Antimicrobial Resistance and Infection Control

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Trends of antibiotic use for acute upper respiratory infections in Chinese emergency departments and the impact of COVID-19: a cross-sectional study

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Abstract

Background The emergence of Coronavirus Disease 2019 (COVID-19) has impacted antibiotic use; however, studies on antibiotic use for acute upper respiratory infections (AURIs) in Chinese emergency department (ED) settings are still scarce.

Objective This study aimed to explore trends and patterns in antibiotic use and the impact of COVID-19 in Chinese ED settings.

Methods A cross-sectional, retrospective analysis was conducted using prescriptions for ED visits due to AURIs through the Hospital Prescription Analysis Cooperative Project Database between 2018 and 2023. We examined patterns of antibiotic use for AURIs and employed an interrupted time series analysis to assess the impact of the COVID-19 pandemic on antibiotic use. The proportion of antibiotic prescriptions adhering to first-line guideline recommendations was also evaluated.

Results A total of 1,972,270 prescriptions for AURIs from 108 hospitals in EDs were extracted. The antibiotic prescription rate (APR) was 58.44%. The predominant antibiotics prescribed for AURIs were second- and third-generation cephalosporins and azithromycin. Among these prescriptions, only 22.26% adhered to first-line guideline recommendations, while 83.82% involved Watch-group antibiotics. A substantial decrease in antibiotic consumption was observed at the onset of the pandemic, but no significant changes were found in the APR. After the relaxation of anti-COVID-19 measures, both antibiotic consumption and the APR exhibited an upward trend. However, neither returned to pre-pandemic levels.

Conclusion Antibiotic use for AURIs was prevalent in ED settings, with a predominant use of broad-spectrum and Watch-group antibiotics. After the lifting of pandemic control measures, both antibiotic consumption and the APR exhibited an upward trend, underscoring the need to reinforce antimicrobial stewardship, particular targeting broad-spectrum and Watch-group antibiotic use.

Keywords Antibiotics, Acute upper respiratory infections, Emergency department, COVID-19, Interrupted time series

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Introduction

Acute respiratory infections are the leading cause of disability and death among children under 5 years of age and adults in developing countries [1]; however, evidence-based guidelines emphasize that uncomplicated self-limiting acute respiratory infections, especially acute upper respiratory infections (AURIs), should not be treated with antibiotics routinely. AURIs are predominantly viral, with only a minority caused by bacterial pathogens. Nonetheless, the misuse and overprescription of antibiotics for these conditions remains prevalent in clinical practice, especially in emergency department (ED) settings [2, 3].

The overuse of antibiotics is a key driver of antimicrobial resistance (AMR), exacerbating the burden on healthcare systems, escalating medical costs, and increasing mortality related to infectious diseases [3–5]. The incidence of inappropriate antimicrobial treatment in ED settings ranges from 40 to 60%, similar to that in inpatient settings; however, ED is a frequently overlooked yet crucial targets for AMR interventions [6]. Moreover, studies indicated that antibiotic prescription rate (APR) for AURIs are notably higher in developing countries [7]. As a large consumer of antibiotics, China has a high rate of antibiotic overprescribing among outpatients with AURIs, with a noteworthy overreliance on broad-spectrum antibiotics [8–10].

The Coronavirus Disease 2019 (COVID-19) pandemic may have exacerbated AMR due to the high use of antibiotics among COVID-19 patients, posing a significant threat to the ongoing AMR crisis [11]. However, the impact of the pandemic on antibiotic utilization remains uncertain. For example, a study in Brazil reported an increase in outpatient antibiotic prescribing, particularly azithromycin, while prescribing rates for other antibiotics, such as amoxicillin-clavulanate and respiratory fluoroquinolones, declined [12]. Conversely, another study observed reductions in overall antibiotic consumption, suggesting a potential mitigation of overprescribing [13]. Similar research in China has reported a decline in antibiotic consumption in public medical institutions during the pandemic [14, 15]; however, these findings have been limited by geographic scope or small sample sizes. Nationwide surveillance of Chinese public medical institutions revealed an overall decline in antibiotic consumption since 2020, but it relied on drug procurement data, which could not assess antibiotic use patterns for specific diseases [16]. To our knowledge, no studies have specifically examined the impact of the COVID-19 pandemic on antibiotic use for AURIs in ED settings in China. This study aimed to address these gaps by using a nationwide prescription surveillance system to analyze trends and patterns of antibiotic use for AURIs in Chinese EDs during the COVID-19 pandemic. Additionally, the study evaluated the adherence of antibiotic prescriptions to clinical guidelines. These findings may offer support for strengthening clinical surveillance and promoting rational antibiotic use in ED patients with AURIs.

Materials and methods

Data sources

This retrospective study was undertaken to assess antibiotic use for AURIs in the ED settings from 2018 to 2023. Data were extracted from the Hospital Prescription Analysis Cooperative Project Database, which is managed by the Chinese Pharmaceutical Association. In the database, prescriptions are randomly selected from a 10-day period each quarter, excluding national statutory holidays. Each prescription includes the following information: patient demographics (encrypted code, sex, and age), prescribing information (diagnose, generic drug name, dosage, usage, total amount, and cost), and additional information (hospital's regional location and prescription date).

