Appropriate use of antibiotics for acute respiratory infections at primary healthcare facilities in China: a nationwide cross-sectional study from 2017 to 2019

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Summary

Background The appropriateness of antibiotic use for acute respiratory infections (ARIs) in Chinese primary healthcare facilities (PHFs) remained uncertain. We aimed to evaluate to what degree antibiotic prescribing for ARIs were aligned with guideline recommendations in primary settings across China.

Methods We collected outpatient prescriptions from 262 Chinese PHFs in 27 cities of six provinces between 2017 and 2019. The appropriate antibiotic prescribing was defined as prescribing antibiotic classes that were recommended by Chinese clinical guidelines, if patients were prescribed antibiotics. We evaluated the magnitude of antibiotics prescribed for acute upper respiratory infections (AURIs), acute bronchitis, and community-acquired pneumonia (CAP) and their appropriateness.

Findings Overall, 55.1% (87,684/159,150), 66.8% (30,836/46,153), and 68.5% (4615/6733) of outpatients with AURIs, acute bronchitis, and CAP treated at PHFs in China were prescribed with antibiotics. Of all antibiotic prescriptions, only 20.0% (17,542/87,684), 18.6% (5724/30,836) and 69.6% (3211/4615) used antibiotic classes that were recommended by the guidelines for AURIs, acute bronchitis, and CAP, respectively. Patients residing in the Chinese central region (17.0%, 15.4%, 69.3% for AURIs, acute bronchitis, and CAP, respectively) were less likely to be prescribed with antibiotics that were appropriately selected.

Interpretation Unnecessary antibiotics were widely prescribed for patients with AURIs or acute bronchitis and most patients with ARIs did not receive guideline-recommended antibiotic classes in Chinese PHFs. Interventions to promote evidence-based treatment and the appropriate use of antibiotics are urgently needed at the primary level across China.

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Keywords: Antibiotic; Primary health care; Respiratory tract infections; Guideline; Prescriptions

Introduction

Acute respiratory infections (ARIs) are the most common diseases leading to primary healthcare visits and patients with such conditions are usually prescribed with antibiotics.[1] However, clinical guidelines emphasize that antibiotics are unnecessary for routine treatment of uncomplicated self-limiting ARIs, including acute upper respiratory infections (AURIs) and acute bronchitis, which are mostly caused by the viruses, unless there is evidence of the bacterial infection (e.g., suppurative symptoms).[2,3] Antibiotic treatment could neither shorten the course of the disease nor prevent secondary bacterial infections.[4,5] Previous studies have identified that extremely high proportion of ARIs patients received inappropriate antibiotic treatment.[6–8] The number could range from 3% to 78% for AURIs and 25%–94% for acute bronchitis across countries.[3,8–12] In contrast, community-acquired pneumonia (CAP) is mostly caused by *Streptococcus pneumoniae* and always requires antibiotic treatment.[13,14] Nevertheless, under-

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Research in context

Evidence before this study

We searched PubMed for research articles published in English, and CNKI for articles in Chinese, using search terms "antibiotic" ("antibacterial" OR "antimicrobial"), "appropriate*" ("inappropriate*", "rational*", OR "irrational*"), "primary" ("community" OR "township"), "facilit*" ("healthcare", OR "setting*", OR "institution*"), AND "acute respiratory infections" ("respiratory tract infections" OR "acute respiratory illnesses"), with no date restrictions on January 1, 2023, and used the snowball process to identify additional relevant publications. A growing body of literature has shown that inappropriate antibiotic prescribing for acute respiratory infections (ARIs) was highly prevalent in primary healthcare setting in the US. and European countries. However, studies focusing on Chinese primary healthcare facilities (PHFs) typically covered limited geographical areas or had small prescription samples. How antibiotic class selection for ARI treatment align with guideline recommendations was not comprehensively assessed in China.

Added value of this study

We analyzed the magnitude and appropriateness of antibiotic prescribing for ARIs treatment in primary healthcare settings in China. Our analyses encompassed 212,036 outpatient visits with acute upper respiratory infections (AURIs), acute bronchitis, or community-acquired pneumonia (CAP) at Chinese primary healthcare facilities. We found 55.1% (87,684/159,150), 66.8% (30,836/46,153), and 68.5% (4615/6733) of outpatients with AURIs, acute bronchitis, and CAP treated at primary healthcare facilities in China were prescribed with antibiotics. Of all antibiotic prescriptions, only 20.0% (17,542/87,684), 18.6% (5724/30,836) and 69.6% (3211/4615) used antibiotic classes that were recommended by the guidelines for AURIs, acute bronchitis and CAP, respectively. In particular, excessive and inappropriate antibiotic prescribing were more commonly observed in children, with only 10% of children with acute bronchitis receiving appropriate antibiotics classes. Disparity was also found across regions, with the central and western regions having the lowest and highest prescribing rates of guideline-recommended antibiotics.

