

# Trends in Consumption of Quinolones in Chinese Healthcare Institutions: Results of National Procurement Data Analysis (2015–2018)

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## Research

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# Abstract

## Background

There is widespread use of quinolones to treat various infectious diseases due to their broad-spectrum nature and optimal pharmacokinetic characteristics. Nevertheless, the risk of bacterial resistance has also amplified as a consequence of their judicious use in hospitals and the community. The current study investigated the consumption and expenditure of quinolone antibiotics during 2015–2018 in various health settings in China.

## Methods

We used the China Drug Supply Information Platform (CDSIP) to analyze the drug procurement data of national healthcare institutions, focusing on determining the trend and pattern of quinolone consumption. The standard Anatomical Therapeutic Chemical (ATC)/Defined daily dose (DDD) methodology was opted to quantify antibiotic usage.

## Results

A slight decrease in J01M antibiotics consumption (25.7% to 23.5%) was observed over four years (2015–2018). The use of quinolones was significantly higher in rural primary health centers (53.9%) and tertiary hospitals (22.1%). In 2017, levofloxacin (61.4%) was the most commonly consumed quinolone, followed by norfloxacin (27.1%) and moxifloxacin (4.1%). The total spending on J01M antibiotics gradually increased from 21.4% in 2015 to 27.9% in 2018.

## Conclusions

From 2015 to 2018, the general use of J01M antibiotics decreased marginally, but the use of the paternal type of J01M and its expenditure is continuously growing. There is a need to enforce stringent antibiotic management programs to restrict the irrational use of antibiotics.

## Introduction

Antimicrobial resistance (AMR) is among the world's leading threats to public health, which has also amplified the healthcare cost significantly (1). One of the critical drivers of AMR is the overuse of antibiotics. A strong association between AMR and antibiotic consumption has been highlighted by numerous studies (2, 3). To cope with this increasing use of antibiotics globally, the World Health Organization (WHO) launched a set of global strategies at the start of the 21st century. According to an estimation, the rate of mortality attributed to AMR could increase from 700,000 in 2015 to 10 million in 2050 without effective control policy (4).

The intensity of the AMR problem is higher among low- and middle-income countries, possibly due to the higher consumption of antibiotics (5). China is among the top countries globally in terms of antibiotic

production and consumption, which are widely used in the human and animal sector for the cure, treatment, and prophylaxis of infectious diseases (6). In 2010, China was ranked second in antibiotic consumption by volume in humans (7). A study in 2013 concluded that each of the Chinese residents had used a mean value of 25 grams of antibiotics (8). Surprisingly, the rate of antibiotics prescribing to treat common cold was higher than 80% in China, which should be under 30% as recommended by WHO (9). A significant number of factors that trigger the consumption of antibiotics in China include inadequate knowledge of healthcare professionals, patient's pressure to prescribe antibiotics, and financial compensation for the sale of drugs (10, 11).

The rate of AMR is higher in China, owing to a lack of prudent use of antibiotics. A report of the national antimicrobial surveillance system, which used data of 1427 secondary and tertiary hospitals, affirmed the presence of 36% MRSA, 59% third generation, and 54% quinolone-resistant *Escherichia coli* (12). This increasing rate in AMR compelled the Chinese government to launch several interventions on the prudent use of antibiotics (13, 14). In recent health system reforms, the authority to prescribe antibiotics in primary health-care settings was limited to only those drugs that were listed in the National Essential Medicines List (NEML); the sale of these medicines was based on a zero markup policy, thus eliminating the probability of financial benefit (15). Nowadays, this policy has been implemented in all public sector hospitals. In 2011, a three-year nationwide campaign was launched by the Chinese Ministry of Health to prevent the judicial use of antibiotics, specifically in secondary and tertiary hospitals (16). In 2012, China's government issued guidelines about the clinical use of antimicrobial drugs to further eradicate the risk of antibiotic sale without prescription (17). There were three categories of antibiotics, including non-restricted, restricted, and controlled. All antibiotics of the controlled list were removed from the NEML for use in primary healthcare settings. Administrative restrictions were made to prescribe antibiotics from the restricted and controlled category. Various punishments and penalties were imposed for non-compliance (18). In the recent five-year national action plan, the Chinese government made antibiotics a prescription-only medicine by 2020 to combat AMR (19).

