Evaluation of appropriateness of antibiotic prescribing in primary healthcare institutions in China using proxy indicator

Haishaerjiang Wushouer,[a,b,d] Junxuan Yu,[a,d] Kexin Du,[a] Weihsin Ko,[a] Weibin Li,[a] Kairui Zhang,[a] Shuo Chen,[a] Bo Zheng,[c] Luwen Shi,[a,b] and Xiaodong Guan[a,b,*]

[a]Department of Pharmacy Administration and Clinical Pharmacy, School of Pharmaceutical Sciences, Peking University, Beijing, 100191, China
[b]International Research Center for Medicinal Administration (IRCMA), Peking University, Beijing, 100191, China
[c]Institute of Clinical Pharmacology, Peking University First Hospital, Beijing, 100034, China

The Lancet Regional Health - Western Pacific 2024;49: 101132

Published Online xxx
https://doi.org/10.1016/j.lanwpc.2024.101132

Summary

Background Our objectives were to develop a set of proxy indicators (PIs) suited for assessing antibiotic use appropriateness in China's primary healthcare institutions (PHIs), and assess performance scores of these PIs while exploring factors that influence the antibiotic appropriateness.

Methods We selected potential PIs for the PHIs through a RAND–modified Delphi procedure, and assessed clinimetric properties, focusing on measurability, applicability, and potential for improvement. PIs with favorable clinimetric properties were used to evaluate antibiotic prescription appropriateness by calculating performance scores of each PI. Institutions were categorized into three clusters representing different levels of appropriateness. We used the chi–square test and an ordinal logistic regression model at PHI level to explore factors influencing antibiotic appropriateness.

Findings Eighteen PIs were developed through two rounds of online surveys and one face–to–face meeting involving 20 stakeholders. All PIs met the clinimetric properties criteria and were used to analyze 209,662 antibiotic prescriptions across 269 PHIs. The percentage of PHIs meeting the target ranged from 3.1% to 69.3%, with 6 PIs below 10%. The appropriateness of antibiotic prescriptions was significantly associated with percentages of patients' gender of the PHIs.

Interpretation The varied and suboptimal performance of the PIs indicated the need for diverse efforts to enhance the rational antibiotic use at PHI level. It was necessary to devise distinct sets of PIs for diverse settings in future endeavors.

Funding This work was supported by the National Natural Science Foundation of China (grant numbers 72374009, 81973294).

Keywords: Antibiotic prescriptions; Appropriateness; Proxy indicators; Primary healthcare institutions; Clusters

Introduction

Inappropriate antibiotic use significantly contributes to antimicrobial resistance (AMR).[1] In low– and middle–income countries, the lack of surveillance networks magnifies the urgency of identifying and addressing this issue. Assessing antibiotic utilization commonly relies on the percentage of antibiotic prescriptions, a metric introduced by the World Health Organization and the International Network of Rational Use of Drugs.[2] However, the appropriateness cannot be solely reflected based on prescription volume. High–income countries in Europe have adopted Quality Indicators (QIs) to reflect the degree of appropriateness of antibiotic prescription.[3–7] Yet, since QIs evaluated appropriateness at the per–prescription level, such as prescription compliant with guidelines, they implied poor operability. Additionally, some QIs relied on clinical indication whereas most European countries lacked computerized systems that routinely linked antibiotic prescriptions to clinical diagnoses.[7] In response, Thilly

*Corresponding author. Peking University Health Science Center, 38 Xueyuan Road, Haidian District, Beijing, 100191, China.
E-mail address: guanxiaodong@pku.edu.cn (X. Guan).
[d]These authors contributed equally to this study.

Research in context

Evidence before this study

Initially, we conducted a systematic literature review on PubMed, Embase, and Web of Science Core Collection until 1st January 2023 focusing on quality metrics of antibiotics applied in the outpatient setting. Our findings revealed that high–income countries in Europe and South Korea use Quality Indicators (QIs) to assess appropriateness. However, the evaluation of appropriateness at the per–prescription level by QI implied poor operability, with some relying on clinical indications, a challenge exacerbated by the lack of computerized systems in most European countries that routinely link antibiotic prescriptions to clinical diagnoses. To address this, Thilly et al. introduced proxy indicators (PIs) in the French primary care setting. These PIs were derived from quantity metrics (QMs) and did not rely on clinical indication data but they shared characteristics of both QMs and QIs. However, there's limited evidence regarding the adoption of PIs within China's healthcare settings.

Added value of this study

To the best of our knowledge, this study represented the first attempt to develop, measure, and apply the PIs at the level of primary healthcare institutions (PHIs) in China using nationally representative sample data. Eighteen PIs were developed through two rounds of online surveys and one face–to–face meeting involving 20 stakeholders. The robustness and validity of these PIs were confirmed through RAND–modified Delphi procedure. Notably, all PIs were found to be measurable and applicable, showing substantial room for improvement. The percentage of PHIs met the target ranged between 3.1% and 69.3%, with 6 PIs below 10%, which highlighted significant variations in the performance of each PI among the sample PHIs and notable differences in performance across various PIs. Furthermore, our study revealed that the appropriateness of antibiotic prescriptions was significantly associated with percentages of patients' gender of the PHIs.

Implications of all the available evidence

The varied and suboptimal performance of the PIs indicated the need for diverse efforts to enhance the rational antibiotic use at PHI level. These collective findings underscore the necessity of devising distinct sets of PIs for diverse settings in future endeavors.

et al. introduced a set of proxy indicators (PIs) in the French primary care setting, derived from quantity metrics (QMs) without clinical indication data but sharing characteristics of both QMs and QIs.[8] While PIs offer aggregated insights rather than prescription–level accuracy like QIs, their adoption provided an opportunity to broadly analyze antibiotic use appropriateness, particularly in primary care settings.

China, known as one of the world's largest consumers of antibiotics, faces significant challenges related to inappropriate antibiotic use, particularly in primary care settings.[9] A study found that 70.5% of antibiotic prescriptions from 269 primary healthcare institutions (PHIs) across China were deemed inappropriate.[10] While diagnosis is a requirement in China's regulations according to the *Prescription Management Methods* issued by the former Ministry of Health of China, PHIs struggle due to their lower level of informatization. Unlike secondary and tertiary medical institutions, PHIs lack standardized International Classification of Diseases (ICD) codes for diagnoses in their electronic prescription systems. Additionally, PHIs are not integrated into national surveillance networks for monitoring antibiotic use and AMR. In response, the National Health Commission has implemented a prescription review and feedback policy for PHIs to promote the rational use of antibiotics. This policy involves experts from higher–level hospitals assessing sampled antibiotic prescriptions in PHIs. However, the resource–intensive nature of this intervention hinders its widespread implementation due to concerns about homogenization. As a result, the use of PIs emerges as a potential solution for evaluating the appropriateness of antibiotic prescriptions in China's primary care settings. Despite this potential, there's a dearth of evidence concerning the adoption of PIs within China's healthcare settings. Our study aimed to address this gap by pursuing three key objectives: (i) developing a tailored set of PIs specifically suited for assessing antibiotic use appropriateness in China's PHIs; (ii) evaluating the clinimetric properties of these PIs using outpatient prescription data obtained from a nationwide survey spanning PHIs in China; and (iii) assessing the performance scores of these PIs at the PHI level while exploring the factors that influence the appropriateness of antibiotic prescriptions.