Implications of all the available evidence

Antibiotic stewardship programs and interventions aimed to promote evidence-based treatment should be designed and implemented. Tailored training and continuous education for physicians and improvement for accessibility to laboratory services or quality of laboratory test are urgently needed at primary healthcare settings. Future work should design, implement and assess the effect of multidimensional interventions.

prescribing of antibiotics for pneumonia was prevalent globally, with 22%–34% of CAP patients not receiving antibiotic treatment according to previous reports.[15–18]

Inappropriate antibiotic prescribing, including overuse, underuse, and irrational selection of antibiotics (i.e., the choice of antibiotics deviates from guideline recommendations), could contribute to adverse clinical outcomes and antimicrobial resistance (AMR).[19,20] Assessing the patterns and appropriateness of antibiotic prescribing for ARIs is necessary to promote the rational use of antibiotics and inform strategies to tackle AMR. In China, primary healthcare facilities (PHFs) held over half of annual outpatient visits (53.2% of 7.7 billion in 2020),[21] however, inappropriate antibiotic prescribing was more severe in PHFs than upper-level hospitals.[6,8] Studies conducted at Chinese PHFs typically covered limited geographical areas or had small prescription samples.[18,22–24] Only two studies reported the prescribing rate of antibiotics for ARIs at PHFs nationwide, however, they did not assess the alignment of ARI treatment with guideline recommendations,[8,25] which is a significant research gap. Therefore, this study aimed to address this gap by generating comprehensive estimates of the prescribing rates of antibiotics for ARIs and evaluating the appropriateness of antibiotic selection at PHFs in China using current clinical guidelines.

Methods

Sampling and data collection

Sampling

We extracted outpatient prescription data from a national survey for PHFs in China. In the survey, we systematically sampled Chinese PHFs using a two-step method that has been described in detail in our previous study and Supplementary Materials.[26] In brief, urban community health centers and rural township hospitals were randomly sampled based on their ratio (1:4) across China in 2017, from 31 cities of six (out of 31) provinces (three from the twelve developing provinces in western region, one from the eight less developed provinces in central region, and two from the eleven relatively developed provinces in eastern region) in China (Supplementary Figure S1, Supplementary Table S1).[27] Using a 5% confidence level and a 2.5% margin of error, with an expected rate of antibiotic prescriptions for acute respiratory infections (ARIs) based on a previous study at 20%,[8] the minimum sample size was calculated to be 984 prescriptions at primary healthcare facilities per year. For the convenience of data collection, we designed to collect 100 prescriptions on the second Tuesday of each month (1200 prescriptions per year) at each facility from 2017 to 2019 (detailed in Supplementary Methods). In this study, the term "prescription" refers to all drugs

prescribed for one patient during one outpatient visit in a single day.

Data collection and quality control

Two trained investigators extracted outpatient records from the electronic prescribing system of sampled facilities. Extracted data included visit date, patient demographics (gender and age), diagnoses, medications, and costs. All data were de-identified. Double data extraction for a proportion of the prescriptions was applied to ensure the accuracy of extraction. All data were checked for completeness by the investigators and digitally transferred under password-protection. Then, four data quality specialists inspected manually for data errors and made necessary corrections for all collected prescriptions. Errors, outliers for each continuous variable, and illogical association between variables in the records were noted for quality control to determine the authenticity of the data. The ethical approval was obtained from the Peking University Institution Review Board (IRB00001052-17019-m).

Inclusion and exclusion criteria

PHFs that recorded prescriptions every year from 2017 to 2019 were sampled facilities in our analysis (262/371 [70.6%], Supplementary Table S1). All outpatient prescriptions of sampled facilities with a diagnosis of AURIs, acute bronchitis, or CAP were eligible for inclusion. Prescriptions that contained diagnoses of multiple ARIs or infections other than the three conditions mentioned above were excluded. Detailed inclusion and exclusion criteria of prescriptions by diagnostic category are presented in Supplementary Table S2 and Supplementary Figure S2. Vaccines and antiviral drugs were excluded from the analyses. Herbal medicines and traditional Chinese medicines (TCMs) were also excluded because there are no systemic frameworks to categorize TCMs and thus it is difficult to quantify the use of TCMs for the treatment of acute respiratory tract infections as the substitution for antibiotics.

