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Carriage of plasmid-mediated *qnr* determinants and quinolone efflux pump (*qepA*) by ciprofloxacin-resistant bacteria recovered from Urinary Tract Infection (UTI) samples

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Abstract

Background: Bacterial resistance to commonly-used antibiotics has been on the increase especially in the clinical settings. This study focused on the detection of plasmid-mediated quinolone resistance (PMQR) determinants in ciprofloxacin-resistant bacteria recovered from Urinary Tract Infection (UTI) samples.

Results: Already characterized isolates from urine samples of UTI-diagnosed in- and out- patients were obtained from the culture pool of the Department of Medical Microbiology and Parasitology, University College Hospital (UCH), Ibadan, Nigeria. A total of seventy-three ciprofloxacin-resistant isolates were used in this study. Of the 73 UTI isolates, 43 carried at least one of the four PMQR genes targeted and they belonged to eight bacterial genera namely: *Escherichia* (25), *Klebsiella* (10), *Pseudomonas* (2), *Proteus* (2) and one isolate each belonging to *Enterobacter*, *Acinetobacter*, *Citrobacter* and *Salmonella* genera. *qnrA* was detected in 10.9% (8/73) of the isolates while the occurrence of *qnrB* and *qnrS* was 32.9% (24/73) and 20.5% (15/73), respectively. The quinolone efflux pump (*qepA*) was detected in 9/73 (12.3%) of the isolates. Thirty of the isolates carried only one PMQR gene, while thirteen carried two PMQR genes. There was no carriage of more than two PMQR genes in the forty-three isolates from which PMQR genes were detected.

Conclusion: This study reports the carriage of PMQR determinants by eight of the nine Gram-negative bacterial genera from urinary sources in patients attending the University College Hospital, Ibadan over the four-month period of study. This is quite worrisome as it suggests a high contribution of UTI cases to the burden of quinolone resistance. There is a need for more studies of this nature in other hospitals in Nigeria, to develop a database on the contribution of UTI cases to quinolone resistance.

Keywords: Quinolone resistance, Urinary Tract Infection (UTI), Antibiotic resistance, PMQR genes, Tertiary Hospital

Background

Urinary tract infections (UTIs) are one of the most common group of bacterial infections worldwide. It is estimated that the proportion of UTIs remains at a high level reaching 150 million episodes per year worldwide and accounting for an estimated $6 billion in health care expenditures (Foxman 2014; AUA 2016). Resistance to beta-lactam antibiotics and fluoroquinolones, which are the most widely used therapeutics against UTI has

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skyrocketed lately (Grabe et al. 2015). The past 30 years have led to an explosive increase in quinolone resistance, especially among the Enterobacterales. This has been brought about by the acquisition of plasmid-mediated quinolone resistance genes (Briales et al. 2012; Alikhani et al. 2013).

Quinolone antibiotics have shown high effectiveness in the treatment of UTIs and other diseases as a result of their broad spectrum of activity, good oral absorption and unnoticeable side effects, making them the drug of choice in the treatment of a variety of infections (Mandell 2005; Shahcheraghi et al. 2013). The mechanisms used by bacteria to resist quinolones include alteration in the genes encoding quinolone target enzymes, regulation of proteins responsible for overexpression of quinolone efflux pumps and intake system (Hooper and Jacoby 2015); in addition to the possession of plasmid-mediated quinolone resistance (PMQR) determinants (Strahilevitz et al. 2009).

The first plasmid–mediated resistance gene in quinolones; *qnrA1* was reported in 1998 from a clinical strain of *Klebsiella pneumoniae* and ever since then, more plasmids-transferable resistance mechanisms to quinolones have been identified (Poirel et al. 2005; Jacoby et al. 2008; Hernández et al. 2011; Ade et al. 2014; Ohene et al. 2019). In addition to this, other elements such as efflux pumps (*oqxAB* and *qepA*), and the possession of aminoglycoside acetyltransferase (*aac(6')-Ib-cr*) have been reported to contribute to the resistance of bacteria to the quinolone antibiotics (Jacoby 2005; Strahilevitz et al. 2009). Before the 2000s, studies carried out in Nigeria have shown reports of low-level resistance to the quinolones among isolates of clinical origin probably because of the low patronage of the drugs back then (Lamikanra et al. 2011), but currently, there have been increasing reports of quinolone resistance in Nigeria and other neighboring countries in West Africa (Aibinu et al. 2004, 2008; Ogbolu et al. 2011, 2016). In lieu of this fact, this study aimed to determine the prevalence of plasmid-mediated *qnr* and *qepA* quinolone resistance genes among ciprofloxacin-resistant uropathogens obtained from the urine of patients attending a University Teaching hospital in Nigeria over a 4-month period.

