

# Assessment of the Frequency of *qnrS* and *qnrA* Genes in Clinical Isolates of *Klebsiella pneumoniae* and Their Relationship with Antibiotic Resistance Patterns and Iron Oxide Nanoparticles

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## Abstract

**Background:** *Klebsiella pneumoniae* is a gram-negative, short, facultative anaerobic bacillus that commonly grows in laboratory culture environments, including blood agar, EMB, Mueller-Hinton agar, and nutrient agar. As an opportunistic pathogen, it poses significant treatment challenges due to increasing antibiotic resistance.

**Objectives:** The purpose of this study is to determine the relationship between antibiotic resistance and the frequency of *qnrS* and *qnrA* genes in clinical isolates of *Klebsiella pneumoniae*.

**Methods:** In this study, 100 patients referred to Sina Hospital in Tabriz due to urinary tract infections (UTIs) were examined. Common biochemical tests confirmed the presence of *Klebsiella* in 20 samples. The antibiotic sensitivity pattern of the isolates was determined using the disc diffusion method, and the results of the antibiogram test were analyzed. The resistance of the samples to five different types of antibiotics was assessed.

**Results:** In this study, the highest antibiotic resistance was observed against nalidixic acid. The presence of the *qnrS* gene was confirmed in five isolates of *Klebsiella pneumoniae*, while the *qnrA* gene was absent in all isolates. The sensitivity of the *Klebsiella pneumoniae* strain to iron oxide nanoparticles was evaluated using the well method at a concentration of 0.08 g in 100 ml of water. One sample in a volume of 100 ml and two samples in a volume of 200 ml formed halos with diameters of 11 mm, 14 mm, and 12 mm, respectively.

**Conclusion:** The findings of the present study showed that the frequency of *qnrS* genes was high in fluoroquinolone-resistant samples of *Klebsiella pneumoniae*, and this factor could lead to progressive antimicrobial resistance in different hospital departments.

**Keywords:** *Klebsiella pneumoniae*, Antibiotic Resistance, *qnrA* Gene, *qnrS* Gene, Iron Oxide Nanoparticles

## 1. Background

*Klebsiella* is a non-motile, gram-negative, capsule-shaped, rod-shaped bacterium characterized by parallel sides and rounded, sharp ends. It is considered one of the important members of the *Enterobacteriaceae* family and is shorter and narrower than other members of this family. This bacterium is one of the gram-negative bacteria commonly associated with hospital infections and can cause severe infections accompanied by high fever. The genus includes seven different species: *Klebsiella ozonae*, *Klebsiella rhinoscleromatis*, *Klebsiella oxytoca*, *Klebsiella trigena*, *Klebsiella planticola*, *Klebsiella ornithinolytica*, and *Klebsiella pneumoniae*.<sup>1</sup> *Klebsiella pneumoniae* is a gram-negative bacillus that is short, facultatively anaerobic, non-spore-forming, and non-motile, featuring a polysaccharide capsule. It is recognized as the most significant

genus and the most common pathogenic member of the *Klebsiella* species.<sup>2</sup> *Klebsiella pneumoniae* resides in the digestive tract, respiratory tract, and genitourinary tract of humans, its primary host. It can cause a wide range of infections, including septicemia, pneumonia, urinary tract infections, and meningitis.<sup>3</sup> *Klebsiella pneumoniae* can ferment sugars such as glucose and lactose and hydrolyze urea. It can be cultured in various laboratory media, including blood agar, Mueller-Hinton agar, nutrient agar, and MacConkey agar. This bacterium possesses several pathogenic factors encoded by virulence genes, including a polysaccharide capsule, lipopolysaccharides, pili, and siderophores. A wide range of antibiotics is used to treat infections caused by *Klebsiella pneumoniae*, including beta-lactams, aminoglycosides, quinolones, and fluoroquinolones.<sup>4</sup> Quinolones and fluoroquinolones

