Appropriateness of antibiotic prescriptions in China ambulatory care visits: a nationwide descriptive study

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Research in context

Evidence before this study

We searched PubMed and Embase for articles in English and CNKI and Wanfang for articles in Chinese published up to December 31, 2019, using the terms: “antibiotic” (“antibacterial”, or “antimicrobial”), “prescription” (“prescrib*”), “appropriate*” (“inappropriate*”, “rational*”, or “irrational*”), “outpatient” (“ambulatory”), and “China” (“Chinese”). There were only two studies that described the appropriateness of outpatient antibiotic prescriptions in multiple provinces of China. One study estimated that in primary health care settings in China, more than 60% of antibiotic prescriptions were inappropriate by using a sample of only 7311 outpatient visits from six provinces. The other study reported the appropriateness of antibiotic prescriptions in tertiary-level hospitals in 25 provinces of Mainland China, with 0·45 million prescriptions. Both studies were conducted through manual prescription review, of which the review scheme was not clearly described and validated. No study investigated the antibiotic prescription rates for various diagnoses at the national level in China.

Added value of this study

We analyzed a prescription data of 173 million outpatient visits from 28 provinces collected during October 2014 and April 2018 in China. Using a well established and validated approach, we established the baseline of outpatient antibiotic prescription rates for various diagnoses and the proportion of inappropriate antibiotic prescribing, and our results suggested that over 50% of outpatient antibiotic prescribing in China was inappropriate. To the best of our knowledge, no previous studies analyzed such a big prescription data to investigate antibiotic prescribing in China. This study provides the most recent and comprehensive evaluation of the appropriateness of outpatient antibiotic prescriptions in China, which can be benchmark for future studies to assess the progress of China curbing antibiotic misuse and overuse.

Implications of all the available evidence

Although years of efforts to curb antibiotic use have significantly reduced antibiotic prescription rate, the inappropriate antibiotic prescribing is still prevalent in China. Our findings inform policy makers in China, as well as other countries with high prevalence of inappropriate antibiotic prescribing, carrying out more in-depth antibiotic stewardship programs focusing on reducing inappropriate antibiotic prescribing to achieve the goals of optimizing antibiotic use and curbing antimicrobial resistance. This study also provides a precedent for the use of large-scale prescription data and a well-established methodological framework to evaluate the appropriateness of antibiotic prescriptions in China. Future studies focusing on antibiotic use in China can apply our methods to evaluate the appropriateness of antibiotic prescribing by using big electric medical records or administrative data.

Summary

Background

Inappropriate antibiotic use greatly accelerates antimicrobial resistance. The appropriateness of antibiotic prescriptions is well evaluated, using big observational data, in some high-income countries (HICs), whereas the evidence of this appropriateness is very limited in China. We aimed to assess the appropriateness of antibiotic prescriptions in China ambulatory care settings.

Methods

We used a data from the Beijing Data Center for Rational Use of Drugs, which was a national database designed for monitoring rationality of drug use. Hospitals that uploaded diagnosis and prescription information were included, resulting in 172·7 million outpatient visits from 139 hospitals in 28 provincial-level regions of Mainland China. Prescription diagnoses were classified as appropriate, potentially appropriate, inappropriate, or not linked to any diagnosis for antibiotic use by following a published classification scheme. Antibiotic prescription rates for various diagnosis categories and proportions of inappropriate antibiotic prescriptions for different subgroups were estimated. Antibiotic prescribing pattern and proportions of individual antibiotics prescribed for different diagnosis categories were analyzed and reported.

Findings

Among the 172704117 outpatient visits, 18848864 (10·9%) ended with antibiotic prescriptions. For conditions for which antibiotic use was appropriate, potentially appropriate, and inappropriate, 42·2%, 30·6%, and 7·6% of visits were associated with antibiotic prescriptions, respectively. Among all 18848864 antibiotic prescriptions, 9689937 (51·4%) were inappropriate, 5354224 (28·4%) were potentially appropriate, 2893102 (15·3%) were appropriate, and 911601 (4·8%) could not be linked to any diagnosis. A total of 23266533 individual antibiotics were prescribed, among which 80·0% belonged to broad-spectrum and the top four most prescribed antibiotics were the third-generation cephalosporins (21·7%), second-generation cephalosporins (16·4%), macrolides (15·3%), and fluoroquinolones (14·1%).