There is extensive use of quinolones to treat a large number of infectious diseases, owing to their broad-spectrum and optimal pharmacokinetic characteristics. Nevertheless, their widespread and irrational use is also augmenting the risk of bacterial resistance (20, 21). Currently, the literature lacks studies designed to determine the trends in antibiotics, specifically fluoroquinolone consumption at a national level by using ATC/DDD methodology, which could frame the picture of antibiotic resistance with higher resolution. Previously, researchers have given more attention to investigating antibiotics prescription changes, coupled with its cost (22, 23). Therefore, the current study was designed to measure the trend and pattern of fluoroquinolone consumption in China over four years from 2015 to 2018.

## Methods

### Study settings

China is a developing country covering nearly 9,600,000 square kilometers, with a population of 1.428 billion inhabitants (24). In 2019, China's gross domestic product (GDP) was 99 trillion yuan (14.3 trillion USD) (25).

## Data collection

As of 2015, the China Drug Supply Information Platform (CDSIP) was launched in China to gather information about drug storage, drug order, and drug delivery. It was made mandatory for healthcare institutions to upload this information regularly. By using CDSIP, the government could update the quantity, price, distribution, and arrangement of drugs. Furthermore, CDSIP helped strengthen the management of drugs. Since 2017, the CDSIP has drug procurement data of 80% of the national healthcare institutions. Therefore, CDSIP is the most comprehensive and reliable data source for national drug procurement data. In this study, we used CDSIP to analyze drug procurement data of 51,935 national healthcare institutions, focusing on determining the trend and pattern of fluoroquinolone consumption. For longitudinal analysis, we used procurement data of 41,306 healthcare institutions that had not undergone any change in the four years.

Healthcare institutions were categorized into different types, including primary hospitals, secondary hospitals, tertiary hospitals, upgraded hospitals, urban, and rural primary healthcare centers (PHCs). Various other hospitals included are traditional Chinese hospitals, general hospitals, specialized hospitals, and nursing homes. Community health centers, township health centers, clinics, and village clinical stations were classified as PHCs.

The information which was extracted from the database includes the name of the province, the name of the institution, the name of the drug, dosage form, the strength of the drug, pack size, the total number of packs, name of the manufacturer, and the order time.

## Data analysis

In the first step, the procurement data were normalized in accordance with Anatomical Therapeutic Chemical (ATC)/DDD methodology by the WHO Collaborating Center for Drug Statistics Methodology (WHOCC).

We calculated the antibiotic consumption in a defined daily dose (DDD) as a unit of measurement as per WHO guidelines. DDD is the average daily dose maintained by adults with primary indications; DDDs represent the amount of DDD consumed to measure the frequency of antibiotic use. The formula for DDDs is the number of packages sold  $\times$  the number of drugs  $\times$  the strength of each drug/DDD.

Although the CDSIP covers more than 80% of all healthcare institutions in China, the different proportions of healthcare institutions across provincial-level regions and levels of institutions are excluded in this platform owing to a lack of information system infrastructure within those institutions. Hence, the current analysis cannot cover all healthcare institutions in China. We assumed that there is no systematic difference in antibiotic use patterns between the healthcare institutions included and those not included

in the CDSIP. We, therefore, used a simple extrapolation to account for the antibiotics consumed by institutions that were excluded from the CDSIP.

## Results

A total of 19 specific chemical substances were identified in single or combine antibiotics.

### Overall consumption of J01M antibiotics

The use of J01M class of antibiotics was the highest in 2015, with a peak value of 120 million DDDS, however, in the last quarter of 2015, its consumption was reduced to 112 million DDDS. This decline in quinolones' use continues in 2016 with a total consumption of 82 million DDDS in the last quarter. Unfortunately, the use of antibiotics rose abruptly in 2017, with a peak level of 112 million DDDS. However, there was a marked reduction in consumption in the subsequent year (Fig. 1a). The overall J01M antibiotic use was declined from 25.7–23.5% over four years (2015–2018).

The top seven quinolone antibiotics consumed from 2015 to 2018 were levofloxacin, norfloxacin, moxifloxacin, ciprofloxacin, ofloxacin, lomefloxacin and gatifloxacin. Out of total antibiotics, levofloxacin was the most commonly used antibiotic in 2017 with a total share of 61.4%, followed by norfloxacin 27.1% and moxifloxacin 4.1%. Additionally, the use of levofloxacin was continuing to rise from 59.3% in 2015 to 61.3% in 2018 (Fig. 1b). However, the use of ciprofloxacin was significantly reduced from 4.9% in 2015 to 2.6% in 2018. Complete information about the consumption of all J01M antibiotics is available as a supplementary file.