Methods

Bacteria used for the study

This study was carried out in April, 2021, and the isolates used for this study were ciprofloxacin-resistant uropathogens isolated from urine samples of UTI- diagnosed population attending the University College Hospital, over a period of 4 months. The Teaching hospital is located in Ibadan, a city in the South-western part of Nigeria. The uropathogenic bacteria were obtained with written approval, from the culture collection of the Department of Microbiology and Parasitology, University College Hospital (UCH). The Microbact™ Gram Negative System Identification kit (Thermo Scientific-Oxoid, UK) was used in the identification of the uropathogenic bacteria.

Table 1 Oligonucleotide primers and amplicon sizes of PMQR genes targeted in this study

Target gene	Primer sequence (5′ to 3′)	Amplicon size (bp)	References
qnrA	TTCAGCAAGAGGATTTCTCA	608	Wu et al. (2007)
	GGCAGCACCATTACTCCCAA		
qnrB	CCTGAGCGGCACTGAATT CAT	389	Wu et al. (2007)
	GTTTGCTGCTCGCCAGTCGA		
qnrS	CAATCATACATATCGGCACC	621	Wu et al. (2007)
	TCAGGATAAACAACAATA CCC		
qepA	GCAGGTCCAGCAGCGGGT AG	218	Wu et al. (2007)
	CTTCCTGCCCGAAGTATC GTG		

Table 2 Frequency of ciprofloxacin-resistant bacterial genera and their carriage of PMQR genes

Bacteria	Frequency	Percentage occurrence	No. of isolates showing carriage of PMQR genes
Escherichia spp.	31/73	42.5	25
Klebsiella spp.	27/73	36.9	10
Pseudomonas spp.	4/73	5.5	2
Enterobacter spp.	3/73	4.1	2
Proteus spp.	3/73	4.1	1
Acinetobacter spp.	2/73	2.7	1
Citrobacter spp.	1/73	1.4	1
Salmonella spp.	1/73	1.4	1
Morganella spp.	1/73	1.4	0
Total	73	100	43

DNA extraction and PCR amplification of plasmid-mediated quinolone resistance (PMQR) genes

The genomic DNA of the seventy-three ciprofloxacin-resistant bacteria was extracted using the boiling lysis method (Gugliandolo et al. 2010). The methods described by Wu et al. (2007) were used in the amplification of the targeted PMQR genes (*qnrA*, *qnrB*, *qnrS* and *qepA* genes). The oligonucleotide primers and amplicon sizes of PMQR genes targeted in this study are highlighted in Table 1.

Table 3 Distribution of *qnr* determinants and *qepA* in the Urinary Tract Infection isolates showing the carriage of PMQR genes

Lab code	Isolate identity	*qnrA*	*qnrB*	*qnrS*	*qepA*
UP1	*Escherichia coli*	−	−	−	+
UP2	*Escherichia coli*	−	+	−	−
UP3	*Escherichia coli*	−	+	−	+
UP4	*Enterobacter cloacae*	−	−	+	+
UP5	*Escherichia coli*	−	+	−	+
UP6	*Acinetobacter baumannii*	−	+	−	−
UP7	*Escherichia coli*	−	+	−	−
UP9	*Klebsiella pneumoniae*	+	−	−	−
UP10	*Escherichia coli*	−	−	−	+
UP13	*Klebsiella pneumoniae*	−	−	+	−
UP20	*Escherichia coli*	−	−	+	−
UP21	*Escherichia coli*	−	−	+	−
UP22	*Escherichia coli*	−	+	−	−
UP23	*Escherichia coli*	−	+	−	−
UP24	*Pseudomonas aeruginosa*	−	+	+	−
UP25	*Escherichia coli*	−	+	−	−
UP26	*Citrobacter amalonaticus*	−	+	−	−
UP27	*Escherichia coli*	−	+	−	−
UP28	*Escherichia coli*	−	+	−	−
UP29	*Klebsiella oxytoca*	−	+	+	−
UP36	*Escherichia coli*	−	+	−	−
UP38	*Klebsiella pneumoniae*	−	−	+	−
UP40	*Escherichia coli*	−	−	+	−
UP41	*Escherichia coli*	+	−	−	−
UP42	*Klebsiella pneumoniae*	−	−	+	−
UP43	*Pseudomonas aeruginosa*	+	+	−	−
UP44	*Escherichia coli*	+	+	−	−
UP45	*Klebsiella pneumoniae*	−	+	+	−
UP46	*Escherichia coli*	−	+	−	+
UP47	*Escherichia coli*	−	+	−	+
UP48	*Klebsiella pneumoniae*	+	−	−	−
UP50	*Klebsiella pneumoniae*	−	+	−	−
UP51	*Klebsiella pneumoniae*	+	−	+	−
UP53	*Salmonella enterica*	−	−	+	−
UP54	*Escherichia coli*	−	−	+	−
UP59	*Escherichia coli*	−	−	+	−
UP60	*Enterobacter cloacae*	+	+	−	−
UP61	*Escherichia coli*	−	+	+	−
UP62	*Klebsiella pneumoniae*	−	+	−	−
UP63	*Escherichia coli*	−	−	−	+
UP64	*Escherichia coli*	−	−	−	+
UP66	*Escherichia coli*	+	−	−	−
UP67	*Proteus mirabilis*	−	+	−	−