Methods

Study design

The study was structured into three main sections. The first part involved the establishment of PIs by a RAND–modified Delphi procedure, which is one of the premier methods for developing QIs.[3] We developed a comprehensive set of PIs through a systematic review to identify from the QIs. Following this, two rounds of online surveys and a consensus meeting were conducted to finalise the PIs. The second part focused on the assessment of three clinimetric properties (measurability, applicability, and potential for improvement) of the aforementioned PIs to determine their suitability for the sampled PHIs.[8] In the third section, we applied these PIs to evaluate the appropriateness of antibiotic prescriptions at the PHI level. Initially, we calculated the results for each PHI using the PIs. Subsequently, we categorised the PHIs into three clusters, representing varying levels of prescription appropriateness. Further, we compared the characteristics of PHIs across these clusters and subsequently explored factors influencing the appropriateness of antibiotic prescriptions. The flowchart of the study was depicted in Fig. 1.

Study sampling and data collection

We obtained outpatient prescription data from a national survey conducted across PHIs in China from 2017 to 2019. Urban community health centers and rural township hospitals were systematically selected using a two–step method from 6 out of the 31 provinces in China mainland, selected based on economic status. Within each selected institution, 100 outpatient prescriptions were randomly sampled from patient visits occurring on the second Tuesday of each month. Subsequently, two investigators independently extracted and cross–verified the data.[10] The detailed data sampling and collection were provided in Supplementary Methods.

Definition

In this study, the term "prescription" encompassed all medications prescribed to a single patient during a single visit to a PHI clinic. Antibiotic prescriptions referred to the prescriptions containing at least one antibiotic classified according to Anatomical Therapeutic and Chemical classification J01.[11] Narrow–spectrum antibiotics included tetracyclines, narrow–spectrum penicillins, first–generation cephalosporins, aminoglycosides, sulphonamides, and nitroimidazoles. Broad–spectrum antibiotics included penicillins with extended spectrum, combination of penicillins and beta–lactamase inhibitors, second–generation to four–generation cephalosporins, macrolides, quinolones, and other antibiotics.[12] The first–line antibiotics was determined according to *Chinese Guidelines for Clinical Use of Antibiotics* (2015 edition).[13] The PHIs in the study included community health centers in urban areas and township hospitals in rural areas for the basic medical needs of the community and rural residents respectively.[14] "Urban" and "rural" areas were classified based on Chinese administrative division standards. Urban areas include city districts, unincorporated municipalities, and resident committees, as well as other areas physically connected by construction to the seats of district and municipal governments. These areas typically boast more developed economic and cultural facilities. In contrast, rural areas include the physically connected neighborhood committees, areas where county people's governments are located, and other townships. These areas are primarily agricultural and often lag behind in terms of economic development.

Establishment of PIs

To thoroughly assess the appropriateness of antibiotic prescriptions at the PHI level, we formulated a set of PIs using the RAND–modified Delphi method (see Supplementary Table S1 for further details). Initially, we conducted a systematic literature review encompassing reviews, observational studies, guidelines, and expert

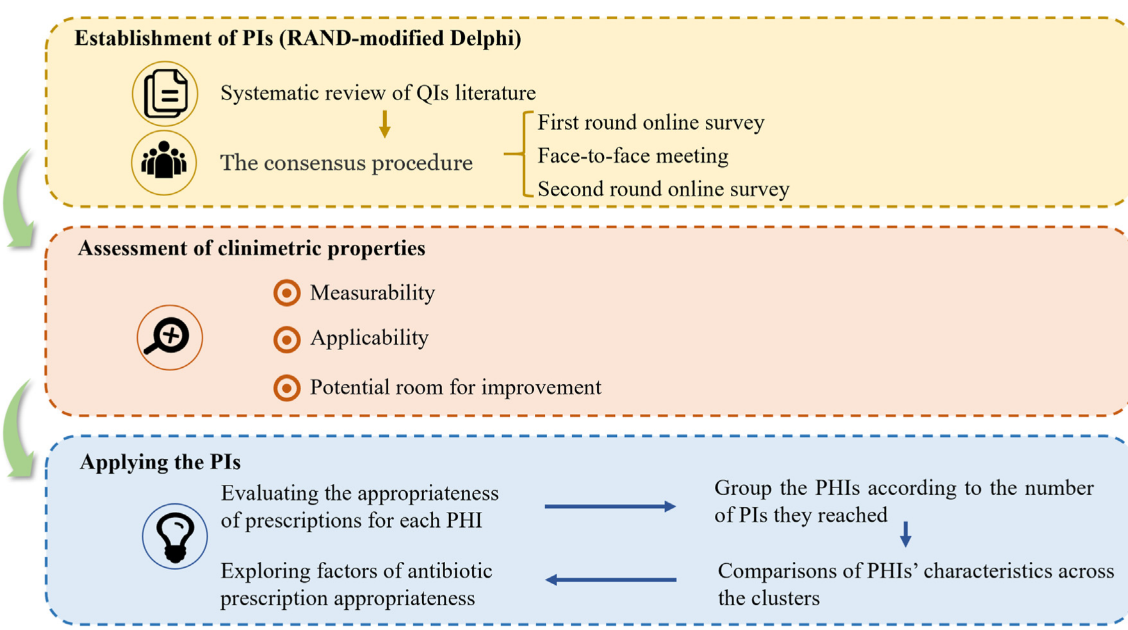

Fig. 1: **Flowchart of the study**. Abbreviations: PI, proxy indicator; QI, Quality indicator; PHI, primary healthcare institution.

consensus.[13,15–18] Our search spanned PubMed, Embase, and Web of Science Core Collection until 1st January 2023 (see Supplementary Methods for detailed review process, Supplementary Table S2 for search strategies, Supplementary Table S3 for included articles, and Supplementary Table S4 for characteristics of these articles). Additionally, we complemented our search by scouring authoritative websites in the field of anti–infectives (National institute for Health and Care Excellence, Centers for Disease Control and Prevention, European Surveillance of Antimicrobial Resistance Consumption, Infectious Diseases Society of America) and the relevant guidelines. QIs were extracted from these sources for outpatient settings. Those incalculable QIs, namely without numerators and denominators, were excluded. The remaining QIs were regarded as potential PIs. Subsequently, the list of potential PIs was circulated among experts (see Supplementary Methods for detailed process of selecting expert panels). Two online surveys and a face–to–face meeting were conducted to finalise the PIs, encompassing their definitions, numerators, and denominators. Specifically, we initially briefed the experts on the study background, providing them with data of antimicrobial resistance pharmacoepidemiology, medicine use and existing studies on QIs and PIs (Supplementary Table S3). Subsequently, we asked them to select PIs from QIs that best reflected antibiotic prescription appropriateness. The target values were confirmed based on their professional expertise, and primary care experience with reference to the evidence we provided and synthesized from the literature review through two rounds of online questionnaires, designed based on Likert scale (see Supplementary data 1 for sample of the questionnaire). PIs that were received five or more points (on a scale ranging from zero to nine points) from each expert were included. Two online surveys were completed in March 2023 and April 2023 respectively, with the face–to–face meeting taking place on April 6, 2023.