Interpretation

Inappropriate antibiotic prescribing was highly prevalent nationwide in China, over half of the antibiotic prescriptions were inappropriate in secondary- and tertiary-level hospitals, suggesting an urgent need for outpatient antibiotic stewardship aimed at optimizing antibiotic prescribing to achieve the goals set in the National Action Plan.

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Key Words: Antibiotic use; Prescription; Outpatients; Antibiotic stewardship program

Introduction

Antimicrobial resistance (AMR) affects all areas of health and incurs high economic costs to the society.[1,2] It could cause 10 million deaths per year by 2050 if no action is taken to stop the spread of AMR.[2] The United Nations General Assembly has recognized AMR as a global priority health issue,[3] as it cannot be single-handedly managed or mitigated by any organization or nation.[1] High AMR rates are a particular issue in low- and middle-income countries (LMICs), where antibiotic overuse is highly prevalent.[4] Inappropriate use of antibiotics greatly accelerates AMR and reducing overuse and misuse of antibiotics is essential for combatting AMR.[1,5,6] The surveillance of antibiotic use and appropriateness of prescribing is necessary to inform the strategies of AMR prevention and containment.[3]

China is one of the countries that consume the most antibiotics and have high prevalence of AMR in the world.[7,8] About 162000 tons of antibiotics were consumed in 2013 in China, and the average consumption is six folds higher than that in the United States and Europe.[7] In 2016, 14 ministries of China jointly issued the National Action Plan to Contain Antimicrobial Resistance (NAP),[9] in line with the WHO Global Action Plan (GAP)[1] regarding AMR control. Promoting appropriate use of antibiotics and establishing the antimicrobial stewardship program in secondary and tertiary hospitals are the two national targets in the NAP,[9] which is in accordance with the strategic objective of optimizing the use of antimicrobial medicines in the GAP.[1] However, comprehensive assessment of inappropriate use of antibiotics in LMICs is relatively scarce. In the past decade, the evaluation of appropriateness of antibiotic prescriptions in China has occurred mainly through manual prescription review (MPR),[10] which is very time-consuming and thus infeasible for evaluating large-scale prescription data. Furthermore, there was no standard measure across different regions and hospitals and the results of MPR largely depend on pharmacists' or physicians' experience. Consequently, there is no reliable overall estimate of inappropriate antibiotic prescribing at the national level in China. In this study, we aimed to use a well-established classification approach[5,6,11-14] to estimate the antibiotic prescription rates for common diagnosis categories and to assess the appropriateness of outpatient antibiotic prescriptions using a large database for monitoring the rational use of drugs in China.

Methods

Data source and participants

We used all the outpatient prescriptions from the Beijing Data Center for Rational Use of Drugs (BDCRUD), a national database for monitoring the rational use of drugs. The process of recruiting hospitals, collecting data and the representativeness of the database are given in the appendix (pp 2-4). In total, 194 public general hospitals from all 31 provincial-level regions were recruited and required to upload all the data from the hospital information system since October 2014 to the data center. We focused on secondary- and tertiary-level hospitals (appendix pp 5-6), because the policies of antibiotic management in recent years in China were mainly aimed at these hospitals (appendix pp 7-12) and over two-thirds of antibiotic consumption occurred in these hospitals.[15,16].

The prescription data for each visit consisted of three parts (appendix p 13), which included diagnosis and drug information. Outpatient diagnosis was in the format of Chinese narrative free text.[14] Chemical drugs including antibiotics were coded according to the Anatomical Therapeutic Chemical (ATC) classification system. Drug prescriptions and diagnosis records were linked through a unique identifier consisting of the hospital code, patient identification number, and date of visit. All the visits to outpatient clinics and emergency departments from October 2014 to April 2018 were included.

In this study, we excluded 55 hospitals that did not submit diagnosis records, leaving 139 hospitals (45 secondary and 94 tertiary) from 28 provincial-regions and 96 cities. In these hospitals, 66% of outpatient visits ended with drug prescriptions. Comparisons between the included and excluded hospitals are given in the appendix (pp 14-15).