Results

Thirty-one (42.5%) of the ciprofloxacin-resistant bacteria were identified as *Escherichia coli*, while twenty-seven (36.9%) were *Klebsiella* spp., four (5.5%) were *Pseudomonas* spp., while there were three isolates (4.1%) each of *Proteus* spp. and *Enterobacter* spp. There were two *Acinetobacter* spp. isolates (2.7%), with *Citrobacter* spp., *Morganella* spp. and *Salmonella* spp. having one isolate (1.4%) each. Forty-three of the total isolates carried at least one of the targeted PMQR genes (Table 2).

The distribution of PMQR genes in the forty-three of the seventy-three UTI isolates showing the carriage of PMQR genes is shown in Table 3. Of the forty-three isolates showing the carriage of PMQR genes, 25 were *Escherichia coli*, 10 were *Klebsiella* spp., two each for *Pseudomonas* spp. and *Proteus* spp., while *Enterobacter* spp., *Acinetobacter* spp., *Citrobacter* spp. and *Salmonella* spp. had one isolate each. All the bacteria genera used in this study with the exception of the genus *Morganella* had at least one isolate showing the carriage of the targeted PMQR genes. The remaining thirty isolates did not carry any of the PMQR genes and were not presented in the Table.

Eight of the isolates representing 10.9% of the total 73 ciprofloxacin-resistant bacteria carried the *qnrA* gene,

Table 4 Frequency of occurrence of PMQR genes in the ciprofloxacin-resistant bacteria

PMQR gene	Frequency	Percentage occurrence (%)
qnrA	8/73	10.9
qnrB	24/73	32.9
qnrS	15/73	20.5
qepA	9/73	12.3

Table 5 Carriage of different PMQR gene combination by the forty-three isolates carrying PMQR genes

PMQR gene combinations	Frequency of occurrence
qnrA only	4
qnrB only	13
qnrS only	9
qepA only	4
qnrA + *qnrB*	3
qnrA + *qnrS*	1
qnrB + *qnrS*	4
qnrA + *qepA*	0
qnrB + *qepA*	4
qnrS + *qepA*	1
qnrA + *qnrB* + *qnrS*	0
qnrA + *qnrB* + *qnrS* + *qepA*	0

which is the gene with the least frequency of occurrence among the uropathogenic isolates. *qnrS* was detected in fifteen isolates (20.5%), with *qepA* being harboured by nine of the isolates (12.3%). The predominant gene of the PMQR genes targeted in this study was *qnrB*, which was detected in 24/73 (32.9%) of the isolates as shown in Table 4. Thirty of the isolates carried only one of the PMQR genes targeted, while thirteen carried two of the four PMQR genes. There was no carriage of more than two PMQR genes in the forty-three isolates detected to harbour the genes.

Table 5 is showing the carriage of different PMQR gene combination by the forty-three from which PMQR genes were detected. Four isolates carried *qnrA* only, while thirteen, nine and four isolates, respectively, carried *qnrB*, *qnrS* and *qepA* only. The combination of *qnrA* + *qnrB* was carried by three isolates, one isolate carried the *qnrA* + *qnrS* combination and four of the isolates carried the *qnrB* + *qnrS* combination. There was no carriage of a combination of *qnrA* + *qepA*, while four isolates carried a combination of *qnrB* + *qepA*. One of the forty-three isolates carried *qnrS* + *qepA* concurrently, while none of the isolates carried more than a combination of two PMQR genes.