Assessment of clinimetric properties

To validate the significance of the PIs assessing the appropriateness of antibiotic prescription in PHIs, we assessed the subsequent clinimetric properties for each PI[4,19]:

i. Measurability: Measurability was defined as the availability of data necessary to calculate the indicator. An indicator was deemed measurable if the required data were available for more than 75% of prescriptions, i.e. data were missing in <25% of cases.[8]
ii. Applicability: The applicability of a PI was determined by its meaningfulness for the PHI, i.e. it reflected at least 10 clinical situations. In practice, a PI score could not be calculated for a given PHI if (i) fewer than 10 prescriptions were identified for the denominator for PIs focusing on suboptimal practices i.e. drugs that should not be prescribed (e.g. PI 3, 4, 5, 6, 7, 11, 13, 18), where the optimal target value was close to 0, or (ii) less than 10 prescriptions were identified for either the numerator or the denominator for PIs describing both suboptimal and good practices (e.g. PI 1, 2, 8, 9, 10, 12, 14, 15, 16, 17), with the denominator being different from null. A PI was considered applicable if it could be calculated from data extracted for more than 75% of the PHIs.[8]
iii. Potential for improvement: The potential for improvement measured the sensitivity of a PI to detect variability in appropriateness of prescriptions between PHIs and over time. It was calculated as 100% minus the performance score, where performance represented the percentage of PHIs reaching the PI target among the applicable PHIs. High performance scores indicated less sensitivity, making indicators less useful in routine practice. The potential room for improvement for a PI was considered as low if it was ≤15%.[8]

Data analysis

Firstly, we presented the findings regarding the potential PIs, estimating their clinimetric properties——— measurability, applicability, and improvement potential as percentages. Secondly, for each PHI, we computed the median, maximum and minimum based on individual PI results. Thirdly, we categorised all PHIs into three clusters based on the number of PIs that met the targets. PHIs reaching 0–3, 4–6, and 7–11 PIs targets were classified into cluster 1 (indicating practices below average), cluster 2 (representing average practice), and cluster 3 (signifying practices above average) respectively.

Each PHI received an appropriateness score, expressed as a percentage, calculated as follows: [(number of applicable PIs for the PHI meeting targets)/(total number of applicable PIs for the PHI)] × 100. Subsequently, performance scores for each PI within every cluster were computed, indicating the percentage of PHIs that achieved their respective target. To explore potential factors that influenced the appropriateness of antibiotic prescription, we identified various characteristics of PHIs, including area (rural or urban), region, economic status, percentages of patients' gender and age at PHI level. The Chi–square test was employed to compare the PHIs' characteristics among the clusters. Then we applied an ordinal logistic regression model to further explore the factors. The model met the proportional odds assumption (see Supplementary Table S5 for results of the proportional odds assumption). A P–value<0.05 was considered statistically significant. All analyses were conducted with using Stata version 17.

Ethics approval
Not applicable.

Role of the funding source
The funders had no role in study design, data collection, data analysis, interpretation, writing of the report.

Results

Results of RAND–modified Delphi procedure
Fifteen potential key PIs initially identified from 103 studies underwent evaluation by 20 multidisciplinary expert panels. The characteristics of the stakeholders were presented in Table 1. A total of 20 experts were included in the first–round survey, 19 (95%) experts aged 40–60 years, 14 (70%) holding senior titles, and having practiced for more than 20 years. Most of these experts were hospital administrators (40%), hospital antimicrobial stewardship (AMS) team members (45%), and infectious disease physician (35%). In the second–round survey, one of the hospitals AMS team members withdrawn due to time constraints. Following an initial online survey, all 15 PIs were retained, with a notable consensus (12/15 accepted, 3/15 rephrased). Subsequently, face–to–face discussions led to the addition of three more key PIs related to first–line antibiotic prescriptions for acute bacterial conditions (acute bacterial otitis media, acute bacterial rhinosinusitis, acute bacterial pharyngitis/tonsillitis). Post the online survey and face–to–face meetings, namely through the second–round online survey, all 18 PIs garnered acceptance from the expert panels. The methodology for the selection of potential PIs and the results of the consensus procedure were presented in Supplementary Fig. S1 and Supplementary Table S6. Ultimately, a total of 18 PIs were identified to assess the appropriateness of antibiotic prescriptions in PHIs, with detailed specifications available in Supplementary Table S7.

Clinimetric properties of the PIs
We computed the clinimetric properties of these potential PIs in our sample PHIs (see Table 2). The measurability of the PIs was 100% as no missing data was observed for PI score calculation. Similarly, all PIs demonstrated highly applicability across the sampled PHIs, surpassing the 75% threshold, ranging from 77.0% for PI 11 to 98.1% for PI 10. Moreover, the potential for improvement across all PIs exceeded 15%, ranging from 30.7% (PI 13) to 96.9% (PI 1), suggesting a measurable sensitivity to detect variability of these PIs. Consequently, all the 18 PIs met the criteria for three clinimetric properties, validating their use in measuring the appropriateness of prescriptions at the PHI level.

Characteristics of the study prescriptions
During the period from 2017 to 2019, a total of 641,732 prescriptions were collected from 269 sampled PHIs in China, comprising 212 community health centres and 57 township hospitals. Among these prescriptions, 32.7% (209,662/641,732) were antibiotic prescriptions

	First–round		Second–round	
	n (N = 20)	%	n (N = 19[b])	%
Age				
< 40	0	0.0	0	0.0
40~45	9	45.0	9	47.4
50~60	10	50.0	9	47.4
> 60	1	5.0	1	5.2
Title				
Deputy senior	6	30.0	6	31.6
Full senior	14	70.0	13	68.4
Years of practice				
< 10	0	0.0	0	0.0
10~20	6	30.0	5	26.3
> 20	14	70.0	14	73.7
Expertise[a]				
Infectious disease physician	7	35.0	7	36.8
Clinical pharmacist	5	25.0	5	26.3
Hospital administrators	8	40.0	8	42.1
Hospital AMS team members	9	45.0	8	42.1
Hospital infection control staff	5	25.0	5	26.3

Abbreviation: AMS, Antimicrobial Stewardship. [a]The expertise of stakeholders are crossed, so the totals do not add up to 20 or 19. [b]One of the hospital AMS team member withdrawn due to time constraints.