Data were collected from 108 general hospitals across nine major regions in China, including Beijing, Shanghai, Shenyang, Haerbin, Tianjin, Zhengzhou, Hangzhou, Chengdu, and Guangzhou. Only prescriptions for patients diagnosed as AURIs were included in our study. According to Chinese guidelines [17, 18] and prior research [19], AURIs was defined as the acute nasopharyngitis (common cold), acute pharyngitis, acute tonsillitis, acute laryngitis and tracheitis, acute obstructive laryngitis and epiglottitis, and acute upper respiratory infections of multiple and unspecified sites, corresponding to International Classification of Diseases (ICD-10) codes J00 and J02-J06 in this study. Prescriptions with missing data were excluded.

Drug classification and guideline recommendations

First, antibiotic data were encoded using the WHO Anatomical Therapeutic and Chemical (ATC) classification system, focusing specifically on antibiotics for systemic use, categorized under ATC code J01. Second, in accordance with the WHO Access, Watch, and Reserve (AWaRe) categories [20], antibiotics were classified into four categories: Access, Watch, Reserve and Others. Third, according to Chinese guidelines [17, 18], antibiotics were further grouped into first-line and second-line categories. Amoxicillin, azithromycin, and first-generation cephalosporins were classified as first-line antibiotics for AURIs, while levofloxacin was classified as second-line antibiotic.

Outcome measures

The primary outcome was the APR for AURIs, calculated as the proportion of AURI prescriptions containing at least one antibiotic divided by the total number of AURI

prescriptions. Subsequently, the proportions of antibiotic-containing prescriptions were analyzed to identify disparities in antibiotic usage patterns, including the route of administration (parenteral *vs*. oral antibiotics), type of antibiotic therapy (monotherapy *vs*. combination therapy), and the distribution of antibiotics according to the ATC classification, the WHO AWaRe categories, and guideline-recommended antibiotics. Monotherapy was defined as the use of a single antibiotic, while combination therapy referred to the use of two or more different antibiotics. Additionally, we assessed the impact of the COVID-19 pandemic on the antibiotic use, including the APR and antibiotic consumption. In our study, antibiotic consumption was quantified using Defined Daily Doses (DDDs) obtained from the ATC/DDD Index of the WHO Collaborating Centre for Drug Statistics.

Statistical analysis

Descriptive analyses were performed to examine trends in APR among ED patients with AURIs and the patterns of antibiotic use. The covariates included patients' age group (0 ~ < 5, 5 ~ < 8, 8 ~ < 18, 18 ~ < 65, 65 ~ < 80, and ≥ 80 years), and diagnosis.

A single-group Interrupted Time Series (ITS) analysis using linear regression models was performed to assess the impact of the pandemic on antibiotic use. ITS analysis is a powerful tool for evaluating the real-world impact of public health interventions, allowing researchers to move beyond simple pre-post comparisons and gain a nuanced understanding of how these programs affect the population over time [21]. 2020Q1 and 2023Q1 were chosen as key time points for analysis, as China officially declared the COVID-19 outbreak on 20 January 2020, and significant adjustments to pandemic control measures were implemented on 8 January 2023. The study period was divided into three phases: pre-pandemic period (2018–2019), pandemic period (2020–2022), and post-pandemic period (2023).

The ITS model is calculated as follows:

$$Y_t = \beta_0 + \beta_1 T_{t1} + \beta_2 X_{t1} + \beta_3 X_{t1} T_{t1} + \beta_4 X_{t2} + \beta_5 X_{t2} T_{t2} + \varepsilon_t$$

where Y_t represents the outcome variable (APR or antibiotic consumption), β_0 represents the baseline level at time = 0 (pre-pandemic), β_1 represents the trend prior to COVID-19, β_2 represents the level change in 2020Q1, β_3 represents the trend change before and after the outbreak of pandemic, β_4 represents the level change in 2023Q1, β_5 represents the trend change before and after policy adjustments; X_t is a dummy variable; T represents the elapsed time (in quarters) during the observation period, ranging from 1 to 24, corresponding to the 24 consecutive quarters included in the analysis. The Cumby-Huizinga test was conducted to examine the presence of autocorrelation.

The analysis was performed using R software (version 4.1.2), and a *P*-value < 0.05 was considered statistically significant.

Results

Trends in antibiotic prescription rate

A total of 1,972,270 prescriptions for 768,781 ED patients diagnosed with AURIs were extracted from 108 hospitals across 9 provinces between 2018 and 2023. The annual number of prescriptions for AURIs was 167,169 in 2018 and 206,193 in 2019. A significant decline in the number of prescriptions occurred in 2020, and by 2023, the total had partially rebounded to 146,798; however, it remained below pre-pandemic levels. Over the study period, 58.44% of ED visits for AURIs were treated with at least one antibiotic, with the APR ranging from 62.16% in 2018 to 53.33% in 2023. Stratified by age, adult patients had a significantly higher APR than patients aged under 18 years (Table 1). Regarding diagnosis, the APR for common cold (J00) was 31.83%, showing a consistent decline throughout the study period (Table 1 and Table S1).