This study was approved by the Ethical Review Board of Peking University Health Science Center (approval number: IRB00001052-18013-Exempt). Informed consent was not required owing to the use of anonymized routine data.

Definition of antibiotics and outpatient visits

We used ATC code of J01 for systemic antibiotic use. We also included four other antibiotics, namely metronidazole, tinidazole, ornidazole, and furazolidone.[14] The appendix (pp 16-17) gives a full list of antibiotics in this study.

Following previous studies,[17,18] second- to four-generation cephalosporins, fluoroquinolones, macrolides, combinations of penicillins, and streptomycins were classified as broad-spectrum antibacterial agents. Other antibiotics were classified as narrow-spectrum, such as beta-lactamase sensitive penicillins and first-generation cephalosporins.

We treated multiple prescriptions of drugs and diagnoses from the same patient on the same day in the same hospital as one visit.

Diagnosis classification

By following the approach applied in previous studies,[5,6,11-13] we used the standard description of codes in Chinese version of ICD-10 (International Classification of Diseases, 10th revision)[19] to classify the first five diagnoses of each visit. Three categories of diagnosis were defined as 1) “tier 1” if the condition almost always justifies antibiotics, 2) “tier 2” if the condition only sometimes justifies antibiotics, and 3) “tier 3” if the condition almost never justifies antibiotics.[5,11] We first used the ICD-10 to establish the standard tiers of all conditions (step 1), which was then used for constructing the regular expressions (REs) in the step 2. Then, the REs were used for mapping information in the raw diagnostic text and classifying diagnoses into standard tiers (step 3). Details of the algorithm and how the diagnostic classification was done have been published elsewhere.[14] The first five diagnoses were chosen because the regulations on drug prescribing in China stipulate that no more than five kinds of drugs can be prescribed in a single visit (appendix pp 8, 13). Hence, for a clinician to prescribe antibiotics, infectious diseases should be part of the first five diagnoses. In addition, among all the 169·7 million diagnosis records, only 1·9% contained >5 diagnoses (appendix p 18). Furthermore, diagnoses were classified into 30 different categories (appendix pp 19-25), following the ICD-10 chapters and classification in previous studies.[5,6,19,20] For some conditions, it is sometimes difficult to make a definite diagnosis due to insufficient evidence, and physicians would write some supplemental descriptions (e.g. 'maybe', 'likely') to indicate the uncertainty. These diagnoses of tier 1 and tier 2 were identified by detecting the uncertainty modifiers.[14] After all the first five diagnoses were classified, the tier-fashion method[5,11] was applied to assign a single diagnosis category to each prescription. That is, for multiple diagnoses in the same prescription, priority was given to certain tier 1 diagnosis, followed by uncertain tier 1 diagnosis, certain tier 2 diagnosis, uncertain tier 2 diagnosis, and finally tier 3 diagnosis. If multiple diagnoses of the same tier existed in a visit, the first-listed certain diagnosis was assigned. Linking multiple diagnoses to a single visit is conservative because only one diagnosis that justifies antibiotics is required to classify the visit as appropriate or potentially appropriate.[12] According to our validation study, the sensitivities, specificities, positive predictive values, and negative predictive values of the algorithm used for classifying diagnoses into three tiers were all over 98%.[14]

Antibiotic prescription rates and appropriateness of antibiotic prescriptions

We calculated the antibiotic prescription rates as the percentage of outpatient visits ended with antibiotic prescriptions, for different diagnosis categories of outpatient and emergency departments. Outpatient visits with antibiotic prescriptions were assigned into one of the four mutually exclusive categories as applied by Chua et al[11]: "appropriate" if associated with "tier 1" diagnosis, "potentially appropriate" if associated with no "tier 1" but "tier 2" diagnosis, "inappropriate" if associated with only "tier 3" diagnosis, and "not-linked to any diagnosis" if not associated with any visit-level diagnosis. The proportion of visits ended with antibiotic prescriptions in each appropriateness category for different subgroups was calculated.