Discussion

Unrestricted access to antimicrobials over the counter coupled with the unguided use of antibiotics in developing countries especially Nigeria, has contributed in no small portion to the rapid rise in antibiotic resistance. This has negatively affected the efficacy of most antibiotics in the treatment of infections, such as UTIs. Owing to the increased patronage of fluoroquinolone antibiotics since the 2000s, there has been an uncontrollable rise in the level of resistance shown to these agents in Nigeria. This has also fueled the need for bacteria to evolve several coping mechanisms to deal with the increased exposure to these antibiotics (Lamikanra et al. 2011; Chattaway et al. 2016; Ogbolu et al. 2016).

In this study, the most frequently isolated uropathogenic bacteria were from the genus *Escherichia*, which accounted for 42.5% (31/73) of the ciprofloxacin-resistant uropathogens. This was followed by the genus *Klebsiella* with 27/73 (36.9%). Pasom et al. (2013) reported the recovery of *Escherichia coli* and *Klebsiella* spp. in samples of urinary origin obtained from a Teaching Hospital in Thailand. In their study, 49/75 (65.3%) of *Klebsiella* spp. obtained were resistant to quinolone antibiotic, with 22.3% (27/121) of the *Escherichia coli* isolates showing resistance to the quinolone antibiotic used in the study. The only difference between their study and this current study is that *Klebsiella* spp. occurred more frequently in their study as against *Escherichia coli* in this present study. Numerous studies have reported the predominance of *Escherichia coli* in samples of clinical origin, and they even went ahead to conclude that the organism accounts for a very high percentage of Urinary Tract Infections (UTIs).

A study carried out by Marei et al. (2019) on ESBL- and non-ESBL- producing Enterobacteriaceae from UTI reported a percentage occurrence of 61.2% of *Escherichia coli*, followed by *Klebsiella* spp., accounting for 21.8% of the total isolates obtained. This same trend of *Escherichia coli* and *Klebsiella* spp. dominating in isolates from urinary sources was observed in this study. Other bacteria notably the members of the Enterobacterales have also been recovered from samples of UTI infected patients. In a study carried out by Ezeh et al. (2017), bacteria of the genera *Salmonella*, *Enterobacter*, *Serratia*, *Klebsiella*, *Escherichia* and *Acinetobacter* were encountered from urinary sources, with *Acinetobacter* being prevalent. This is in concordance with this study, where all the aforementioned genera with the exception of *Serratia* spp., and inclusive of *Citrobacter* spp. were also obtained in the urine samples of patients diagnosed with UTI infections.

The occurrence of PMQR determinants in isolates obtained from urine samples of patients diagnosed with UTI has been well documented in several countries of the world. In a study carried out in Italy by Musumeci et al. (2012), the carriage of PMQR genes by uropathogenic *Escherichia coli* was reported, while Deepak et al. (2009), Nazik et al. (2011), Sheikh et al. (2019), Badamchi et al. (2019), Hashemizadeh et al. (2019), Kammili et al. (2020), in their respective studies have all reported the prevalence and distribution of PMQR determinants in bacteria from urinary sources in different parts of the globe. This current study reports the occurrence of PMQR genes in bacteria obtained from urine samples of patients diagnosed with UTI and attending the University College Hospital (UCH), Ibadan, South-west Nigeria, over a period of 4 months.

The *qnr* genes are pentapeptide proteins whose major function is the protection of the quinolone targets, topoisomerase IV and DNA gyrase. They have been reported in bacteria from different compartments including human, animal and environment (Briales et al. 2012; Chen et al. 2012). The genes which are housed on mobile genetic elements (MGE) have five major phylogenetic groups. In this present study, three *qnr* genes (*qnrA*, *qnrB* and *qnrS*) were targeted in the ciprofloxacin-resistant uropathogens. Of these three genes, *qnrB* was predominant, as it was detected in 32.9% of the isolates, followed by *qnrS* (20.5%) and *qnrA* (10.9%). The predominance of the *qnrB* among the *qnr* genes is consistent with the study of Badamchi et al. (2019) who reported a percentage occurrence of 41.8% of the gene, making it the most

predominant PMQR gene in their study. This is in addition to the work of Nourozi et al. (2020), who reported the detection of *qnr* genes among *Klebsiella* spp. isolated from different clinical samples, including urine. The predominant quinolone resistance gene in their study was *qnrB* (43%), followed by *qnrS* (34%) and *qnrA* (23%). Several other studies have reported the detection of *qnr*-encoding genes in isolates of urinary origins. Notable among them were Nazik et al. (2011), Pasom et al. (2013), Hashemizadeh et al. (2019) and Salah et al. (2019).