Patterns of antibiotics use

Regarding the route of administration, oral antibiotics were the predominant choice (60.78%), with 92.04% of patients receiving monotherapy. The most frequently prescribed antibiotics were cephalosporins (56.27%), macrolides, lincosamides and streptogramins (21.23%), and quinolones (15.08%). Among cephalosporins, third-generation cephalosporins were the most commonly prescribed (50.57%), followed by second-generation cephalosporins (43.90%). In addition to cephalosporins, azithromycin and levofloxacin were commonly prescribed (Fig. 1a). When stratified by age, patients under 18 years exhibited a higher use of azithromycin (23.90%), cefixime (14.40%), and cefaclor (12%). In contrast, quinolones were commonly prescribed to patients aged 65 years and older. Of note, 52 children aged 8–18 years received systemic fluoroquinolone therapy for AURIs (Fig. 1b). Similar antibiotic prescription patterns were observed across diagnoses, with second- and third-generation cephalosporins being the most frequently prescribed (Fig. 1c).

Watch-group antibiotics accounted for the majority of prescriptions for the treatment of AURIs (83.82%), followed by Access-group antibiotics (13.52%) and Reserve-group antibiotics (0.21%). Elderly patients were more likely to be prescribed Watch-group antibiotics for AURIs (Fig. 2).

Table 1 Characteristics of patients prescribed antibiotics for AURIs in Chinese ED settings, 2018 to 2023

Characteristics	No. patients with AURIs	Antibiotics given	APR (%)
Overall	768,781	449,288	58.44
Sex			
Female	376,838	221,598	58.80
Male	391,943	227,690	58.09
Age group			
0 ~ < 5	234,021	110,130	47.06
5 ~ < 8	93,531	50,789	54.30
8 ~ < 18	94,379	53,031	56.19
18 ~ < 65	289,159	196,915	68.10
65 ~ < 80	38,607	26,379	68.33
> = 80	19,084	12,044	63.11
Diagnosis[a]			
J00	4,024	1,281	31.83
J02	32,547	21,813	67.02
J03	81,181	53,573	65.99
J04	258,198	170,971	66.22
J05	397	345	86.90
J06	414,316	215,708	52.06
Year			
2018	167,169	103,914	62.16
2019	206,193	123,644	59.97
2020	80,076	46,236	57.74
2021	85,286	51,145	59.97
2022	83,259	46,068	55.33
2023	146,798	78,281	53.33

[a] A patient may have multiple AURIs diagnoses. *APR* Antibiotic prescription rate, *AURIs* Acute upper respiratory infections; J00: Acute nasopharyngitis (common cold), J02: Acute pharyngitis, J03: Acute tonsillitis, J04: Acute laryngitis and tracheitis, J05: Acute obstructive laryngitis and epiglottitis, J06: Acute upper respiratory infections of multiple and unspecified sites

Proportion of antibiotic prescriptions adhering to first-line recommendations in the guidelines

The overall proportion of antibiotic prescriptions for AURIs adhering to first-line guideline recommendations was 22.26%, increasing from 16.51% in 2018 to 21.45% in 2023 (Fig. 3). The characteristics of guideline-recommended antibiotics were summarized in Table S2. Guideline adherence rates were higher among male patients (51.66%) compared with female patients (48.34%). Among therapy regimens, azithromycin—a first-line antibiotic for AURIs—was the most frequently prescribed agent for monotherapy (15.50%). Notably, levofloxacin—a second-line recommended antibiotic—ranked third in monotherapy use (9.86%) and was also frequently prescribed antibiotics in combination therapy regimens.

Interrupted time series analysis

The APR for AURIs was not significantly impacted by the COVID-19 outbreak. Following adjustments to COVID-19 mitigation measures, the APR declined by 11.67% ($P < 0.001$), followed by a quarterly increase of 5.65% ($P < 0.001$), as shown in Fig. 4. Notably, the pandemic had no significant impact on the APR among patients under 18 years, which contrasted with trends in other age groups (Table S4).

ITS analysis of antibiotic consumption patterns for AURIs revealed a statistically significant decline at the onset of the pandemic, with an estimated reduction of 41,255.23 DDDs ($P < 0.001$), as listed in Table S5. This decrease was observed across multiple antibiotic classes, including cephalosporins, macrolides, lincosamides and streptogramins, as well as quinolones (Fig. 5). Among cephalosporins, the consumption of third-generation cephalosporins declined less during the pandemic than first- and second-generation cephalosporins. However, following the relaxation of COVID-19 containment measures, there was a general resurgence in antibiotic consumption, with the notable exception of extended-spectrum penicillins, which remained relative stable ($P = 0.087$) (Table S6).

Comparative analysis of antibiotic classification groups revealed distinct patterns in prescribing behavior. Compared to Access-group antibiotics, Watch-group antibiotics exhibited a less pronounced decline during the initial pandemic phase (Access: −0.42; $P < 0.001$; Watch: −0.38; $P < 0.001$). Notably, the consumption of antibiotics prescribed for patients aged over 80 years was unaffected. However, in the post-restriction period, Watch-group antibiotics demonstrated a more substantial rebound (0.24; $P < 0.001$) than their Access-group counterparts (0.13; $P < 0.001$) (Fig. 6, and Table S7).