Antibiotic prescribing was examined by hospital level (secondary or tertiary), patient's gender, age groups (< 6, 6–17, 18–45, 46–64, and ≥ 65 years), year of outpatient visits (2014–2018), and China economic regions, which are the Eastern, Central, Western and Northeastern (appendix pp 26-27). Antibiotic prescribing patterns for all diagnosis categories were identified by calculating the proportions of different antibiotic categories (4th level ATC code,) and broad-spectrum agents. We also identified the most common used individual antibiotics for all appropriateness categories, by calculating the proportion of each antibiotic relative to the total antibiotics prescribed.

Statistical analysis

We calculated descriptive statistics of outcome measures for different diagnosis categories and subgroups. Formal significance testing was not conducted and the 95% confidence intervals (CIs) were not reported, because many clinically insignificant differences may have been statistically significant[12] and the vast majority of the 95% CIs were extremely narrow (most had a width of about 0·1 to 0·2 percentage points) due to the overwhelming sample size of the database.

Five sensitivity analyses by imputing the proportions of different appropriateness categories in the excluded hospitals were conducted to assess the impacts of excluding hospitals. First, each of the excluded hospitals was matched to the included hospitals in the same region and of the same hospital level, then four strategies were applied to impute missing proportions and for each of the excluded hospitals: 1) proportions of the included hospital with the nearest distance, calculated by using antibiotic prescription rate, average monthly visits and percentage of visits associated with drugs, were used; 2) the medians, 3) 25th percentiles, and 4) 75th percentiles of the proportions of different appropriateness categories among the matched included hospitals were used. In the fifth sensitivity analysis, after transforming the proportions using the additive logratio transformation (appendix pp 28-29), multiple imputation using the hospital level characteristics, including region of location, hospital level, antibiotic prescription rate, average monthly visits and percentage of visits ended with drugs, by imputing the data 10 times were conducted. Then prescription numbers of each appropriateness categories in the excluded hospitals and the overall proportions for all appropriateness categories by including all hospitals were calculated. Bootstrapping method with 1000 times replacement was used for the estimation of the 95% CIs of the proportions.

We estimated the quarter changes of inappropriate antibiotic prescribing by using generalized estimating equations with adjustment of quarter effects. In order to avoid the influence of the prescriptions that cannot be linked to any diagnosis, the logratio of inappropriate prescribing to the appropriate and potentially appropriate prescribing was used as the dependent variable. Sensitivity analyses were conducted for the year changes and for different hospital levels (appendix p 39).

Data extraction and diagnosis classification were done by using Oracle 11gR2 and PLSQL Developer V.11.0 (Oracle

Corp). Statistical analyses were performed by using SAS 9.4 (SAS Institute Inc).

Role of the funding source

The funder had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or decision to submit the article for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit the article for publication.

Results

Overall, 172704117 visits, of which 92·0% (158828268 visits) occurred in outpatient clinics, were included. Of these visits, 16215279 (9·4%) were made by children, 89686644 (51·9%) were by women, and 158646196 (91·9%) occurred in tertiary-level hospitals. Most outpatient visits were from the Eastern and Western regions, which accounted for 54·9% and 30·0% of all the visits respectively (**Table 1**).

Antibiotics were prescribed for 18848864 visits (10·9%) for all conditions at the national level. The antibiotic prescription rates were 9·3% and 29·6% for outpatient clinics and emergency departments, respectively (Figure 1 and appendix pp 30-31). Among the visits of tier 1 diagnoses, 616404 (66·4%) of 928676 visits for pneumonia and 792844 (51·1%) of 1551374 visits for urinary tract infection (UTI) were associated with antibiotic prescriptions. Acute otitis media (AOM), acute pharyngitis, and acute sinusitis were the top three diagnoses with the highest antibiotic prescription rates among tier 2 conditions. From our analysis, 131832 (43·4%) of 303474 visits for AOM, 823850 (43·1%) of 1909806 visits for acute pharyngitis, and 139903 (37·8%) of 370511 visits for acute sinusitis ended with antibiotic prescriptions. Antibiotic prescribing was even prevalent for tier 3 conditions. For patients with acute bronchitis, viral upper respiratory tract infections (URTI), unspecific fever, influenza, and non-suppurative otitis media, antibiotic prescription rates were 55·6% (1237999 out of 2225138 visits), 40·9% (2508630 out of 6134757 visits), 48·9% (242914 out of 496753 visits), 14·4% (866 out of 6024 visits), and 36·2% (64170 out of 177390 visits), respectively..

