

# Association between the rate of fluoroquinolones-resistant Gram-negative bacteria and antibiotic consumption from China based on 145 tertiary hospitals data in 2014

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## Research

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# Abstract

This study aimed to investigate the relationship between the rate of fluoroquinolones-resistant (FQR) gram-negative bacteria and antibiotic consumption intensity in 145 tertiary hospitals from China in 2014. Methods A retrospective study using national surveillance data from 2014 was conducted. Data on the annual consumption of each antibiotic, and the rate of FQR gram-negative bacteria, were collected from each participating hospital, and the correlation between antibiotic consumption and FQR rate was simultaneously investigated. Results The overall antibiotic consumption intensity among the hospitals varied between 23.93 and 115.39 defined daily dosages (DDDs) per 100 patient-days (median, 46.30 DDDs per 100 patient-days). Cephalosporins were the most commonly prescribed antibiotics, followed by fluoroquinolones, penicillins, and carbapenems, and the rate of FQR gram-negative bacteria from each hospital varied. The correlation analysis showed significantly relationship between the percentage of FQR *E. coli* and the consumption of FQs consumption ( $r=0.308$ ,  $p<0.01$ ) and levofloxacin ( $r=0.252$ ,  $p<0.01$ ). For FQR *K. pneumoniae*, not only FQs ( $r=0.291$ ,  $p<0.01$ ) and levofloxacin ( $r=0.260$ ,  $p<0.01$ ) use but also carbapenems ( $r=0.242$ ,  $p<0.01$ ) and overall antibiotics ( $r=0.247$ ,  $p<0.01$ ) use showed significant correlation. A strong correlation was observed between the resistant proportion of FQR *P. aeruginosa* and the consumption of all antibiotics ( $r=0.260$ ,  $p<0.01$ ), FQs ( $r=0.319$ ,  $p<0.01$ ) and levofloxacin ( $r=0.377$ ,  $p<0.01$ ). The percentage of levofloxacin-resistant *A. baumannii* was significantly correlated with the consumption of all antibiotics ( $r=0.282$ ,  $p<0.01$ ), third-generation cephalosporins excluding combinations with beta-lactamase inhibitors ( $r=0.246$ ,  $p<0.01$ ), FQs ( $r=0.254$ ,  $p<0.01$ ) and levofloxacin ( $r=0.336$ ,  $p<0.01$ ). However, the correlation of the ciprofloxacin-resistant *A. baumannii* and the antibiotics consumption was not found. Conclusions A significant relationship was demonstrated between the antibiotic consumption and the rates of FQR gram-negative bacteria. As unreasonable antibiotics usage remains crucial in the proceeding of resistant bacteria selection, our study could greatly promote the avoidance of unnecessary antibiotic usage.

## Background

Fluoroquinolones (FQs) were introduced as broad-spectrum antibiotics. Because of their excellent oral bioavailability, FQs have been widely prescribed to patients with bacterial infections. With the widespread use of FQs, FQs-resistant (FQR) gram-negative bacteria are gradually increasing, limiting the choices of antibiotics available for treating infections.

According to surveillance report of China in the first half of 2018, the overall prevalence of ciprofloxacin-resistant strains was 57.8% in *Escherichia coli*, 35.4% in *Klebsiella* spp., 17.1% in *P. aeruginosa* and 75.4% in *A. baumannii* respectively. FQR gram-negative bacteria isolates were reported as independent risk factors for in-hospital mortality, which have been associated with greater hospital expenses and poor clinical outcomes<sup>1-5</sup>. Moreover, compared with other phenotypic resistance patterns, FQR *E. coli* and *Klebsiella* spp hospital-onset bacteremia had a larger relative impact on mortality<sup>6</sup>. It is reported that previous colonization of FQR *E. coli* can lead to the spread of extended-spectrum beta-lactamase (ESBL) after the use of quinolone prophylaxis<sup>5,7</sup>. The high probability of ESBL production by FQR gram-negative

bacteria makes anti-infective treatment more difficult. The risk of gram-negative bloodstream infection increased over time in parallel with an increased FQR rate, and the unadjusted mortality rate was 18% for FQR gram-negative bloodstream infections<sup>1,8</sup>.

It is plausible that the irrational use of antibiotics can increase selective pressure of bacterial resistance, which is considered to be the main factor contributing to the emergence of resistance. In this study, we investigated the correlation between the FQR rate of gram-negative bacteria and antibiotic consumption.

## Methods

### 2.1 Study design

A cross-sectional study including 145 voluntarily participating hospitals was conducted. Data on antibiotic consumption and the FQR rate of gram-negative bacteria from inpatients at each participating hospital in 2014 were collected. Then the correlation between antibiotic consumption and resistant rate was performed.

### 2.2 Data collection

Each participating hospital reported annual data of 2014. They were required to report antibiotic consumption data to national antibacterial drug clinical consumption survey network. While bacterial resistance data were obtained from China antimicrobial resistance surveillance system.

Administrative data of each participating hospital, including hospital type, administrative region, number of beds, admissions and patient-days was recorded.