Discussion

To our knowledge, this retrospective study is the first to comprehensively analyze changes in antibiotic use for AURIs in Chinese EDs during the COVID-19 pandemic, based on a national prescription dataset. The findings indicated that antibiotic prescriptions for AURIs were prevalent in ED settings across China, with 58.44% of patients with AURIs receiving antibiotics, the majority of which were administered orally. Only 22.26% of the antibiotic prescriptions adhered to first-line recommendations in the clinical guidelines, while most involved Watch-group antibiotics. At the onset of the pandemic, ITS analysis showed no significant changes in the APR for AURIs but a significant reduction in antibiotic consumption. However, following the relaxation of pandemic

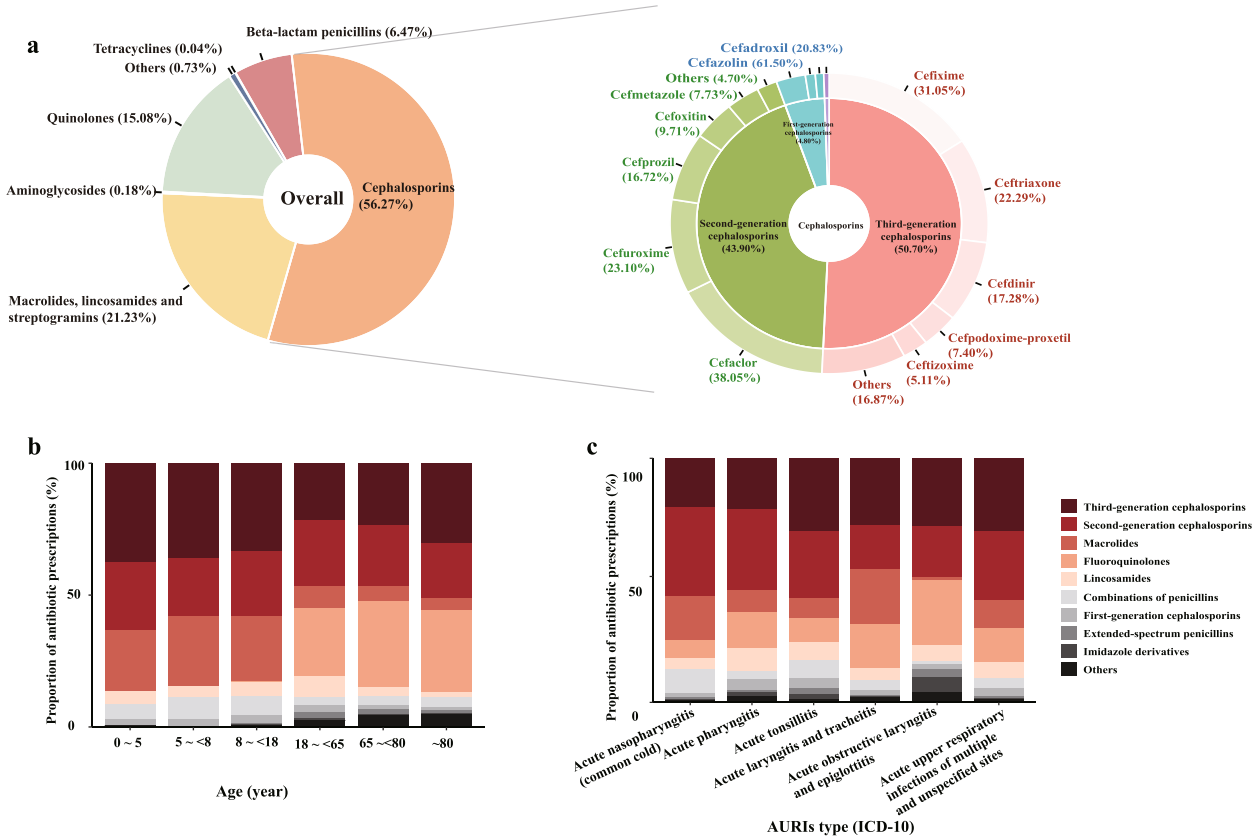

Fig. 1 Patterns of antibiotic use for AURIs according to ATC classification. **a** Overall. **b** By age. **c** By diagnosis (ICD-10)

control measures, both the APR and antibiotic consumption exhibited a substantial upward trend.

Large variations in the APR of AURIs have been reported across regions in China. Two national studies on antibiotic use found APRs of 40.8% and 55.1% for Chinese outpatients with AURIs, respectively [5, 19]. Similarly, our study revealed that more than half of ED patients with AURIs received at least one antibiotic. When compared with data from other countries, such as the United States (57.2%) and Europe (31.9%) [22, 23], the APR in Chinese ED settings is concerning. According to the guidelines from the European Surveillance of Antimicrobial Consumption (ESAC), the proportion of patients with AURIs receiving systemic antibiotics should not exceed 20% [24]. Evidence suggests that antibiotic treatment initiated in the ED played an increasingly prominent role in its continuation. Compared with outpatient and inpatient settings, antibiotic stewardship in the ED is particularly challenging owing to its unique operational characteristics [3].