### Consumption and expenditure of J01M antibiotics based on the institution

The use of quinolones was found to be higher in rural PHCs (53.9%) and tertiary hospitals (22.1%) followed by secondary hospitals (14.8%), primary hospitals (13.8%), urban hospitals (6.8%) and ungraded hospitals (0.8%). Despite this, a reduction in overall quinolone consumption was noted in rural PHCs from 58.4% in 2015 to 48.4% in 2018. Surprisingly, there was a marked increase in quinolone consumption in tertiary hospitals from 18.9% in 2015 to 26.4% in 2018. Figure 2a illustration information about J01M antibiotic consumption in DDDs. The detail about J01M consumption in percentage DDDs based on different healthcare settings is available in a supplementary file.

The overall quinolone expenditure was found to be consistently increasing from 21.4% in 2015 to 27.9% in 2018, and the highest expenditure occurred in tertiary care hospitals (56.4%) followed by secondary hospitals (25.6%), and rural PHC (12.8%), (Fig. 2b).

### Consumption and expenditure of J01M antibiotics based on the dosage form

Oral consumption of quinolones was predominant than the parenteral form in selected hospitals (72.8% vs 27.2%). In 2015, 295 million DDDs of oral quinolones were used; however, this was slightly reduced to 280 million DDDs in 2018, as shown in Fig. 3a. The expenditure of parenteral quinolones was significantly higher compared to oral quinolones (83.4% vs 16.6%). However, a decreasing trend was noted in parenteral quinolone consumption from 85.0% in 2015 to 82.2% in 2018 (Fig. 3b).

## Discussion

This national-level study is the first of its kind, which reports on the trend, consumption, and expenditure of quinolone antibiotics over a period in China, providing an opportunity to restructure their policies regarding antibiotic use. Quinolones are broad-spectrum antibiotics widely used to treat multiple infectious diseases due to their optimal pharmacokinetic characteristics. Unfortunately, their irrational use is continuously increasing worldwide, including China; thus, amplifying antibiotic resistance risk (26).

From 2015 to 2018, there is a slight decrease in the consumption of J01M antibiotics in China (25.7% in 2015 vs 23.5% in 2018). Like our results, a decreasing pattern in the use of quinolones was reported in a recent study conducted in Shandong province of China, which analyzed the antibiotic procurement data from 2012 to 2017 (27). These results could be attributed to the implementation of numerous interventions including strict antibiotic use policies including hospital-based antimicrobial stewardship programs implemented by the Chinese government to restrict the irrational use of antibiotics in hospitals and community (28, 29). Besides, in 2012, the Ministry of Health launched Administrative Rules for the Clinical Use of Antibiotics which is playing a pivotal role in minimizing the antibiotic use in different hospital settings as reported in other studies (30). The government has implemented punishments if healthcare professionals and institutions violate the laws and rules of rational antibiotic use, including the loss of accreditation, downgrade in service fees, and dismissal of managers. In severe cases, the doctors could be stopped to prescribe antibiotics, and their medication registration could be revoked. Still, there is a need to do more work to minimize the level of all antibiotics, including quinolones in all hospital settings of China, to meet the recommendations of the WHO.

Furthermore, since 2015, a systematic restructuring of public hospitals has been undertaken nationally. The most integral component of these reforms is the extension of Zero Mark-up Drug Policy (ZMDP) to prevent antibiotic misuse in secondary and tertiary hospitals. ZMDP has clearly shown a reduction in irrational prescribing of antibiotic use as found in various studies (27, 31).

Levofloxacin was the most frequently used quinolone antibiotic in our study from 2015–2018 (59.3% in 2015 to 61.3% in 2018). Similar results were found by a previous study where the use of levofloxacin was greater than 30% of the total consumption of quinolones in each year (32). Likewise, levofloxacin was among the top five most-used antibiotics in a Shandong study (27). This increasing use of levofloxacin has also amplified the risk of resistance in different infections, including tuberculosis (33).

