jacoby (2015)
		CrpP	*crpP*	Ciprofloxacin	0.008 (J53-3 pUCP20)	0.06 (J53-3 pUC_*crpP*))	7.5	Chávez-Jacobo et al. (2018)
	Efflux pumps	QepA	*qepA*	Multiple antibiotics including quinolones	0.008 (J53)	0.064 (J53 pAT851_*qepA*)	32	Hooper and Jacoby (2015)
		OqxAB	*oqxAB*		0.0078 (N43 pLOW2)	0.125 (N43 pLOW2_*oqxAB*)	16	Hansen et al. (2007)

–: There is no study showing the impact of occurrence of a single mutation in the *parE* gene on the MIC of quinolones (*parE* mutation is always accompanied with *gyrA* or *parC* mutations).
EUCAST and CLSI susceptibility breakpoints for ciprofloxacin in *E. coli* were: S ≤ 0.25 mg/l, *R* > 0.5 mg/l.

[a] Example of the MIC of deficient OmpF *E. coli*.

[b] Example of effect of *marR* mutation on the MIC.

Table 2
Epidemiology of plasmid-mediated quinolone resistance (PMQR) among clinical isolates in the Arab countries.

Country	Year of study	Setting	Species (Nb)	PMQR genes (%)									Mutations in QRDR		Associated genes	Ref
				qnr genes					*aac (6′)-Ib-cr*	*oqxA*	*oqxB*	*qepA*	*gyrA*	*ParC*		
				A	*B*	*C*	*S*	*D*								
Lebanon	1997–2002 and 2004–2005	Beirut	EC (50) and KP (50)	0	0	NT	0	NT	68.8	NT	NT	NT	NT		$bla_{CTX-M-15}$, $bla_{SHV-1,\ -5,\ -28}$, bla_{OXA-1}, bla_{TEM-1}, *aac(3)-II*	Kanj et al. (2008)
	2017	Beirut	EC (9)	0	0	0	0	0	55.5	0	0	0	NT		$bla_{CTX-M-15}$, bla_{TEM-1}, bla_{OXA-1}, *aac(3)-IIa*, *catB3*, *tet(A)*,	Tokajian et al. (2017)
Syria	2010–2011	Aleppo	EC (99) and KP (24)	0	24.4	NT	16.3	NT	75.6	NT	NT	0	NT		NT	Alheib et al. (2015)
Palestine	2013	Gaza	CTX- and CAZ-resistant KP (16)	NT	12.5	NT	31.2	NT	43.7	NT	NT	0	NT		$bla_{CTX-M-14,\ -15}$, bla_{TEM-1}, bla_{SHV-1}, *aac(3)-II*, *sul1*, *sul2*, *aadA1,-5*, *dfrA12,-17*, *tetA*, *tetB*	Tayh et al. (2017)
Saudi Arabia	2009	Riyadh	ESBL Ent (160)	2.5	10.6	NT	0	NT	47.5	NT	NT	NT	S83Y S83L S83F D87N D87A D87G	S80I E84K	$bla_{CTX-M-15}$	Shibl et al. (2012)
	2014	Riyadh	EC (10) and KP (21) with IMP MIC ≥0.5 μg/ml	0	3.2	NT	58	NT	51.6	0	0	0	NT		bla_{NDM}, $bla_{CTX-M-1,\ -9}$, bla_{TEM}, $bla_{OXA-48,\ -1}$, bla_{SHV-1}	Al-Agamy et al. (2018)
