

A Systematic Review of Antibiotic Prescription Associated With Upper Respiratory Tract Infections in China

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Abstract: Overuse of antibiotics among patients with upper respiratory tract infection (URTI) is a worldwide problem, and the problem is especially serious in developing countries, such as China. This systematic review is aimed at summarizing previous findings on outpatient prescriptions of antibiotics associated with URTI in China in order to help policymakers and the public understand and tackle the problem.

We systematically searched and reviewed studies of antibiotic prescribing patterns for outpatients with URTI in China that were published in Chinese or English before December 31, 2014. The study quality was assessed, and the overall rates of URTI cases prescribed antibiotics were calculated by using random-effects model. Subgroup analyses were performed to explore the potential sources of heterogeneity among studies.

We included 45 eligible studies with a total of 52,072 URTI outpatients. The overall percentage of URTI outpatients prescribed antibiotics was 83.7% (95% confidence interval [CI]: 80.6%–86.4%). Of the URTI outpatients prescribed antibiotics, 79.7% (95% CI: 72.8%–85.2%) were prescribed 1 antibiotic, 18.4% (95% CI: 13.6%–24.5%) prescribed 2 antibiotics, and 1.1% (95% CI: 0.7%–1.6%) prescribed 3 or more antibiotics. The rates of antibiotic prescription varied greatly across hospitals and showed a downward trend over time.

An extremely high percentage of URTI patients in China were prescribed antibiotics and, the overuse is especially problematic in

lower-level hospitals. Although there appears a downward trend, likely attributable to China's recent efforts in curbing antibiotic abuse, greater efforts are needed to promote the rational use of antibiotics.

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Abbreviations: CI = confidence interval, ESAC = European surveillance of antimicrobial consumption, INRUD = International Network for the Rational Use of Drugs, URTI = upper respiratory tract infection, USAID = United States Agency for International Development, WHO = World Health Organization.

INTRODUCTION

Overuse of antibiotics is a serious public health problem worldwide, which not only results in waste of healthcare resources but also leads to the development of antibiotic resistance.^{1–4} The most common condition associated with excessive use of antibiotics is upper respiratory tract infections (URTIs). Etiological studies suggest that the main cause of URTI is virus; only less than 10% of URTI cases are caused by bacteria, which require antibiotic treatment.⁵ Therefore, the percentage of URTI cases prescribed antibiotics has been used as a key indicator for assessing overuse of antibiotics.⁶ The World Health Organization (WHO) has been using this indicator to systematically review the use of antibiotics for URTI cases.^{7–9} In a report entitled, *Medicines Use in Primary Care in Developing and Transitional Countries*, the WHO estimated that the percentage of URTI cases prescribed antibiotics increased over time from 43% to 71% during the 1982 to 2006 period,¹⁰ despite systematic that reviews have shown that antibiotics are of limited effectiveness in the treatment of URTI.¹¹

China is one of the countries with severe abuse of antibiotics.¹² Many studies have been conducted on the overuse of antibiotics in China. However, there are few articles were published in English, and most of these studies were published in Chinese. Because of the limited publication in English literature, global antibiotic researchers have not appreciated the relevant data from China.¹³ For example, the 2004 World Medicines Situation Report stated that reliable data about antibiotic utilization in the large pharmaceutical market of the world's most populous country, the People's Republic of China, were in short supply.⁷ This is not conducive to a comprehensive understanding of the global antibiotics usage and to a comparative analysis between research results from China and those from other countries. In view of this, we conducted a meta-analysis about the use of antibiotics in China in 2013 and found that 50.3% of Chinese outpatients were prescribed 1 or more antibiotics.¹⁴ Recently, the number of studies published in English about antibiotic utilization in China has been increasing;^{14–17} however, such studies have not been extended to particular diseases or conditions. Our current meta-analysis focuses on the use of antibiotics for URTI outpatients in China, for which the overuse is most prevalent worldwide.