### 2.3 Measurement of Antibiotic Consumption

Hospital pharmacists reported each antibiotic consumption to the national antibacterial drug clinical consumption survey network annually. According to Anatomic Therapeutic Chemical (ATC) classification system<sup>9</sup>, data on consumption of all antibiotics (J01), beta-lactams (J01C+J01D), beta-lactam-beta-lactamase inhibitor combinations, beta-lactams excluding combinations with beta-lactamase inhibitors (CBLI), penicillins (J01C), penicillins excluding CBLI (J01C-J01CR), cephalosporins (J01DB+J01DC+J01DD+J01DE), cephalosporins excluding CBLI, third-generation cephalosporins (J01DD), third-generation cephalosporins excluding CBLI, fourth-generation cephalosporins (J01DE), carbapenems (J01DH), FQs (J01MA), ciprofloxacin, levofloxacin and moxifloxacin were analyzed. Antibiotic consumption was expressed as antibiotics consumption intensity, which was indicated as the number of defined daily dose (DDDs) per 100 patient-days. According to the World Health Organization ATC/DDD classification, DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. Patient-days were defined as number of discharged patients during the same period multiplied by the average length of stay of hospitalized patients in the same period. Then, data on antibiotic consumption were analyzed, according to the main classes.

## 2.4 Antibiotic resistance

Each participating hospital was required to report data about *E. coli*, *K. pneumoniae*, *P. aeruginosa* and *A. baumannii*, isolated from all sample sources (e.g., bloodstream, respiratory tract, urinary tract, wound pus, other sterile body fluids, cerebrospinal fluid, genital tract and others). The duplicate strains were excluded, isolates of each species from each patient who recovered within 7 days were considered duplicate. Then, the number of isolates that were FQR and the total number of bacterial strain isolated from clinical specimens were collected. All hospitals must adhere to the Clinical and Laboratory Standards Institute 2014 guidelines and antibiotic susceptibility tests are performed with a routine laboratory method. FQs-resistance was defined as a strain resistant to levofloxacin or ciprofloxacin. If the resistance rates were different, the higher resistance rate was considered as the resistance rate of the strain to FQs. The FQR rate was calculated as the number of FQR isolates divided by the total number of the isolates of the same species tested multiplied by 100. For *A. baumannii*, ciprofloxacin and levofloxacin-resistant rate were derived separately because of their great differences. Each laboratory can ensure the consistency and standardized assessment of the antimicrobial resistance data through quality control. The antibiotic resistance data were processed by Whonet 5.6 software. Quality control bacterial strains were *E. coli* ATCC25922, *K. pneumoniae* ATCC700603, *P. aeruginosa* ATCC27853 and *A. baumannii* ATCC19606. The hospital with isolated strains less than 50 isolates per year was excluded from the study.

## 2.5 Statistical analysis

With Pearson's correlation analysis, the association between annual antibiotic consumption and FQR rate of gram-negative bacteria from 145 hospitals of China was performed. The relationship between the FQR rate of gram-negative bacteria and the consumption intensity of overall antibiotics, beta-lactams, beta-lactam-beta-lactamase inhibitor combinations, beta-lactams excluding CBLI, penicillins, penicillins excluding CBLI, cephalosporins, cephalosporins excluding CBLI, third-generation cephalosporins, third-generation cephalosporins excluding CBLI, fourth-generation cephalosporins, carbapenems, FQs, ciprofloxacin, levofloxacin and moxifloxacin were analyzed individually. Statistical significance was defined as  $p < 0.05$ . All the analyses were performed using Microsoft Excel 2013 and STATA 20.0 (StataCorp LLC, Texas, USA).

# Results

## 3.1 Participating hospitals

A total of 145 hospitals were included in this study. 141 of the participating hospitals were tertiary hospitals, which are the highest quality hospitals in China. There are 29 hospitals in North China, 29 hospitals in East China, 22 hospitals in Central China, 25 hospitals in Southern China, 12 hospitals in the southwest of China, 15 hospitals in the northwest of China, and 13 hospitals in northeast of China. These hospitals had a median of 2356 beds (range, 720-8475 beds). The median number of inpatients per year reached 88.3 thousands (range, 10-410 thousands).

### 3.2 Antibiotics consumption

During the study period, the overall antibiotics consumption intensity for the participating hospitals varied from 23.93 to 115.39 DDDs/100 patient-days, the median was 46.30 DDDs/100 patient-days. Among them, cephalosporins were the most commonly prescribed antibiotics, followed by fluoroquinolone, penicillins and carbapenems. The antibiotics consumption intensity for the main antibiotic classes was depicted in Table 1.

### 3.3 Correlation between antibiotics consumption intensity and FQR *E. coli*

138 hospitals were included to perform the correlation between antibiotics consumption intensity and rate of FQR *E. coli*. 158866 strains of *E. coli* were isolated, and 94247 strains of them were FQR. The percentage of *E. coli* isolates that were resistant to FQs at each hospital was 44.96-82.2%, and the median value was 61.67%. The percentage of FQR *E. coli* was significantly positively correlated with the consumption of FQs ( $r=0.308$ ,  $p<0.01$ ) and levofloxacin ( $r=0.252$ ,  $p<0.01$ ). As shown in table 2 and figure 1.

