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

Houyu Zhao, Li Wei, Hui Li, Mei Zhang, Bin Cao, Jiaming Bian, Siyan Zhan**

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, whereas the evidence of this appropriateness is scarce in China. We aimed to assess the appropriateness of antibiotic prescriptions in ambulatory care settings in China to inform future antimicrobial stewardship.

Methods We used data from the Beijing Data Center for Rational Use of Drugs, which was a national database designed for monitoring rationality of drug use. 139 hospitals that uploaded diagnosis and prescription information were included from 28 provincial-level regions of mainland China. Outpatient prescriptions 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 patterns and proportions of individual antibiotics prescribed for different diagnosis categories were analysed and reported.

Findings Between Oct 1, 2014, and April 30, 2018, 18 848 864 (10·9%) of 172 704 117 outpatient visits 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. Of all 18 848 864 antibiotic prescriptions, 9 689 937 (51·4%) were inappropriate, 5 354 224 (28·4%) were potentially appropriate, 2 893 102 (15·3%) were appropriate, and 911 601 (4·8%) could not be linked to any diagnosis. A total of 23 266 494 individual antibiotics were prescribed, of which 18 620 086 (80·0%) were broad-spectrum and the top four most prescribed antibiotics were third-generation cephalosporins (5 056 058 [21·7%]), second-generation cephalosporins (3 823 410 [16·4%]), macrolides (3 554 348 [15·3%]), and fluoroquinolones (3 285 765 [14·1%]).

Interpretation Inappropriate antibiotic prescribing was highly prevalent nationwide in China. Over half of the antibiotic prescriptions were inappropriate in secondary-level and tertiary-level hospitals, suggesting an urgent need for outpatient antibiotic stewardship aimed at optimising antibiotic prescribing to achieve the goals set in China's 2016 national action plan to contain antimicrobial resistance.

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For the Chinese translation of the abstract see Online for appendix 1

*Contributed equally

Department of Epidemiology and Biostatistics, School of Public Health (H Zhao PhD, Prof S Zhan PhD) **and Center for Intelligent Public Health, Institute for Artificial Intelligence** (Prof S Zhan), **Peking University, Beijing, China; Research Department of Practice and Policy, School of Pharmacy, University College London, London, UK** (L Wei PhD); **Department of Pulmonary and Critical Care Medicine, Center for Respiratory Diseases, China–Japan Friendship Hospital, Beijing, China** (H Li MD, Prof B Cao MD); **Department of Pharmacology, 7th Medical Center of Chinese PLA General Hospital, Beijing, China** (J Bian PhD, Prof M Zhang MS); **Research Center of Clinical Epidemiology, Peking University Third Hospital, Beijing, China** (Prof S Zhan)

Correspondence to: Prof Siyan Zhan, Department of Epidemiology and Biostatistics, School of Public Health, Peking University, Beijing 100191, China **siyan-zhan@bjmu.edu.cn**

or

Dr Jiaming Bian, Department of Pharmacology, 7th Medical Center of Chinese PLA General Hospital, Beijing 100700, China **bianbenjamin@163.com**

Introduction

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

China is one of the countries that consumes the most antibiotics and has one of the highest prevalences of antimicrobial resistance in the world.[7,8] About 162 000 tons of antibiotics were consumed in 2013 in China, and the average consumption is six times higher than that in the USA and Europe.[7] In 2016, 14 ministries of China jointly issued a 5-year national action plan to contain antimicrobial resistance (NAP),[9] in line with the WHO Global Action Plan (GAP)[1] regarding antimicrobial resistance control. Promoting appropriate use of antibiotics and establishing the antimicrobial stewardship programme in secondary and tertiary hospitals are the two national targets in the NAP,[9] which is in accordance with the strategic objective of optimising 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

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 to Dec 31, 2019, with no restriction on the starting date, 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 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 done through manual prescription review, and 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 analysed a prescription data of 173 million outpatient visits from 28 provinces collected between Oct 1, 2014, and April 30, 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 have analysed such a large prescription database 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 a benchmark for future studies to assess the progress of China in curbing antibiotic misuse and overuse.

Implications of all the available evidence

Although years of efforts to curb antibiotic use have substantially reduced the numbers of antibiotics that are being prescribed, inappropriate prescribing is still prevalent in China. Our findings inform policy makers in China, and other countries with a high prevalence of inappropriate antibiotic prescribing, to implement more in-depth antibiotic stewardship programmes that focus on reducing inappropriate antibiotic prescribing to optimise antibiotic use and curb 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 electronic medical records or administrative data.

occurred mainly through manual prescription review,[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 manual prescription review 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 outpatient prescriptions from the Beijing Data Center for Rational Use of Drugs, a national database. The process of recruiting hospitals, collecting data, and the representativeness of the database are given in the appendix 2 (pp 2–4). In total, 194 public general hospitals from all 31 provincial-level regions in mainland China were recruited and required to upload all data from the hospital information system since Oct 1, 2014, to the data centre. We focused on secondary-level and tertiary-level hospitals (appendix 2 pp 5–6), because the policies of antibiotic management in recent years in China were mainly aimed at these hospitals (appendix 2 pp 7–12), and over two-thirds of antibiotic consumption occurred in these hospitals.[15,16]

See Online for appendix 2

Prescription data for each visit consisted of three parts (appendix 2 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 visits to outpatient clinics and emergency departments from Oct 1, 2014, to April 30, 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. Comparisons between the included and excluded hospitals are given in the appendix 2 (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 anonymised routine data.