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METHODS

We conducted the meta-analysis according to the Meta-analysis of Observational Studies in Epidemiology guidelines.¹⁸

Search Strategy

To identify relevant studies, we searched 4 Chinese biomedical databases and PubMed up to December 31, 2014. The 4 Chinese databases are the China National Knowledge Infrastructure, WANFANG database, VIP Information/Chinese Scientific Journals database, and Chinese Biomedical Literature database. We searched the Chinese databases using the following terms (in Chinese): “antibiotic,” “antibacterial,” “anti-infective/anti-infection,” “rational drug use,” “prescription,” “upper respiratory infection,” “acute upper respiratory infections,” “acute nasopharyngitis,” “acute sinusitis,” “acute pharyngitis,” “acute tonsillitis,” “acute laryngitis,” “acute tracheitis,” “acute obstructive laryngitis,” “acute epiglottitis,” “common cold,” or “acute laryngotracheitis.”

PubMed was searched using the following terms: ((antibacterial[Title/Abstract] OR antibiotic[Title/Abstract] OR antimicrobial[Title/Abstract] OR antibiotics[Title/Abstract]) AND (Upper respiratory tract infections[Title/Abstract] OR Acute upper respiratory tract infections[Title/Abstract] OR Acute nasopharyngitis[Title/Abstract] OR Acute sinusitis[Title/Abstract] OR Acute pharyngitis[Title/Abstract] OR Acute tonsillitis[Title/Abstract] OR Acute laryngitis[Title/Abstract] OR Tracheitis[Title/Abstract] OR Acute obstructive laryngitis[Title/Abstract] OR Epiglottitis[Title/Abstract] OR Cold[Title/Abstract])) AND (China[Title/Abstract] OR Chinese[Title/Abstract]) AND (“humans”[MeSH Terms] AND English[lang]).

Identification of relevant studies was accomplished by 1 researcher and checked by 2 other researchers. First, we examined the titles and abstracts yielded by searching bibliographic databases. Then, we retrieved and examined the full publications of possibly relevant studies for inclusion or exclusion. In addition, lists of references of the extracted articles were reviewed, and relevant studies were extracted and added into the meta-analysis.

Inclusion and Exclusion Criteria

Observational studies, published in Chinese or English before December 31, 2014 were included, and the theme of published research should be the percentage of URTI outpatients prescribed antibiotics in Mainland China. The site must be hospital outpatient departments, community health service centers, or township hospitals. A study would be included; if it have used the WHO/International Network for the Rational Use of Drugs (INRUD) methods and followed the guideline to determine what antimicrobial agents could be counted as antibiotics for prescribing indicators analysis, which was recommended by WHO.¹⁹ In addition, the study should have the following information: study site, enrolment time, the total number of sampled outpatient encounters with URTI, the total number of outpatient antibiotic encounters with URTI, the number of outpatient encounters with URTI with 1 antibiotic, and the number of outpatient encounters with URTI with 2 antibiotics and with more than 2 antibiotics. For duplicate publications of the same study, we included the version published first or published in English. Conference abstracts, review articles, and data from regions of China other than the Mainland (Hong Kong, Macao, and Taiwan) were excluded.

Quality Assessment of Included Studies

We assessed the methodological quality of the included studies according to the WHO/INRUD methods and United States Agency for International Development (USAID) methods.^{19,20} Six criteria in the quality assessment were defined as follows:

- (1) Whether a study gave the definition which drugs to be considered as antibiotics according to the WHO/INRUD indicator methodology.
- (2) Whether the sample size was adequate. According to the survey methods on “How to Investigate Antimicrobial Use in Hospitals: Selected Indicator,” which were recommended by the USAID, the number of prescribing encounters should be ≥ 100 in any retrospective or prospective study.
- (3) Whether the study gave a definition of URTI.
- (4) Whether a study described the data collection methods. For instance, data may be collected retrospectively or prospectively.
- (5) Whether the statistical methods were eligible according to the WHO/INRUD indicator methodology.
- (6) Whether the study period was appropriate. According to the survey methods on “How to Investigate Antimicrobial Use in Hospitals: Selected Indicators,” which were recommended by the USAID, antimicrobial assessments should cover 12 consecutive months to ensure that any seasonal variations are taken into consideration.