**Table 1. Antibiotics consumption intensity for the main classes of antibiotics in 145 hospitals**

Class (ATC category)	Antibiotics consumption intensity, median value (range, DDDs per 100 patient-days)
All antibiotics[J01]	46.30 (23.93-115.39)
Beta-lactams[J01C+J01D]	33.03 (19.35-67.05)
Beta-lactam-beta-lactamase inhibitor combinations	7.34 (0.73-34.33)
Beta-lactams excluding CBLI	25.95 (13.48-58.82)
Penicillins[J01C]	5.69 (0.99-23.21)
Penicillins excluding CBLI	2.40 (0.02-21.89)
Cephalosporins[J01DB+J01DC+J01DD+J01DE]	24.70 (10.81-52.52)
Cephalosporins excluding CBLI	19.82 (9.20-51.38)
3-GC[J01DD]	10.99 (2.57-38.98)
3GC excluding CBLI	5.99 (1.05-20.99)
4-GC[J01DE]	0.30 (0-5.98)
Carbapenems[J01DH]	1.95 (0.17-10.06)
Fluoroquinolones[J01MA]	5.70 (1.58-19.25)
Ciprofloxacin (J01MA02)	0.09 (0-2.80)
Levofloxacin (J01MA12)	3.73 (0.01-13.56)
Moxifloxacin (J01MA14)	1.41 (0-6.74)

ATC: Anatomic Therapeutic Chemical; DDDs: defined daily dosages; CBLI: combinations with beta-lactamase inhibitors; 3-GC: the third generation cephalosporins; 4-GC: the fourth generation cephalosporins.

### **3.4 Correlation between antibiotics consumption intensity and FQR *K. pneumoniae***

139 hospitals were included to analyze the correlation between antibiotic consumption intensity and rate of FQR *K. pneumoniae*. 194957 strains of *K. pneumoniae* were isolated, and 48287 strains of them were FQR. The percentage of *K. pneumoniae* isolates that were resistant to FQs at each hospital was 5.3-66.9%, and the median value was 23.1%. The percentage of FQR *K. pneumoniae* was significantly correlated with the consumption of all antibiotics ( $r=0.247$ ,  $p<0.01$ ), carbapenems ( $r=0.242$ ,  $p<0.01$ ), FQ ( $r=0.291$ ,  $p<0.01$ ) and levofloxacin ( $r=0.260$ ,  $p<0.01$ ). As demonstrated in table 2 and figure 2.

### **3.5 Correlation between antibiotics consumption intensity and FQR *P. aeruginosa***

139 hospitals were included to analyze the correlation between antibiotic consumption intensity and rate of FQR *P. aeruginosa*. 111711 strains of *P. aeruginosa* were isolated, and 27171 strains of them were FQR. The percentage of *P. aeruginosa* isolates that were resistant to FQs at each hospital was 7.7-65.2%, and the median value was 22.4%. The percentage of FQR *P. aeruginosa* was significantly correlated with the consumption of all antibiotics ( $r=0.260$ ,  $p<0.01$ ), FQs ( $r=0.319$ ,  $p<0.01$ ) and levofloxacin ( $r=0.377$ ,  $p<0.01$ ). As demonstrated in table 2 and figure 3.

### **3.6 Correlation between antibiotics consumption intensity and FQR *A. baumannii***

131 hospitals were included to analyze the correlation between antibiotic consumption intensity and rate of levofloxacin-resistant *A. baumannii*. 93114 strains of *A. baumannii* were isolated, and 52695 strains of them were levofloxacin-resistant. The percentage of *A. baumannii* isolates that were resistant to levofloxacin at each hospital was 16.1-93.9%, and the median value was 59.3%. The percentage of levofloxacin-resistant *A. baumannii* was significantly correlated with the consumption of all antibiotics ( $r=0.282$ ,  $p<0.01$ ), third-generation cephalosporins excluding CBLI ( $r=0.246$ ,  $p<0.01$ ), FQs ( $r=0.254$ ,  $p<0.01$ ) and levofloxacin ( $r=0.336$ ,  $p<0.01$ ). As demonstrated in table 2 and figure 4.

133 hospitals were included to analyze the correlation between antibiotic consumption intensity and rate of ciprofloxacin-resistant *A. baumannii*. 101374 strains of *A. baumannii* were isolated, and 80032 strains of them were ciprofloxacin-resistant. The percentage of *A. baumannii* isolates that were resistant to ciprofloxacin at each hospital was 28.7-95%, and the median value was 77.6%. The percentage of ciprofloxacin-resistant *A. baumannii* was not significantly correlated with the antibiotics consumption. As demonstrated in table 2.