	2015	Alkhobar and Dammam	FOX-resistant EC, KP, and PM (200)	0	26	0	0	0	64	NT	NT	0	NT		*pAmpC*, *aacA4*, *aacC2*, *aadA1*, *aphA6*, *armA*, *rmtB*	Abdalhamid et al. (2017)
Iraq	2010–2011	Baghdad	Quinolone-resistant *Shigella* (34)	29.4	2.9	NT	20.6	NT	NT	NT	NT	NT	NT		NT	Abdulrahman et al. (2015)
	2011–2012	Al-najaf	Quinolone-resistant KP (34)	NT	2.9	NT	50	NT	94	NT	NT	11.7	NT		NT	Alshammari and Al-Skhattat (2015)
	2012–2013	Al-najaf	Quinolone-resistant KP (74)	2.7	23	0	1.4	0	NT	NT	NT	NT	NT		NT	Hadi et al. (2016)
Kuwait	2002–2004	Kuwait City	ESBL Ent (64)	0	4.7	NT	0	NT	NT	NT	NT	NT	NO		bla_{VEB-1b}, bla_{SHV-12}	Cattoir et al. (2007)
	2010–2012	National study	EC (83)	0	3.6	NT	4.81	NT	67.5	NT	NT	NT	NO		$bla_{CTX-M-56,\ -15}$, bla_{CMY-2}, bla_{TEM-1}, bla_{OXA-1}	Dashti et al. (2014)
	2010–2012	National study	ESBL and qnr-positives KP (27)	3.7	78	NT	18.5	NT	96	NT	NT	NT	NO		$bla_{CTX-M-15}$, bla_{TEM-1}, bla_{SHV}	Vali et al. (2015)
Yemen	2013	Sana'a	Ent with a reduced susceptibility to carbapenems (10)	20	50	0	20	0	60	NT	NT	0	NT		bla_{NDM-1}, bla_{TEM-1}, $bla_{CTX-M-15}$, $bla_{SHV-11,-76,-184}$	Gharout-Sait et al. (2014)
	2013	Sana'a	CIP-resistant EC (41)	0	0	0	12.2	0	100	0	0	0	S83L D87N	S80I E84V	$bla_{CTX-M-15}$	Alsharapy et al. (2018)
Egypt	2012–2013	Cairo	CIP- or LVX- resistant KP (57)	0	74	1.7	49	40	61	88	30	12	NT		*ant(3″)-I*, *aac(6′)-Ib*, *aac(3)-II*, *aph(3h(3I*, *armA*	El-Badawy et al. (2017)
	2014–2015	Cairo	Gram-negatives (239)	0.4	7.1	NT	24.3	NT	36.8	92.5[a]	92.5[a]	0	NT		NT	Hamed et al. (2018)
	2015–2016	Cairo	MDR Gram-negatives (70)	2.8	12.8	NT	27.1	NT	NT	NT	NT	NT	NT		bla_{TEM}, bla_{SHV}, bla_{CTX-M} *aac(6′)-Ib*	Tohamy et al. (2018)
	2018	Cairo	Ent (57)	15.7	56.1	NT	50.8	NT	29.8	NT	NT	NT	NT		$bla_{CTX-M-15}$, bla_{TEM}, bla_{SHV}	Galal et al., 2018
Libya	2016–2017	Refugee (Germany)	Gram-negatives bacteria (39)	0	10.2	NT	0	NT	61.5	NT	NT	NT	NT		bla_{SHV}, bla_{NDM}, bla_{TEM}, $bla_{CTX-M-1}$, $bla_{OXA-1,\ -9,\ -48}$	Lohr et al. (2018)