The ITS analysis indicated a notable divergence in trends between antibiotic consumption and the APR. At the onset of the pandemic, overall antibiotic consumption exhibited a substantial decline, while the APR remained relatively stable. Notably, this period was marked by significant fluctuations and overall decline in both total prescriptions for AURIs and antibiotic-containing prescriptions. However, variations in APR during this phase did not reach statistical significance. Several factors likely contributed to these patterns. China's stringent anti-COVID-19 measures at the onset of the pandemic may have reduced healthcare utilization. Furthermore, the dramatic decline in respiratory virus transmission, as documented in recent literature [25], likely resulted in fewer ED visits [26]. These concurrent factors may explain the decline in both antibiotic-containing prescriptions and overall antibiotic consumption. However, based on the available evidence, we cannot conclusively determine whether individual patients with AURIs were more likely to receive antibiotic treatment during the pandemic. The epidemiological landscape shifted dramatically after the relaxation of control measures in the first quarter of 2023. Our data showed statistically significant increases in both the APR and antibiotic consumption. This pattern aligns with findings from the European Surveillance of Antimicrobial Consumption Network (ESAC-Net), which reported a transient

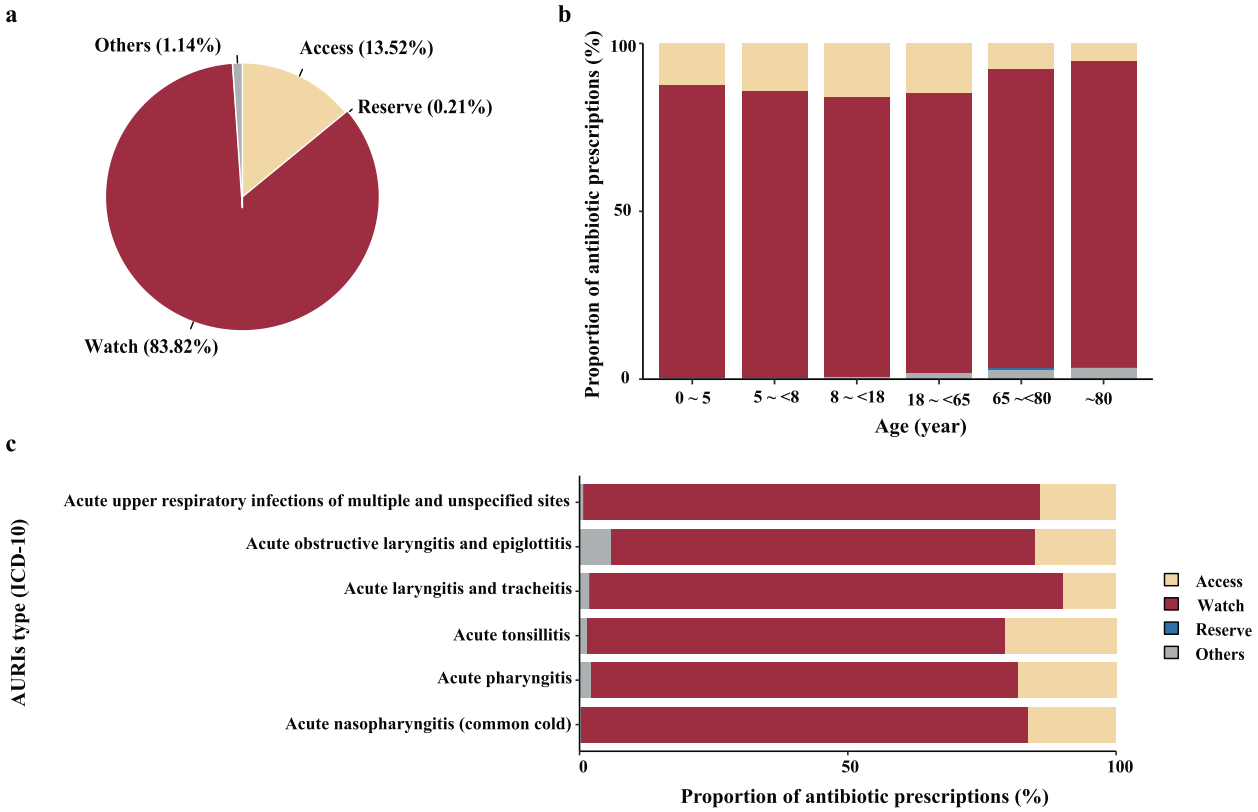

Fig. 2 Patterns of antibiotic use for AURIs according to the WHO AWaRe classification. **a** Overall. **b** By age. **c** By diagnosis (ICD-10)

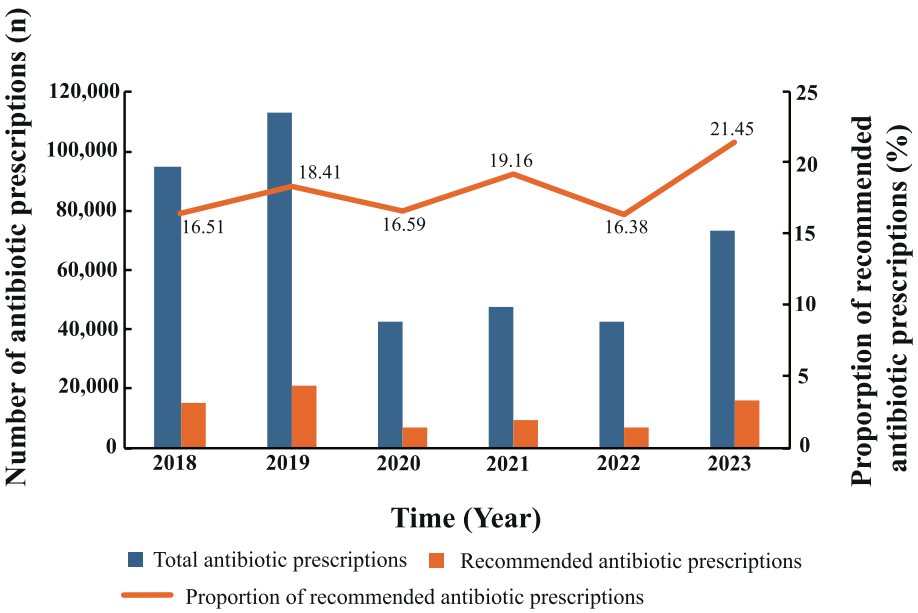

Fig. 3 The trends for the proportion of antibiotic prescription adhering to first-line recommendations in clinical guidelines, 2018 to 2023