**Table 2 Correlations between main classes of antibiotics consumption intensity and the rate of fluoroquinolone-resistant gram-negative bacteria**

Classes (ATC category)	Correlation									
	fluoroquinolone-resistant <i>E. coli</i> n=138		fluoroquinolone-resistant <i>K. pneumoniae</i> n=139		fluoroquinolone-resistant <i>P. aeruginosa</i> n=139		Levofloxacin-resistant <i>A. baumannii</i> n=131		Ciprofloxacin-resistant <i>A. baumannii</i> n=133	
	$r^a$	$p^*$	$r$	$p$	$r$	$p$	$r$	$p$	$r$	$p$
All antibiotics[J01]	0.174	0.062	0.247*	0.003	0.260*	0.002	0.282*	0.001	0.194	0.055
Beta-lactams[J01C+J01D]	-0.035	0.682	0.116	0.173	0.109	0.202	0.165	0.060	0.165	0.058
Beta-lactam-beta-lactamase inhibitor combinations	-0.176	0.093	0.135	0.113	-0.046	0.589	-0.039	0.656	0.037	0.671
Beta-lactams excluding CBLI	0.118	0.167	0.088	0.303	0.152	0.075	0.200	0.072	0.154	0.077
Penicillins[J01C]	-0.118	0.169	0.040	0.643	0.126	0.140	0.081	0.359	0.036	0.678
Penicillins excluding CBLI	0.004	0.964	0.046	0.590	0.212	0.072	0.215	0.064	0.078	0.371
Cephalosporins[J01DB+J01DC+J01DD+J01DE]	-0.014	0.873	0.068	0.426	0.061	0.478	0.157	0.074	0.185	0.053
Cephalosporins excluding CBLI	0.095	0.269	0.034	0.693	0.091	0.286	0.139	0.112	0.141	0.106
3-GC[J01DD]	-0.055	0.524	0.147	0.085	0.063	0.459	0.194	0.067	0.156	0.073
3GC excluding CBLI	0.093	0.276	0.131	0.125	0.109	0.203	0.246*	0.005	0.133	0.127
4-GC[J01DE]	0.037	0.671	-0.063	0.460	0.044	0.611	-0.182	0.077	-0.028	0.748
Carbapenems[J01DH]	0.129	0.131	0.242*	0.004	-0.065	0.445	-0.003	0.975	0.002	0.983
Fluoroquinolones[J01MA]	0.308**	0.000	0.291*	0.001	0.319*	0.000	0.254*	0.003	0.159	0.068
Ciprofloxacin (J01MA02)	-0.014	0.869	0.075	0.383	0.054	0.532	-0.021	0.811	0.077	0.376
Levofloxacin (J01MA12)	0.252*	0.003	0.260*	0.002	0.377*	0.000	0.336*	0.000	0.157	0.072

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ATC: Anatomic Therapeutic Chemical; CBLI: combinations with beta-lactamase inhibitors; 3-GC: the third generation cephalosporins; 4-GC: the fourth generation cephalosporins.

## Discussion

The present study reflects the current status of antibiotic usage and antimicrobial resistance patterns at the hospital level in China. During the study period, cephalosporins were found to be the most commonly prescribed antibiotics, followed by fluoroquinolone, penicillins, and carbapenems. The percentage of FQR gram-negative bacteria from each hospital varied. Our data demonstrated that the percentage of FQR *E. coli* was significantly positively correlated with the consumption of FQs and levofloxacin while the rate of FQR *K. pneumoniae* was significantly correlated with the consumption of all antibiotics, carbapenems, FQs and levofloxacin. When it comes to FQR *P. aeruginosa*, the resistant rate was significantly correlated with the consumption of all antibiotics, FQs and levofloxacin. Furthermore, the percentage of levofloxacin-resistant *A. baumannii* was significantly correlated with the consumption of all antibiotics, third-generation cephalosporins excluding combinations with beta-lactamase inhibitors, FQs and levofloxacin. However, the correlation of ciprofloxacin-resistant *A. baumannii* and the antibiotics consumption was not found.

In accordance with previous studies, our results found that the FQR *E. coli* was significantly associated with FQs consumption<sup>9-18</sup>. The most important resistance mechanism of *E. coli* to quinolones is mutation of target gene DNA gyrase and topoisomerase IV. Further, up expression of active efflux pump, changes in membrane permeability of bacteria and plasmid-mediated quinolone resistance are the main mechanism of FQR *E. coli* production<sup>19</sup>. However, the emergence of FQR *E. coli* occurs as a multistep process, with increasing numbers of target gene mutations leading to progressively higher minimum inhibitory concentrations<sup>20</sup>. Not surprisingly, the most important risk factor for FQR *E. coli* appears to be previous FQs use<sup>21-23</sup>. Restriction of quinolone use can offer opportunities to reduce the prevalence of FQR *E. coli*<sup>24-26</sup>.

However, data from 42 Spanish hospitals collected by the European Antimicrobial Surveillance Network indicate that amoxicillin clavulanic acid use is the main driving force for the progression of FQR *E. coli*, possibly due to its high consumption in Spain<sup>12</sup>. 36 acute care hospitals from France indicated the level of first, second and third-generation cephalosporins, as well as tetracycline's usage influenced the incidence of FQR *E. coli*<sup>14</sup>. As *E. coli* are less often resistant to third-generation cephalosporins than to quinolones, infections due to FQR *E. coli* may be treated with third-generation cephalosporins. Hence, the use of third-generation cephalosporins might be higher because the incidence of FQR *E. coli* has increased. The author believe that the reason for the correlation between FQR *E. coli* and tetracycline use is that FQR *E. coli* is plausibly associated with resistance to tetracyclines.