Table 1: **Characteristics of the stakeholders that participated in the different steps of the RAND–modified Delphi method.**

Proxy indicator	Measurability missing data (%) Target: < 25%	Applicability n (%) target: > 75%	Improvement potential 1– performance[a] (%) target: > 15%
PI 1 Prescriptions of quinolones (%)	0	258 (95.9)	96.9
PI 2 Prescriptions of cephalosporins (%)	0	260 (96.7)	78.1
PI 3 Prescriptions of aminoglycosides (%)	0	255 (94.8)	71.8
PI 4 Co–prescription of antibiotic with systemic corticosteroids (%)	0	225 (83.6)	62.7
PI 5 Co–prescription of antibiotic with systemic NSAIDs (%)	0	244 (90.7)	45.9
PI 6 Duration of antibiotic prescriptions against acute URTIs >10 days (%)	0	262 (97.4)	76.0
PI 7 Contraindications of antibiotic prescriptions (%)	0	256 (95.2)	65.2
PI 8 Prescriptions of narrow–spectrum antibiotics (%)	0	251 (93.3)	92.8
PI 9 Amoxicillin/broad–spectrum antibiotics (ratio)	0	233 (86.6)	80.3
PI 10 Prescriptions of essential antibiotics (%)	0	264 (98.1)	31.1
PI 11 Prescription of highly–restricted antibiotics (%)	0	207 (77.0)	79.7
PI 12 Seasonal variation of total antibiotic prescriptions (%)	0	252 (93.7)	41.7
PI 13 Seasonal variation of quinolone prescriptions (%)	0	257 (95.2)	30.7
PI 14 First–line antibiotics prescriptions against acute URTIs (%)[b]	0	250 (93.3)	96.4
PI 15 First–line antibiotics prescriptions for acute bacterial otitis media (%)[c]	0	256 (95.2)	96.5
PI 16 First–line antibiotics prescriptions for acute bacterial rhinosinusitis (%)[d]	0	255 (94.8)	96.5
PI 17 First–line antibiotics prescriptions for acute bacterial pharyngitis/tonsillitis (%)[e]	0	253 (94.1)	96.4
PI 18 Antibiotic prescriptions without indication (%)	0	211 (78.4)	75.4

Abbreviations: PI, proxy indicator; NSAID, non–steroidal anti–inflammatory drug; URTI, upper respiratory tract infection. [a]Performance (percentage of PHIs reached the target) results were displayed in Table 3. [b]First–line antibiotics for PI14 (acute URTIs): Amoxicillin, Cefalexin, Azithromycin. [c]First–line antibiotics for PI15 (acute bacterial otitis media): Amoxicillin. [d]First–line antibiotics for PI16 (acute bacterial rhinosinusitis): Amoxicillin/Clavulanate. [e]First–line antibiotics for PI17 (acute bacterial pharyngitis/tonsillitis): Penicillin.

Table 2: **Clinimetric properties of the proxy indicators.**

and were included for analysis. Among the total antibiotic prescriptions, 20.1% (42,177/209,662) included more than one antibiotic, 88.5% (185,514/209,662) consisted of broad–spectrum antibiotics, and 45.4% (95,196/209,662) contained injectable antibiotics (Supplementary Table S8).

Concerning the characteristics of PHIs, the antibiotic prescribing rate in urban areas (32.8%, 42,315/128,939) was comparable to that in rural areas (32.6%, 167,347/512,793). Notably, PHIs situated in the central region exhibited a higher antibiotic prescribing rate compared to other regions (eastern region, 29.8%, 50,765/170,230; central region, 50.3%, 135,293/268,960; western region, 23.0%, 23,604/102,542). Moreover, PHIs in cities with lower–middle economic development status prescribed more antibiotics than cities in other economic categories (low, 33.3%, 49,587/148,830; low–middle, 39.2%, 53,666/136,927; middle–high, 28.9%, 39,779/137,685; high, 30.5%, 66,630/218,290). In terms of patient demographics, 322,061 prescriptions were for males, 307,920 for females, and 11,751 with unknown gender. The antibiotic prescribing rate was higher in males than in females (males, 31.0%, 95,344/322,061; females, 34.4%, 95,344/307,920). Regarding patient age, the antibiotic prescribing rate was higher in children compared to adults (0–5 years, 44.3%, 26,799/62,143; 6–17 years, 48.1%, 28,902/62,003; 18–44 years, 35.9%, 44,471/126,736; 45–64 years, 30.0%, 60,297/199,402; ≥65 years, 25.2%, 45,495/178,423; unknown age, 28.4%, 3698/13,025).

Appropriateness of antibiotic prescriptions

The performance results for the 18 PIs were presented in Table 3. These findings revealed variable and suboptimal practices across PIs, ranging from 3.1% (PI 1) to 69.3% (PI 13). The substantial range for each PI underscored disparities in prescription practice among various PHIs. Specifically, the performance of only 2 PIs———PI 10 and PI 13, exceeded 60%. The majority of PIs (10 out of 18) demonstrated performances ranging between 20% and 60%. Notably, 6 PIs displayed considerable room for improvement, with performances below 10%. These were related to the prescriptions of quinolones (PI 1), narrow–spectrum antibiotics (PI 8), first–line antibiotics prescriptions against acute URTIs (PI 14), first–line antibiotics for acute bacterial otitis media (PI 15), first–line antibiotics for acute bacterial rhinosinusitis (PI 16), first–line antibiotics for acute bacterial pharyngitis/tonsillitis (PI 17).

Grouping results

The distribution of diagnoses in PI 14–PI 17 across the three clusters was presented in Supplementary Table S9. Table 4 exhibited the appropriateness scores of the three clusters and their respective performances across each PI. Among the PHIs, 72 (26.8%) were classified into clusters 1 (worse than average practices), 159 (59.1%) into cluster 2 (average practices), and 38 (14.1%) into cluster 3 (better than average practices). The appropriateness scores were 15.38% (cluster 1), 27.78% (cluster 2), and 41.18% (cluster 3) respectively.

Proxy indicator	Median	Range (Minimum, Maximum)		Target value	% of PHIs met the target
PI 1 Prescriptions of quinolones (%)	4.9%	0.5%	44.3%	20–40%	3.1
PI 2 Prescriptions of cephalosporins (%)	14.6%	0.5%	82.5%	20–40%	21.9
PI 3 Prescriptions of aminoglycosides (%)	0.8%	0.1%	18.3%	<5%	28.2
PI 4 Co-prescription of antibiotic with systemic corticosteroids (%)	1.4%	0.1%	9.3%	<5%	37.3
PI 5 Co-prescription of antibiotic with systemic NSAIDs (%)	4.6%	0.1%	23.1%	<5%	54.1
PI 6 Duration of antibiotic prescriptions against acute URTIs >10 days (%)	20.9%	0.9%	81.8%	<15%	24.0
PI 7 Contraindications of antibiotic prescriptions (%)	6.7%	0.1%	23.1%	<5%	34.8
PI 8 Prescriptions of narrow-spectrum antibiotics (%)	5.9%	0.2%	48.1%	>20%	7.2
PI 9 Amoxicillin/broad-spectrum antibiotics (ratio)	1.15	0.1	2.9	0.2–0.4	19.7
PI 10 Prescriptions of essential antibiotics (%)	11.8%	1.0%	55.5%	>10%	68.9
PI 11 Prescription of highly-restricted antibiotics (%)	0.6%	0.0%	7.8%	<5%	20.3
PI 12 Seasonal variation of total antibiotic prescriptions (%)	7.8%	−25.4%	375.0%	<10%	58.3
PI 13 Seasonal variation of quinolone prescriptions (%)	2.0%	0.1%	18.2%	<2.5%	69.3
PI 14 First-line antibiotics prescriptions against acute URTIs (%)	3.6%	0.1%	17.0%	>70%	3.6
PI 15 First-line antibiotics prescriptions for acute bacterial otitis media (%)	3.5%	0.0%	18.0%	>60%	3.5
PI 16 First-line antibiotics prescriptions for acute bacterial rhinosinusitis (%)	3.6%	0.0%	17.4%	>70%	3.5
PI 17 First-line antibiotics prescriptions for acute bacterial pharyngitis/tonsillitis (%)	3.6%	0.1%	18.3%	>70%	3.6
PI 18 Antibiotic prescriptions without indication (%)	0.6%	0.0%	7.2%	<1%	25.1

Abbreviations: PHI, primary healthcare institution; PI, proxy indicator; NSAID, non-steroidal anti-inflammatory drug; URTI, upper respiratory tract infection.