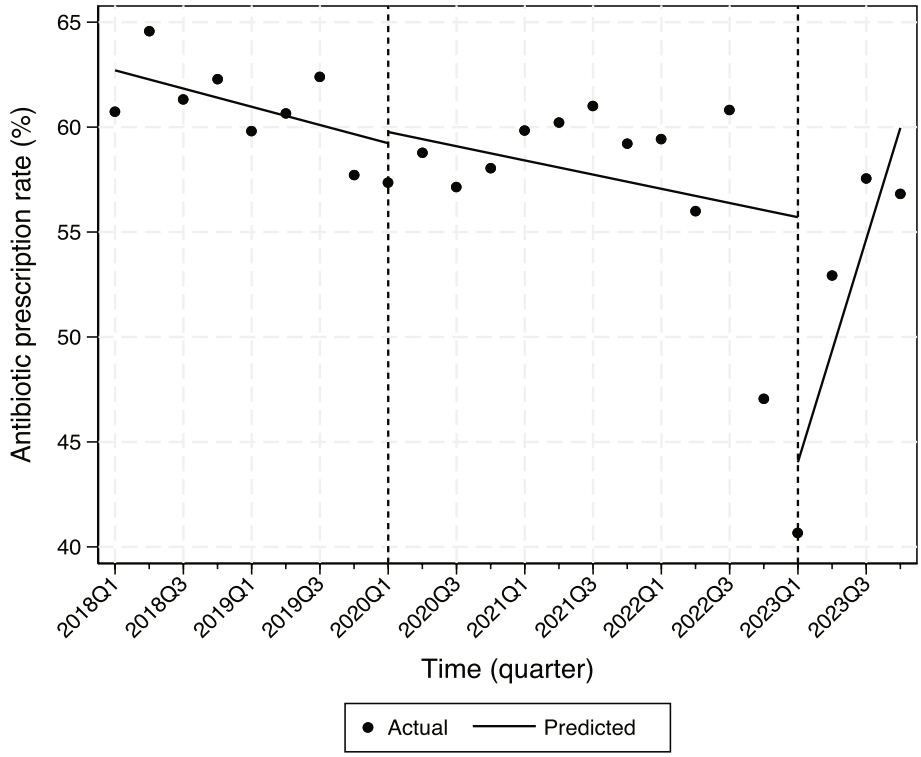

Fig. 4 Changes in the APR for AURIs in Chinese ED settings, 2018 to 2023. Note: Dashed vertical lines indicate first change point and second change point, respectively

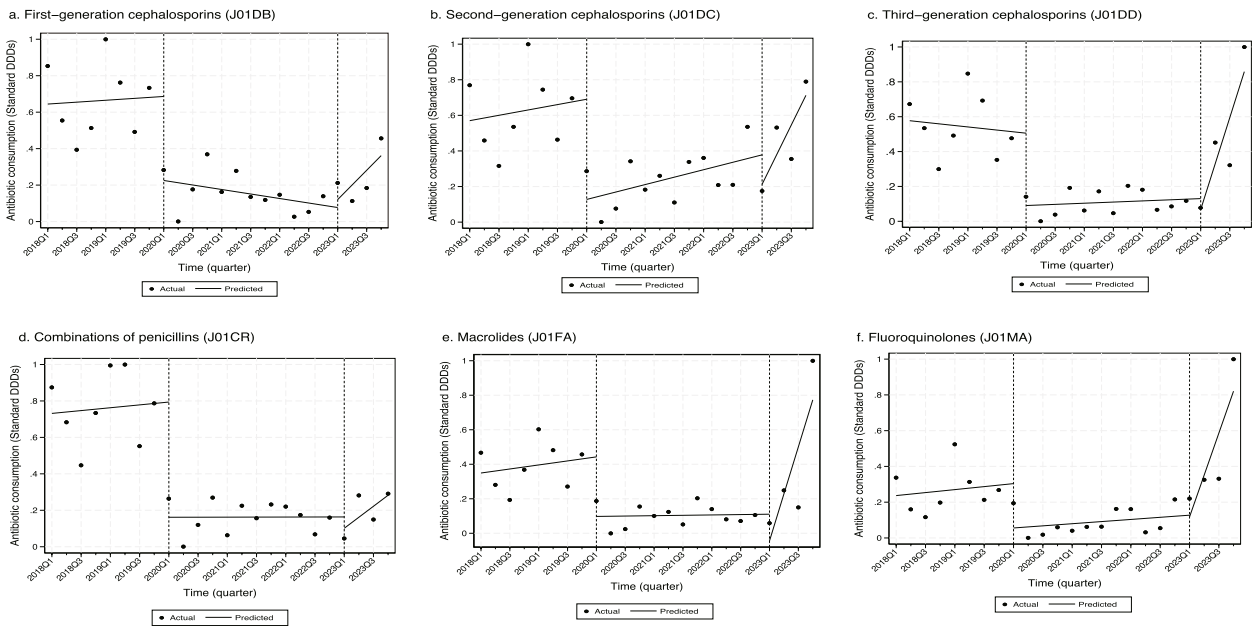

Fig. 5 Changes in the consumption of the most commonly prescribed antibiotics for AURIs in Chinese ED settings, measured in standard DDDs and classified according to the ATC classification, 2018 to 2023. **a**-**c** Cephalosporins. **d** Combinations of penicillins. **e** Macrolides. **f** Fluoroquinolones. Note: Dashed vertical lines indicate first change point and second change point, respectively