Each criterion was assigned 1 point if a study met a WHO or USAID recommendation. The qualities of the included studies were assessed by 2 independent reviewers. Studies that scored 5 or higher were considered as high quality, 3 or 4 as moderate quality, and 2 or lower as low quality. The results of quality assessment are shown in Supplemental Digital Content-Table 1, <http://links.lww.com/MD/A952>.

Data Extraction

The following data from each included study were extracted: first author, year of publication, enrolment time, sample size (number of URTI outpatients), the total number of URTI outpatients who were prescribed antibiotics, and the number of URTI outpatients who were prescribed 1, 2, and more antibiotics. We also extracted data on study designs, settings, and regions.

Statistical Analysis

Following standard meta-analysis methodology, we obtained summary rates of URTI outpatients who were prescribed 1, 2, and 3, or more antibiotics. Subgroup analyses were conducted by hospital type, geographical area, and study period. Studies were divided into 3 geographical regions: western, central, and eastern China. Chinese hospitals are divided into 3 levels, level 1 (1–100 beds), level 2 (101–500 beds), and level 3 (>500 beds), according to size, technology, equipment, and management level. Level 3 hospitals are the highest level with the best medical technology and equipment, while level 1 hospitals include community health service centers and township hospitals. All these hospitals have outpatient departments in addition to hospital wards.

Statistical analyses were conducted using R-3.1.3 statistical software package. Meta-analyses were conducted using Logit transformed proportions and the pooled estimates were back-transformed to ordinary proportions.²¹ Heterogeneity

across the studies was evaluated by using the Q statistic and I^2 statistic.²² For publication bias, we used Egger's weighted regression methods to assess. Pooled rates were calculated with 95% confidence interval (CI) using random-effects model.

Ethical Review

We have submitted the study design to “the Research Ethics Committee in Huazhong University of Science and Technology, Wuhan, China”. As the data this study needed have been published and can be freely accessed, the Research Ethics Committee considered that our study does not need Ethics Committee review.

RESULTS

Figure 1 shows the process of study selection and inclusion. In the end, 45 articles met the inclusion criteria,

and all were published in Chinese. The main characteristics of the included studies are shown in Supplemental Digital Content-Table 2, <http://links.lww.com/MD/A952> and Supplemental Digital Content-Table 3, <http://links.lww.com/MD/A952>. Of these studies, 18 were scored as high-quality studies, 24 moderate-quality studies, and 3 low-quality studies. Both of the overall and subgroup analyses were all observed significant heterogeneity ($P < 0.001$). The Egger's test result showed that there may be a publication bias ($P < 0.001$).

Figure 2 reports the percentages of URTI cases prescribed antibiotics from the studies included. Table 1 shows the pooled percentage of the URTI outpatient who were prescribed antibiotics. The overall average was 83.7% (95% CI: 80.6%–86.4%). Table 1 further shows that the percentages of antibiotics prescription for URTI vary substantially by level of hospital, geographic area, and study period. The proportion of URTI cases prescribed antibiotics was on average 76.7% in level 3