In our study, the use of the parenteral form of quinolone antibiotics remains nearly static from 2015 to 2018 (27.9% in 2015, 27.1% in 2018). This slight decline is still far from the standard limits. A high

proportion of parenteral quinolone expenditure (more than 80% of the total expenditure in 2018) were found in our study, which is as per previous studies (27). In developing countries, including China, people often prefer the injectable form of antibiotics as they consider them more potent and effective to eradicate their infections. Therefore, some patients force healthcare professionals to prescribe the parenteral form of antibiotics, only (34).

There is a significantly higher consumption of quinolones in rural PHCs and tertiary hospitals than in other healthcare settings, which is alarming. A large number of studies have also reported similar results (35, 36). The management and use of quinolones in these hospital settings should be controlled by enforcing strict policies launched by the Chinese government. It is advisable that an optimal and effective system should be enforced to determine the irrational use of antibiotics within hospital (37, 38). Those antibiotics, used irrationally should be placed on the restricted list, and only written permission should be obtained from the doctors whenever they need such type of antibiotics. This will help in the prudent use of antibiotics within the hospital. Besides, continuous training programs should be launched for all healthcare professionals aimed at the judicious use of antibiotics and antibiotic resistance to equip them with the latest advancements (39, 40). To enhance health literacy specifically about antibiotics, public education campaigns should be instituted regularly to provide awareness of the prudent use of antibiotics (41). This will also help in reducing the pressure of patient demands about prescribing antibiotics.

Certain limitations should be taken into consideration. First, the antibiotic purchase record of the institution is unable to differentiate between inpatient medication and outpatient medication. Therefore, this study could not investigate the use of antibiotics in outpatient and inpatient settings. Second, this study could not find the antibiotics, which were expired or discarded during storage; likewise, it's difficult to estimate the length of time of storage of antibiotics in the inventory after purchasing by using sales data. Despite the above limitations, this is a pioneer national-level study, which has highlighted the expenditure and consumption of quinolones from 2015 to 2018 in China.

## **Conclusions**

The overall consumption of quinolones was reduced slightly between 2015 and 2018. A decreasing trend in the use of the parenteral form of quinolones and its expenditure was also noted. However, the overall quinolone expenditure is continuously increasing with the parenteral quinolone expenditure greater than 80% of the total expenditure. There is a need to implement a strict antibiotic management system to control the irrational use of antibiotics. Regular education sessions for all healthcare professionals, including physicians, should be arranged.

## **Declarations**

## **Ethics approval and consent to participate**

Not applicable.

## Availability of data and material

The dataset used in this publication will be available from the corresponding author upon a reasonable request.

## Consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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## Contributions

C.C. and K.H. were involved in the concept or design of the study. All authors were involved in the interpretation of the data.

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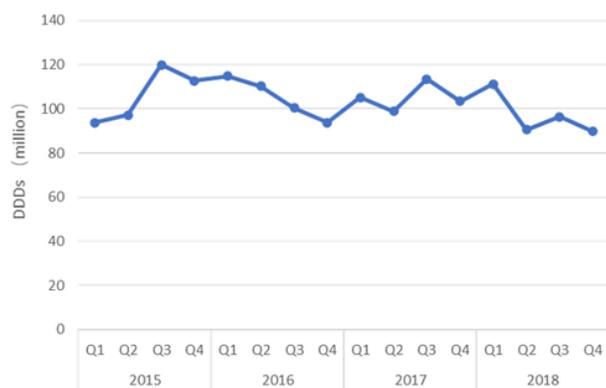
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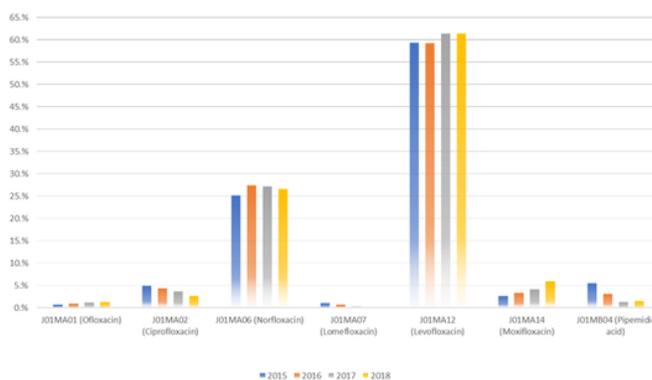
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## Figures



**a**



**b**

### Figure 1

1a: Seasonal variation in overall consumption of J01M during 2015-2018 1b: consumption of the top seven J01M antibiotics in China from 2015–2018