Definition of antibiotics and outpatient visits

We used ATC code J01 for systemic antibiotic use. We also included four other antibiotics, namely metronidazole, tinidazole, ornidazole, and furazolidone.[14] Appendix 2 (pp 16–17) gives a full list of antibiotics in this study. Following previous studies,[17,18] second-generation to four-generation cephalosporins, fluoroquinolones, macrolides, combinations of penicillins, and streptomycins were classified as broad-spectrum antibacterial drugs. Other antibiotics were classified as narrow-spectrum, such as β-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

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 ICD-10 to establish the standard tiers of all conditions (step 1), which was then used to construct the regular expressions in step 2. Then, the regular expressions 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 2 pp 8, 13). Hence, for a clinician to prescribe antibiotics, infectious diseases should be part of the first five diagnoses. In addition, of all 169 650 641 diagnosis records, only 3 237 350 (1·9%) contained more than five diagnoses in the database (appendix 2 p 18). Furthermore, diagnoses were classified into 30 different categories (appendix 2 pp 19–25), following the ICD-10 chapters and classification in previous studies.[5,6,19,20] For some conditions, a definite diagnosis is sometimes difficult to make because of insufficient evidence, and physicians would write supplemental descriptions (eg, maybe or likely) to indicate the uncertainty. These diagnoses of tier 1 and tier 2 were identified by detecting the uncertainty modifiers.[14] After 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 higher than 98%.[14]

Antibiotic prescription rates and appropriateness of antibiotic prescriptions

We calculated the antibiotic prescription rates as the percentage of outpatient visits ending 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 and colleagues:[11] appropriate if associated with tier 1 diagnosis, potentially appropriate if associated with tier 2 but not tier 1 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 ending with antibiotic prescriptions in each appropriateness category for different subgroups was calculated.

Antibiotic prescribing was examined by hospital-level (secondary or tertiary), patient's sex, age groups (<6, 6–17, 18–45, 46–64, and ≥65 years), year of outpatient visits (2014–18), and Chinese economic regions (eastern, central, western, and northeastern; appendix 2 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 drugs. 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 done and the 95% CIs were not reported, because many clinically insignificant differences might 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) because of the overwhelming sample size of the database.

Five sensitivity analyses were done to assess the effect of excluding hospitals, by imputing the proportions of different appropriateness categories in the excluded 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

	Outpatient clinic visits (n=158 828 268)	Emergency department visits (n=13 875 849)	All outpatient visits (n=172 704 117)
Age group, years			
<6	7 079 809 (4·5%)	1 013 600 (7·3%)	8 093 409 (4·7%)
6–17	7 234 312 (4·6%)	887 558 (6·4%)	8 121 870 (4·7%)
18–44	69 566 763 (43·8%)	6 204 861 (44·7%)	75 771 624 (43·9%)
45–64	49 084 298 (30·9%)	3 605 035 (26·0%)	52 689 333 (30·5%)
≥65	25 234 835 (15·9%)	2 084 848 (15·0%)	27 319 683 (15·8%)
Unknown	628 251 (0·4%)	79 947 (0·6%)	708 198 (0·4%)
Sex of patients			
Female	83 532 856 (52·6%)	6 153 788 (44·3%)	89 686 644 (51·9%)
Male	75 147 915 (47·3%)	7 709 499 (55·6%)	82 857 414 (48·0%)
Unknown	147 497 (0·1%)	12 562 (0·1%)	160 059 (0·1%)
Hospital level			
2nd	12 365 680 (7·8%)	1 692 241 (12·2%)	14 057 921 (8·1%)
3rd	146 462 588 (92·2%)	12 183 608 (87·8%)	158 646 196 (91·9%)
Regions of China			
Eastern	86 840 743 (54·7%)	8 018 768 (57·8%)	94 859 511 (54·9%)
Central	8 452 692 (5·3%)	721 786 (5·2%)	9 174 478 (5·3%)
Western	48 343 649 (30·4%)	3 474 219 (25·0%)	51 817 868 (30·0%)
Northeastern	15 191 184 (9·6%)	1 661 076 (12·0%)	16 852 260 (9·8%)
Year of visit*			
2014	11 001 719 (6·9%)	909 713 (6·6%)	11 911 432 (6·9%)
2015	45 885 211 (28·9%)	3 854 264 (27·8%)	49 739 475 (28·8%)
2016	45 297 698 (28·5%)	3 935 806 (28·4%)	49 233 504 (28·5%)
2017	43 957 728 (27·7%)	3 988 636 (28·7%)	47 946 364 (27·8%)
2018	12 685 912 (8·0%)	1 187 430 (8·6%)	13 873 342 (8·0%)

Data are n (%). For rounding reasons, the sum of the percentages of some subgroups might not be exactly equal to 100%. *For years 2014 and 2018, only prescriptions in October, November, and December of 2014 and January, February, March, and April of 2018 were available.