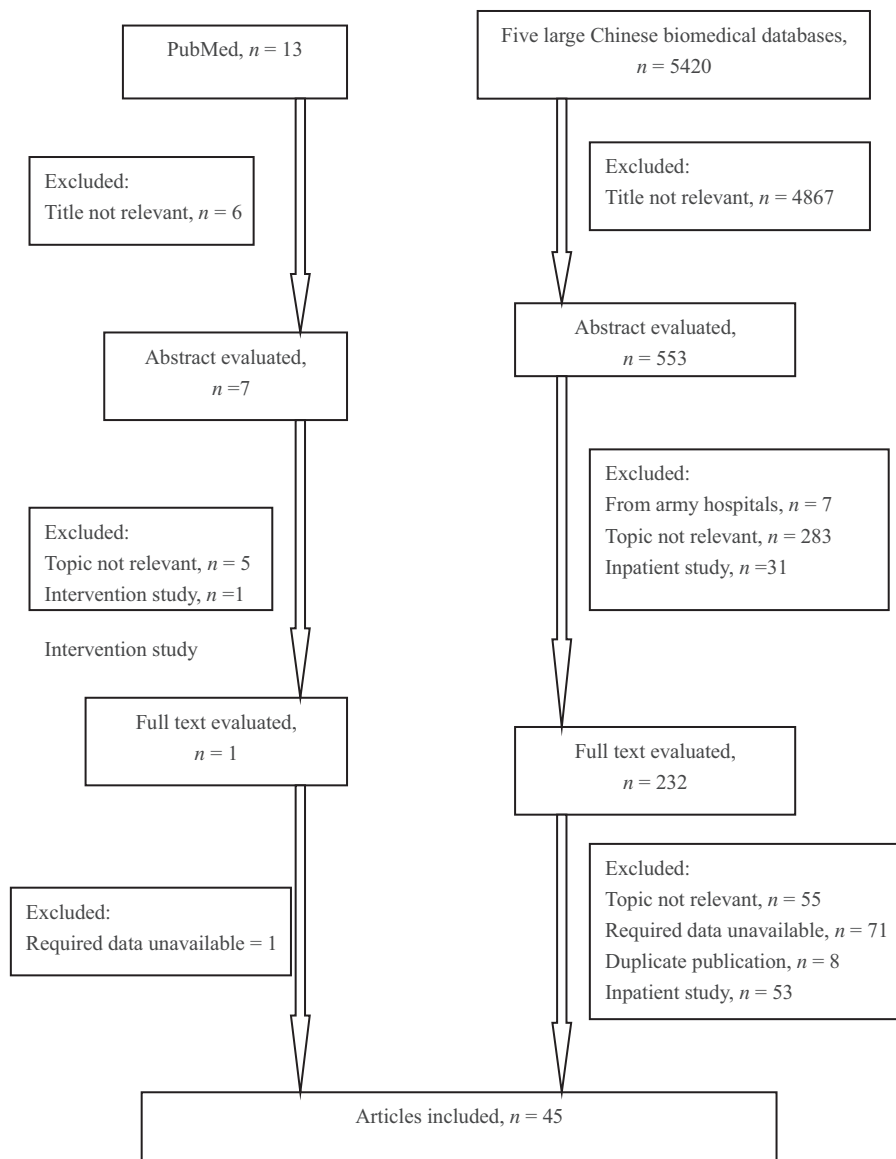


FIGURE 1. Flow diagram of study identification.