were first introduced by George Lasher et al. to treat infections caused by *Klebsiella pneumoniae*. These antibiotics target both gram-positive and gram-negative bacteria by inhibiting DNA replication. Fluoroquinolones are a subclass of quinolones, modified by adding fluorine at position number six. Their positive attributes, such as broad-spectrum activity, high potency, and suitability for oral consumption, have contributed to their widespread use.<sup>5</sup> Resistance to quinolones is primarily caused by mutations in the DNA gyrase A subunit. Topoisomerase IV, often a tetrameric enzyme, consists of two ParC subunits and two ParE subunits. In gram-negative bacteria, topoisomerase IV serves as a secondary target for quinolones. Additionally, *qnr* is responsible for plasmid-mediated resistance to quinolones, as it prevents the inhibitory effects of these antibiotics on both DNA gyrase and topoisomerase IV enzymes.<sup>6</sup> Excessive and incorrect use of antibiotics has resulted in the emergence of bacterial resistance, creating a significant global challenge. Researchers are actively seeking suitable alternatives with fewer side effects. Nanoparticles, which are particles with dimensions ranging from 1 to 100 nm, possess a high surface-to-volume ratio and exhibit distinct characteristics compared to larger particles. These unique properties make them promising candidates for developing new antimicrobial agents and therapies.<sup>7</sup> Nanoparticles possess the ability to kill microorganisms, making them a promising alternative to traditional antibiotics. Metal oxide nanoparticles, including zinc oxide, aluminum oxide, and iron oxide, are particularly favored in medical and chemical sciences due to their biocompatibility, chemical stability, and low toxicity. These properties enhance their potential for safe and effective applications in combating infections and improving health outcomes.<sup>8</sup> Iron oxide nanoparticles, typically prepared in sizes smaller than 20 nm, are regarded as a suitable option for combating pathogenic agents. Their high reactivity allows iron ions to adhere to cell wall proteins, leading to cellular damage and death by altering the cell wall structure. This mechanism highlights their potential as effective antimicrobial agents in addressing bacterial infections.<sup>9</sup> The *qnr* gene encodes a protein approximately 200 amino acids in length, belonging to the pentapeptide repeating protein family. This protein plays a role in bacterial resistance to quinolone antibiotics, contributing to the challenge of treating infections caused by resistant strains. Understanding the structure and function of the *qnr* protein can provide insights into developing strategies to combat antibiotic resistance.<sup>10</sup> This protein comprises two domains separated by a glycine amino acid and contains a cysteine amino acid at position i. *Qnr* proteins confer resistance to quinolones through two distinct mechanisms: First, they reduce the binding of DNA gyrase and topoisomerase IV to DNA. Second, these proteins bind to DNA gyrase and

topoisomerase IV, preventing quinolones from accessing the sites where the enzymes have induced breaks in the DNA.<sup>11</sup> Antibiotic resistance in *Klebsiella pneumoniae* against quinolones has raised significant concerns regarding the treatment of hospital infections. There are limited reports on the prevalence of plasmid-dependent quinolone resistance genes in *Klebsiella pneumoniae* isolates from Iran. This gap in knowledge highlights the need for further research to understand the extent of resistance and to inform treatment strategies effectively.

## 2. Objectives

The purpose of this study is to investigate the relationship between antibiotic resistance and the frequency of *qnrS* and *qnrA* genes in clinical isolates of *Klebsiella pneumoniae*. As antibiotic resistance continues to pose a significant challenge in healthcare settings, understanding the genetic factors contributing to this resistance is crucial. By analyzing the prevalence of *qnrS* and *qnrA* genes, which are known to play a role in quinolone resistance, this research aims to provide insights into the mechanisms of resistance in *Klebsiella pneumoniae*. The findings may help inform treatment options and strategies to combat infections caused by this pathogen in clinical settings.

## 3. Methods

### 3.1. Sample Collection

To conduct this study, a sample of 100 patients with urinary tract infections was collected from Sina Hospital in Tabriz over a four-month period, from September 2023 to January 2024. Various biochemical tests were performed to identify *Klebsiella pneumoniae* isolates, including sugar fermentation in Triple Sugar Iron (TSI) agar, indole production and motility in Sulfur, Indole, Motility (SIM) medium, and reactions in the Methyl Red and Voges-Proskauer (VP-MR) tests. Growth was also assessed in Simmons citrate and urea media, with a standard strain used as a control. The clinical isolates of *Klebsiella pneumoniae* were cultured in trypticase soy broth (TSB) and Muller-Hinton broth (MHB) with 30% glycerol, then stored at -70 °C.