(*continued on next page*)

Table 2 (*continued*)

Country	Year of study	Setting	Species (Nb)	PMQR genes (%)									Mutations in QRDR		Associated genes	Ref
				qnr genes					*aac (6′)-Ib-cr*	*oqxA*	*oqxB*	*qepA*	*gyrA*	*ParC*		
				A	*B*	*C*	*S*	*D*								
Morocco	2006–2007	Casablanca	ESBL Ent (39)	10.2	23	NT	2.5	NT	NT	NT	NT	NT	NT		$bla_{CTX\text{-}M\text{-}15,\ -28}$, $bla_{SHV\text{-}1,\text{-}12}$, $bla_{TEM\text{-}1}$, bla_{DHA1}	Bouchakour et al. (2010)
	2008–2009	El Jadida, and Settat-Berrechid)	Ent (237)	0	0.9	NT	1.7	NT	8.5	0	NT	NT	NT		$bla_{CTX\text{-}M\text{-}15}$, $bla_{SHV\text{-}12}$, $bla_{TEM\text{-}1}$	Jamali et al. (2014)
	2010–2011	National study	ESBL EC (49)	0	8.1	NT	2	NT	61.2	NT	NT	NT	NT		$bla_{CTX\text{-}M\text{-}15}$, $bla_{TEM\text{-}1}$, $bla_{OXA\text{-}1}$	Barguigua et al. (2013)
	2011	Casablanca	Case KP (11)	0	18.1	0	27.2	NT	72	NT	NT	NT	NT		$bla_{CTX\text{-}M\text{-}15,\ -28}$, $bla_{SHV\text{-}1}$, $bla_{OXA\text{-}1}$, $_{-48}$ $bla_{TEM\text{-}1}$, *aac(3)-II*,, $bla_{NDM\text{-}1}$	Barguigua et al. (2015)
	2012–2015	North-west of Morocco	EC (398) and K spp. (118)	0	6.5	0	2.5	NT	12.6	NT	NT	0	NT		NT	Benaicha et al. (2017)
Tunis	2007	Tunisia	ESBL EC (18)	0	0	NT	0	NT	83.3	NT	NT	NT	NT		$bla_{CTX\text{-}M\text{-}15}$, $bla_{OXA\text{-}1}$, $bla_{TEM\text{-}1b}$, *aac(3)-II*, *sul2*, *−3*, *tetB*, *tetA*, *aadA*, *dfrA17*	Jouini et al. (2010)
	2003, 2007–2009	Tunisia	Qnr-positives Ent (40)	0	95	0	7.5	0	77.5	NT	NT	0	NT		NT	Jlili et al. (2014)
	2005–2007	Sousse	NAL-resistant Ent (281)	4.2	9.2	NT	2.5	NT	0	NT	NT	0	NT		$bla_{CTX\text{-}M\text{-}15}$, $bla_{SHV\text{-}2,\text{-}12,\text{-}28}$, $bla_{TEM\text{-}1}$	Dahmen et al. (2010)
	2006–2009	Tunisia	EC (300)	0.3	1	0	0.3	0	22	0	NT	0	S83LD87N	S80IE84V E84G	$bla_{CTX\text{-}M\text{-}15}$, $bla_{TEM\text{-}1}$, $bla_{CMY\text{-}4,\ -38}$	Sana et al. (2014)
	2010	Tunisia	ESBL Ent (120)	0	24	0	1.6	0	19.2	21.6		0	S83L S83Y S83FD87A D87N	S80I E84VE84G	$bla_{CTX\text{-}M\text{-}15}$, $bla_{SHV\text{-}12,\ -17}$	Ferjani et al. (2015)
	2011	Sfax	ESBL PS (11) [!]	100	0	NT	0	NT	NT	NT	NT	0	NT		$bla_{OXA\text{-}48}$, $bla_{CMY\text{-}4}$, $bla_{PER\text{-}1}$, *aac (6′)-Ib*	Mnif et al. (2013)
	2012–2013	Manouba	CTX-resistant EC (7)	0	0	0	0	0	14.2	0	0	0	NI		$bla_{CTX\text{-}M\text{-}15}$	Ferjani et al. (2017)
	2014–2015	Sousse	MDR Ent (102)[!]	0	70	NT	0	NT	59	0	0	NT	NI		NI	Yosra et al. (2017)
Algeria	2010–2011	Bejaia	NAL-resistant EC (30)	0	3.3	NT	6.6	NT	NT	NT	NT	NT	S83L D87N	S80I E84K	$bla_{CTX\text{-}M\text{-}15}$	Yanat and Viñas (2014)
	2010–2014	Bejaia	NAL-resistant Ent (141)	0	2.8	0	1.4	1.4	7.8	0	0	0	S83L S83I D87N	S80I E84V V87A	$bla_{CTX\text{-}M\text{-}15}$, $bla_{TEM\text{-}1}$	Yanat et al. (2017a)
Mauritania	2009	Nouakchott	ESBL EC (5)	0	0	0	NT	NT	100	NT	NT	0	NT		$bla_{CTX\text{-}M\text{-}15}$, $bla_{TEM\text{-}1b}$, $bla_{OXA\text{-}1}$, *dfrA1–17*, *aadA1,-5*, *tetA*, *tetB*, *sul2*, *−3*, *strA*, *strB*	Ben Sallem et al. (2015)

The *qnrE* and *crpP* genes are not included in this table, because they are not tested in any study.