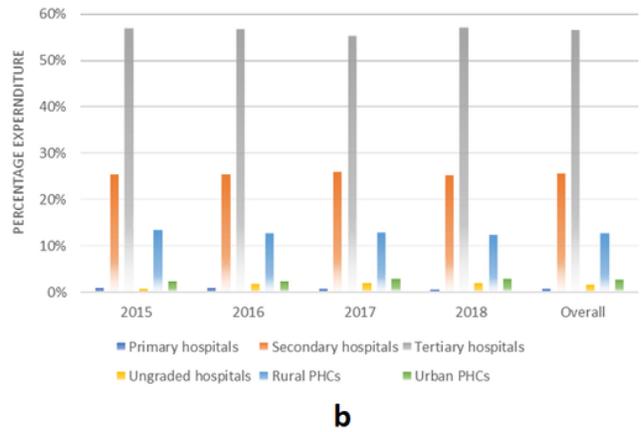
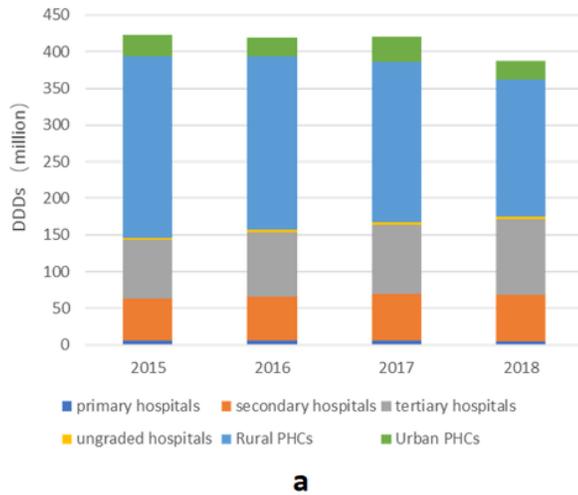


Figure 2

2a: J01M consumption based on different healthcare settings from 2015–2018 (DDDs, defined daily doses). 2b: J01M expenditure based on different healthcare settings from 2015–2018

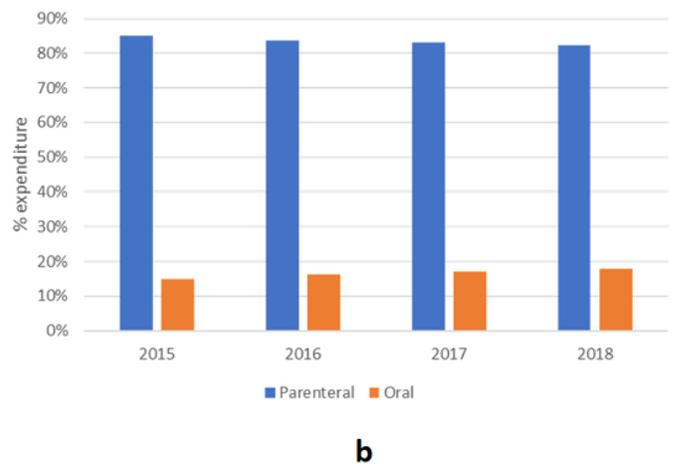
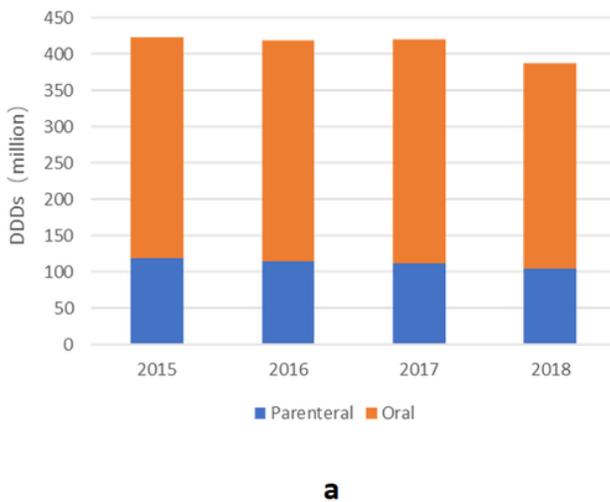


Figure 3

3a: J01M antibiotics consumption based on the dosage form from 2015–2018 (DDDs, defined daily doses) 3b: J01M expenditure from 2015–2018

## Supplementary Files

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