Table 3: **Performance of the 18 proxy indicators calculated at primary healthcare institution level (n = 269 PHIs).**

Proxy indicator	Target value	Cluster 1[a] N = 72 PHIs appropriateness score[d] 15.38% (10.83%, 16.67%)	Cluster 2[b] N = 159 PHIs appropriateness score 27.78% (23.58%, 31.25%)	Cluster 3[c] N = 38 PHIs appropriateness score 41.18% (38.89%, 50.00%)
		Performance: % of PHIs reached the target		
PI 1 Prescriptions of quinolones (%)	20–40%	1.6	4.5	0.0
PI 2 Prescriptions of cephalosporins (%)	20–40%	20.3	22.6	21.6
PI 3 Prescriptions of aminoglycosides (%)	<5%	10.6	32.7	41.7
PI 4 Co-prescription of antibiotic with systemic corticosteroids (%)	<5%	17.9	38.0	68.8
PI 5 Co-prescription of antibiotic with systemic NSAIDs (%)	<5%	17.2	58.8	92.1
PI 6 Duration of antibiotic prescriptions against acute URTIs >10 days (%)	<15%	15.9	25.6	32.4
PI 7 Contraindications of antibiotic prescriptions (%)	<5%	7.9	36.1	73.7
PI 8 Prescriptions of narrow-spectrum antibiotics (%)	>20%	3.6	8.2	8.1
PI 9 Amoxicillin/broad-spectrum antibiotics (ratio)	0.2–0.4	3.8	21.5	36.1
PI 10 Prescriptions of essential antibiotics (%)	>10%	40.0	75.0	97.4
PI 11 Prescription of highly-restricted antibiotics (%)	<5%	5.7	22.0	35.5
PI 12 Seasonal variation of total antibiotic prescriptions (%)	<10%	18.2	69.6	86.8
PI 13 Seasonal variation of quinolone prescriptions (%)	<2.5%	66.2	69.5	71.1
PI 14 First-line antibiotics prescriptions against acute URTIs (%)	>70%	0.0	0.7	21.6
PI 15 First-line antibiotics prescriptions for acute bacterial otitis media (%)	>60%	0.0	0.6	21.1
PI 16 First-line antibiotics prescriptions for acute bacterial rhinosinusitis (%)	>70%	0.0	0.6	21.1
PI 17 First-line antibiotics prescriptions for acute bacterial pharyngitis/ tonsillitis (%)	>70%	0.0	0.6	21.1
PI 18 Antibiotic prescriptions without indication (%)	<1%	5.9	22.6	58.3

Abbreviations: PHI, primary healthcare institution; PI, proxy indicator; NSAID, non-steroidal anti-inflammatory drug; URTI, upper respiratory tract infection. [a]The PHIs that reached 0–3 PIs' target were grouped into cluster 1. [b]The PHIs that reached 4–6 PIs' target were grouped into cluster 2. [c]The PHIs that reached 7–11 PIs' target were grouped into cluster 3. [d]The appropriateness score is expressed as a percentage, displayed using medians (1st quartile; 3rd quartile) and calculated as [(number of PIs applicable for each PHI and for whom the acceptable target is reached)/(number of PIs applicable for each PHI)] × 100.

Table 4: **Description of the three clusters reflecting the appropriateness of antibiotic prescriptions and their performances for the 18 proxy indicators (n = 269 PHIs).**

Notably, none of the 72 PHIs in cluster 1 reached the targets set for PI 14–PI 17, which pertained to the percentage of first–line antibiotic prescriptions. Within cluster 3, PI 1 (prescriptions of quinolones) was the only PI that all 38 PHIs did not meet the target. Almost all PHIs (97.4%) in cluster 3 met the target of PI 10 (prescriptions of essential antibiotics). Furthermore, 92.1% and 86.8% of PHIs in cluster 3 reached the target of PI 5 (Co–prescription of antibiotic with systemic NSAIDs) and PI 12 (seasonal variation of total antibiotic prescriptions), respectively. Additionally, the difference of performances between the clusters was greater than 10% in most PIs other than PI 1 (prescriptions of quinolones), PI 2 (prescriptions of cephalosporins), PI 6 (duration of antibiotic prescriptions against acute URTIs >10 days), PI 8 (prescriptions of narrow–spectrum antibiotics), and PI 13 (seasonal variation of quinolone prescriptions).

Factors of antibiotic prescription appropriateness

Table 5 provided the comparative results of PHIs' characteristics among the three clusters. There were no significant differences in the characteristics of all PHIs' characteristics (urban or rural areas, region, economic status, percentages of patients' gender and age) across the three clusters.

Fig. 2 illustrated the findings from the ordinal logistic regression analysis investigating factors influencing the appropriateness of antibiotic prescriptions. Percentages of patients' gender considered in the model showed significant associations with the clusters. Specifically, after adjusting for other factors, PHIs in the cluster with better practices prescribed antibiotics to a higher proportion of male patients compared to those in the cluster with poorer practices. (OR = 1.04, P = 0.042).

Discussion

In summary, our study introduced 18 PIs aimed at evaluating the appropriateness of antibiotic use in China's PHIs, displaying favorable clinimetric properties derived from nationwide outpatient prescription data. However, the performance scores of these PIs at the PHI level exhibited variability and suboptimal outcomes. Moreover, the appropriateness of antibiotic prescriptions could be associated with percentages of patients' gender of PHIs.

To assess the antibiotic prescription appropriateness using prescription data without clinical indication,

PHIs' characteristics	Cluster 1 N = 72	Cluster 2 N = 159	Cluster 3 N = 38	P–value
	n (%)	n (%)	n (%)	
Area				
Urban	21 (29.2)	30 (18.9)	6 (15.8)	0.141
Rural	51 (70.8)	129 (81.1)	32 (84.2)	
Region				
East	23 (31.9)	48 (30.2)	8 (21.1)	0.672
Central	40 (55.6)	86 (54.1)	22 (57.9)	
West	9 (12.5)	25 (15.7)	8 (21.1)	
Economic status				
Low	19 (26.4)	21 (13.2)	10 (26.3)	0.100
Middle low	19 (26.4)	34 (21.4)	6 (15.8)	
Middle high	11 (15.3)	41 (25.8)	8 (21.1)	
High	23 (31.9)	63 (39.6)	14 (36.8)	
Patients' characteristics	**Cluster 1 N = 72**	**Cluster 2 N = 159**	**Cluster 3 N = 38**	**P–value**
	Median (1st quartile; 3rd quartile)	Median (1st quartile; 3rd quartile)	Median (1st quartile; 3rd quartile)	
Gender				
% of male patients	49.2 (45.8, 52.8)	50.1 (47.1, 54.0)	52.5 (48.6, 56.5)	0.468
% of female patients	50.3 (47.1, 53.5)	49.3 (44.9, 52.4)	47.1 (42.3, 50.8)	0.468
% of unknown–gender patients	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.677
Age				
% of patients < 5 years old	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.730
% of patients aged 6–17	6.7 (0.9, 13.4)	7.6 (3.3, 13.5)	7.8 (4.2, 16.6)	0.503
% of patients aged 18–44	8.1 (2.7, 12.7)	9.4 (4.5, 12.8)	11.4 (5.9, 16.2)	0.509
% of patients aged 45–64	14.3 (9.0, 20.3)	19.3 (13.8, 26.4)	18.9 (15.0, 25.8)	0.468
% of patients ≥65 years old	31.9 (25.5, 36.2)	30.8 (27.2, 35.7)	30.0 (25.8, 35.0)	0.468
% of unknown–age patients	32.4 (22.8, 41.0)	25.0 (19.9, 34.1)	22.9 (16.8, 31.2)	0.468

Abbreviation: PHI, primary healthcare institution.