Case for carbapenemase-producing isolate, CAZ for ceftazidime, CTX for cefotaxime, CIP for ciprofloxacin, EC for *Escherichia coli*, Ent for *Enterobacteriaceae*, FOX for cefoxitin, IMP for imipenem, K for *Klebsiella*, KP for *Klebsiella pneumoniae*, MDR for Multi-drug resistant, NA for not available, NAL for Nalidixic acid, Nb for numbers, NI for not indicated among PMQR positive isolates, NO for no mutation was detected in the QRDR of *gyrA* and *parC* genes, NT for not tested, PM for *Proteus mirabilis*, PS for *Providencia stuartii*, SE for *Salmonella enterica*, [!]: clinical and environmental isolates.

[a] Among *K. pneumoniae* only.

quinolone resistance phenotypes (Rodríguez-Martínez et al., 2016a,b).

The *qnr* genes are mostly identified by PCR. The presence of different groups of *qnr* genes makes their separate detection by simplex PCR an expensive and time-consuming process. For this purpose and in order to facilitate a higher throughput, several multiplex PCR have been developed aiming to detect most of *qnr* genes and alleles (Cattoir et al., 2007; Kim et al., 2009a; Robicsek et al., 2006). Recently, an updated multiplex PCR has been developed to detect all *qnr* families described at that time including *qnrA*, *qnrB*, *qnrS*, *qnrC*, *qnrD*, and *qnrVC* (Kraychete et al., 2016). To the best of our knowledge, there is no multiplex PCR described until now that can detect the seven *qnr* families. In 2011, Guillard et al., have developed a multiplex Real-time PCR (RT–PCR) using SYBR Green I to identify *qnrA*, *qnrB*, *qnrS*, *qnrD*, and *qnrC* in clinical Extended-Spectrum β-Lactamase (ESBL)–producing *Enterobacteriaceae* isolates (Guillard et al., 2011). Another RT-PCR has also been developed to detect and quantify *qnr* genes (*qnrA*, *qnrB*, and *qnrC*) in environmental samples and chicken feces (Marti and Balcázar, 2013). A multiplex RT-PCR coupled with high resolution melting analysis was also described to detect and characterize *qnrA*, *qnrB*, and *qnrS* alleles (Guillard et al., 2012).

AAC(6′)-Ib-cr detection is difficult because it differs from AAC(6′)-Ib in only 2 amino acid mutations at codons 102 and 179. It was traditionally done by amplification of the *aac(6′)-Ib* gene by PCR followed by restriction endonuclease analysis using Bstf5Ia enzyme (Kim et al., 2009; Park et al., 2006; Pitout et al., 2008), pyrosequencing (Guillard et al., 2010, 2013) or high resolution melting analysis (Hidalgo-Grass and Strahilevitz, 2010) to distinguish between the wild-type AAC(6′)-Ib and the cr variant. Due to the cost, and the need for specific equipment, simpler methods were needed. A gap ligase chain reaction (gap -LCR) (Warburg et al., 2009) and an allele-specific simple PCRs (Andres et al., 2013; Wareham et al., 2010) have been developed to rapidly detect this variant. In 2011, Wachino et al., developed a simple, and practical phenotypic disc method test to screen for AAC(6′)-Ib-cr producers with high sensitivity and specificity (Wachino et al., 2011). Similarly, a new disc diffusion method, based on the detection of a difference of at least 5 mm between the inhibition zones of levofloxacin and ciprofloxacin, was proposed for the prediction of the presence of *acc(6′)-Ib-cr* gene (Andres et al., 2013). In the last few years, a fast, affordable, and easy method based on Matrix Assisted Laser Desorption Ionization-Time Of Flight (MALDI-TOF) MS strategy has been developed to detect AAC(6′)-Ib-cr enzymes by measuring acetyltransferase activity against fluoroquinolones such as norfloxacin and ciprofloxacin. This new method is based on the detection of peaks corresponding to the acetylated forms of norfloxacin and ciprofloxacin, which have an increased molecular weight of 42 Da (Oviaño et al., 2017a,b; Pardo et al., 2016).