The appendix shows the antibiotic prescription rates by diagnosis and age group (pp 32-34), by diagnosis and hospital level (pp 35-36), and for uncertain diagnoses (pp 37-38). For children, 323687 (57·5%) of 562761 visits for tier 1 conditions and 2240606 (18·8%) of 11939098 visits for tier 3 conditions ended with antibiotic prescriptions, both obviously higher than that of adult patients. Visits in secondary hospitals resulted in higher antibiotic prescription rates for tier 2 and tier 3 diagnose compared with tertiary hospitals. In addition, for tier 1 and tier 2 conditions, the antibiotic prescription rate for visits of uncertain diagnoses was 5·8% less than that of certain diagnoses. This discrepancy was particularly prominent among tier 1 diagnoses and for visits of pneumonia, UTI, and certain bacterial diseases, uncertain diagnoses resulted in 16·9%, 14·4%, and 15·4% less antibiotic prescribing.

Among the 18848864 visits ended with antibiotic prescriptions, only 2893102 (15·3%) were appropriate, 5354224 (28·4%) were potentially appropriate, 9689937 (51·4%) were inappropriate, and the other 911601 (4·8%) were not linked to any diagnosis (**Table 2**). In the subgroup analysis, 48·4% (7139299 out of 14736483 visits) and 62·0% (2550638 out of 4112381 visits) of visits in outpatient clinic and emergency department were inappropriate, respectively. Children under the age of six had the highest proportion of inappropriate antibiotic prescriptions at 71·1% (1422464 out of 2000957 visits). Furthermore, 60·1% (841337 out of 1399031 visits) of antibiotic prescriptions in Northeastern China were inappropriate, ranking the first among all the four economic regions. In addition, 49·2% (864285 out of 1756646 visits) of antibiotic prescriptions in secondary hospitals were inappropriate, compared with 51·6% in tertiary hospitals. Furthermore, the proportions of inappropriate antibiotic prescriptions were similar for the visits of female and male patients.

The sensitivity analyses (Table 3) show that the results of inappropriate antibiotic prescribing were robust for excluding hospitals that did not submit diagnosis information. The differences of the proportions of all appropriateness categories between the 139 included hospitals and all 194 hospitals after imputation were not significantly different from zero. Furthermore, the ratio of inappropriate antibiotic prescribing to appropriate/potential appropriate prescribing has not changed significantly during the study period (Figure 2; p=0.1862). Results of sensitivity analyses for trends of inappropriate antibiotic prescribing (appendix p 39) were consistent with the primary analysis. A list of the national-level policies and actions associated with the management of antibiotic use is given in the appendix (pp 7-12).

Among all the 18848864 outpatient visits ended with antibiotics, 3393302 (18·0%) were prescribed two and 465966 (2·5%) were prescribed three or more antibiotics. The appendix (pp 40-41) shows the combined use of antibiotics for different diagnosis categories. In total, 23266494 individual antibiotics were prescribed, among which 18620086 (80·0%) belonged to broad-spectrum (appendix pp 42-43). The most commonly prescribed antibiotics were the third-generation cephalosporins (J01DD, 21·7%), followed by second-generation cephalosporins (J01DC, 16·4%), macrolides (J01FA, 15·3%), and fluoroquinolones (J01MA, 14·1%) (**Figure 3**). For visits associated with pneumonia and UTI, fluoroquinolones and third-generation cephalosporins were the most prescribed antibiotics, which accounted for 49·0% and 57·9% of all individual antibiotics for these two conditions, respectively. For most conditions in which antibiotic use is potentially appropriate or inappropriate, third- and second-generation cephalosporins were the most used antibiotics. The most frequent individual antibiotics associated with appropriate, potentially appropriate, and inappropriate prescriptions are given in the appendix (p 44).

