



Molecular Detection of *qnr* Genes in Multidrug-Resistant *E. coli* from Punjab, Pakistan: A Rising Threat of Quinolone Resistance

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ABSTRACT

Escherichia coli is a primary causative agent of urinary tract infections (UTIs) and has shown rising multidrug resistance (MDR) worldwide. Prevalence and molecular characteristics of plasmid-mediated quinolone resistance (PMQR) in 43 collected MDR clinical isolates of *E. coli* have been studied. Using the E-test, antimicrobial susceptibility testing was performed to determine the minimum inhibitory concentrations (MICs) of Ciprofloxacin, Levofloxacin, and Ofloxacin. Among 30 quinolone-resistant isolates, resistance rates were 73% for Ofloxacin, 75% for Levofloxacin, and 83% for Ciprofloxacin. Molecular characterization using polymerase chain reaction (PCR) revealed a high prevalence of the *qnrB* gene (76.7%), followed by *qnrS* (6.97%) and *qnrA* (4.7%). Notably, 11.2% of resistant isolates lacked detectable *qnrA*, *qnrB*, or *qnrS*, suggesting the possible presence of lesser-known *qnrC* or *qnrD* genes. These findings emphasize the growing challenge of PMQR in the region and highlight the need for regular molecular surveillance to guide public health strategies and antibiotic stewardship.

INTRODUCTION

A widely used class of broad-spectrum antibiotics, quinolones, has substantial therapeutic value against a range of bacterial infections. Their clinical utility was initially developed to treat Gram-negative bacterial infections. Still, through structural modifications, such as fluorination, which led to the development of fluoroquinolones, their use was later extended to Gram-positive pathogens [1,2]. These synthetic derivatives exert potent antibacterial effects by inhibiting essential bacterial enzymes involved in DNA replication and transcription, primarily targeting DNA gyrase in Gram-negative bacteria and topoisomerase IV in Gram-positive species [3,4].

Over time, the widespread and often unregulated use of quinolones has led to the emergence of resistance, posing a serious public health concern. To date, four primary mechanisms of quinolone resistance have been identified: i) chromosomal mutations in *gyrA*, *gyrB*, *parC*, or *parE* genes of the quinolone resistance-determining regions (QRDRs) [5]; ii) overexpression of chromosomally encoded efflux pumps [6]; iii) DNA gyrase and topoisomerase IV are protected from quinolone binding by plasmid-mediated quinolone resistance (PMQR), which

involves the *qnr* family of proteins[7]; and iv) enzymatic modification of fluoroquinolones by the acetyltransferase variant AAC(6')-Ib-cr [8].

The first plasmid-mediated quinolone resistance gene, *qnrA*, was discovered in 1998 in a clinical isolate of *Klebsiella pneumoniae* in the United States.[9]. Since then, several *qnr* variants (*qnrB*, *qnrS*, *qnrD*, and others) have been reported across diverse Enterobacteriaceae species. These PMQR genes contribute to low-level resistance but are of clinical importance as they can facilitate the selection of high-level resistance when combined with chromosomal mutations.

Accurate detection of quinolone resistance is necessary for antimicrobial stewardship and effective therapy. While phenotypic methods such as disc diffusion, broth microdilution, and gradient diffusion assays (e.g., E-test) remain standard tools for determining minimum inhibitory concentrations (MICs), molecular methods, especially polymerase chain reaction (PCR), have greatly enhanced the ability to detect and characterize resistance determinants [10].

In this study, we employed both phenotypic (E-test MIC) and genotypic (PCR) methods to characterize

plasmid-mediated quinolone resistance in multidrug-resistant *Escherichia coli* isolates from clinical samples collected in Pakistan. To our knowledge, this is among the first molecular studies in this region to investigate the prevalence and distribution of *qnr* genes in clinical *E. coli*, highlighting an emerging resistance threat with significant implications for local antimicrobial policies.