Table 1: Basic characteristics of outpatient visits

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 2 pp 28–29), multiple imputation was done, imputing data ten times using hospital-level characteristics including region of location, hospital level, antibiotic prescription rate, average monthly visits, and percentage of visits ended with drugs. 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 to estimate 95% CIs of the proportions.

We estimated the quarter changes of inappropriate antibiotic prescribing by using generalised estimating equations with adjustment of quarter effects. To avoid the influence of prescriptions that cannot be linked to any diagnosis, the logratio of inappropriate prescribing to appropriate and potentially appropriate prescribing was used as the dependent variable. Sensitivity analyses were done for year changes and for different hospital levels (appendix 2 p 39).

Data extraction and diagnosis classification were done using Oracle 11gR2 and PLSQL Developer V.11.0. Statistical analyses were done using SAS 9.4.

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, 172 704 117 outpatient visits took place between Oct 1, 2014, and April 30, 2018, of which 92·0% (158 828 268 visits) occurred in outpatient clinics. Of all the visits, 16 215 279 (9·4%) were made by children, 89 686 644 (51·9%) were by women, and 158 646 196 (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).

In all hospitals included in the database, 113 844 978 (65·9%) of 172 704 117 outpatient visits ended with at least one drug prescription. Antibiotics were prescribed at 18 848 864 (10·9%) of all outpatient visits for all conditions at the national level. Antibiotic prescription rates were 9·3% (14 736 483 of 158 828 268 visits) for outpatient clinics and 29·6% (4 112 381 of 13 875 849 visits) for emergency departments (figure 1; appendix 2 pp 30–31). Among the included visits of tier 1 diagnoses, 616 404 (66·4%) of 928 676 visits for pneumonia and 792 844 (51·1%) of 1 551 374 visits for urinary tract infection were associated with antibiotic prescriptions. Acute otitis media, acute pharyngitis, and acute sinusitis were the top three diagnoses with the highest antibiotic prescription rates among tier 2 conditions. From our analysis, 131 832 (43·4%) of 303 474 visits for acute otitis media, 823 850 (43·1%) of 1 909 806 visits for acute pharyngitis, and 139 903 (37·8%) of 370 511 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, unspecific fever, influenza, and non-suppurative otitis media, antibiotic prescription rates were 55·6% (1 237 999 of 2 225 138 visits), 40·9% (2 508 630 of 6 134 757 visits), 48·9% (242 914 of 496 753 visits), 14·4% (866 of 6024 visits), and 36·2% (64 170 of 177 390 visits), respectively.

Appendix 2 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, 323 687 (57·5%) of 562 761 visits for tier 1 conditions and 2 240 606 (18·8%) of 11 939 098 visits for tier 3 conditions ended with antibiotic prescriptions, both obviously higher than that of adult patients. Visits in