Similarly, *crpP*, *oqxAB* and *qepA* genes are detected by PCR (Chávez-Jacobo et al., 2019; Guillard et al., 2011; Kim et al., 2009b; Liu et al., 2011; Taherpour and Hashemi, 2013; Yamane et al., 2008). Subsequently, several reported multiplex PCR assays are able to detect the different PMQR genes (Ciesielczuk et al., 2013; Kim et al., 2009a; Rodríguez-Martínez et al., 2016a,b).

However, there is still no method that can detect all PMQR genes. Therefore, whole genome sequencing remains the best way not only to detect the known PMQR genes, but it would also be ideal for the identification of new alleles and for overriding the problems related with primer design to detect all *qnr* alleles.

5. Epidemiology

Over the past decade, the intensive use of quinolones in human and veterinary medicines as well as in food animals has led to the rapid emergence of quinolones resistance (Acar and Goldstein, 1997; World Health Organization (WHO), 1998). The rate of quinolone resistance differs widely from one country to another. According to the Center for Disease Dynamics, Economics and Policy the percentage of fluoroquinolone-resistant *E. coli* among invasive isolates was 29% in United States of America, ranged from 7% to 46% in European countries, and reached > 70% in some countries as India (78%) and Pakistan (72%). However, the quinolone resistance rates in Arab countries are moderately high and reached up to 31% and 45% in Tunisia and Lebanon, respectively (The Center for Disease Dynamics, Economics and Policy, 2017). Although, there are multiple quinolone resistance mechanisms, attention should be paid to those mediated by plasmid-carried genes (Robicsek et al., 2006a). Nevertheless, even with the increased rates of PMQR witnessed worldwide, limited data are available in Arab countries. Overall, the majority of these countries are reeling under the consequences of the Arabic Spring (particularly the Syrian conflict) among many other problems. Most notable are health problems particularly the high antimicrobial resistance rates, the low-level of antibiotic awareness, and the high rate of self-prescribed antibiotics (Al Omari et al., 2018). This part of the review will gather the scattered epidemiological studies conducted in the Arab countries to determine the prevalence of PMQR genes in clinical and environmental isolates (Table 2,3). We searched the Pubmed, Google Scholar, and Sciences web for investigations that tackled the epidemiology of PMQR in Arab countries. All studies stating the prevalence of at least one PMQR genes until September 2018 are included. Data was double-checked by two authors. It is worth noting that of the 22 Arab countries no data were found for nine of these countries which are Oman, Bahrain, Jordan, United Arab Emirates, Qatar, Sudan, Comoros, Djibouti, and Somalia.

Among 34 clinical studies, *aac(6′)-Ib-cr* was the predominant PMQR gene in most of the studies with a prevalence varying from 7.8% to 100% depending on selection criteria of studied strains. PMQR genes were recovered from diverse specimens and ages. Strikingly, multiple studies highlighted the presence of PMQR genes in isolates recovered from children raising an undeniable alarm of the emergence of PMQR genes among such population (Ferjani et al., 2017; Hamed et al., 2018; Jlili et al., 2014; Tohamy et al., 2018). In Tunisia, a high prevalence of *aac(6′)-Ib-cr* (77.5%) was found in *qnr*-positive *Enterobacteriaceae* isolated from children even those not overtreated with quinolones (Jlili et al., 2014). Similarly, the *aac(6′)-Ib-cr* gene was identified from the intestinal microbiota of healthy children (Ferjani et al., 2017). An interesting study conducted between 2014 and 2015 among Gram-negative infected cancer patients, showed that 66.9% of isolates were resistant to all quinolones while 51.4% had a high-level of quinolone-resistance. The prevalence of PMQR genes was 53.6% including ciprofloxacin-susceptible isolates of which *aac(6′)-Ib-cr* was the most PMQR gene detected followed by *qnrS*, *qnrB*, and *qnrA* genes. Interestingly, the isolates recovered from pediatric patients showed a higher prevalence of PMQR genes than among adult patients (Hamed et al., 2018). Similar results have been reported in febrile neutropenic cancer patients (Tohamy et al., 2018) (Table 2).