Measurements

Definition of acute respiratory infections

Based on guidelines and previous research,[25,28–30] we defined AURIs as J00 and J02-06 (common cold, tonsillitis, pharyngitis, laryngitis, and pharyngoconjunctival fever) of the International Classification of Diseases (ICD-10) system, acute bronchitis as J20, and CAP as J13-J15 and J18 (Supplementary Table S2). Sinusitis (J01) and otitis media (H65) were excluded because they were not included as AURIs in Chinese guidelines.[29,30] Diagnoses in the database were presented in the form of Chinese narrative free text. We used a regular expression algorithm, validated and applied in previous research, to extract diagnosis information from natural language and map to the ICD-10 codes.[16,31]

Definition of antibiotics and guideline recommendations

Drugs in the database were coded according to the World Health Organization (WHO) Anatomical Therapeutic Chemical (ATC) classification system, as recommended by the WHO Collaborating Centre for Drug Statistics Methodology.[32] We classified systemic antibiotics according to the ATC classification J01 (antibacterial for system use) and also classified antibiotics into Access, Watch, Reserve, and Not recommended categories according to the WHO AWaRe classification.[32,33] We evaluated the selection of antibiotic classes based on Chinese guidelines for the primary care of AURIs, acute bronchitis, and CAP.[14,30,34] Antibiotic classes recommended by the guideline are presented in Supplementary Table S3.

Outcomes

Antibiotic prescription rate (APR) was calculated for AURIs, acute bronchitis, and CAP, with the numerator being the number of prescriptions that contained at least one antibiotic and the denominator being the total number of prescriptions for a specific condition.[8,16] Then, for prescriptions containing antibiotics, we reported the rate of guideline-recommended antibiotics for each condition, with the numerator being the number of prescriptions that contained antibiotics classes aligned with the guideline recommendations and the denominator being the number of prescriptions that contained at least one antibiotic. The frequency proportion of each antibiotic class prescribed was calculated to describe the distribution of prescribed antibiotics by class (ATC system or WHO AWaRe system), with the numerator being the frequency of a specific antibiotic class and the denominator being the frequency of all antibiotic classes.

Statistical analysis

Covariates in our analysis were region, located area of the facility, and patient gender and age. Descriptive statistics were used to describe facility and patient characteristics, with counts and proportions reported. Prescription rates were calculated and adjusted by a generalized linear model, using logistic regression as link function with error variance that allows for intra-group correlation in facilities. The linear regression form of generalized linear model was conducted to confirm the robustness of logistic link function form (Supplementary Table S5). The variance inflation factors (VIF) were calculated to test potential multicollinearity. The VIF of variables were less than five and suggest slight correlation and thus no correction was conducted (Supplementary Table S6).[35] We also conducted the regression including the interaction between region and area, or between region and age, to further explore the potential interactions between these variables (Supplementary Tables S8 and S9). The level of statistical significance was defined as $p < 0.05$ (two-sided). We

conducted statistical analyses using Stata version 16 and created plots using Microsoft Excel.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Study sample and characteristics

We included 212,036 prescriptions with a diagnosis of acute respiratory infection for visits that occurred at 262 PHFs in 27 cities of six provinces between 2017 and 2019 (Supplementary Figures S1 and S2, Supplementary Table S1). Of these prescriptions, 159,150 (75.1%) were with a diagnosis of AURIs, 46,153 (21.8%) with acute bronchitis, and 6733 (3.2%) with CAP; 44,610 (21.0%) were prescribed in urban community healthcare centers and 167,426 (79.0%) in rural township hospitals; 41,454 (19.6%), 133,413 (62.9%), and 37,169 (17.5%) prescriptions were from facilities located in the western, central, and eastern regions, respectively; 99,249 (46.8%) prescriptions were prescribed for female patients and 133,023 (62.7%) were for patients aged 18 years and above (Table 1).