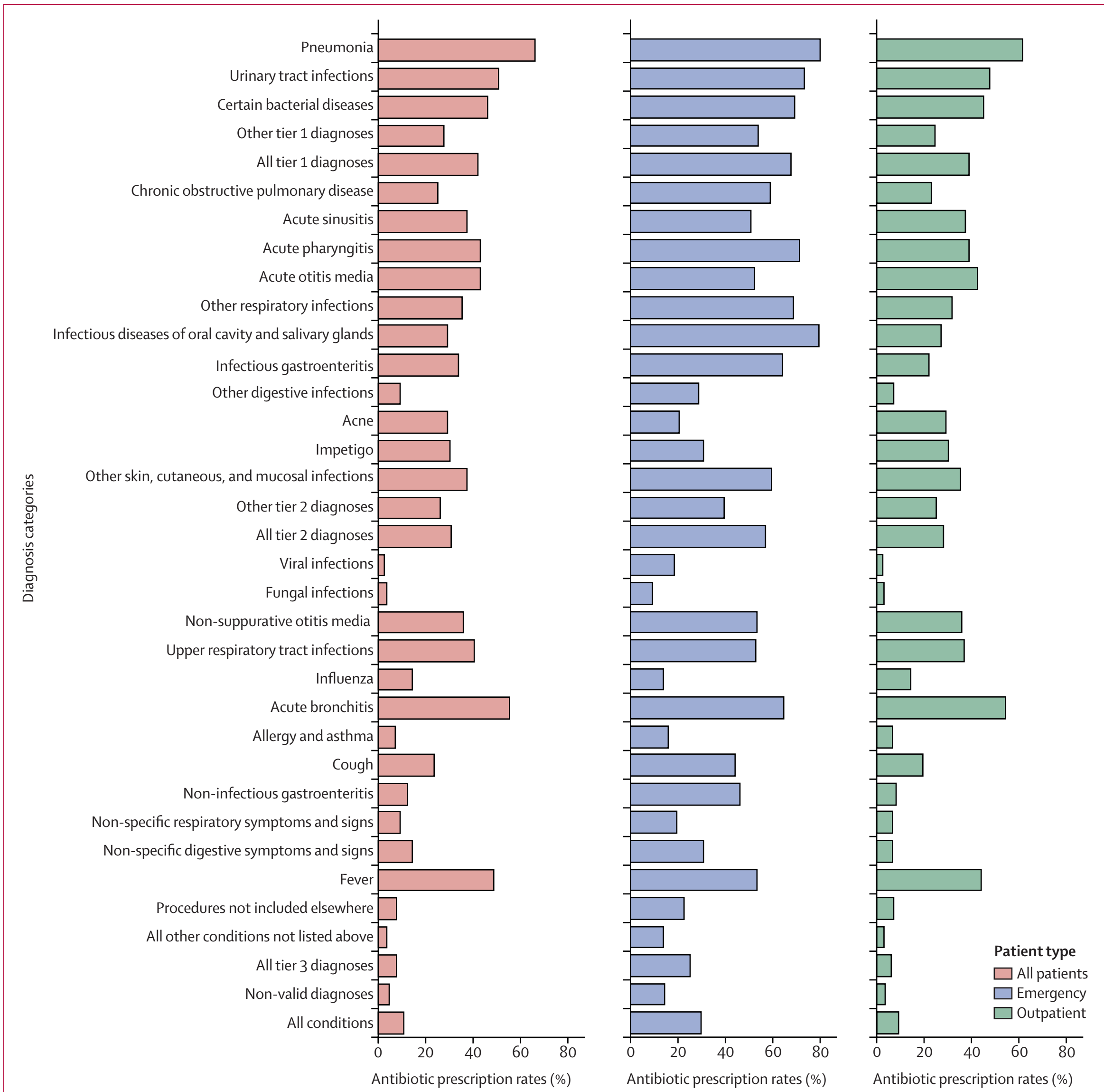

Figure 1: **Antibiotic prescription rates for various diagnosis categories of patient visits at the outpatient clinics and emergency departments**
Other tier 1 diagnoses=other tier 1 bacterial infections. Other respiratory infections=other infectious diseases of the respiratory system categorised in tier 2. Other tier 2 diagnoses=other tier 2 infectious diseases for which an antibiotic might be indicated. See appendix 2 (pp 19–25) for more details of all diagnosis categories.

secondary hospitals resulted in higher antibiotic prescription rates for tier 2 and tier 3 diagnoses 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, urinary tract infection, and certain bacterial diseases, uncertain diagnoses resulted in 16·9%, 14·4%, and 15·4% less antibiotic prescribing.

Of 18 848 864 visits that ended with antibiotic prescriptions, only 2 893 102 (15·3%) were appropriate, 5 354 224 (28·4%) were potentially appropriate, 9 689 937 (51·4%) were inappropriate, and the other 911 601 (4·8%) were not linked to any diagnosis (table 2). In the subgroup analysis, 7 139 299 (48·4%) of 14 736 483 visits to an outpatient clinic and 2 550 638 (62·0%) of 4 112 381 visits to an emergency department were inappropriate. Children younger than 6 years had the highest proportion of inappropriate antibiotic prescriptions at 71·1% (1 422 464 of 2 000 957 visits). Furthermore, 60·1% (841 337 of 1 399 031 visits) of antibiotic prescriptions in northeastern China were inappropriate, ranking the first among all of four economic regions. In addition, 49·2% (864 285 of 1 756 646 visits) of antibiotic prescriptions in secondary hospitals were inappropriate, compared with 51·6% (8 825 652 of 17v 092 218 visits) in tertiary hospitals. Furthermore, the