Discussion

In this analysis of a large, nationally representative outpatient prescription data, we estimated that 11% of outpatient visits ended with antibiotic prescriptions in Chinese hospitals. Our results indicated that 51·4% of outpatient antibiotic prescriptions in China were inappropriate, while only 15·3% were appropriate. To the best of our knowledge, this study is the first in China to investigate antibiotic prescription for various diagnoses and assess appropriateness of antibiotic prescriptions by using such a big prescription data covering almost all provinces of China. Following a valid approach,[5,6,11-14] we established the baseline of outpatient antibiotic prescription rates for various diagnosis categories and estimated the proportion of inappropriate antibiotic prescriptions.

Current comprehensive estimates of inappropriate antibiotic prescribing at the national level mainly come from some HICs. It is estimated that for people of different ages in the US, around 13% of outpatient visits for all conditions end with antibiotic prescriptions,[5,13] among which 23-40% are inappropriate.[5,11-13] Whilst 23% of antibiotic prescriptions for all ages in the UK primary care are defined as inappropriate.[6,21] However this proportion is much higher in Japan, where 56% of antibiotic prescriptions in outpatient visits for infectious diseases are estimated as inappropriate.[17] Our findings that 11% of outpatient visits resulted in antibiotic prescriptions was comparable to the prescription rate in US, however that 51·4% of antibiotic prescriptions were inappropriate was obvious higher than that in the US and UK, and approximated that in Japan. Part of this discrepancy can be attributed to different methodology, data, and populations.[11] For example, two studies in US used claim data and linked antibiotic claims occurring within specific days before prescription fills[11] or after outpatient encounters.[12] However, the study in Japan which also used claim data only considers antibiotic prescriptions occurring at the same day of the diagnosis.[17] In our study, we applied a similar strategy to the study in Japan, because our data came from electric medical records and in China ambulatory cares drug prescribing and dispensing almost always happen on the same day. Furthermore, several studies classified diagnoses according to the ICD-9 codes,[5,12,13] other studies,[11,17] including ours, were based on the ICD-10 codes or corresponding descriptions. The impacts of these differences on the estimation of inappropriate antibiotic prescribing are difficult to assess, further studies on this issue are needed in the future.

Inappropriate use of antibiotics is a great concern in LMICs.[22,23] In the past two decades the global consumption of antibiotics in humans has risen dramatically, primarily driven by an increased use in LMICs.[23,24] However, not only misuse and overuse, but underuse of antibiotics due to lack of access is common in LMICs.[3] Using antibiotics appropriately is at the cornerstone of tackling antibiotic resistance in LMICs.[3,25] Therefore, it is very important and necessary to estimate the prevalence of inappropriate antibiotic use for informing actions to combat AMR in LMICs.

However, this evidence at the national level is limited in LIMCs, including China. Appropriateness assessment of antibiotic prescribing based on MPR exists in China,[26] but the results varied across different researches and the review scheme was not clearly described and validated. A study based on MPR in 2016 using nearly 0·45 million outpatient prescriptions from 25 provinces found that the inappropriate prescribing accounted for <5% of all antibiotic prescriptions,[26] which is is incredibly low compared to the available evidence in different countries. Further, this study shows huge regional variations with a highest inappropriate prescription rate of 30% in Guangdong and the lowest rate of 0% in Hubei.[26] Science this study did not report detail evaluation scheme, direct comparison is impossible. However, we used a comprehensive ICD-10 and natural language processing based classification scheme, which has been well validated[14] to evaluate the appropriateness of antibiotic prescriptions. Our method can be used by other researchers, making our results repeatable by using other kind of data. Furthermore, our study provided a successful precedent for assessing inappropriate outpatient antibiotic prescribing in LMICs.

A range of policies have been introduced to curb antibiotic overuse in the past decade in China (appendix pp 6-11). However, inappropriate antibiotic prescribing did not change significantly during the study period. In 2009, the national essential medicines (NEM) and zero-mark-up policy was issued to improve rational use of medicines by disengaging prescribing from profits,[27,28] which is considered as important driver of antibiotic overuse.[29] However, available evidence indicates that the NEM policy has small or no significant impact on the use of antibiotics.[27,28] In 2011, the Ministry of Health of China carried out the three-year national antimicrobial stewardship programme (ASP). With a series of compulsory measures, this was considered to be the most stringent ASP in China in history. Whilst the effects of the ASP were quite obvious and antibiotic prescription rate was reduced dramatically below a predetermined level during the ASP, antibiotic use has remained at a stable level or decreased slightly after 2013.[30,31] This may explain why inappropriate antibiotic prescribing have not changed significantly after 2014 in this study. Since we only had access to the data after 2013, direct evaluation of the impacts of ASP and NEM on inappropriate antibiotic prescribing is not feasible in this study.