Table 5: **Description of characteristics of Primary Healthcare Institutions and patients for the three identified clusters (n = 269 PHIs).**

		Odds ratio (95% CI)	p Value
Area	Urban	1·00 (reference)	
	Rural	1.64(0.88;3.05)	1.121
Region	East	1·00 (reference)	
	Central	1.01(0.53;1.90)	0.984
	West	2.00(0.91;4.39)	0.084
Economic Status	Low	1·00 (reference)	
	Middle Low	1.05(0.48;2.28)	0.911
	Middle High	1.71(0.80;3.68)	0.167
	High	1.49(0.72;3.11)	0.283
Gender	% of male patients	1.04(1.00;1.09)	0.042
Age	% of patients over 65	0.97(0.95;1.00)	0.083

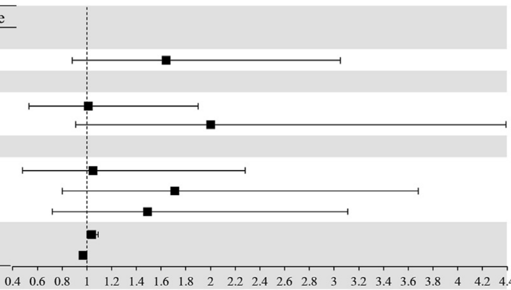

Fig. 2: **The factors of antibiotic prescription appropriateness—ordinal logistic regression analysis (n = 269 PHIs)**. Abbreviation: PHI, primary healthcare institution.

Thilly et al. pioneered and introduced 10 PIs among French general practitioners.[8] Several French PIs resembled our study's findings, such as seasonal variations in total antibiotic and quinolone prescriptions, antibiotic use without clear indications, and co–prescriptions with non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids. However, while French PIs mainly addressed urinary tract infections, ours focused on acute upper respiratory tract infections (URTIs), bacterial otitis media, rhinosinusitis, and pharyngitis/tonsillitis (PI 6 and PI 14–PI 17). In China's primary care, antibiotics were frequently used for acute respiratory tract infections, otitis media, and bronchitis,[10,20] despite many cases not requiring antibiotics.[13,15–18,21] It was crucial to measure the clinimetric properties of the PIs before their application, ensuring their relevance and utility in specific context. Our study found all 18 PIs had measurable, applicable aspects, but also substantial room for improvement, indicating suboptimal performance across the PHIs. PI 11 (Prescription of highly-restricted antibiotics) and PI 18 (Antibiotic prescriptions without indication) demonstrated larger variations. The variation of applicability for PI 11 could be attributed to imbalanced implementation of regulatory measures limiting highly restricted antibiotics in PHIs mandated by the National Health Commission.[22] Similarly, the uneven implementation of the prescription review and feedback (PRF) policy might contribute to the variability of applicability for PI 18. Regions with well–resourced settings where the PRF policy was effectively implemented tended to use antibiotics more appropriately.[23] While regional differences in medicine supply and restriction lists may contribute to variations, especially considering that antibiotic restriction lists are developed provincially,[24] their effect might be limited. Since the implementation of the essential medicines system in 2009, all government–organized PHIs are mandated to utilize essential medicines.[25] Additionally, most first–line medications recommended by primary care infectious diseases guidelines are included in the list, providing guidance for antibiotic selection for common infectious diseases at the primary care level. Moreover, the lack of essential diagnoses may also contribute to the variation, particularly for PI 14–PI 17. However, China's prescription regulations mandate the inclusion of diagnoses in the information system, ensuring that necessary diagnostic information is available. Therefore, the impact of lacking essential diagnoses in information systems (for PI 14–PI 17) is limited.

The performance evaluation of PIs showed that the percentage of prescriptions of essential antibiotics and seasonal variation of quinolone prescriptions displayed comparatively better results than other PIs in our study. The higher usage of essential antibiotics could be linked to the extensive availability of essential medicines in China's healthcare system. Notably, our study revealed a higher performance (69.3%) for seasonal variation of quinolone prescriptions in PHIs in China compared to French setting (38.2%),[8] indicating potentially more appropriate seasonal usage of quinolone in China than in French. However, challenges remained with the excessive use of broad–spectrum formulations and unnecessary antibiotic prescriptions for URTIs. We observed the worst performance in the percentage of quinolones prescriptions (3.1%). The widespread use of quinolones in China might be driven by the mandatory requirement for patients to undergo a skin test before prescribing oral or injectable penicillin prescriptions, creating inconvenience and yielding unreliable results. This could deter primary care clinicians from prescribing penicillins in their clinical practice.[26] Furthermore, five PIs (PI 8, 14–17) exhibited performances below 10%, suggesting that the primary issue with irrational antibiotic prescriptions in China's PHIs was antibiotic selection for URTIs. In line with these observations, a study conducted by our colleagues revealed that diseases such as URTIs, acute bacterial otitis media, acute bacterial rhinosinusitis, and acute bacterial pharyngitis/tonsillitis were most commonly treated with broad–spectrum antibiotics instead of the narrow–spectrum ones recommended in the guidelines.[27] Additionally, another study by our colleagues found that prescription rate of quinolones for acute bronchitis in PHIs in China was approximately 7.2%, falling outside our target range of 20%–40%.[28] Therefore, the indicators indicating that over 90% of PHIs failed to meet the targets were consistent with findings from other studies. These collective findings emphasized the need for heightened attention from the Chinese government and PHIs toward antibiotic selection for these specific diseases in the future.

The grouping results demonstrated that the majority (59.1%) of PHIs fell into cluster 2 (average practices), illustrating the centralized distribution of the PHIs' practices. The appropriateness scores validated the three clusters can reflect the levels of prescription appropriateness. We found that none of the PHIs in cluster 1 (worse than average practices) reached the targets set for percentage of first–line antibiotic prescriptions, highlighting significant issues with guideline compliance for the PHIs in cluster 1. Importantly, even within cluster 3 (better than average practices), none of the PHIs met the target for PI 1 (prescriptions of quinolones), revealing an urgent need to address quinolone abuse across primary care settings in China. Additionally, there was a substantial variability of over 10% in the performances between the clusters across most PIs, except for PI 1, PI 2, PI 6, PI 8, and PI 13. This variability was consistent with the diverse performances observed among the PIs before the grouping. Interestingly, we observed that clusters 1 & 2 had a higher frequency of prescriptions associated with the four diagnoses (acute URTIs, acute bacterial otitis media, acute bacterial rhinosinusitis, acute bacterial pharyngitis/tonsillitis) compared to cluster 3. Thus, the elevated scores of cluster 3 for PI 14–PI 17 cannot be attributed to more comprehensive diagnoses. Instead, they indicate variability in the appropriateness of antibiotic prescribing practices across the PHIs.