	All visits with antibiotics prescribed	Proportion of appropriate antibiotic use	Proportion of potentially appropriate antibiotic use	Proportion of inappropriate antibiotic use	Proportion of visits not linked to diagnosis
Overall	18 848 864	2 893 102 (15·3%)	5 354 224 (28·4%)	9 689 937 (51·4%)	911 601 (4·8%)
Type of patients					
Outpatient	14 736 483	2 366 494 (16·1%)	4 543 942 (30·8%)	7 139 299 (48·4%)	686 748 (4·7%)
Emergency	4 112 381	526 608 (12·8%)	810 282 (19·7%)	2 550 638 (62·0%)	224 853 (5·5%)
Age group, years					
<6	2 000 957	216 534 (10·8%)	273 453 (13·7%)	1 422 464 (71·1%)	88 506 (4·4%)
6–17	1 328 278	107 153 (8·1%)	341 345 (25·7%)	818 142 (61·6%)	61 638 (4·6%)
18–44	8 991 249	1 365 898 (15·2%)	2 941 486 (32·7%)	4 238 146 (47·1%)	445 719 (5·0%)
45–64	4 236 194	784 219 (18·5%)	1 148 981 (27·1%)	2 100 647 (49·6%)	202 347 (4·8%)
≥65	2 229 790	414 299 (18·6%)	639 412 (28·7%)	1 068 030 (47·9%)	108 049 (4·8%)
Unknown	62 396	4999 (8·0%)	9547 (15·3%)	42 508 (68·1%)	5342 (8·6%)
Sex of patients					
Female	8 459 258	1 642 520 (19·4%)	2 061 727 (24·4%)	4 362 649 (51·6%)	392 362 (4·6%)
Male	10 368 810	1 248 784 (12·0%)	3 289 821 (31·7%)	5 315 980 (51·3%)	514 225 (5·0%)
Unknown	20 796	1798 (8·6%)	2676 (12·9%)	11 308 (54·4%)	5014 (24·1%)
Hospital level					
2nd	1 756 646	275 103 (15·7%)	467 936 (26·6%)	864 285 (49·2%)	149 322 (8·5%)
3rd	17 092 218	2 617 999 (15·3%)	4 886 288 (28·6%)	8 825 652 (51·6%)	762 279 (4·5%)
Regions of China					
Eastern	11 791 704	1 930 262 (16·4%)	3 472 908 (29·5%)	6 136 962 (52·0%)	251 572 (2·1%)
Central	1 044 778	122 052 (11·7%)	287 082 (27·5%)	566 391 (54·2%)	69 253 (6·6%)
Western	4 613 351	684 811 (14·8%)	1 270 792 (27·5%)	2 145 247 (46·5%)	512 501 (11·1%)
Northeastern	1 399 031	155 977 (11·1%)	323 442 (23·1%)	841 337 (60·1%)	78 275 (5·6%)
Year of visit*					
2014	1 529 384	235 064 (15·4%)	410 118 (26·8%)	716 469 (46·8%)	167 733 (11·0%)
2015	5 639 535	869 462 (15·4%)	1 577 452 (28·0%)	2 843 928 (50·4%)	348 693 (6·2%)
2016	5 266 957	807 623 (15·3%)	1 504 493 (28·6%)	2 755 437 (52·3%)	199 404 (3·8%)
2017	4 935 667	758 437 (15·4%)	1 429 966 (29·0%)	2 591 781 (52·5%)	155 483 (3·2%)
2018	1 477 321	222 516 (15·1%)	432 195 (29·3%)	782 322 (53·0%)	40 288 (2·7%)

Data are n (%). For rounding reasons, the sum of the proportions of diagnosis categories for some subgroups might not be exactly equal to 100%. Outpatient visits were assigned into one of four mutually exclusive categories as applied by Chua and colleagues:[11] appropriate if assigned with at least one tier 1 diagnosis, potentially appropriate if assigned with at least one tier 2 diagnosis but not assigned any tier 1 diagnoses, inappropriate if assigned with only tier 3 diagnosis, and not linked to any diagnosis if the prescription cannot be linked with any valid diagnosis. *For year 2014 and 2018, only prescriptions in October, November, and December of 2014 and January, February, March, and April of 2018 were available.

Table 2: **Proportion of antibiotic prescriptions in each appropriateness category for various subgroups**

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 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 and potentially appropriate prescribing did not change significantly during the study period (figure 2; p=0·186). Results of sensitivity analyses for trends of inappropriate antibiotic prescribing (appendix 2 p 39) were consistent with the primary analysis. A list of national-level policies and actions associated with the management of antibiotic use is given in appendix 2 (pp 7–12).

Of 18 848 864 outpatient visits that ended with antibiotics being prescribed, 3 393 302 (18·0%) visits ended with two antibiotics and 465 966 (2·5%) with three or more antibiotics. Appendix 2 (pp 40–41) shows the combined use of antibiotics for different diagnosis categories. In total, 23 266 494 individual antibiotics were prescribed, of which 18 620 086 (80·0%) were broad-spectrum (appendix 2 pp 42–43). The most commonly prescribed antibiotics were third-generation cephalosporins (J01DD, 5 056 058 [21·7%]), followed by second-generation cephalosporins (J01DC, 3 823 410 [16·4%]), macrolides (J01FA, 3 554 348 [15·3%]), and fluoroquinolones (J01MA, 3 285 765 [14·1%]; figure 3). For visits associated with pneumonia and urinary tract infection, fluoroquinolones and third-generation cephalosporins were the most prescribed antibiotics, accounting for 49% (395 478 of 807 036) and 57·9% (569 166 of 982 373) of all individual antibiotics for these two