Antibiotic prescribing and influencing factors

Before adjusted by generalized linear model for covariates, the unadjusted APRs were 55.1%, 66.8%, and 68.5% for AURIs, acute bronchitis, and CAP, respectively (Supplementary Table S4). After the adjustment (Table 2, Supplementary Table S7), facilities located in the western region had a lower adjusted APR for all three conditions (27.5% [reference], 43.2% [reference], 40.2% [reference] for AURIs, acute bronchitis, and CAP, respectively) than those in the central (64.5% [OR = 5.06; 95% CI 3.34–7.65], 68.3% [OR = 3.01; 95% CI 1.90–4.78], 74.9% [OR = 5.00; 95% CI 2.85–8.79]) or eastern regions (58.1% [OR = 3.83; 95% CI 2.35–6.22], 70.5% [OR = 3.37; 95% CI 2.13–5.33], 67.6% [OR = 3.41; 95% CI 1.87–6.15]). Adults (18–64 years: 70.2% [OR = 1.76; 95% CI 1.50–2.08]) and elders (65–79 years: 70.2% [OR = 1.76; 95% CI 1.46–2.13], ≥80 years: 67.2% [OR = 1.52; 95% CI 1.23–1.89]) were more likely to be prescribed with antibiotics for acute bronchitis than children (0–5 years: 57.9% [reference]; 6–17 years: 66.4% [OR = 1.47; 95% CI 1.26–1.71]). In the eastern and central regions, the increase of age accompanied by higher rise in the antibiotic prescription rate, which is supported the positive interaction terms in the models (Supplementary Table S8).

Guideline-recommended antibiotic prescription rate

Before adjusted by the generalized linear model for covariates, the rates of guideline-recommended antibiotic in the antibiotic prescriptions (assuming antibiotics were indicated) were 20.0%, 18.6%, and 69.6% for AURIs, acute bronchitis, and CAP, respectively (Supplementary Table S4). After the adjustment (Table 2, Supplementary Table S7), facilities located in the western region had a higher adjusted rate of guideline-recommended antibiotic in the antibiotic prescriptions for AURIs and acute bronchitis (31.5% [reference], 32.8% [reference] for AURIs and acute bronchitis, respectively) than those in the central (17.0% [OR = 0.44; 95% CI 0.30–0.64], 15.4% [OR = 0.36; 95% CI 0.26–0.49]) or eastern regions (24.5% [OR = 0.70; 95% CI 0.44–1.11], 22.5% [OR = 0.58; 95% CI 0.41–0.82]). Adults (18–64 years: 22.6% [OR = 2.62; 95% CI 2.02–3.41]) and elders (65–79 years: 24.1% [OR = 2.85; 95% CI 2.02–3.41]; ≥80 years: 24.7% [OR = 2.94; 95% CI 2.17–3.98]) with acute bronchitis were more likely to be prescribed with guideline-recommended antibiotics than children (0–5 years: 10.2% [reference]; 6–17 years: 9.8% [OR = 0.95; 95% CI 0.77–1.18]). Elders with CAP were more likely to be prescribed with guideline-recommended antibiotics (65–79 years: 82.6% [OR = 3.49; 95% CI 2.12–4.61]; ≥80 years: 84.5% [OR = 4.07; 95% CI 2.16–6.14]) than children (0–5 years: 64.9% [reference]; 6–17 years: 65.0% [OR = 1.00; 95% CI 0.74–1.35]) and adults (18–64 years: 60.8% [OR = 0.92; 95% CI 0.63–1.30]).

Distribution of prescribed antibiotics by drug class

For CAP, the most frequently prescribed antibiotics were third-generation cephalosporins (J01DD, 1350 [21.5%]), followed by combinations of penicillin and beta-lactamase inhibitors (J01CR, 970 [15.5%]), and second-generation cephalosporins (J01DC, 959 [15.3%]). For acute bronchitis, second-generation cephalosporins (J01DC, 6650 [17.5%]) were the most commonly used antibiotics, closely followed by third-generation cephalosporins (J01DD, 6346 [16.7%]) and macrolides (J01FA, 5309 [14.0%]). However, all third-generation cephalosporins were not recommended for acute bronchitis, and only some of the second-generation cephalosporins or macrolides were recommended for acute bronchitis. For AURIs, second-generation cephalosporins (J01DC, 18,705 [17.6%]) also shared the largest proportion of antibiotics prescriptions, followed by third-generation cephalosporins (J01DD, 16,301 [15.3%]) and combinations of penicillin and beta-lactamase inhibitors (J01CR, 15,482 [14.5%]). Nevertheless, all the three antibiotic classes above were not recommended for AURI (Supplementary Table S10). Antibiotics classified as Access accounted for 42.2%, 34.5%, and 31.5% of all antibiotics prescribed for AURIs, acute bronchitis, and CAP, respectively. By contrast, Watch-class antibiotics constituted 55.1%, 61.9%, and 62.8% of all antibiotics prescribed for AURIs, acute bronchitis, and CAP, respectively (Supplementary Table S12).