MATERIALS AND METHODS

Samples

A total of 43 clinical isolates of *Escherichia coli* were obtained from urine samples of patients collected between March and December 2023 from two hospitals and two private diagnostic laboratories located in Multan and Lahore, major cities of Punjab, Pakistan. All isolates were confirmed as *E. coli* using standard biochemical and microbiological procedures. Antimicrobial susceptibility testing was performed following the guidelines described by Ericsson and Sherris [11].

Antimicrobial Susceptibility Testing

MICs for ofloxacin, levofloxacin, and ciprofloxacin were determined for 30 out of 43 isolates that were randomly selected (based on geographical representation) by the E-

test method (AB Biodisk, Solna, Sweden), following the manufacturer's instructions [12]. MIC values were interpreted according to the Clinical and Laboratory Standards Institute (CLSI) guidelines.

Plasmid DNA Extraction

For plasmid analysis, isolates were cultured in 25 mL Luria Bertani (LB) broth and incubated at 37 °C for 18–24 hours on an orbital shaker (GFL, Germany). Bacterial cells were harvested using a microcentrifuge (Eppendorf, Germany) and centrifuged at 16,000 × g for 30 seconds. Plasmid DNA was extracted using a modified version of the Kado and Liu method [13], optimized for high-yield recovery from Gram-negative bacteria.

PCR Amplification of *qnr* Genes

All 43 isolates were screened for the presence of PMQR (*qnrA*, *qnrB*, and *qnrS*) using gene-specific primers listed in Table 1. PCR amplification was performed under standardized conditions as described by Cattoir et al. [14]. Positive control strains for *qnrA* and *qnrS* were kindly provided by Dr. Patrice Nordmann (Paris, France). Amplified products were analyzed via agarose gel electrophoresis to confirm the presence of target gene fragments.

Table 1

PCR Primers used for qnr Gene Detection

Primer Name	Sequence (5'→3')	Target Gene	Tm (°C)	GC %	Amplicon Size (bp)	Reference
QnrA 1-6 F	AGAGGATTCTCAGCCAGG	qnrA A1-A6	62	52	580	Cattoir et al., 2007
QnrA 1-6 R	TGCCAGGCACAGATCTTGAC	qnrA A1-A6	62	52		
QnrB 1-6 F	GGMATHGAAATTCGCCACTG	qnrB B1-B6	58	43	264	Cattoir et al., 2007
QnrB 1-6 R	TTTGCYGYCGCCAGTCGAA	qnrB B1-B6	66	65		
QnrS 1-2 F	GCAAGTTCATTGAACAGGGT	qnrS S1-S2	58	43	428	Cattoir et al., 2007
QnrS 1-2 R	TCTAAACCGTCGAGTTCGGCG	qnrS S1-S2	66	57		

RESULTS

Antibiotic Susceptibility Profiles

Multidrug resistance was observed in all 43 clinical *Escherichia coli* isolates obtained from urine samples collected between March and December 2023 from Multan and Lahore, Punjab, Pakistan.

Table 2

Antibiotic Resistance Profile of Escherichia coli Isolates (n=43)

Antibiotic Class	Antibiotic	Susceptible (S)	Intermediate (I)	Resistant (R)
Fluoroquinolones	Ofloxacin (OFX)	4 (9.3%)	3 (7.0%)	36 (83.7%)
	Ciprofloxacin (CIP)	6 (14.0%)	1 (2.3%)	36 (83.7%)
	Levofloxacin (LEV)	6 (14.0%)	0 (0.0%)	37 (86.0%)
	Amoxicillin (AMC)	2 (4.7%)	7 (16.3%)	34 (79.0%)
Cephalosporins	Ceftazidime (CTX)	11 (25.6%)	2 (4.7%)	30 (69.8%)
Aminoglycosides	Amikacin (AK)	15 (34.9%)	14 (32.6%)	14 (32.6%)
Bacteriostatic	Sulfamethoxazole (STX)	9 (20.9%)	0 (0.0%)	33 (79.1%)
Analog	Tetracycline (TE)	0 (0.0%)	0 (0.0%)	43 (100.0%)

Disc diffusion testing revealed high resistance rates ranging from 70% to 86% against fluoroquinolones

(ofloxacin, ciprofloxacin, levofloxacin) as well as other commonly used antibiotics, including amoxicillin, ceftazidime, and sulfamethoxazole (Table 2). Resistance to amikacin was comparatively lower, observed in 32% of isolates. These results indicate a widespread multidrug resistance phenotype in this population.