	Proportion of appropriate antibiotic use	Proportion of potentially appropriate antibiotic use	Proportion of inappropriate antibiotic use	Proportion of visits not linked to diagnosis
Imputation by nearest distance*				
Estimation after imputing	14·3% (13·1 to 15·6)	27·8% (25·8 to 30·1)	52·5% (50·0 to 55·1)	5·3% (3·6 to 7·3)
Differences to 139 included hospitals	−1·0% (−2·2 to 0·3)	−0·6% (−2·6 to 1·7)	1·1% (−1·4 to 3·7)	0·5% (−1·2 to 2·5)
Imputation by median				
Estimation after imputing	14·9% (13·9 to 16·0)	28·5% (26·8 to 30·4)	52·7% (50·6 to 54·7)	3·9% (2·6 to 5·5)
Differences to 139 included hospitals	−0·4% (−1·4 to 0·7)	0·1% (−1·6 to 2·0)	1·3% (−0·8 to 3·3)	−0·9% (−2·2 to 0·7)
Imputation by 25th percentile				
Estimation after imputing	14·5% (13·5 to 15·7)	29·0% (27·2 to 30·8)	52·8% (50·7 to 54·9)	3·7% (2·4 to 5·3)
Differences to 139 included hospitals	−0·8% (−1·8 to 0·4)	0·6% (−1·2 to 2·4)	1·4% (−0·7 to 3·5)	−1·1% (−2·4 to 0·5)
Imputation by 75th percentile				
Estimation after imputing	15·0% (14·0 to 16·2)	28·0% (26·3 to 29·9)	51·4% (49·4 to 53·4)	5·6% (4·2 to 7·3)
Differences to 139 included hospitals	−0·3% (−1·3 to 0·9)	−0·4% (−2·1 to 1·5)	0·0% (−2·0 to 2·0)	0·8% (−0·6 to 2·5)
Multiple imputation				
Estimation after imputing	15·6% (14·3 to 17·1)	28·9% (26·9 to 31·2)	51·4% (48·8 to 53·9)	4·1% (2·5 to 6·0)
Differences to 139 included hospitals	0·3% (−1·0 to 1·8)	0·5% (−1·5 to 2·8)	0·0% (−2·6 to 2·5)	−0·7% (−2·3 to 1·2)

Data are % (95% CI). *Distance between matched hospitals was calculated using antibiotic prescription rate, average monthly visits, and percentage of visits associated with prescribed drugs.

Table 3: **Sensitivity analyses for exclusion of hospitals that did not submit diagnostic information**

conditions, respectively. For most conditions in which antibiotic use is potentially appropriate or inappropriate, third-generation 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 appendix 2 (p 44).

Discussion

In this analysis of a large, nationally representative database of outpatient prescriptions, we estimated that 10·9% of outpatient visits ended with antibiotic prescriptions in Chinese hospitals. Our results indicated that 51·4% of outpatient antibiotic prescriptions in China were inappropriate, whereas only 15·3% were appropriate. To the best of our knowledge, this study is the first in China to investigate antibiotic prescriptions for various diagnoses and assess appropriateness of antibiotic prescriptions using such extensive prescription data covering almost all provinces of China. Following a validated approach,[5,6,11,14] we established the baseline of outpatient antibiotic prescription rates for various diagnosis categories and estimated the proportion of antibiotic prescriptions that were inappropriate.

Current comprehensive estimates of inappropriate antibiotic prescribing at the national level mainly come from high-income countries. For people of different ages in the USA, around 13% of outpatient visits for all conditions are estimated to end with antibiotic prescriptions,[5,13] of which 23–40% are inappropriate,[5,11–13]

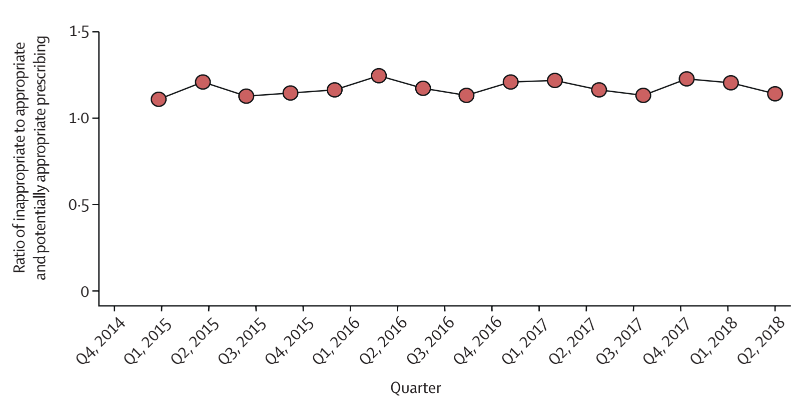

Figure 2: **Trend in inappropriate antibiotic prescribing**

whereas 23% of antibiotic prescriptions for all ages in 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 finding that 10·9% of outpatient visits resulted in antibiotic prescriptions was similar to the prescription rate in the USA; however, our finding that 51·4% of antibiotic prescriptions in China were inappropriate was higher than that in the USA and UK, and approximated the rate in Japan. Part of this discrepancy can be attributed to different methods, data sources, and populations.[11] For example, two studies in the USA used insurance claim