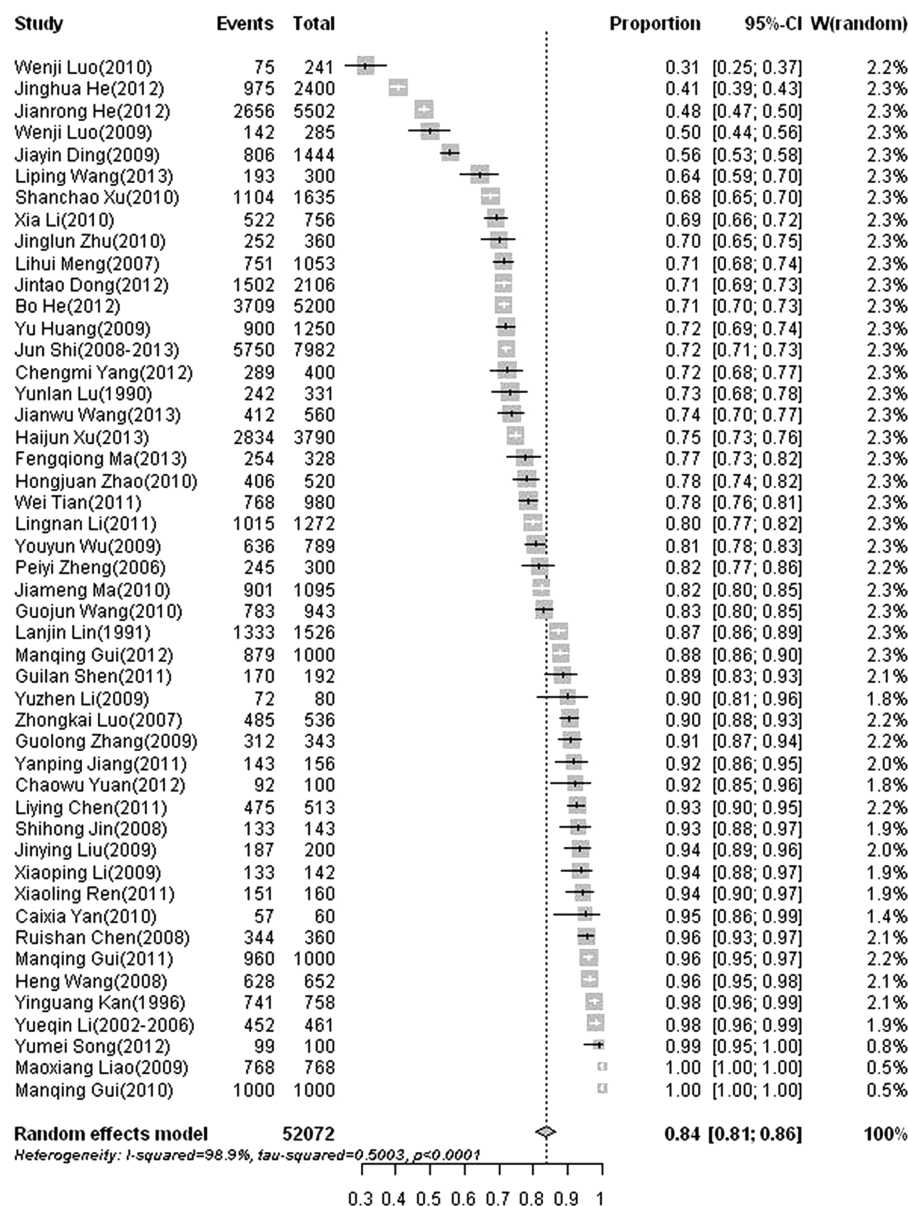


FIGURE 2. Forest plot of reported percentage use of antibiotics with URTI in China. One included study (a034-Wenji Luo) was divided into 2 different subgroups in groupwise analysis, and the other one (a083-Manqing Gui) was divided into 3 different subgroups in groupwise analysis.

hospitals, 84.8% in level 2 hospitals, and 91.1% in level 1 hospitals. The reported antibiotic prescriptions of lower-level hospitals were much higher than higher-level hospitals, and the differences between hospital levels were statistically significant ($P=0.0009$). Antibiotic prescription for URTI outpatients in western region (83.9%) and central region (86.6%) was higher than that in the eastern China (82.3%), but no statistically significant differences were found among geographical regions. The percentages of antibiotic prescription for URTI outpatients showed a downward trend, with the percentage of antibiotics before 2008 being statistically significantly higher than that in the subsequent years ($P<0.001$).

Table 2 shows that of the URTI outpatients prescribed antibiotics in China, 79.7% were prescribed 1 antibiotic, 18.4% prescribed 2 antibiotics, and 1.1% prescribed 3 or more antibiotics. The proportion of URTI outpatients with 1 antibiotic prescribed in central (87.3%) and eastern (78.5%) China was higher than that in western (69.6%) China, the proportion of URTI outpatients with 2 antibiotics prescribed in central (11.7%) and eastern (19.4%) China was apparently lower than that in western (28.1%) China, while the proportion of URTI outpatients with 3 and more antibiotics prescribed was 1.3% in the eastern region, 0.5% in the central region, and 1.4% in the western region, though no statistically significant differences