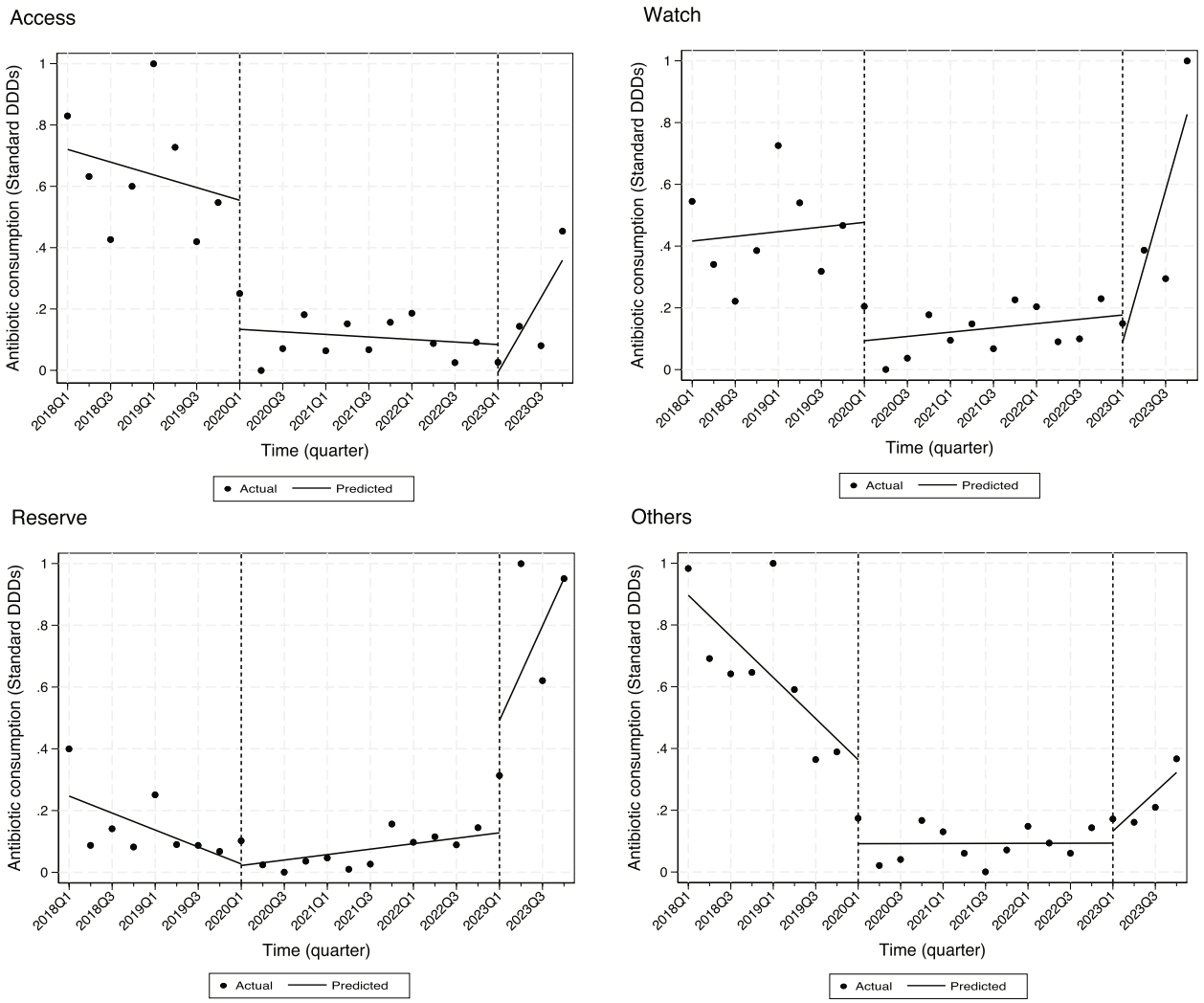

Fig. 6 Changes in the consumption of antibiotics for AURIs in Chinese ED settings, measured in standard DDDs and classified according to the WHO AWaRe categories, 2018 to 2023. Note: Dashed vertical lines indicate first change point and second change point, respectively

pandemic-related decline in antibiotic use followed by a rebound to pre-pandemic levels after the cessation of non-pharmaceutical interventions [27]. While the resurgence of respiratory infections (both viral and bacterial) may partially explain this trend, the significant increase in antibiotic use for AURIs highlights the urgent need for reinforced antimicrobial stewardship initiatives [27, 28].