MIC Determinations

Minimum inhibitory concentrations (MICs) for ofloxacin, ciprofloxacin, and levofloxacin were determined using the E-test on 30 selected isolates, confirming the high-level resistance observed phenotypically. Approximately 60% of isolates were resistant to ofloxacin and levofloxacin, while ciprofloxacin showed an even higher resistance rate of 80% (Table 3a). These findings corroborate the disc diffusion data, highlighting significant fluoroquinolone resistance among clinical isolates (Table 3b).

Table 3a

Fluoroquinolone MIC Results by E-Test (n=30)

Antibiotic	Susceptible (%)	Intermediate (%)	Resistant (%)
Ofloxacin (OFX)	2 (6.7%)	11 (36.7%)	17 (56.7%)
Ciprofloxacin (CIP)	0 (0.0%)	6 (20.0%)	24 (80.0%)
Levofloxacin (LEV)	1 (3.3%)	11 (36.7%)	18 (60.0%)

Table 3b
Fluoroquinolone Resistance by Disc Diffusion (n=30)

Antibiotic	Susceptible (%)	Intermediate (%)	Resistant (%)
Ofloxacin (OFX)	2 (6.7%)	1 (3.3%)	27 (90.0%)
Ciprofloxacin (CIP)	4 (13.3%)	0 (0.0%)	26 (86.7%)
Levofloxacin (LEV)	3 (10.0%)	0 (0.0%)	27 (90.0%)

Molecular Characterization of *qnr* Genes

Molecular screening via PCR using specific primers (Table 1) revealed that plasmid-mediated quinolone resistance genes were prevalent among the isolates. The *qnrB* gene was the most frequently detected, present in 79.2% of Multan isolates and 73.7% of Lahore isolates (Table 4). In contrast, *qnrS* and *qnrA* genes were less common, with *qnrS* detected in 4.2% and 10.5%, and *qnrA* in 4.2% and 5.3% of isolates from Multan and Lahore, respectively. Notably, 12.5% of isolates from Multan and 10.5% from Lahore did not harbor any of the tested *qnr* genes, suggesting the possible presence of novel or less characterized plasmid-mediated quinolone resistance determinants in this region.

Table 4
*Prevalence of *qnr* Determinants in *E. coli* Isolates from Multan and Lahore*

<i>qnr</i> Determinant	Multan (n=24)	Lahore (n=19)
<i>qnrA</i>	1 (4.2%)	1 (5.3%)
<i>qnrB</i>	19 (79.2%)	14 (73.7%)
<i>qnrS</i>	1 (4.2%)	2 (10.5%)
Not grouped	3 (12.5%)	2 (10.5%)

Statistical Analysis

All experiments were performed in triplicate, and results are presented as means $\pm$ SEM. Pearson's correlation coefficient analysis using IBM SPSS 21.0 revealed a strong positive correlation ($r = 0.85$, $p < 0.01$) between the presence of the *qnrB* gene and elevated ciprofloxacin MIC values, indicating that *qnrB* significantly contributes to high-level fluoroquinolone resistance in these clinical isolates.

DISCUSSION

Antibiotics were once hailed as "magic bullets" that would decisively end bacterial infections. However, the early optimism of the 1960s and 1970s has given way to a sobering reality: over 40 years later, infectious diseases remain among the top causes of mortality worldwide, exacting a heavy toll in both developing and developed nations [15]. The rapid emergence of multidrug-resistant (MDR) bacteria has compromised the efficacy of many frontline antibiotics, dramatically narrowing therapeutic options and, in some cases, leaving clinicians powerless against persistent infections. Urinary Tract Infections (UTIs), one of the most common bacterial infections globally, exemplify this growing crisis with escalating resistance trends reported across diverse geographical and socioeconomic contexts [16].