There is mounting evidence demonstrating that the prevalence of ciprofloxacin-resistant *K. pneumoniae* was associated with use of ciprofloxacin and FQs<sup>17,26,27</sup>. A study from database of the Korean Health Insurance Review and Assessment Service suggested that the consumption of all third-generation cephalosporins was significantly correlated with resistance rates of *K. pneumoniae* to levofloxacin with a quarter lag<sup>28</sup>. The resistance mechanism of *K. pneumoniae* to FQs is the change of target sites, the change of outer membrane protein permeability, the effect of efflux pump and the transfer of resistant plasmids among bacteria. Our study results suggested that the percentage of FQR *K. pneumoniae* was significantly correlated with the consumption of all antibiotics, carbapenems, FQs and levofloxacin. The use of FQs is a risk factor for the incidence of FQR *K. pneumoniae*<sup>29</sup>. Therefore, it is no doubt that the overuse of FQs increases FQR *K. pneumoniae*.

The drug resistance of *K. pneumoniae* is mostly mediated by plasmids. Plasmid DNA can carry multiple drug-resistant genes such as ESBLs, Amp C enzyme and metalloenzyme-coded genes at the same time. As a mobile genetic primitive, plasmids can transmit carbapenemase-producing resistance genes, resulting in the outbreaks of multidrug-resistant *K. pneumoniae*<sup>30</sup>. Therefore, it is credible that the production of multidrug-resistant *K. pneumoniae* was correlated with the use of carbapenems and all antibiotics.

Resistance to fluoroquinolones developed in *P. aeruginosa* by various mechanisms: mutations in the genes encoding bacterial DNA topoisomerase II and topoisomerase IV is a major cause of resistance to fluoroquinolones in *P. aeruginosa* isolates. Meanwhile, overexpression of active efflux systems can reduce the permeability of the membrane. Furthermore, the plasmid carries the gene of beta-lactamase, which leads to the high level of resistance to quinolones in ESBL-producing strains<sup>31</sup>.

Consistent with our study, the positive correlation between FQs consumption and the rates of FQR *P. aeruginosa* was described<sup>17,26,32-34</sup>. Moreover, the increased consumption of levofloxacin but not ciprofloxacin was associated with an increased incidence of FQR *P. aeruginosa*<sup>35-39</sup>. The differential effects of ciprofloxacin and levofloxacin on the risk of isolating FQR *P. aeruginosa* might be related to the greater intrinsic in vitro activity of ciprofloxacin against *P. aeruginosa* than that of levofloxacin. With higher minimum inhibitory concentration against *P. aeruginosa*, levofloxacin might have been more likely than ciprofloxacin to select for colonization or infection with FQR *P. aeruginosa*. However, various studies indicated that the consumption of ceftazidime, anti-pseudomonal cephalosporin and ciprofloxacin was positively correlated with the incidence rates of ciprofloxacin-resistant *P. aeruginosa*<sup>34,37,40</sup>. As we known, the use of certain antibiotics could be both a cause and a consequence of the resistance emergence. So it seems reasonable to explain higher rates of consumption of ceftazidime, anti-pseudomonal cephalosporin and ciprofloxacin in hospitals is likely to be a result of the high prevalence of FQR organisms and the use of alternative drugs to treat infection with these organisms.

*A. baumannii* has become a difficult bacteria in clinical treatment because of its complex drug resistance mechanism and high drug resistance rate. The use of widespectrum antibiotics will further screen out multidrug-resistant bacteria. Our study showed that the resistance rate of *A. baumannii* to ciprofloxacin

was higher than that of levofloxacin, probably because ciprofloxacin is easier to detect the overexpression of pumps<sup>41</sup>. Our study illustrated the selection pressure of FQs use in the development of FQR *A. baumannii*, which is in accordance with a nationwide multicenter study from Korea<sup>17</sup>. The drug resistance mechanism of *A. baumannii* to quinolones modified the bacterial DNA helix enzyme through the mutation of quinolone resistance gene cluster, thus reducing the affinity between the drug and the enzyme-DNA complex and leading to drug resistance. Also, some efflux systems affect the drug sensitivity. Up to now, three types of plasmid-mediated quinolone resistance genes have been identified, namely aminoglycoside acetyltransferase AAC (6') - Ib-cr, specific efflux systems Qep A and Oqx AB and Qnr family<sup>42</sup>. Furthermore, simultaneous mutations in *gyrA* and *parC* genes are expected to play a major role in high-level fluoroquinolone resistance in *A. baumannii*<sup>43</sup>.

Amp C enzyme is a cephalosporin enzyme encoded by chromosomes inherent in all *A. baumannii*. Adding the promoter insertion sequence ISAb1 beside the Amp C gene increases the production of beta-lactamase, which leads to resistance to cephalosporins. This also explains the correlation between drug resistance and consumption of 3GC excluding CBLI<sup>44</sup>. A domestic research report that the consumption of carbapenem has a significant positive relationship with *A. baumannii* resistance to levofloxacin<sup>45</sup>. A retrospective study manifested the consumption of cefmetazole and total cephamycin positively correlated with the resistance rates of *A. baumannii* to levofloxacin. The author believed that these consequences may be partly due to production of AmpC enzymes<sup>46</sup>.

With the extensive use of FQs, their adverse reactions and the harm caused by irrational use have become increasingly prominent in recent years. Therefore, drug regulatory agencies at home and abroad frequently issued drug safety warnings, demanding the discontinuation or restriction of the FQs use. In our survey, the resistant rates of all gram-negative bacteria were significantly correlated with the FQs consumption, which is consistent with previous study. It is more likely that the resistance mechanism of gram-negative bacteria to FQs leads to a correlation between resistance and FQs consumption. Therefore, in view of the adverse reactions of FQs and the increasing drug resistance, controlling FQs consumption should be taken seriously.