Characteristics	Samples, n (%)							
	Total	Proportion (%)	AURIs	Proportion (%)	Acute bronchitis	Proportion (%)	CAP	Proportion (%)
Total	212,036 (100.0)	100.0	159,150 (75.1)	100.0	46,153 (21.8)	100.0	6733 (3.2)	100.0
Year								
2017	71,737 (100.0)	33.8	54,903 (76.5)	34.5	14,609 (20.4)	31.7	2225 (3.1)	33.0
2018	70,704 (100.0)	33.3	53,103 (75.1)	33.4	15,415 (21.8)	33.4	2186 (3.1)	32.5
2019	69,595 (100.0)	32.8	51,144 (73.5)	32.1	16,129 (23.2)	34.9	2322 (3.3)	34.5
Area								
Urban	44,610 (100.0)	21.0	34,711 (77.8)	21.8	9023 (20.2)	19.6	876 (2.0)	13.0
Rural	167,426 (100.0)	79.0	124,439 (74.3)	78.2	37,130 (22.2)	80.4	5857 (3.5)	87.0
Region								
Western	41,454 (100.0)	19.6	36,572 (88.2)	23.0	3963 (9.6)	8.6	919 (2.2)	13.6
Central	133,413 (100.0)	62.9	99,701 (74.7)	62.6	29,400 (22.0)	63.7	4312 (3.2)	64.0
Eastern	37,169 (100.0)	17.5	22,877 (61.5)	14.4	12,790 (34.4)	27.7	1502 (4.0)	22.3
Patient gender								
Male	112,787 (100.0)	53.2	84,422 (74.9)	53.0	24,623 (21.8)	53.4	3742 (3.3)	55.6
Female	99,249 (100.0)	46.8	74,728 (75.3)	47.0	21,530 (21.7)	46.6	2991 (3.0)	44.4
Patient age[a]								
0–5	34,553 (100.0)	16.3	23,783 (68.8)	14.9	9459 (27.4)	20.5	1311 (3.8)	19.5
6–17	44,460 (100.0)	21.0	34,757 (78.2)	21.8	8678 (19.5)	18.8	1025 (2.3)	15.2
18–64	101,428 (100.0)	47.8	79,879 (78.8)	50.2	18,909 (18.6)	41.0	2640 (2.6)	39.2
65–79	25,491 (100.0)	12.0	17,072 (67.0)	10.7	7123 (27.9)	15.4	1296 (5.1)	19.2
≥80	6104 (100.0)	2.9	3659 (59.9)	2.3	1984 (32.5)	4.3	461 (7.6)	6.8

Abbreviations: AURIs, acute upper respiratory tract infections; CAP, community-acquired pneumonia. [a]The stratification of patient age was base on recommendations in Chinese guidelines.

Table 1: **Characteristics of outpatient-visit prescriptions for acute respiratory infections at primary healthcare facilities in China, 2017–2019.**

Discussion

This study comprehensively compared antibiotic prescribing for ARIs at PHFs in China against guideline recommendations using a nationally representative sample of prescription data. We found an excessive use of antibiotics for patients with AURIs or acute bronchitis and underuse for patients with CAP. Among all patients with AURIs or acute bronchitis who received antibiotics, only one-fifth were prescribed with antibiotics that were recommended by the Chinese guideline. Second- and third-generation cephalosporins were the most commonly prescribed antibiotics, accounting for one-third of antibiotic prescriptions, despite that they were not recommended for treatment of the three conditions, except in cases where patients with CAP were either over 65 years old or with comorbidities. Children were less likely to receive guideline-recommended antibiotics than adults (aged of 18–64) and elders (aged of 65 and above), with only 10% of children with acute bronchitis receiving appropriate antibiotics classes. Disparity was also found across regions, with the central and western regions having the lowest and highest prescribing rates of guideline-recommended antibiotics for AURIs and acute bronchitis.