The *qnr* genes have also been widely reported in other isolates apart from the usual suspects, *Escherichia coli* and *Klebsiella* spp., which are the major organisms extensively worked upon by most researchers. In a study by Yang et al. (2015), the detection of plasmid-mediated *qnr* genes was reported in *Acinetobacter baumannii*, with *qnrB* frequently occurring having been detected in 92/95 (96.8%) of the isolates obtained, while the other variants, *qnrA* and *qnrS*, were not detected. In this present study, only one of the two ciprofloxacin-resistant *Acinetobacter baumannii* showed the carriage of *qnrB*. Bacteria of the following genera: *Enterobacter*, *Pseudomonas*, *Proteus*, *Salmonella* and *Citrobacter* were also found to carry the targeted PMQR genes in this study. The isolation of *Acinetobacter baumannii* and *Salmonella* spp., showing the carriage of PMQR genes is in concordance with the work of Ezeh et al. (2017) who reported the isolation of *Acinetobacter baumannii* and *Salmonella* species showing the carriage of PMQR determinants from uropathogens isolated from the urine samples of asymptomatic female students in a University in Northern Nigeria.

Apart from the *qnr* genes which were detected in the ciprofloxacin-resistant isolates from this study, the quinolone efflux pump (*qepA*) was also detected in the isolates. Until 2007, when the *qepA* gene was detected in a clinical *Escherichia coli* isolate from Japan, as a novel plasmid-mediated efflux pump, no PMQR efflux pump was in existence. The gene, which is responsible for the reduction of quinolone accumulation in bacteria cell has been widely detected in many Gram-negative genera in many Asian countries and Africa, most notably Nigeria. There is a relative low occurrence of the gene in quinolone-resistant strains, and this has been largely attributed to its limited host spectrum, as a result of its newness in comparison with other PMQR genes (Chen et al. 2007, 2012; Yamane et al. 2007; Ogbolu et al. 2011). In this study, nine of the seventy-three ciprofloxacin-resistant isolates (12.3%) carried *qepA* gene, with eight of them identified as *Escherichia coli* and the ninth being *Enterobacter cloacae*. The frequency of occurrence of the gene in this study is higher than what was reported in some other studies on uropathogenic bacteria. Nazik et al. (2011) reported a frequency of 5.7% in their study carried out at two Turkish hospitals, while Badamchi et al. (2019) detected *qepA* in 7.3% of the isolates in their study. Pasom et al. (2013) on the other hand reported the absence of the gene in uropathogenic isolates obtained from a Teaching hospital in Thailand, same as Ehwarieme et al. (2021). In contrast however, Ezeh et al. (2017) reported the occurrence of the gene in 70% of the isolates obtained in their study, while Ogbolu et al. (2016) in their study on gram-negative bacteria from a Nigerian hospital reported 18.7% occurrence of *qepA*. There was co-occurrence of PMQR genes in thirteen of the seventy-three ciprofloxacin-resistant bacteria in this study, and this presents a rather worrisome situation, as these genes could be transmitted to bacteria in other compartments notably the environment, which could further facilitate the proliferation of quinolone resistance.

Conclusions

Enterobacteriaceae are commonly recovered from of UTIs, however the high carriage of PMQR genes which confer resistance to first line treatment drug (quinolones) is quite alarming. This study showed that 73 (60.8%) of the uropathogens obtained from the hospital showed resistance to ciprofloxacin while 43/73 (58.9%) showed the presence of at least one PMQR genes, with *qnrB* being the most prevalent. There is, therefore, a need to regulate the use of quinolone drugs in UTI treatment, to clamp down on the increasing tide of resistance to these drugs.

Abbreviations

PMQR: Plasmid-Mediated Quinolone Resistance; UTI: Urinary Tract Infection; CLSI: Clinical and Laboratory Standards Institute; ARG: Antibiotic Resistance Gene; PCR: Polymerase Chain Reaction.

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Authors' contributions

AOA conceived the study. AOA and OCA designed the study. AOA, SU, OCA and AVO carried out the laboratory work. AOA, SU, OCA, AVO and AAO wrote the first draft of the manuscript. AOA and AVO did the article formatting. AOA, OCA and AAO read the final version of the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used and/or analysed during the current study are included in the article.

Declarations

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Not applicable.

Consent for publication
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Competing interests
The authors declare that they have no competing interests.

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