Our findings aligned with a body of existing research that highlighted various factors influencing antibiotic prescriptions. Pandolfo et al. revealed that diagnostic uncertainty complicated antibiotic overuse, as clinicians often lean toward antibiotic prescriptions due to safety concerns for both patients and themselves, fearing potential adverse outcomes.[29] Wang et al. identified factors contributing to high antibiotic usage, including inadequate knowledge, resistance to change, complacency with satisfied patients, low household income, and rural areas.[30] Other studies also delved into factors impacting the appropriateness of antibiotic prescriptions.[31–34] These encompassed physicians' educational background, practice volume, years of experience, age, pharmaceutical expenses per patient, training exposure, as well as patients' age, gender, comorbidities. Interestingly, in concurrence with our study, patients' gender emerged as a significant factor associated with the appropriateness of antibiotic prescriptions.[34]

Since the health system reform in 2009, China has placed significant emphasis on antibiotic regulation by enhancing national AMS efforts and instituting the National Essential Medicines System. Although the reform effectively reduced antimicrobial consumption in tertiary hospitals, the restructuring of drug policies did not address the persistent issue of antibiotic overuse in primary care and rural areas.[9] Moreover, PHIs were not covered by China Antimicrobial Resistance Surveillance System, despite accounting for 94.84% of medical institutions and providing basic clinical care and public health services to 50.17% of the population.[35] Therefore, the development and utilization of PIs in the study offer a scalable solution with ensured measurement accuracy. The annually calculated appropriateness scores can be compared horizontally among PHIs and vertically within them, enabling the identification of problems in antibiotics prescribing practices. A comprehensive assessment of target achievement, the impact on bacterial resistance, and the effectiveness of diverse incentives would offer invaluable insights. Vigilance regarding potential unintended repercussions of reduced antibiotic prescribing is imperative and necessitating ongoing monitoring and documentation. The amalgamation of such endeavors could fortify the evidential base and facilitate the establishment of pertinent future objectives.

Limitations

The study had several limitations. Firstly, despite our comprehensive search across PubMed, Embase, Web of Science Core Collection, and authoritative websites, the exclusion of grey literature and non–English–language sources might have impacted the comprehensiveness of our findings. However, within the study's defined scope, we meticulously incorporated all publicly available information regarding QIs and PIs, ensuring the solidity of our findings. Secondly, while we meticulously composed an expert panel by considering factors like age, years of practice, title, and expertise, the panel's composition might have influenced both the development of PIs and the assessment of antibiotic prescriptions. Thirdly, our retrospective data collection limited our access to crucial information that could influence antibiotic prescription, such as clinicians' characteristics, knowledge, and patient socio–economic characteristics details. Additionally, the applicability of our PIs might be confined to our study setting only and might not be transferable to other regions within China or foreign countries due to potential variations in clinimetric properties. However, the methodology adopted in the study could be replicated in other settings. Finally, the absence of case–mix stability analysis, owing to data limitation, was a noteworthy limitation.

Conclusions

The study developed 18 PIs with favorable clinimetric properties for China's primary care context to evaluate antibiotic prescription appropriateness. The varied and suboptimal performance of the PIs indicated the need for diverse efforts to enhance the rational antibiotic use at PHI level. The appropriateness of antibiotic prescriptions was significantly associated with percentages of patients' gender of the PHIs. These collective findings underscore the necessity of devising distinct sets of PIs for diverse settings in future endeavors.

Contributors

Conceptualisation of the study: H.W., J.Y., and X.G.; Data curation: K.D., B.Z., and L.S.; Formal analysis: K.D., B.Z., and L.S.; Funding acquisition: L.S. and H.W.; Investigation: J.Y., W.K., W.L., K.Z., and S.C.; Methodology: H.W., J.Y., and K.D.; Project administration: H.W.; Resources: L.S., X.G., B.Z., and H.W.; Software: J.Y. and K.D.; Supervision: X.G.; Validation: H.W. and X.G.; Visualisation: J.Y.; Writing—original draft: H.W. and J.Y.; Writing—review & editing: L.S. and X.G.; H.W., K.D., and L.S. have directly accessed and verified the underlying data reported in the manuscript; H.W. and J.Y. contributed equally to this work. X.G. was responsible for the decision to submit the manuscript.

Data sharing statement

Data collected for the study including individual participant data and a data dictionary defining each field in the set will not be made available to others. The raw prescription level data used to generate the results cannot be shared publicly because of the associated legislation. The datasets used and analysed in the study are available from the corresponding author on reasonable request.

Declaration of interests

The authors declare no conflicts of interest.

Acknowledgements

This work was supported by the National Natural Science Foundation of China (grant numbers 72374009, 81973294). The funding source had no involvement in the manuscript. All authors were not precluded from accessing data in the study, and they accept responsibility to submit for publication.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2024.101132.

References

1 Adjei A, Kukula V, Narh CT, et al. Impact of point-of-care rapid diagnostic tests on antibiotic prescription among patients aged <18 years in primary healthcare settings in 2 peri-urban districts in Ghana: randomized controlled trial results. *Clin Infect Dis*. 2023;77:S145–S155. https://doi.org/10.1093/cid/ciad328.

2 World Health Organization. How to investigate drug use in health facilities: selected drug use indicators. https://www.who.int/publications–detail–redirect/who–dap–93.1. Accessed December 15, 2023.

3 Berrevoets MAH, Ten Oever J, Oerlemans AJM, Kullberg BJ, Hulscher ME, Schouten JA. Quality indicators for appropriate outpatient parenteral antimicrobial therapy in adults: a systematic review and RAND-modified Delphi procedure. *Clin Infect Dis*. 2020;70:1075–1082. https://doi.org/10.1093/cid/ciz362.

4 van den Bosch CMA, Hulscher MEJL, Natsch S, Wille J, Prins JM, Geerlings SE. Applicability of generic quality indicators for appropriate antibiotic use in daily hospital practice: a cross-sectional point-prevalence multicenter study. *Clin Microbiol Infect*. 2016;22:888.e1–888.e9. https://doi.org/10.1016/j.cmi.2016.07.011.

5 van den Bosch CMA, Geerlings SE, Natsch S, Prins JM, Hulscher MEJL. Quality indicators to measure appropriate antibiotic use in hospitalized adults. *Clin Infect Dis*. 2015;60:281–291. https://doi.org/10.1093/cid/ciu747.

6 Monnier AA, Schouten J, Le Maréchal M, et al. Quality indicators for responsible antibiotic use in the inpatient setting: a systematic review followed by an international multidisciplinary consensus procedure. *J Antimicrob Chemother*. 2018;73:vi30–v39. https://doi.org/10.1093/jac/dky116.

7 Howard P, Huttner B, Beovic B, et al. ESGAP inventory of target indicators assessing antibiotic prescriptions: a cross-sectional survey. *J Antimicrob Chemother*. 2017;72:2910–2914. https://doi.org/10.1093/jac/dkx243.