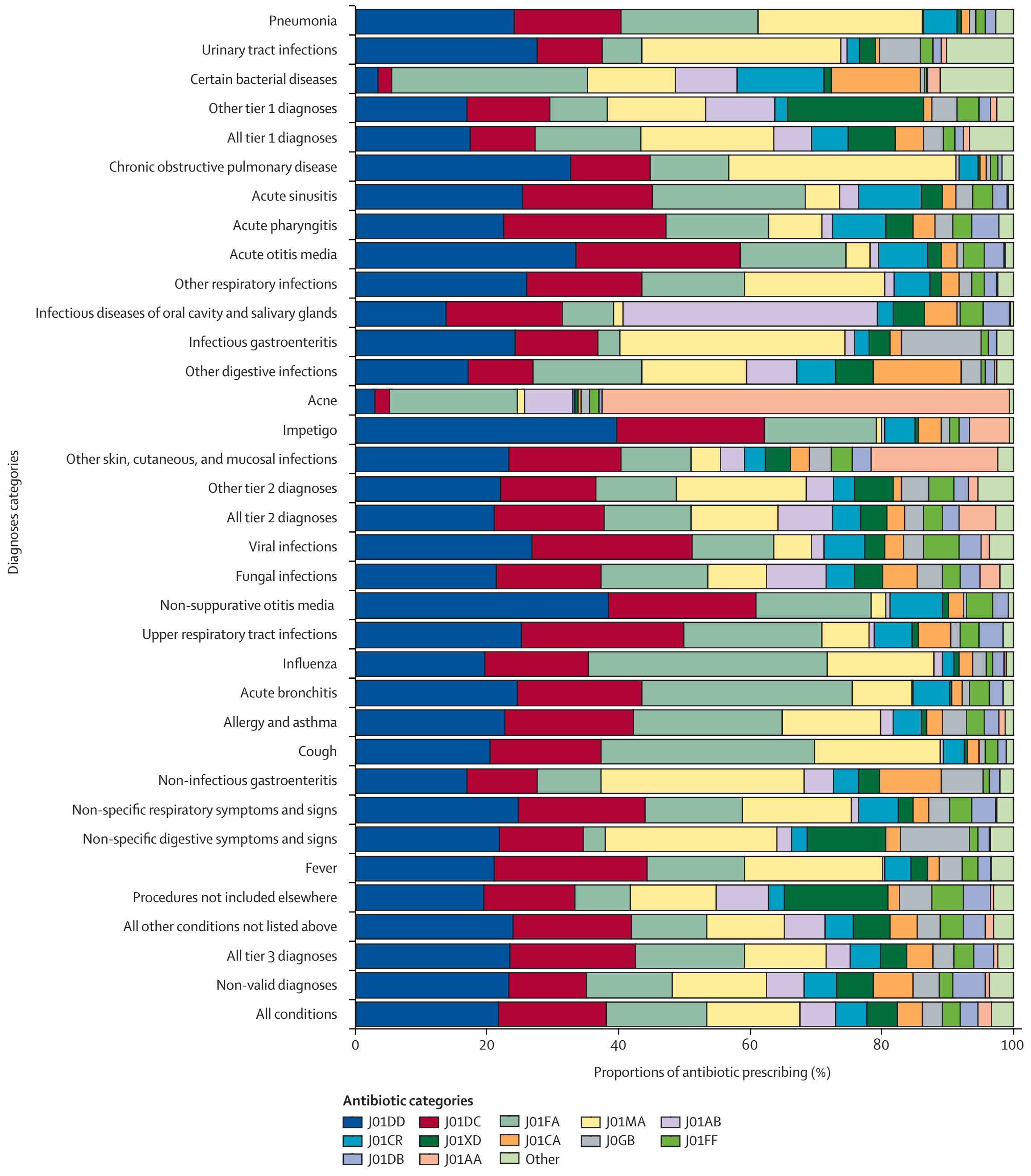

Figure 3: **Types of antibiotics prescribed for different diagnostic categories**

Other tier 1 diagnoses=other tier 1 bacterial infections. Other respiratory infections=other infectious diseases of the respiratory system categorised in tier 2. Other tier 2 diagnoses=other tier 2 infectious diseases for which an antibiotic might be indicated. See appendix 2 (pp 19–25) for more details of all diagnosis categories. J01AA=tetracyclines. J01CA=penicillins with extended spectrum. J01CR=combinations of penicillins, including beta-lactamase inhibitors. J01DB=first-generation cephalosporins. J01DC=second-generation cephalosporins. J01DD=third-generation cephalosporins. J01FA=macrolides. J01FF=lincosamides. J01MA=fluoroquinolones. J01GB=other aminoglycosides. J01XD=imidazole derivatives. P01AB=nitroimidazole derivatives. Others=include G01AX, J01BA, J01CE, J01CF, J01CG, J01DE, J01DF, J01DH, J01DI, J01EE, J01GA, J01MB, J01XA, J01XB, J01XC, J01XE, and J01XX.

data and linked antibiotic claims occurring within specific days before prescription fills[11] or after outpatient visits.[12] However, the study in Japan, which also used insurance claim data, only considered antibiotic prescriptions occurring on the same day as the diagnosis.[17] In our study, we applied a similar strategy to the study in Japan, because our data came from electronic medical records and in China ambulatory care drug prescribing and dispensing almost always happen on the same day. Furthermore, several studies classified diagnoses according to ICD-9 codes;[5,12,13] other studies,[11,17] including ours, were based on ICD-10 codes or corresponding descriptions. The effects of these differences on the estimation of inappropriate antibiotic prescribing are difficult to assess, and further studies on this issue are needed.