We observed that 55.1% of patients with AURIs and 66.8% of patients with acute bronchitis were prescribed with antibiotics at PHFs in China. These rates were higher than those reported by PHFs in Canada (18.0% for AURIs, 60.5% for acute bronchitis, 2011–2016), Switzerland (2.7% for AURIs, 41.5% for acute bronchitis, 2015), and Sweden (4.5% for AURIs, 26.2% for acute bronchitis, 2013), though the clinical significance of the comparison could be weakened due to difference in time spans, clinical guidelines, and clinical settings.[9–11] Compared with previous studies in China, our rates were lower than those reported by studies investigating PHFs in six provinces in China (78.0% for AURIs, 93.5% for acute bronchitis, 2009–2011) and in Shandong province (61.4% for AURIs, 78.2% for acute bronchitis, 2015–2017),[8,18] which could be partly explained by the Chinese antibiotic stewardship programs since 2011.[36] However, the rates were higher than those shown by a study evaluating outpatient prescriptions in secondary and tertiary hospitals at the national level (44.9% for AURIs, 50.6% for acute bronchitis, 2014–2018), though variance may arise from disparities in patient characteristic across PHFs and secondary or tertiary hospitals.[16] According to the Cochrane reviews, there was no or limited evidence on the benefit of antibiotic treatment for patients with AURIs or acute bronchitis.[37,38] The current Chinese guidelines for AURIs and acute bronchitis also did not recommend routine use of antibiotics for these conditions, except for specific situations that do indicate antibiotics (e.g., patients with suppurative pharyngitis, or patients with both bronchitis and diabetes).[29,39] Our

Characteristics	Antibiotic prescription (%)						Guideline-recommended antibiotic in the antibiotic prescriptions (%)					
	AURIs		Acute bronchitis		CAP		AURIs		Acute bronchitis		CAP	
	Rate[a]	OR	Rate	OR	Rate	OR	Rate	OR	Rate	OR	Rate	OR
Year												
2017	55.9	Ref.	66.8	Ref.	68.2	Ref.	19.4	Ref.	18.6	Ref.	67.4	Ref.
2018	55.4	0.98	67.6	1.04	68.9	1.04	19.8	1.03	17.5	0.92	69.7	1.12
2019	53.9	0.91	66.0	0.96	68.5	1.02	20.9	1.10	19.6	1.07	71.6	1.24
Area												
Urban	58.9	Ref.	71.1	Ref.	79.5	Ref.	19.2	Ref.	16.6	Ref.	62.4	Ref.
Rural	54.0	0.80	65.7	0.77	66.9	0.48**	20.3	1.07	19.1	1.20	70.9	1.50*
Region												
Western	27.5	Ref.	43.2	Ref.	40.2	Ref.	31.5	Ref.	32.8	Ref.	71.3	Ref.
Central	64.5	5.06***	68.3	3.01***	74.9	5.00***	17.0	0.44***	15.4	0.36***	69.3	0.90
Eastern	58.1	3.83***	70.5	3.37***	67.6	3.41***	24.5	0.70	22.5	0.58**	69.8	0.93
Patient gender												
Male	55.4	Ref.	67.0	Ref.	68.4	Ref.	20.1	Ref.	18.6	Ref.	68.7	Ref.
Female	54.7	0.97	66.6	0.99	68.7	1.01	19.9	0.99	18.5	1.00	70.7	1.11
Patient age												
0–5	48.4	Ref.	57.9	Ref.	60.9	Ref.	18.7	Ref.	10.2	Ref.	64.9	Ref.
6–17	55.7	1.39***	66.4	1.47***	67.8	1.40*	17.4	0.92	9.8	0.95	65.0	1.00
18–64	56.6	1.45***	70.2	1.76***	72.1	1.77***	21.4	1.19	22.6	2.62***	62.7	0.91
65–79	56.4	1.43***	70.2	1.76***	72.6	1.82**	20.8	1.15	24.1	2.85***	85.0	3.13***
≥80	54.0	1.28**	67.2	1.52***	61.5	1.03	19.9	1.09	24.7	2.94***	86.8	3.64***

Abbreviations: AURIs, acute upper respiratory tract infections; CAP, community-acquired pneumonia. *p < 0.05; **p < 0.01; ***p < 0.001. [a]All rates in the table were adjusted by generalized linear model, using logistic regression as link function with error variance that allow for intragroup correlation in facilities.