TABLE 1. Percentage of URTI Outpatients Prescribed Antibiotics

	Number of Study	n/N	Percentage Use of Antibiotics (95% CI)
Overall	48*	37736/52072	83.7 (80.6, 86.4)
Region			
Eastern China	28	19650/27102	82.3 (77.9,86.0)
Central China	12	15305/21539	86.6 (79.8, 91.4)
Western China	8	2781/3431	83.9 (79.4, 87.6)
Hospital level			
Level 3 hospitals	16	13079/20153	76.7 (68.7, 83.2)
Level 2 hospitals	26	23455/30537	84.8 (81.8, 87.4)
Level 1 hospitals	6	1202/1382	91.1 (84.3, 95.2)
Year of study			
Before 2008	10	5354/6120	91.6 (86.0, 95.1)
2009	9	3956/5301	84.3 (75.5, 90.3)
2010	10	5243/6766	78.3 (70.1, 84.8)
2011	6	8814/11586	86.9 (80.1, 91.5)
2012	9	10676/17321	78.2 (68.0,85.7)
2013	4	3693/4978	72.9 (68.5, 76.9)

The differences between hospital levels were statistically significant ($P = 0.009$). The percentage use of antibiotics prescriptions before 2008 was statistically significantly higher than that in other years ($P < 0.0001$). The differences between regions were statistically not significant. CI = confidence interval.

*Two included studies were conducted in different study time: one (a034-Wenji Luo) was divided into 2 different subgroups in groupwise analysis, and the other one (a083-Manqing Gui) was divided into 3 different subgroups in groupwise analysis.

TABLE 2. Percentage of URTI Outpatients With Antibiotic Prescription Prescribed 1, 2, or More Antibiotics

	Number of Study	n/N	Percentage Use of Antibiotics (95% CI)
With 1 antibiotic	48	30725/37736	79.7 (72.8, 85.2)
Region			
Eastern China	28	15108/19650	78.5 (69.4, 85.5)
Central China	12	13441/15305	87.3 (74.8, 94.1)
Western China	8	2176/2781	69.6 (46.1, 86.0)
Hospital level			
Level 3 hospitals	16	10006/13079	82.6 (72.9, 89.4)
Level 2 hospitals	26	20213/23455	83.8 (74.6, 90.2)
Level 1 hospitals	6	506/1202	43.1 (31.0, 56.2)
With 2 antibiotic	48	6478/37736	18.4 (13.6, 24.5)
Region			
Eastern China	28	4184/19650	19.4 (13.2,27.5)
Central China	12	1735/15305	11.7 (5.8,22.2)
Western China	8	559/2781	28.1 (13.2, 50.0)
Hospital level			
Level 3 hospitals	16	2817/13079	15.8 (10.0, 24.0)
Level 2 hospitals	26	3004/23455	14.8 (9.3,22.9)
Level 1 hospitals	6	657/1202	51.7 (35.9, 67.2)
With 3 or more antibiotics	48	533/37736	1.1 (0.7, 1.6)
Region			
Eastern China	28	358/19650	1.3 (0.8, 2.1)
Central China	12	129/15305	0.5 (0.2, 1.2)
Western China	8	46/2781	1.4 (0.5,3.9)
Hospital level			
Level 3 hospitals	16	256/13079	0.9 (0.4,1.9)
Level 2 hospitals	26	238/23455	0.8 (0.5,1.5)
Level 1 hospitals	6	39/1202	3.8 (1.6,8.9)

Compared with level 3 and level 2 hospitals, level 1 hospitals were associated with a statistically significantly lower proportion of 1 antibiotic ($P < 0.0001$) and a statistically significantly higher proportion of 2 antibiotics ($P < 0.0001$). The proportion of URTI outpatients prescribed 3 or more antibiotics by level 3 and level 2 hospitals were statistically lower than that by level 1 hospitals ($P = 0.012$). The differences between regions were statistically not significant. CI = confidence interval.

between the regions were detected. Level 3 and level 2 hospitals had significantly higher proportions of URTI outpatients with 1 antibiotic prescribed ($P < 0.001$), a lower proportion of URTI outpatients with 2 antibiotics prescribed ($P < 0.001$) and with 3 or more antibiotics ($P = 0.012$) than level 1 hospitals.