### 3.2. Sensitivity Assay of *Klebsiella pneumoniae* to Antibiotic and Iron Oxide NPs

The antibiotic resistance pattern was assessed using the disc diffusion method per CLSI guidelines. A 0.5 McFarland bacterial suspension was inoculated on Muller-Hinton agar, followed by the placement of antibiotic discs (nalidixic acid, ciprofloxacin, norfloxacin, levofloxacin, and ofloxacin). After 24 hours at 37 °C, inhibition zones were measured to determine resistance. In this study, a microbial suspension of *Klebsiella pneumoniae* was prepared to a concentration equivalent to 0.5 McFarland and cultured on Mueller-Hinton agar plates using a sterile

swab in three directions. Four wells, each 10 mm in diameter, were created on the plates. Three wells received 50, 100, and 200 µl of a nanoparticle mixture, while the fourth well served as a control with DMSO. The plates were incubated for 24 hours, after which the diameter of the bacterial growth inhibition halo was measured. This experiment was conducted in triplicate to ensure reliability.

### 3.3. Molecular Assays

In this research, a specialized kit for viral gene extraction was utilized. A sample equivalent to 0.5 McFarland ( $10^8$ - $10^9$ ) was prepared, and 200 µl of cell/blood lysis solution was added. Following this, 20 µl of proteinase K was

incorporated, and the mixture was incubated at 70 °C for 10 minutes. Afterwards, 100 µl of isopropanol was added, and the mixture was centrifuged at 1200 rpm, discarding the supernatant. Subsequently, 500 µl of washing solution 1 was added and centrifuged again for one minute at 1200 rpm, followed by the addition of 500 µl of washing solution 2 and another centrifugation at the same speed. A final addition of 100 µl of washing buffer was made, and the centrifugation was repeated. Template DNA was then collected. Primers were prepared based on the literature and subjected to BLAST analysis, as outlined in Table 1. The quality of the extracted DNA and PCR products was assessed using agarose gel electrophoresis.

**Table 1.** Sequence of Primers

Gene name		Seq (5-3)	Lenth (bp)	TM
<i>qnrA</i>	F	AGAGGATTTCACGCC	21	60
	R	TGCCAGGCACAGATCTTGAC	22	
<i>qnrS</i>	F	GCAATTCATTGAACAGGGT	24	58
	R	TCTAAACCGTCGATTCGCG	25	

### 3.4. Statistical Analysis

The data obtained were analyzed using SPSS version 27 statistical software, and corresponding graphs were generated. A one-way ANOVA test was conducted on the data, with a significance threshold set at  $P < 0.05$ .

## 4. Results

### 4.1. Antimicrobial Assay

A total of 100 urine samples from patients referred to the laboratory of Sina Hospital in Tabriz in 1401 were analyzed. Among these samples, 20 were identified as *Klebsiella pneumoniae*. Identification results from staining and biochemical tests indicated that all samples exhibited a pink coloration with Gram staining and were observed as rod-shaped bacteria under a light microscope.

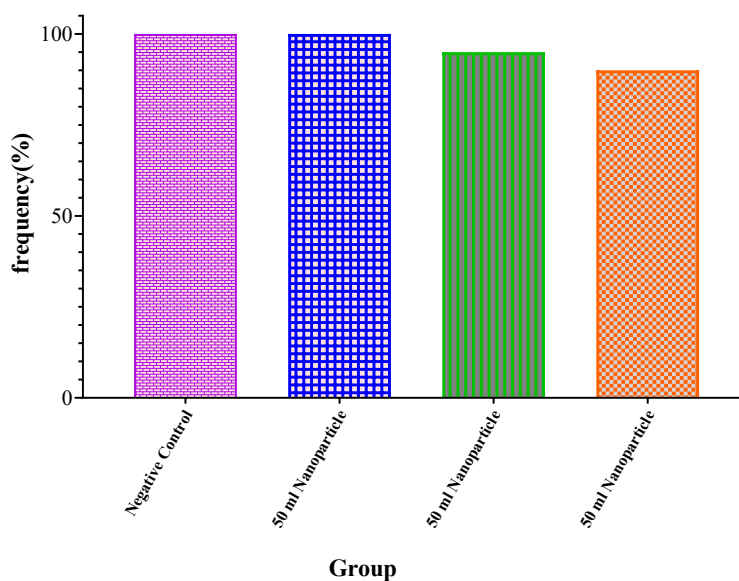
The sensitivity of the *Klebsiella pneumoniae* strain to iron nanoparticles is illustrated in Figure 1.