Table 2: **Adjusted antibiotic prescription rate and the guideline-recommend antibiotic rate in the antibiotic prescriptions for acute respiratory infections at primary healthcare facilities in China, 2017–2019.**

finding suggests that overprescribing of antibiotics for patients with AURIs and acute bronchitis were more common at PHFs in China than secondary or tertiary hospitals in China, and were more common than PHFs in other countries, which could be driven by the lack of physician's knowledge for evidence-based clinical practice and the patient's desire for antibiotics.[16,28]

In contrast to AURIs or acute bronchitis, patients with CAP experienced underuse of antibiotics at Chinese PHFs. We found that 31.5% of patients with CAP were not prescribed with antibiotics and this rate was 33.6% (2014–2018) at secondary and tertiary hospitals across China.[16] The prescribing rate of antibiotics for CAP (68.5%) was slightly higher than rates in research conducted at PHFs in Canada (antibiotic prescription rate for CAP was 63.8%, 2011–2016) and Sweden (62.5%, 2013),[9,11] though the rate was still lower than that in Switzerland (94.6%, 2015).[10] Considering the similitude of prescribing rate and classes distribution of antibiotics for acute bronchitis and CAP at PHFs observed in our study, and also in secondary and tertiary hospital studies in China,[16,40] physicians' diagnostic uncertainty might be an important factor contributing to the inappropriate prescribing of antibiotics for ARIs.[41] Acute bronchitis and CAP are both acute lower respiratory infections that share similar clinical presentations, including cough, dyspnea, and chest pain. A previous survey has reported that nearly half of physicians did not trust that the imaging examination could always rule out CAP for patients with ARIs.[42] The diagnostic uncertainty may lead physicians to prescribe antibiotics for patients that were diagnosed as acute bronchitis as if they have CAP, since physicians worried about risk of undertreating. Conversely, physicians may refrain from prescribing antibiotics for patients diagnosed with CAP due to their concerns about the possibility of overtreatment.[43,44] Consequently, physicians were more inclined to prescribe antibiotics for patients with AURIs or acute bronchitis while being less inclined to prescribe antibiotics for patients with CAP.

Even if all patients that received antibiotics did require antibiotics, we found that only 20.0% of patients with AURIs and 18.6% of patients with acute bronchitis received guideline-recommended antibiotics. This rate was 69.6% for patients with CAP. Second- and third-generation cephalosporins as well as combinations of penicillins and beta-lactamase inhibitors were all not recommended by guidelines. However, these antibiotics accounted for 17.6%, 15.3%, and 14.5% of antibiotics prescribed for patients with AURIs and accounted for

17.5%, 16.7%, and 13.8% for patients with acute bronchitis. Similarly, we found that third-generation cephalosporins, despite not representing a guideline recommendation, were prescribed for nearly 20% of CAP patients under 65 years old. The overuse of second- or third-generation cephalosporins to treat ARIs was consistent with previous findings at PHFs and upper-level hospitals in China.[8,16] This might be explained by the requirement of skin testing before prescribing penicillin for all patients in China.[45] As the mandatory testing is inconvenient and may not be reliable, physicians prefer to prescribe cephalosporins, for which skin testing is not mandatory, rather than penicillin.[46–48] Considering that second- and third-generation cephalosporins are both broad-spectrum antibiotics and that they are associated with increased risk of AMR and development of *clostridioides difficile* infection,[49] further interventions should be implemented to avoid the overuse of broad-spectrum antibiotics.

We observed variations in antibiotic use across different facility characteristics and patient characteristics. We found antibiotic prescription rates in facilities located in the western region were lower than those in the eastern or central regions (31.0%, 64.8%, and 64.2% in the western, central, and eastern region, overall), which is in accordance with previous studies in upper-level hospitals in China (8.9%, 11.4%, and 12.4% in the western, central, and eastern regions, 2014–2018).[16] The disparities could be attributed to variations in the implementation of antibiotic stewardship programs across China, suggesting stricter stewardship in the western region.[36] However, we did not find significant diversity between urban and rural areas for AURIs and acute bronchitis, though antibiotic prescription rate for CAP was lower in rural areas. Due to the unavailability of data, our attempt to comprehend the regional variations was limited, and more in-depth research exploring and interpreting the regional disparities are needed. Besides, we found a lower proportion of children received guideline-recommended antibiotics than adults and elders. A possible explanation is that cephalosporins were prescribed for children more frequently as an alternative to fluoroquinolones, due to the potential risk of severe musculoskeletal disorders associated with fluoroquinolones.[50] However, cephalosporins are not recommended for the routine treatment of AURIs and CAP, as discussed earlier. As a result, a smaller proportion of children received guideline-recommended antibiotic treatment for ARIs. More evidence should be generated to support decisions on treating children with ARIs, given that ARIs is the most common reason for pediatric outpatient visit to PHFs.[51]