DISCUSSION

Based on data from 45 studies that included a total of 52,072 URTI outpatients, this systematic review found that the proportion of URTI cases prescribed antibiotics in China was 83.7%. Although no international standard has been established for the antibiotic prescription for URTI outpatients, the European Surveillance of Antimicrobial Consumption (ESAC) recommended that the proportion of antibiotic use with URTI should be 0%–20% in 2011.²³ Studies elsewhere reported that the percentage of URTI cases prescribed antibiotics was 24.2% in the United States,²⁴ 40% in East Asia,¹⁰ and 45% in India.²⁵ The percentage of URTI cases prescribed antibiotics in China is much higher than the recommended level and those in other countries. Our meta-analysis presents unequivocal evidence that there is substantial over-prescription of antibiotics for URTI patients in China.

Our meta-analysis also revealed that over-prescription of antibiotics is a more serious problem in China's primary care institutions (level 1 hospitals). Clinicians in level 3 hospitals usually have a higher educational levels and better training than those in lower-level hospitals,¹⁴ and recognize better the importance of rational use of antibiotics.^{26,27} In addition, economic incentives may induce clinicians to prescribe antibiotics excessively, and the incentives are expectantly stronger among primary care clinicians since drug prescriptions filled is a major sources of income for them.²⁸ The higher rate of antibiotic prescription for URTI outpatients by primary care clinicians may be explained by a combination of lack of sufficient training and stronger economic incentives. As the primary healthcare centers in China cover a large number of patients, and URTIs are one of the most common health conditions encountered by primary care workers, the excessive use of antibiotics in primary healthcare causes a waste of health resources and the development of antibiotic resistance. Therefore, it is necessary to take measures to control the overuse of antibiotics for URTI cases in primary healthcare facilities in China.

It is worth noting that the percentages of URTI outpatients prescribed antibiotics in China showed a downward trend, which might be associated with the Chinese health authority's recent effort to curb the excessive use of antibiotics. In 2010, the Ministry of Health of China released a ruling, Prescription Management and Evaluation Standards in Clinical Practice. In April 2012, a regulation on the Management Method for Clinical Use of Antimicrobials was issued by the Ministry of Health of China, which established a hierarchical management system for antimicrobials use in clinical practice. The regulation clearly stated the rules for selection, procurement, clinical use, surveillance and early-warning, and intervention and withdrawal of antimicrobial use in healthcare facilities, which was implemented since August 1st, 2012.²⁹ The regulation imposes restrictions on physicians' antibiotics prescribing behaviors and asks them to prescribe antimicrobials judiciously based on the comprehensive assessment for the symptoms and blood and urine test results of patients.³⁰ These guidelines may have reduced the overall antibiotic usage and usage for URTI in China. However, the percentage of URTI cases prescribed

antibiotics in China is still at a very high level. It is imperative that greater efforts are needed to further promote rational use of antibiotics. In addition, although the difference of the percentage of URTI outpatients prescribed antibiotics between the regions was not significant, the combined prescription rate of antibiotics in the western region is high. This should attract the attention of the health administrative department.

This study conducted a comprehensive analysis of antibiotic prescription associated with URTI in China by the method of meta-analysis. However, certain limitations of this study should be noted. Firstly, the heterogeneity across studies was significant and the observed heterogeneity could not be explained by the available data. Secondly, the Egger's test result indicated that the publication bias could not be ruled out. In spite of these limitations, we think that the present study is important to reveal the prevalence of antibiotic utilization for URTI in China. Additionally, all the articles included in this review were retrospective studies. More prospective studies measuring the prescribing indicators are warranted to more accurately investigate the antibiotics utilization for URTI in China.

CONCLUSIONS

The percentage of URTI patients who were prescribed antibiotics in China is extremely high and the overuse is especially problematic in lower-level hospitals. Although our analysis shows a downward trend, likely attributable to China's recent efforts in curbing excessive antibiotic use, more measures are needed to promote the rational use of antibiotics, especially among primary health-care institutions.

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