Among uropathogens, *Escherichia coli* stands out as the dominant and most clinically significant culprit [17]. In our investigation, we meticulously selected quinolone-resistant *E. coli* isolates from two major Punjab cities to

probe the molecular underpinnings of resistance. The isolates displayed alarming levels of resistance not only to fluoroquinolones but also to an array of other antibiotics, including Ampicillin, Augmentin, Amikacin, Amoxicillin, Sulfamethoxazole, Cefixime, and Tetracycline, underscoring the multifaceted challenge posed by MDR strains (Table 2) [18].

The evolutionary trajectory of fluoroquinolone resistance in Pakistan reflects a timeline where older agents such as Ofloxacin and Ciprofloxacin predate Levofloxacin's introduction. Globally, Levofloxacin is often considered more potent than its predecessors [19]. Strikingly, our data reveal that Ciprofloxacin resistance surpasses that of both Levofloxacin and Ofloxacin across clinical isolates—a finding that defies conventional expectations and signals selective pressures unique to this region. Methodologically, while both disc diffusion and E-test methods yielded consistent results, the E-test emerged as superior in precision and reliability, albeit at a higher cost.

A paradigm shift in understanding quinolone resistance centers on plasmid-mediated quinolone resistance (PMQR) genes, particularly the *qnr* family, which act as stealthy genetic weapons disseminating resistance beyond chromosomal mutations [20, 21]. The global distribution of *qnr* variants (*qnrA*, *qnrB*, *qnrS*, among others) in Enterobacteriaceae underscores their role in shaping the antimicrobial resistance landscape [18, 22]. Our study reveals noteworthy prevalence patterns: *qnrA* was detected at 4.65%, echoing reports from France and China but underscoring a worrying foothold within clinical isolates in Pakistan [30, 31]. Notably, *qnrA* appears more dominant in the U.S. compared to Eastern Asia, positioning our findings at a critical intersection of regional and global resistance trends [32].

The prominence of *qnrB* in our isolates is particularly striking, with a prevalence of 76.7%, far exceeding many reports worldwide where values typically range from 3% to 31% [38]. This parallels high prevalence rates documented in Korean hospital isolates [35, 36], positioning Punjab as a potential hotspot for this resistance determinant. Such widespread dissemination of *qnrB* in clinical *E. coli* isolates raises urgent questions about horizontal gene transfer, selective antibiotic pressure, and infection control practices in the region.

QnrS prevalence, though traditionally low worldwide, was found at 6.97% in our cohort, higher than *qnrA* and exceeding rates reported in regions like Morocco and Nigeria [39, 42]. These findings reinforce the notion that plasmid-mediated resistance genes continue to diversify and gain footholds in diverse settings.

Importantly, 10.5-12.5% of isolates lacked amplification for the *qnrA*, *qnrB*, and *qnrS* genes, suggesting the presence of other PMQR variants or alternative resistance mechanisms. Recent literature points to emerging *qnr* variants such as *qnrC*, *qnrD*, and *qnrV*, reflecting an evolving genetic arms race between bacteria and antibiotics [43, 44]. Our data emphasize the urgent need to expand molecular surveillance to encompass these novel determinants, as well as chromosomal mutations that synergistically enhance resistance.

Regional disparities in resistance patterns were evident, with isolates from Multan demonstrating a higher burden of quinolone resistance compared to Lahore, possibly indicating differential antibiotic usage or stewardship practices. While this study represents a critical step in mapping quinolone resistance in Pakistan, its scope was limited to three PMQR genes, underscoring the necessity for broader, integrative studies that incorporate comprehensive genotypic and phenotypic analyses.

In conclusion, our findings highlight an alarming increase in PMQR in *E. coli* clinical isolates from Punjab,

Pakistan, with unprecedented high prevalence of *qnrB* and significant presence of other *qnr* genes. These revelations deepen our understanding of South Asia resistance dynamics and highlight the urgent imperative for improved antimicrobial stewardship, strong surveillance, and novel therapeutic strategies to stop the relentless spread of multidrug resistance.

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