The *qnrB* and *qnrS* genes were the most dominant from the *qnr* genes. Their prevalence ranges from 0% up to 78% for *qnrB* and 58% for *qnrS* (Table 2). The *qnrD* gene was detected in two studies (El-Badawy et al., 2017; Yanat et al., 2017b). The Algerian study was the first study reporting *qnrD* carried on small non-transmissible plasmids in two isolates of *P. mirabilis* and *M. Morganii* (Yanat et al., 2017b). A higher prevalence of *qnrD* (40%) was detected in an Egyptian study identifying for the first time the *qnrC* gene and showing a coexistence between PMQR genes and genes encoding aminoglycoside-modifying enzymes especially *acc(6′)-Ib* (El-Badawy et al., 2017) (Table 2). Although *qnrA* was rarely detected in almost all Arab countries, two outbreaks of *Providencia stuartii* carrying *qnrA6* in burn and intensive care units were reported in Tunisia (Arpin et al., 2012; Mnif et al., 2013).

In very few studies, genes encoding for plasmid-mediated efflux pumps OqxAB (El-Badawy et al., 2017; Ferjani et al., 2015; Hamed et al., 2018) and QepA (Alshammari and Al-Skhattat, 2015; El-Badawy et al., 2017) were identified. In Egypt, a high prevalence of *oqxA* gene (88%) was retrieved among ciprofloxacin- and/or levofloxacin- resistant *K. pneumoniae* isolates whereas *oqxB* was found only in 30% of isolates (El-Badawy et al., 2017). However, a lower frequency of *oqxAB* (21.6%) was obtained in Tunisia among ESBL-producing

Table 3
Epidemiology of plasmid-mediated quinolone resistance (PMQR) among non-clinical isolates in the Arab countries.

Country	Year of study	Setting	Speci-men	Origin of specimen	Species (Nb)	PMQR genes (%)									Associated genes	Ref.
						qnr genes					*aac (6′)-Ib-cr*	*oqxA*	*oqxB*	*qepA*		
						A	*B*	*C*	*S*	*D*						
Lebanon	2014–2015	Tripoli	Water	Dug wells, spring water, estuaries	Ent (33)	0	0	0	21.2	0	24.2	21.2	0	0	$bla_{CTX\text{-}M\text{-}15,\ -55}$, $bla_{CMY\text{-}42}$	Diab et al. (2018)
Egypt	2006–2007	Delta region	Fecal swabs	Diarrheic neonatal calves	EC (182)	0	2.2	NT	2.7	NT	2.7	NT	NT	NT	$bla_{CTX\text{-}M\text{-}15}$, $bla_{TEM\text{-}1}$, $bla_{OXA\text{-}30}$, $bla_{SHV\text{-}12}$, *dfrA1*, −17, −12, *aadA1*, −2, −5, *aac(3)-Id*	Ahmed et al. (2009b)
	2006–2007	National study	Fecal swabs	Diarrheic calves	MDR *Salmonella* spp. (6)	0	16.6	NT	33.3	NT	16.6	NT	NT	NT	$bla_{TEM\text{-}1}$, $bla_{SHV\text{-}12}$, *dfrA1*, *aadA1*	Ahmed et al. (2009a)
	2007	Damietta and Kafr El- Sheikh	Water	Fish farms	Gram-negatives (274)	1.8	1.4	NT	2.5	NT	1.1	NT	NT	NT	*tetA*, *tetE tetD*, *dfrA5*, −7, *aadA5*, $bla_{TEM\text{-}104,\ -1}$, $bla_{OXA\text{-}30}$, $bla_{CTX\text{-}M\text{-}15}$, $bla_{SHV\text{-}89}$	Ishida et al. (2010)
	2008	9 private cow farms	Milk	Cows affected with mastitis	Gram-negatives (112)	2.6	4.4	NT	7.1	NT	3.6	NT	NT	NT	$bla_{TEM\text{-}1}$, $bla_{OXA\text{-}30}$, $bla_{CTX\text{-}M\text{-}15}$, $bla_{SHV\text{-}12,\ -1}$, $bla_{CMY\text{-}2}$, *aadA1,-2,-5–22*, −12, *dfrA12,-17*, −1, −25, −7,, *floR*, *arr-3*	Ahmed and Shimamoto (2011)
	2014	NA	Meat and dairy products	Food	MDR SE (47)	2.1	14.8	NT	10.6	NT	12.7	NT	NT	NT	$bla_{TEM\text{-}1}$, $bla_{CMY\text{-}2}$, $bla_{CTX\text{-}M\text{-}3,\text{-}15}$, $bla_{SHV\text{-}12}$, *floR*, *aadA1*, −2, −5, *dfrA1*, −12, −17,	Ahmed et al. (2014)
Algeria	2010	Boumerdes	Water	Wastewater treatment plant	ESBL EC and KP (40)	0	57.5	0	0	0	NT	NT	NT	0	$bla_{CTX\text{-}M\text{-}3,\text{-}15}$, $bla_{OXA\text{-}1,}$ $bla_{TEM\text{-}1}$	Alouache et al. (2014)
	2012	Annaba	Chicken meat	Butcher shops	NAL-resistant EC (29)	0	6.9	0	3.4	0	0	NT	NT	0	NT	Laarem et al. (2017)
	2012–2014	Setif, Bejaia, Constantine	Swabs	Hospital environment	ESBL KP (44)	0	77	NT	NT	NT	77	NT	NT	NT	$bla_{CTX\text{-}M\text{-}3,\text{-}15}$ $bla_{TEM\text{-}1}$, bla_{SHV}, *aadA2*, *armA*, *aac(6′)-Ib*, *ant(3″)-Ih-aac(6′)-IId*	Zenati et al. (2017)