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 also 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, estimating the prevalence of inappropriate antibiotic use is crucial for informing actions to combat antimicrobial resistance in LMICs. However, this evidence at the national level is scarce in LMICs, including China. Appropriateness assessment of antibiotic prescribing based on manual prescription review exists in China,[26] but the results vary across different pieces of research, and the review scheme is not clearly described and validated. A study based on manual prescription review in 2016 using nearly 0·45 million outpatient prescriptions from 25 provinces found that inappropriate prescribing accounted for less than 5% of all antibiotic prescriptions,[26] which is very low compared with the available evidence in different countries. Furthermore, this study showed huge regional variations with a highest inappropriate prescription rate of 31% in Guangdong and the lowest rate of 0% in Hubei.[26] Since the study did not report a detailed evaluation scheme, direct comparison with our study is impossible. However, we used a comprehensive classification scheme based on ICD-10 and natural language processing, 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 using other kinds 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 2 pp 7–12). However, inappropriate antibiotic prescribing did not change substantially during the study period. In 2009, the national essential medicines and zero mark-up policy was issued to improve rational use of medicines by disengaging prescribing from profits,[27,28] which is considered to be an important driver of antibiotic overuse.[29] However, available evidence indicates that this policy has small or no effect on the use of antibiotics.[27,28] In 2011, the Ministry of Health of China implemented the 3-year national antimicrobial stewardship programme. With a series of compulsory measures, this was the most stringent antimicrobial stewardship programme in China in history. Although the effects of the programme were quite obvious and antibiotic prescription rate was reduced dramatically below a predetermined level during the programme, antibiotic use has remained at a stable level or decreased slightly after 2013.[30,31] This situation might explain why inappropriate antibiotic prescribing has not changed significantly after 2014 in our study. Since we only had access to the data after 2013, direct evaluation of the effects of the antimicrobial stewardship programme and national essential medicines on inappropriate antibiotic prescribing is not feasible in our study.

We found that a substantial amount of antibiotic overuse was driven by tier 3 respiratory conditions, of which viral upper respiratory tract infections and bronchitis were the top two diagnoses with the most antibiotic prescriptions. Similar results were found in Japan, where 40·5% of outpatient visits for upper respiratory tract infections and 58·2% of visits for bronchitis ended with antibiotic prescriptions.[17] Undertreatment for conditions that almost always warrant antibiotics also contributed substantially to inappropriate antibiotic prescribing. For pneumonia and urinary tract infections, 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 high-income countries.[5,17] Diagnostic uncertainty combined with tight restrictions of antibiotic use in the antimicrobial stewardship programme might have discouraged physicians from prescribing antibiotics.[32] For example, in our study, the antibiotic prescription rate for certain pneumonia diagnoses was 68·8% and for the uncertain pneumonia diagnoses was 51·9%.

Several strategies can be taken to remedy these issues. Point-of-care diagnostic tests that can rapidly distinguish between different pathogens causing common infections are needed to allow 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 upper respiratory tract infections and bronchitis is of potential benefit. European countries have established the recommended ideal antibiotic prescription rates for common infectious disease,[6,20] which is a helpful benchmark for assessing and guiding antibiotic prescribing. Similar recommendations are not available in China. Other strategies such as infection prevention and control, audit and feedback, clinician and patient education, and communication training can be used or strengthened to optimise antibiotic use in ambulatory care settings.[33,34]

We found that one in five antibiotic prescriptions contained two or more antibiotics, whereas 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 might also lack appropriateness. For instance, penicillins with extended spectrum (J01CA) and tetracyclines (J01AA) are recommended to account for 80–100% of all antibiotics prescribed for pneumonia,[20] but in China this proportion was just 1·2%, and over 90% of antibiotics for pneumonia had a broad spectrum. Previous studies showed a different prescribing pattern and lower proportions of broad-spectrum antibiotics in some high-income countries than in China.[36,37] However, there has been a shift towards the use of broad-spectrum antibiotics in recent years worldwide, especially in LMICs.[3,24] Misuse of combination therapy and broad-spectrum antibiotics can have crucial impacts on antimicrobial resistance, so actions to promote compliance with guidelines and restrict use of combination therapy and broad-spectrum antibiotics 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 care centres, which are believed to provide most medical care in rural areas,[38] were not available. A previous study reported that over 60% of antibiotic prescriptions were inappropriate in Chinese primary care settings.[38] However, the study was done 10 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 care centres are needed. Second, private hospitals and specialist hospitals, such as traditional Chinese medicine hospitals and maternity hospitals, were not recruited in our study. Comprehensive evaluation of appropriateness of antibiotic use is still scarce in these hospitals. Third, we used Chinese diagnosis text rather than the standard ICD-10 codes because of absence of data standardisation. The diagnosis categories defined as others in this study can be further analysed in the future by using higher standardised prescription data. Last, like previous studies,[5,11–13,17] we used only indications, and not the administration route, dosage, compatibility, and therapy duration (which are also key to assessing inappropriate prescription) to assess the appropriateness of outpatient antibiotic prescriptions. This fact might have resulted 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 programmes focusing on optimising antibiotic prescribing need to be implemented in China to achieve the goals set in the NAP. Our methods can be applied to 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 and designed the work. JB and MZ acquired the data. HZ did the diagnosis classification and analysed 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 interpreta-tion of the data, and revised, and gave final approval of the manuscript.

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 centre, who 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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