The appropriateness of antibiotic use for AURIs was suboptimal. Our findings revealed that the overall guideline adherence was 22.26%. Consistent with previous research, two surveys conducted in China reported that reported that the proportion of antibiotics prescribed for AURIs in accordance with national guidelines ranged from 20.0% to 36.8% [15, 19]. Azithromycin, cefaclor, and levofloxacin were the three most frequently prescribed antibiotics for ED visits with AURIs, partially consistent with prior studies [5, 19]. Among these, only azithromycin is recommended as a first-line treatment. Notably, our findings highlighted a preference for levofloxacin prescribing in ED patients with AURIs, which was not highlighted in previous studies. Levofloxacin, as a second-line antibiotic recommended by national guidelines, was the third most frequently prescribed antibiotic. In addition, the combination of levofloxacin and cefaclor was also commonly prescribed, despite not being recommended. The prevalent use of second-line antibiotic, particularly in combination therapies, raises concerns. Given the association between quinolones overuse and the rise of quinolone-resistant pathogens, reassessing the necessity of prescribing quinolones for AURIs is imperative.

The proportion of Watch-group antibiotics prescribed was 83.82%, closely aligning with the 82.2% rate reported in a study on pediatric antibiotic prescribing in China [29]. The widespread use of broad-spectrum antibiotics,

particularly second- and third-generation cephalosporins, has significantly contributed to the high proportion of Watch-group antibiotics, raising serious concerns about antibiotic overuse in China. Notably, our findings revealed a higher proportion of second- and third-generation cephalosporins prescribed for children. In contrast, amoxicillin remains the most frequently prescribed antibiotic for children with AURIs abroad, often serving as a substitute for broad-spectrum agents [30]. The overuse of broad-spectrum cephalosporins may be partly driven by the mandatory skin testing requirement before prescribing penicillins, making cephalosporins a more convenient choice for clinicians [19, 31]. However, emerging evidence suggests that routine skin testing before prescribing beta-lactam antibiotics, such as amoxicillin, is unnecessary [32] and may hinder access to these first-line treatments. Furthermore, narrow-spectrum antibiotics for AURIs yield similar clinical outcomes with fewer adverse events compared to broad-spectrum agents [33].

To address the overprescribing of antibiotics for AURIs, it is essential to understand the determinants of prescribing practices and implement targeted interventions to optimize antibiotic use. Our study proposes several strategies for improving antibiotic stewardship. First, we recommend establishing and maintaining robust antimicrobial stewardship programs (ASPs) specifically tailored to ED settings. Substantial evidence demonstrates that well-implemented ASPs effectively reduce inappropriate antibiotic use and combat AMR [34]. Second, strict adherence to the WHO AWaRe classification framework should be prioritized [35]. When clinically appropriate, preference should be given to Access-group antibiotics (e.g., amoxicillin) over broad-spectrum alternatives to mitigate resistance development. Third, current evidence challenges the necessity of routine skin testing prior to beta-lactam antibiotic administration (e.g., penicillin, amoxicillin) [32]. Optimizing penicillin skin test requirements in Chinese clinical guidelines may facilitate a shift from broad-spectrum cephalosporins to narrower-spectrum penicillins, enhancing guideline compliance. Fourth, diagnostic uncertainty remains a key driver of antibiotic overprescription, particularly when the infection etiology is unclear. The development and implementation of rapid diagnostic technologies could significantly improve therapeutic decision-making [36], reducing the reliance on empirical antibiotic prescribing. Additionally, we advocate for targeted educational interventions addressing both healthcare providers and patients [37].

Several limitations should be noted. First, the absence of clinical details, such as examination findings, in the prescription data hinders the precise assessment of antibiotic appropriateness. The evaluation of antibiotic use is based on guideline-recommended therapy, which may not fully account for variations in patient severity. Second, the use of ICD-10 coding for diagnostic records can sometimes lead to oversimplification or misrepresentation of complex medical conditions, potentially affecting the accuracy of illness classification. Third, the prescription database primarily includes data from tertiary hospitals, limiting its ability to explore variations in antibiotic use across different hospital levels. Fourth, the study did not account for regional variations in antibiotic use due to disparity in the number of prescriptions, leading to uncertainty regarding regional differences in antibiotic utilization among patients with AURIs in China. Fifth, given the limited study duration and the potential for confounding factors, further research is needed to assess changes in antibiotic use among ED patients with AURIs following the relaxation of COVID-19 restrictions.

Conclusions

Antibiotic prescriptions for AURIs remain prevalent in Chinese ED settings, with a predominant use of broad-spectrum and Watch-group antibiotics. During the COVID-19 pandemic, antibiotic consumption declined significantly, followed by a notable rebound after the lifting of pandemic control measures. Although current usage remains below pre-pandemic levels, this trend underscores the urgent need to maintain robust antibiotic stewardship programs tailored to ED settings.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13756-025-01567-w.

Supplementary Material 1.

Authors'contributions

TXW and YZ designed the research. TXW and TXL wrote the manuscript draft; TXW, HG and TXL contributed to the data collection and analysis; TXW, TXL and HG prepared the tables and figures; BZ, YZ and ZGZ directed the research, reviewed and edited the manuscript. All authors reviewed the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

An ethics review exemption was applicable to this study, as it utilized fully anonymized data obtained from the Hospital Prescription Analysis Cooperative Project Database.

Consent to publication

Not applicable.

Competing interest
The authors declare no competing interests.

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