Antibiotic use is a major risk factor in development of antibiotic resistance but the relationship is complex with additional factors involved such as cross-transmission, interhospital transfer of resistance, a community contribution to resistance, and a complex relationship between resistance and the use of a variety of antibiotics. In our study, the relationships between FQs use and resistance to gram-negative bacteria represent the hospital-level perspective, not that of the patient. Therefore, the results may be subject to ecological bias, meaning that findings may not reflect patient-level relationships. Additionally, lack of data on outpatient use of antibiotics could have led to an underestimation of the magnitude of association between FQs exposure and the subsequent isolation of resistant bacteria. It would be great to know the patterns of the resistant isolates. If so, we can conclude definitely whether any outbreak or clonal spread influenced our results. If clonal dissemination of resistant strains were responsible for some portion of the resistant organisms present, then we might expect to find a weaker association

between antibiotic exposure and resistance. While we acknowledge that our research did not take chronology into account, which is an inevitable defect of the design. This may also be the reason for the not very high correlation coefficient. Even so, it must be stated that the scale of the study made it the most comprehensive investigation reported domestically.

## Conclusion

To summarize, in this study we quantified the associations between antibiotic consumption and the incidence of FQR gram-negative bacteria. As prudent and responsible use of antibiotics remains crucial in preventing the selection of resistant bacteria, our study results could serve as a driving force for implementation of antimicrobial stewardship policies.

## Abbreviations

*A. baumannii*: *Acinetobacter baumannii*; ATC: Anatomic Therapeutic Chemical; DDDs: Defined daily dosages; *E. coli*: *Escherichia coli*; ESBLs: Extended-spectrum beta-lactamase; FQs: Fluoroquinolones; FQR: fluoroquinolones-resistant; *K. pneumoniae*: *Klebsiella pneumoniae*; *P. aeruginosa*: *Pseudomonas aeruginosa*.

## Declarations

### Ethics approval and consent to participate

Given that this study was performed without accessing patient information, approval of the ethics committee was not required

### Consent for publication

Not applicable

### Availability of data and material

The data used in the current study are available from the corresponding author on reasonable request.

### Competing interests

The authors report no conflicts of interest relevant to this article.

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### Authors' contributions

Ping Yang conducted the correlation analysis and prepared the initial drafts of the manuscript. Yunbo Chen and Ping Shen were responsible for the bacterial resistance data analysis. Saiping Jiang contributed in antibiotic consumption analysis. Xiaoyang Lu was responsible for the results interpretation and manuscript review. Yonghong Xiao as a principal investigator designed the study, collected the data and revised the manuscript. All authors contributed to the final version of the manuscript. All authors read and approved the final manuscript.

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Not applicable

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## Figures

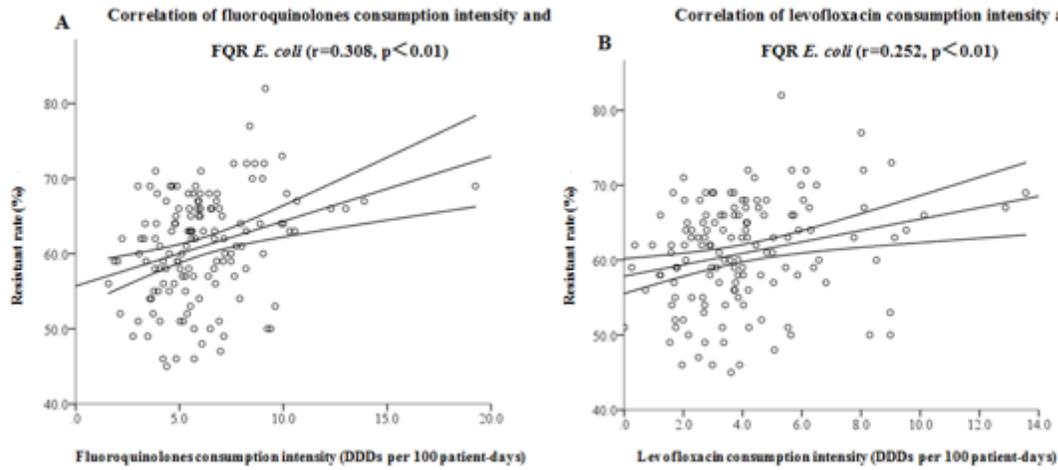


Figure 1

Correlation of FQR *E. coli* and consumption intensity of (A) fluoroquinolones; (B) levofloxacin.