### 4.2. Antibiogram Test Results

The antibiogram results revealed that the highest antibiotic resistance was observed against Nalidixic acid, with 55% of samples showing resistance. Additionally, 35% of samples were resistant to Ciprofloxacin, while resistance to Norfloxacin, Levofloxacin, and Ofloxacin antibiotics was recorded at 30%. The antibiogram test results and the frequency of resistance to antibiotics are illustrated in Figure 2.

### 4.3. Identification of Genes

To validate the results of biochemical tests and accurately



**Figure 1.** The Resistance to iron Oxide Nanoparticles were 95% in 100 ml and 90% in 200 ml. In the 100 ml, iron oxide nanoparticles inhibited growth in one sample and in the 200 ml, iron oxide nanoparticles inhibited growth in two samples.

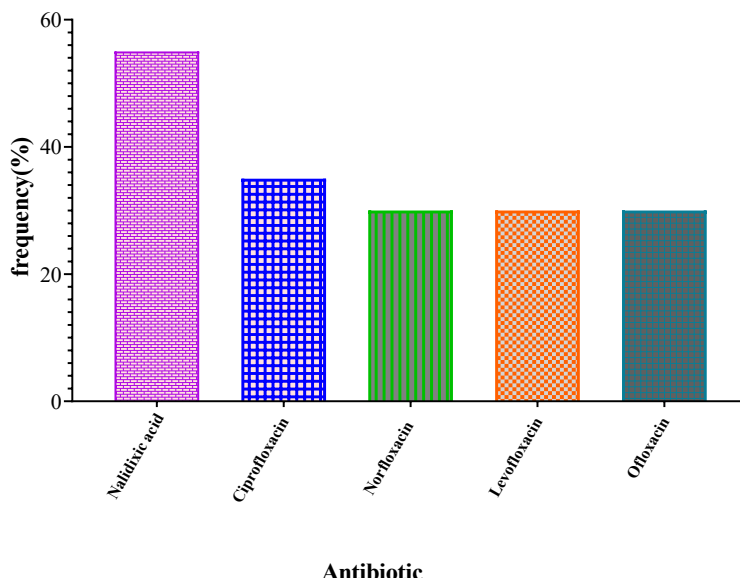


Figure 2. Resistance of Samples to Five Types of Antibiotics.

detect the *qnrS* and *qnrA* genes in clinical isolates of *Klebsiella pneumoniae*, a PCR reaction was performed. The findings revealed that the frequency of the *qnrS* gene

in positive samples of *Klebsiella pneumoniae* was 25%, while the frequency of the *qnrA* gene was found to be zero percent (Figures 3).

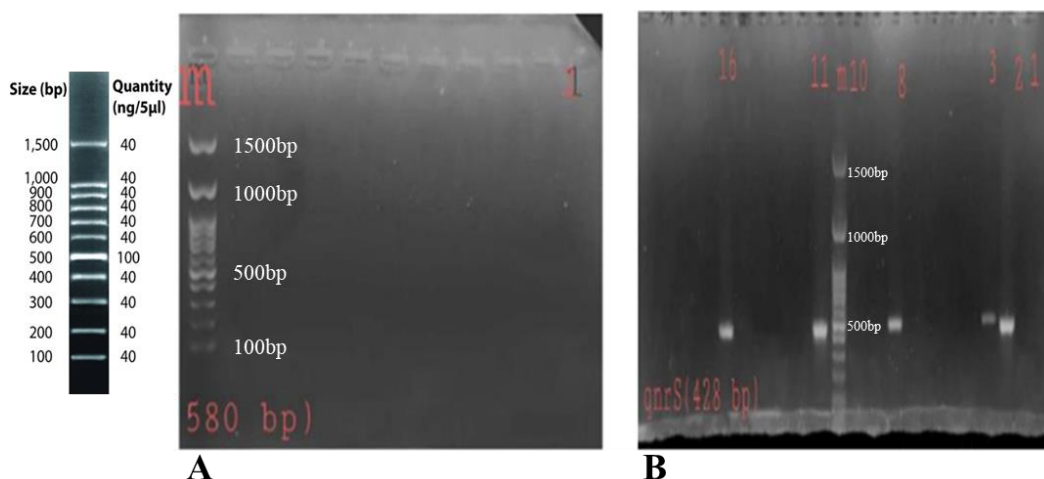


Figure 3. The *qnrA* gene was not found in *Klebsiella pneumoniae* (A), while the frequency of the *qnrS* gene was 25% (B).