We found that a substantial amount of antibiotic overuse was driven by tier 3 respiratory conditions, among which viral URTI and bronchitis were the top two diagnoses with the most antibiotic prescriptions. Similar results were founded in Japan, where 40·5% of outpatient visits for URTI and 58·2% visits for bronchitis ended with antibiotic prescriptions.[17] Whilst undertreatment for conditions that almost always warrant antibiotics also contributed substantially to inappropriate antibiotic prescribing. For pneumonia and UTI, only 66·4% and 51·1% of visits resulted in antibiotic prescriptions, obviously lower than the recommended ideal prescription rates.[6,20] However, underuse of antibiotics for these conditions was also observed in HICs.[5,17] Diagnosis uncertainty combined with tight restrictions of antibiotic use in the ASP may have discouraged physicians from prescribing antibiotics.[32] For example, in our study, the antibiotic prescription rates for certain and uncertain pneumonia diagnoses were 68.8% and 51.9% respectively. Several strategies can be taken to remedy these issues. First, it is needed to develop and apply point-of-care diagnostic test, which can distinguish different pathogens of common infections rapidly, allowing for more accurate diagnosis and targeted antibiotic treatment.[24,33] Such tests, especially those that differentiate bacterial and viral fever, are particularly needed in LMICs.[33] Second, restricting antibiotic use for specific conditions, such as viral URTI and bronchitis is potentially benefit. European countries have established the recommended ideal antibiotic prescription rates for common infectious disease,[6,20] which is helpful for assessing and guiding antibiotic prescribing. Similar recommendations are not available in China. Further, other strategies such as infection prevention and control, audit-and-feedback, clinician and patient education, and communication training can be used or strengthened to optimize antibiotic use in ambulatory care settings.[33,34]

We found that one in five antibiotic prescriptions contained two or more antibiotic agents, whilst few of them had clear indications recommended in the Chinese guidelines such as complicated infections with two or more kinds of bacteria.[35] Furthermore, antibiotic selection for specific conditions may also lacked appropriateness. For instance, penicillins with extended spectrum (J01CA) and tetracyclines (J01AA) are recommended to account for 80–100% among all antibiotics prescribed for pneumonia,[20] however in China this proportions was just 1·2% and over 90% of antibiotics for pneumonia belonged to broad-spectrum. Previous studies showed a different prescribing pattern and lower proportions of broad-spectrum antibiotics in some HICs.[36,37] However, there has been a shift towards the use of broad-spectrum in recent years worldwide, especially in LMICs.[3,24] Science misuse of combination therapy and broad-spectrum antibiotics can have crucial impacts on AMR, actions to promote compliance with guidelines and restrict use of combination therapy and broad-spectrum agents are needed in China.

The main strength of our study is its unprecedentedly large and nationally representative sample of prescription data. Thus, this study provides the most recent and comprehensive estimates of inappropriate antibiotic prescribing in China. However, there were some limitations in our study. First, data were only from public secondary and tertiary general hospitals. Data from primary cares, which are believed to provide the most of medical care in rural areas,[38] were not available. Previous study reported that over 60% of antibiotic prescriptions were inappropriate in Chinese primary care settings.[38] However, this study was conducted ten years ago and used a non-consecutive sample of prescriptions in only six provinces of China. More studies focusing on appropriateness of antibiotic use in the primary cares in recent years are needed. Second, private hospitals and specialized hospitals, such as traditional Chinese medicine hospital and maternity hospital, were not recruited in this study. Comprehensive evaluation of appropriateness of antibiotic use is still very lacking in these hospitals. Third, we used Chinese diagnosis text rather than the standard ICD-10 codes due to lack of data standardization. The diagnosis categories defined as 'others' in this study can be further analyzed in the future by using higher standardized prescription data. Forth, similar to previous studies,[5,11-13,17] we used only indications, and not the administration route, dosage, compatibility, and therapy duration, which are also important for assessing inappropriate prescription, to assess the appropriateness of outpatient antibiotic prescriptions. This may result in underestimation of inappropriate prescribing..