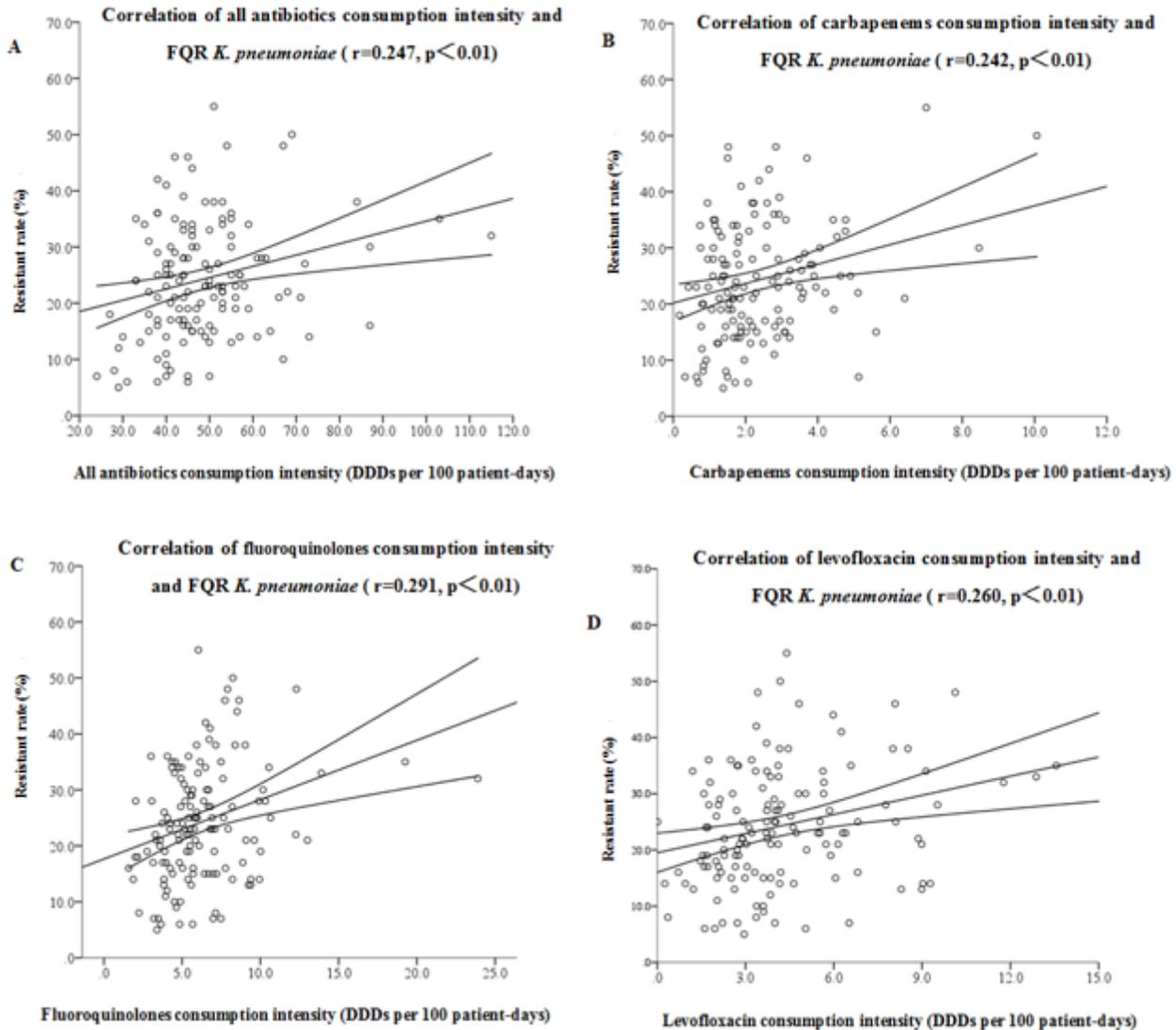


Figure 2

Correlation of FQR *K. pneumoniae* and consumption intensity of (A) all antibiotics; (B) carbapenems; (C) fluoroquinolones; (D) levofloxacin.