As inappropriate antibiotic prescriptions for ARIs at PHFs are prevalent in China, antibiotic stewardship programs and interventions aimed to promote evidence-based treatment should be designed and implemented. Our finding suggested that diagnostic uncertainty could lead to inappropriate antibiotic prescribing and thus improving the accessibility and quality of laboratory services could help limiting inappropriate use of antibiotics. Rapid tests for pathogen of ARIs, such as point-of-care C-reactive protein test, have been proven helpful to reduce diagnostic uncertainty and decrease antibiotic prescribing in primary care,[52,53] yet its feasibility in Chinese primary care settings warrants further research. Introducing a scoring system, such as the FeverPAIN score or Centor score recommended by the NICE (The National Institute for Health and Care Excellence) guideline, could also benefit clinical decision-making concerning antibiotic prescribing.[54] To improve physician's knowledge level and attitude, physician-level strategies, including tailored education with peer-review meetings,[55] public reporting of provider performance,[22] and computer-based feedback system,[56] were proven feasible and effective in primary healthcare settings in China in research. Moreover, surveillance of antibiotic use should also distinguish conditions for which antibiotic treatment is always justified to avoid underuse of antibiotics in certain cases.[16,57] Finally, our finding indicates the need for a long-term, nationwide, government intervened, cross-sectoral antimicrobial stewardship program to promote evidence-based antibiotic use and enhance the consistency in the quality of healthcare services throughout China.[36]

Several limitations of this study should be noted. First, due to the limitation of prescriptions data, our ability to precisely identify patients who were in actual need of antibiotic treatment was restricted. Consequently, we analyzed the prescribing rates of antibiotics (of all prescriptions) and guideline-recommended antibiotics (of all antibiotic prescriptions) separately. The rate of prescriptions adherent to guidelines could be overestimated as there was possible that some patients who were prescribed antibiotics might not actually need them. Therefore, the rate of guideline-recommended antibiotic in the antibiotic prescriptions might be higher than the actual rate of prescriptions adherent to guidelines. Second, although a systematic sampling method was applied to the nationwide survey, the sample might still not be fully representative of all outpatient visits at PHFs across China. Moreover, we excluded village clinics and community health stations from the analyses due to dispersion of institutions and the absence of the electronic health system, which could compromise our sample representativeness and limit the interpretation of results. The deviation from the design during data collection could also impair sample representativeness. Third, our data is up to the year 2019 and thus may not represent the current situation of antibiotic prescribing in China, given that the COVID-19 pandemic might greatly impact clinical arrangement and practices. The use of antibiotics in Chinese primary healthcare settings may have undergone

significant changes during this period. Forth, the quality of diagnosis documentation directly affected the reliability of our results. Inaccurate records of diagnosis are likely to have reduced the robustness of our conclusions, despite that we manually inspected and corrected data errors. Fifth, the assessment of the appropriateness of antibiotic prescribing only evaluated whether antibiotics were needed for certain conditions and whether the antibiotic classes were recommended by the guideline. We did not take administration route, dosage, and therapy duration into consideration. Sixth, due to limited data access, many factors that may affect the quality of prescribing, such as the volume of outpatients and the number of medical staffs in sampled facilities, characteristics and knowledge of clinicians, laboratory tests, local prevalence of antibiotic-resistant bacteria, patient's medical history, prescription time of day of patient visits, drug affordability, smoking, and environmental pollution were not measured. Seventh, we collected de-identified prescription-level records from the sampled facilities. It is possible that patients who did not receive antibiotics in our sample prescriptions, could obtain antibiotics from other hospitals, community pharmacies, or from the same PHFs during another visit.[58,59] Consequently, the prevalence of antibiotic prescribing shown in our study was not equivalent to the actual prevalence of antibiotic use among sample patients. Eighth, we excluded traditional Chinese medicine from our analysis, which might play an important role for ARIs treatment in Chinese PHFs. Consequently, our study may have overlooked valuable insights and introduced bias into the results. Finally, the analysis was fundamentally based on recommendations of the Chinese guidelines and would be affected by the quality of these guidelines. Our results should thus be viewed and interpreted in this light. Further research to evaluate the quality of Chinese guidelines for ARIs are needed.

Contributors

XG, LS, and MF conceived and designed the work. All authors acquired the data. MF, and ZG analyzed the data. XG, MF, and ZG drafted the manuscript. XG and LS critically revised the manuscript for important intellectual content. XG supervised the study. All authors were responsible for the interpretation of the data, and revised, and gave final approval of the manuscript.

Data sharing statement

Data of the research is available upon reasonable request from the corresponding author.

Editor note

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Declaration of interests

The authors declare that there are no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2023.100880.

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