In conclusion, our findings indicate that inappropriate antibiotic prescribing was highly prevalent nationwide in China. More in-depth antibiotic stewardship programs focusing on optimizing antibiotic prescribing are needed to be further implemented in China to achieve the goals set in the NAP,. Our methods can be applied for future studies to assess the appropriateness of antibiotic prescription in primary care settings and to evaluate the effects of policies on outpatient antibiotic appropriateness in China.

Contributors

HZ, JB, and SZ conceived of and designed the work. JB and MZ acquired the data. HZ performed the diagnosis classification and analyzed the data. HZ drafted the manuscript. LW, HL and BC critically revised the manuscript for important intellectual content. JB, MZ, and SZ supervised the study. SZ obtained the funding. All authors were responsible for the interpretation of the data, and revised, and gave final approval of the manuscript.

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Declaration of interests

We declare no competing interests.

Data sharing

Aggregate de-identified patient data with geographical region of outpatient visits masked to the level of China economic region divisions will be available after publication of this study on receipt of a request detailing the study objectives and statistical analysis plan. Requests should be sent to the corresponding authors and the management committee of the data center will discuss the requests and decide whether to share the data on the basis of the feasibility, novelty, and scientific rigor of the proposal. All applicants will need to sign a data access agreement. The core code for diagnosis classification is publicly available online.[14] Other code is freely available to the scientific community.

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Figure Legend

Figure 1. Antibiotic prescription rates for various diagnosis categories of outpatient clinic and emergency department

Abbreviations: UTI: Urinary tract infections; Other tier 1 diagnosis: Other bacterial infections; COPD: Chronic obstructive pulmonary disease; AOM: Acute otitis media; Other respiratory conditions: Other infectious diseases of the respiratory system; OCSG infectious conditions: Infectious diseases of oral cavity and salivary glands; Other digestive infections: Other infectious diseases of the digestive system; Other SCM infections: Other skin, cutaneous, and mucosal infections; Other tier 2 diagnosis: Other infectious diseases that antibiotic may be indicated: URTI: Viral upper respiratory tract infection; Non-infectious gastroenteritis: Other non-infectious gastroenteritis; Respiratory symptoms & signs: Non-specific symptoms, signs of respiratory system; Digestive symptoms & signs: Non-specific symptoms, signs of digestive system.

Figure 2. Trend of inappropriate antibiotic prescribing

Figure 3. Type of antibiotics prescribed for different diagnosis categories

Abbreviations: UTI: Urinary tract infections; Other tier 1 diagnosis: Other bacterial infections; COPD: Chronic obstructive pulmonary disease; AOM: Acute otitis media; Other respiratory conditions: Other infectious diseases of the respiratory system; OCSG infectious conditions: Infectious diseases of oral cavity and salivary glands; Other digestive infections: Other infectious diseases of the digestive system; Other SCM infections: Other skin, cutaneous, and mucosal infections; Other tier 2 diagnosis: Other infectious diseases that antibiotic may be indicated: URTI: Viral upper respiratory tract infection; Non-infectious gastroenteritis: Other non-infectious gastroenteritis; Respiratory symptoms & signs: Non-specific symptoms, signs of respiratory system; Digestive symptoms & signs: Non-specific symptoms, signs of digestive system.

J01AA: Tetracyclines; J01CA: Penicillins with extended spectrum; J01CE: Beta-lactamase sensitive penicillins; J01DC: Second-generation cephalosporins; J01DD: Third-generation cephalosporins; J01FA: Macrolides; J01FF: Lincosamides; J01MA: Fluoroquinolones; J01GB: Other aminoglycosides; J01XD: Imidazole derivatives; J01XX: Other antibacterials; P01AB: Nitroimidazole derivatives; Others: Include G01AX, J01BA, J01CF, J01CG, J01CR, J01DB, J01DE, J01DF, J01DH, J01DI, J01EE, J01GA, J01MB, J01XA, J01XB, J01XC, and J01XE.