5. Discussion

The aim of this study was to determine and investigate the frequency of plasmid-dependent quinolone-resistant (*qnr*) genes in *Klebsiella pneumoniae* isolates isolated from hospitalized patients. Antibiotic sensitivity tests were performed using the disk diffusion method. The resistance of the samples to five types of antibiotics was evaluated, and the size of the non-growth halos created was compared with the CLSI standard table to determine their sensitivity (S), resistance (R), and intermediate (I) status. In this study, the resistance to Nalidixic acid was 55%, ciprofloxacin 35%, levofloxacin 30%, norfloxacin 30%, and ofloxacin 30%. The presence of *qnrA* and *qnrS* genes was evaluated using the PCR method. The *qnrS* gene was found in 25% of the positive bacteria samples, while the *qnrA* gene was not detected. In this study, the

presence of *qnrS* genes and resistance to the studied antibiotics were also evaluated. Among the samples that had the *qnrS* gene, four samples (80%) were resistant to the investigated antibiotics. Hence, the frequency of the *qnrS* gene was higher in antibiotic-resistant strains compared to sensitive strains containing the gene. Following the increase in the prevalence of microbial resistance against chemical antimicrobial agents, the biological effects of metal nanoparticles have recently received special attention from researchers. In this context, the present study was conducted to determine the antimicrobial effects of iron oxide nanoparticles using the well method on *Klebsiella pneumoniae* isolates. The inhibitory effect was observed in only two out of 20 samples. Specifically, samples 6 and 18 showed halos with a diameter of 11, 14, and 12 mm when a concentration of 0.08 grams in 100 µl

of water was used. In this study, the resistance to iron oxide nanoparticles was 95% in 100 ml and 90% in 200 µl. In 100 µl, iron oxide nanoparticles inhibited growth in one sample and in 200 µl, iron oxide nanoparticles inhibited growth in two samples. A study conducted in Kerman investigated the bactericidal effects of iron oxide nanoparticles on six bacteria isolated from urinary tract infections using the well method. Iron nanoparticles were effective on all six bacteria, and the minimum concentration that inhibited the growth of *Proteus mirabilis*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, and *Serratia marcescens* was 1.32, 1.10, 1.12, 1.18, 1.10, and 1.12 mg/ml, respectively. The minimum bactericidal concentration was also determined to be 1.22, 1.10, 1.8, 12.1, 1.32, 1.12, and 1.12 mg/ml, respectively.<sup>12</sup> In our study, we determined the sensitivity of *Klebsiella pneumoniae* strains to iron oxide nanoparticles and their effects using the well method. One sample with a volume of 100 µl created a halo with a diameter of 11 mm, while two samples with volumes of 200 µl created halos with diameters of 14 mm and 12 mm. Salimbahrami et al. (2019) investigated the phenotypic and genotypic resistance to fluoroquinolones in *Klebsiella pneumoniae* isolated from patients hospitalized in educational-therapeutic centers in Sari city. In this descriptive cross-sectional study, bacterial isolates were identified using conventional methods and biochemical tests. Resistance to fluoroquinolone antibiotics was investigated using the disk diffusion method. After evaluating the resistance, the identification and amplification of *qnrA*, *qnrB*, and *qnrS* genes in the isolates were done by PCR. Out of the total 90 tested isolates, the resistance of fluoroquinolone family antibiotics from highest to lowest included nalidixic acid (55%), ciprofloxacin (36%), ofloxacin (31%), levofloxacin (29%) and norfloxacin (22%). Based on the results of the polymerase chain reaction technique, 47 (52%), 22 (25%), and 21 (23%) of the isolates carried *qnrB*, *qnrA*, and *qnrS* genes, respectively.<sup>13</sup> In this study, resistance to nalidixic acid antibiotics was 55%, ciprofloxacin 35%, levofloxacin 30%, norfloxacin 30%, ofloxacin 30%, and 25% of the isolates carried *qnrS* genes. Hashemi et al. (2014) investigated the detection of metallo-beta-lactamases, broad-spectrum beta-lactamases, and outer membrane porins in *Klebsiella pneumoniae* isolates isolated from patients hospitalized in Tehran hospitals. This descriptive cross-sectional study was conducted from March 2011 to March 2012 on 100 isolates of *Klebsiella pneumoniae*. Antibiotic sensitivity tests were performed by disc diffusion and microdilution broth based on CLSI guidelines. The results showed that in this study, the prevalence of wide-spectrum beta-lactamase in *Klebsiella pneumoniae* strains is worrisome and requires infection control measures, including management of antibiotic consumption and rapid