The *qnrE* and *crpP* genes are not included in this table, because they are not tested in any study.
EC for *Escherichia coli*, Ent for *Enterobacteriaceae*, KP for *Klebsiella pneumoniae*, NA for not available, NAL for Nalidixic acid, Nb for numbers, NT for not tested, MDR for Multi-Drug resistant, SE for *Salmonella enterica*.

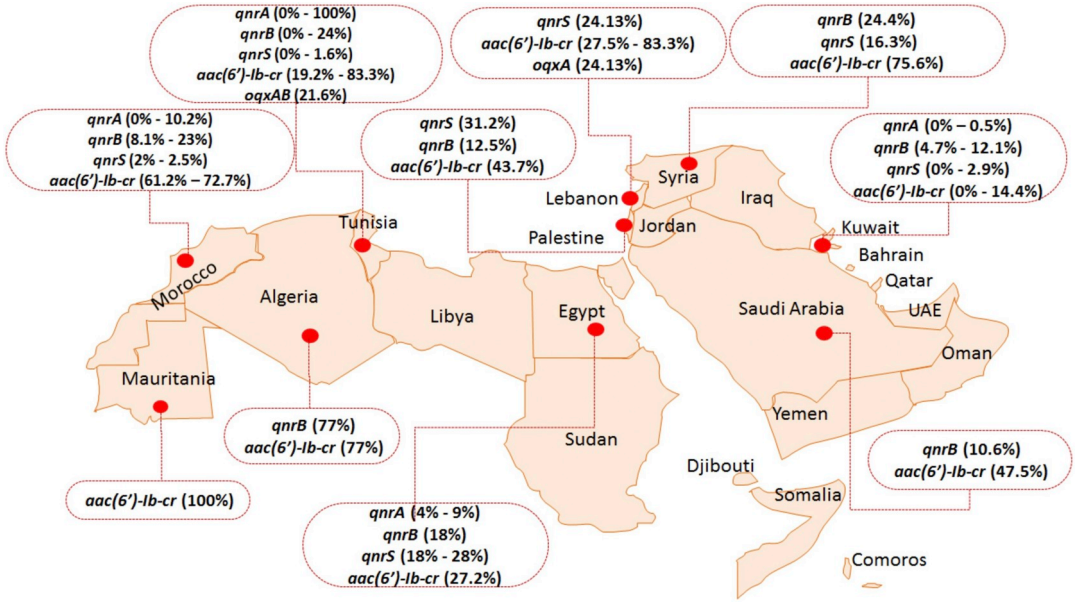

Fig. 1. PMQR genes epidemiology among ESBL-producing *Enterobacteriaceae* isolates in the Arab countries.