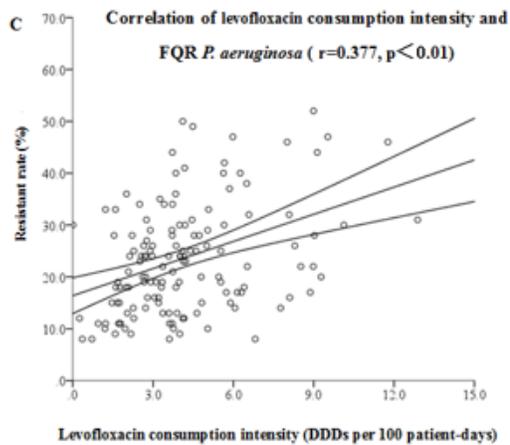
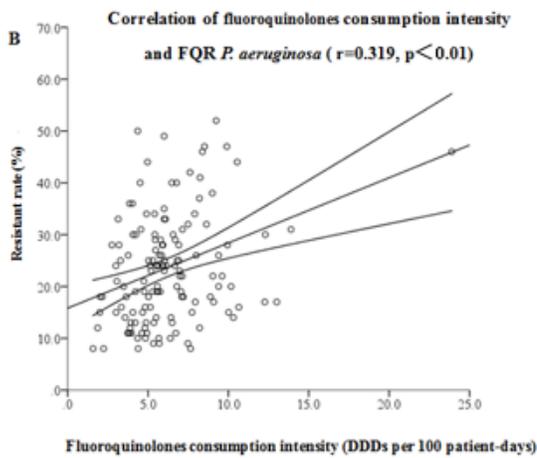
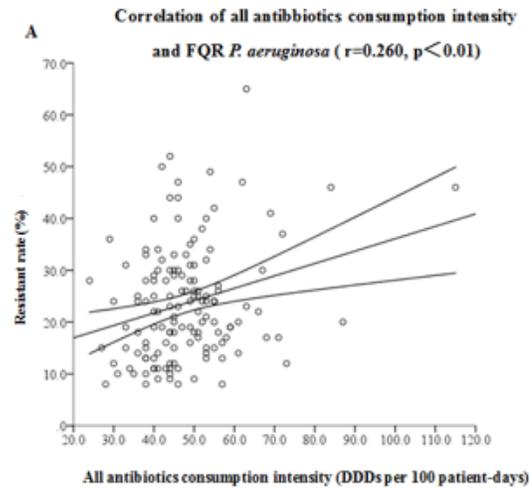
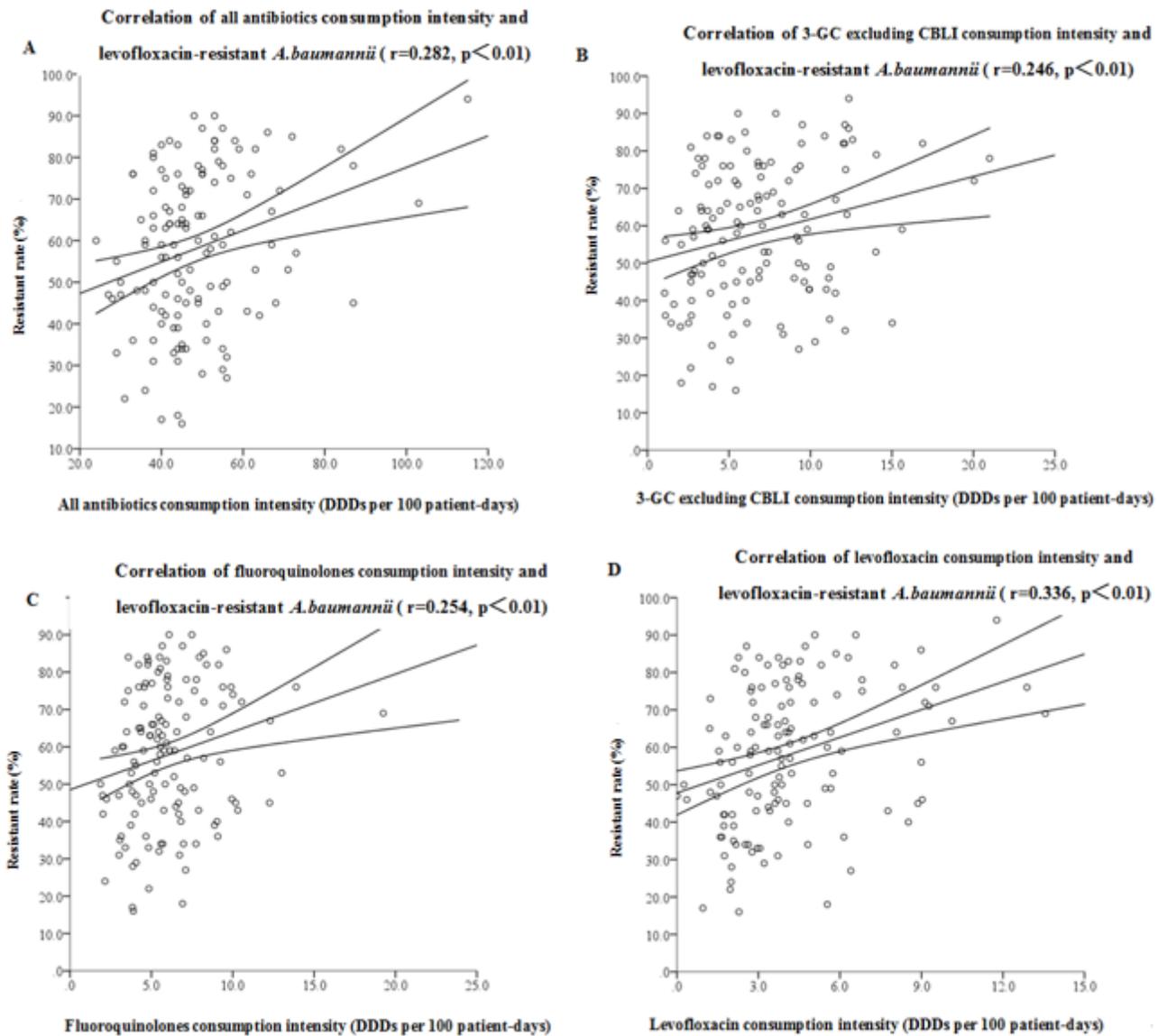


Figure 3

Correlation of FQR *P. aeruginosa* and consumption intensity of (A) all antibiotics; (B) fluoroquinolones; (C) levofloxacin.



**Figure 4**

Correlation of FQR *A.baumannii* and consumption intensity of (A) all antibiotics; (B) combinations of third-generation cephalosporins and beta-lactamase inhibitors; (C) fluoroquinolone; (D) levofloxacin. 3-GC: the third generation cephalosporins; CBLI: combinations with beta-lactamase inhibitors.