identification of resistant isolates.<sup>14</sup> In the Nourozi et al study, 88 isolates of *Klebsiella pneumoniae* were prepared and evaluated. The results of disc diffusion showed that 39.3%, 32.1%, 27.4%, 27.1%, and 22.6% of the strains were completely resistant to nalidixic acid, norfloxacin, ofloxacin, ciprofloxacin, and levofloxacin, respectively. The *qnrB* gene (43% of isolates) was the most common gene identified, followed by *qnrS* (34% of isolates) and *qnrA* (23% of isolates) alone or in combination with other genes.<sup>15</sup> In our study, resistance to nalidixic acid antibiotics was 55%, ciprofloxacin 35%, levofloxacin 30%, norfloxacin 30%, and ofloxacin 30%. The *qnrS* gene (25%) was the most common gene identified. Disc diffusion was performed to determine the drug resistance pattern of 70 isolates of *Klebsiella pneumoniae* prepared from Ilam. The resistance genes were then analyzed using the PCR method. Finally, the PFGE method was used for 40 isolates. Antibiotic resistance results showed that 97.5%, 95%, 100%, 97.5%, 100%, 90%, 100%, and 100% of isolates were resistant to gentamicin, tobramycin, kanamycin, amikacin, norfloxacin, ciprofloxacin, nalidixic acid, and nalidimic acid. The highest frequency was for the gene *qnrB* (92.5%) and *apha6* (12.5%), while the lowest frequency was related to IMP (5.7%), *qnrS* (5%), and *aadB* (2.5%).<sup>16</sup> Unlu et al. (2020) investigated the resistance genes in 22 isolates of *Klebsiella pneumoniae* isolated from ICU hospital patients. The results showed resistance against ciprofloxacin in 72% of the isolates. Moreover, the analysis of quinolone resistance genes revealed that the frequency of *qnrS* and *qnrA* genes was 86% and 27%, respectively.<sup>17</sup> Gholamnejad et al. (2022) studied plasmid-dependent quinolone resistance genes in *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Escherichia coli* from surgical site infections. In their analysis of 7 *Klebsiella pneumoniae* isolates, they found 71% resistance to ciprofloxacin and levofloxacin, and 57% resistance to ofloxacin. The *qnrS* gene was present in 20% of the isolates, while the *qnrA* genes were not detected.<sup>18</sup> In this study, we also examined the presence of *qnrS* genes and their association with resistance to the antibiotics under study. Among the samples that had the *qnrS* gene, 4 samples (80%) were resistant to the antibiotics being studied. Therefore, the frequency of the *qnrS* gene in the strains resistant to the specified antibiotics was more frequent than in the sensitive strains containing the gene.

## 6. Conclusion

According to the results of this study, *qnrS* and *qnrA* are effective genes in *Klebsiella pneumoniae* that have different effects on clinical isolates of *Klebsiella pneumoniae* by influencing the expression of genes involved in these strains. The findings of the present study showed that the frequency of *qnrS* genes was high in fluoroquinolone-resistant samples of *Klebsiella pneumoniae*. This factor

could lead to progressive antimicrobial resistance in different hospital departments.

### Research Highlights

#### What Is Already Known?

- *Klebsiella pneumoniae*, as an opportunistic pathogen, poses significant treatment challenges due to increasing antibiotic resistance.
- The *qnr* gene encodes a protein that plays a role in bacterial resistance to quinolone antibiotics.

#### What Does This Study Add?

- The frequency of *qnrS* genes was high in fluoroquinolone-resistant samples of *Klebsiella pneumoniae*.
- The *qnrS* genes could lead to progressive antimicrobial resistance in different hospital departments.

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### Author Contributions

M.Z, H.B.Z, and S.H developed the theoretical formalism, performed the analytic calculations, and conducted the numerical simulations. The authors contributed to the final version of the manuscript. H.B.Z supervised the project.

### Conflict of Interest Disclosures

All authors declared that they have no conflict of interest.

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