Enterobacteriaceae where *oqxAB* genes were only detected in *K. pneumoniae* isolates (Ferjani et al., 2015). The *qepA* gene was identified only in two studies in Iraq and Egypt with almost the same prevalence (12%) (Alshammari and Al-Skhattat, 2015; El-Badawy et al., 2017) (Table 2).

Besides clinical studies, five articles investigated the presence of PMQR genes in food and animal isolates (Ahmed et al., 2009a,b, 2014; Ahmed and Shimamoto, 2011; Laarem et al., 2017). Among foods of animal origin, PMQR genes were reported in dairy products, beef, and chicken meat. Overall, prevalence of *qnr* genes (*qnrA*, *qnrB*, *qnrS*) varied from 0 to 14.7% and *aac(6′)-Ib-cr* from 0% to 12.7% (Ahmed et al., 2014; Ahmed and Shimamoto, 2011; Laarem et al., 2017). The higher prevalence of PMQR genes was observed in *Salmonella enterica* isolates recovered from meat and dairy products in Egypt (Ahmed et al., 2014). As animal isolates, PMQR genes were reported in *S.* Enteritidis, *S.* Typhimurium, and *E. coli* isolates recovered from diarrheic neonatal calves (Ahmed et al., 2009a,b). Interestingly, *qnrA* was not detected in these studies but lower prevalence of *qnrB* (2.2%), *qnrS* (2.7%) and *aac(6′)-Ib-cr* (2.7%) was observed in case of *E. coli* isolates (Ahmed et al., 2009b) compared to *Salmonella* isolates (*qnrB*:16.6%, *qnrS*: 33.3%, *aac(6′)-Ib-cr*: 16.6%) (Ahmed et al., 2009a) (Table 3).

Few environmental studies were conducted in Arab countries (Diab et al., 2018; Ishida et al., 2010; Mnif et al., 2013; Yosra et al., 2017; Zenati et al., 2017). In Lebanon, a high prevalence of fluoroquinolone resistance (48.5%) was reported among *Enterobacteriaceae* isolates from Lebanese water (rural wells, springs, and estuaries). In addition, 24.2% of the isolates harbored the *aac(6′)-Ib-cr* genes, 21.2% the *qnrS* gene, and 21.2% the *oqxA* gene (Diab et al., 2018). In Egypt, PMQR genes (*qnrA*, *qnrB*, *qnrS*, *aac(6′)-Ib-cr*) were found with a low prevalence in water taken from fish farms (Ishida et al., 2010). On the other hand, a high prevalence of *qnrB* and *aac(6′)-Ib-cr* was seen in Algeria from a hospital environment, thus playing a role in pathogen transmission in health care settings (Zenati et al., 2017) (Table 3).

In addition, almost all studies showed that plasmids harboring the PMQR genes carried other antibiotic resistance genes. Therefore, PMQR genes were identified in association with different types of ESBLs (Fig. 1) especially $bla_{CTX\text{-}M\text{-}15}$ and $bla_{TEM\text{-}1}$, aminoglycosides, rifampicin, chloramphenicol, trimethoprim, and tetracycline genes (Table 2, 3).

6. Conclusion

Although it is difficult to compare and draw conclusions about PMQR trends between the Arab countries due to differences in the number of tested genes, nature of studied strains and design of elaborated studies, it is clear that PMQR genes are widely disseminated in these countries, particularly *aac(6′)-Ib-cr*, with increasing rates over the years. Alarmingly, this widescale dissemination is associated with various resistance genes such as the ESBL $bla_{CTX\text{-}M\text{-}15}$. Other recently described PMQR mechanisms as CrpP and QnrE are not investigated yet in the Arab region. For this, more meticulous molecular studies are required to unveil their exact prevalence and perhaps discover novel mechanisms in these countries. Furthermore, this review presents evidence of the spread of these determinants in different populations (children and adults), environments, animals, and foods. This highlights the pressing need to share and implement the “One Health” concept in these countries and to monitor antibiotics prescription in both human and veterinary medicines.

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Declaration of Competing Interest

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