8 Thilly N, Pereira O, Schouten J, Hulscher ME, Pulcini C. Proxy indicators to estimate appropriateness of antibiotic prescriptions by general practitioners: a proof-of-concept cross-sectional study based on reimbursement data, north-eastern France 2017. *Euro Surveill*. 2020;25:1900468. https://doi.org/10.2807/1560-7917.ES.2020.25.27.1900468.

9 He P, Sun Q, Shi L, Meng Q. Rational use of antibiotics in the context of China's health system reform. *BMJ*. 2019;365:l4016. https://doi.org/10.1136/bmj.l4016.

10 Fu M, Gong Z, Zhu Y, et al. Inappropriate antibiotic prescribing in primary healthcare facilities in China: a nationwide survey, 2017–2019. *Clin Microbiol Infection*. 2023;29:602–609. https://doi.org/10.1016/j.cmi.2022.11.015.

11 WHO Collaborating Centre for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment. https://www.whocc.no/atc_ddd_index_and_guidelines/guidelines/. Accessed December 10, 2023.

12 Zhao H, Bian J, Wei L, et al. Validation of an algorithm to evaluate the appropriateness of outpatient antibiotic prescribing using big data of Chinese diagnosis text. *BMJ Open*. 2020;10:e031191. https://doi.org/10.1136/bmjopen-2019-031191.

13 National Health Commission of the People's Republic of China. Notification on the issuance of guidelines for clinical use of antibiotics. http://www.nhc.gov.cn/yzygj/s3593/201508/c18e1014de6c45ed9f6f9d592b43db42.shtml. Accessed December 20, 2023.

14 Wang Y, Wilkinson M, Ng E, et al. Primary care reform in China. *Br J Gen Pract*. 2012;62(603):546–547. https://doi.org/10.3399/bjgp12X656946.

15 Expert Group of Guidelines for Rational Medication in Primary Care Institution. Guideline for rational medication of acute tracheobronchitis in primary care. *Chin J Gen Pract*. 2020;19(10):882–890.

16 Expert Group of Guidelines for Rational Medication in Primary Care Institution. Guideline for rational medication of acute upper respiratory tract infection in primary care. *Chin J Gen Pract*. 2020;19(8):689–697.

17 Expert Group of Guidelines for Primary Care of Respiratory System Disease. Guideline for primary care of acute upper respiratory tract infection (2018). *Chin J Gen Pract*. 2019;18(5):422–426.

18 Expert Group of Guidelines for Primary Care of Respiratory System Disease. Guideline for primary care of acute tracheobronchitis (2018). *Chin J Gen Pract*. 2019;18(4):314–317.

19 Campbell SM, Braspenning J, Hutchinson A, Marshall M. Research methods used in developing and applying quality indicators in primary care. *Qual Saf Health Care*. 2002;11:358–364. https://doi.org/10.1136/qhc.11.4.358.

20 Taxifulati Y, Wushouer H, Fu M, et al. Antibiotic use and irrational antibiotic prescriptions in 66 primary healthcare institutions in Beijing City, China, 2015–2018. *BMC Health Serv Res*. 2021;21:832. https://doi.org/10.1186/s12913-021-06856-9.

21 Tonkin-Crine SK, Tan PS, van Hecke O, et al. Clinician-targeted interventions to influence antibiotic prescribing behaviour for acute respiratory infections in primary care: an overview of systematic reviews. *Cochrane Database Syst Rev*. 2017;9(9):CD012252. https://doi.org/10.1002/14651858.CD012252.pub2.

22 National Health Commission of the People's Republic of China. Administrative measures for the clinical use of antibacterial drugs. http://www.nhc.gov.cn/yzygj/s3593/201205/e5efd852b86c4afa8b09a0e58e09e10e.shtml. Accessed May 6, 2024.

23 Wushouer H, Du K, Chen S, et al. Evaluation of prescription review and feedback policy on rational antibiotic use in primary healthcare settings in Beijing, China: a qualitative study using the theoretical domains framework and the behaviour change wheel. *JAC Antimicrob Resist*. 2023;5(6):dlad128. https://doi.org/10.1093/jacamr/dlad128.

24 Wushouer H, Yang Y, Deng Y, Zheng B, Shi L, Guan X. A comparative study of antibiotic use in China under Chinese restriction list and world health organization AWaRe classification. *Clin Microbiol Infect*. 2023;29(4):545–547. https://doi.org/10.1016/j.cmi.2022.12.011.

25 National Health Commission of the People's Republic of China. Notification on the issuance of the management of the national essential medicines list (NEML). http://www.nhc.gov.cn/yaozs/s3581/201504/8147002103b741179217eced1ad77efc.shtml. Accessed April 29, 2024.

26 Jiang Z, Zhang H, Xiao H, Xiao X, Meng J. Negative impact of penicillin allergy labels on antibiotic use in hospitalized patients in Chinese Mainland. *World Allergy Organ J*. 2022;15:100677. https://doi.org/10.1016/j.waojou.2022.100677.

27 Fu M, Gong Z, Li C, et al. Appropriate use of antibiotics for acute respiratory infections at primary healthcare facilities in China: a nationwide cross-sectional study from 2017 to 2019. *Lancet Reg Health West Pac*. 2023;40:100880. https://doi.org/10.1016/j.lanwpc.2023.100880.

28 Fu M, Wushouer H, Hu L, et al. Outpatient prescribing pattern for acute bronchitis in primary healthcare settings in China. *NPJ Prim Care Respir Med*. 2021;31(1):24. https://doi.org/10.1038/s41533-021-00234-y.

29 Pandolfo AM, Horne R, Jani Y, et al. Understanding decisions about antibiotic prescribing in ICU: an application of the necessity concerns framework. *BMJ Qual Saf*. 2022;31:199–210. https://doi.org/10.1136/bmjqs-2020-012479.

30 Wang D, Liu C, Zhang X, Liu C. Identifying antibiotic prescribing patterns through multi-level latent profile analyses: a cross-sectional survey of primary care physicians. *Front Pharmacol*. 2020;11:591709. https://doi.org/10.3389/fphar.2020.591709.

31 Degnan KO, Cluzet V, David MZ, et al. Development and validation of antibiotic stewardship metrics for outpatient respiratory tract diagnoses and association of provider characteristics with inappropriate prescribing. *Infect Control Hosp Epidemiol*. 2022;43:56–63. https://doi.org/10.1017/ice.2021.44.

32 Cadieux G, Tamblyn R, Dauphinee D, Libman M. Predictors of inappropriate antibiotic prescribing among primary care physicians. *CMAJ*. 2007;177:877–883. https://doi.org/10.1503/cmaj.070151.

33 Pulcini C, Lions C, Ventelou B, Verger P. Approaching the quality of antibiotic prescriptions in primary care using reimbursement data. *Eur J Clin Microbiol Infect Dis*. 2013;32:325–332. https://doi.org/10.1007/s10096-012-1743-2.

34 Nowakowska M, van Staa T, Mölter A, et al. Antibiotic choice in UK general practice: rates and drivers of potentially inappropriate antibiotic prescribing. *J Antimicrob Chemother*. 2019;74:3371–3378. https://doi.org/10.1093/jac/dkz345.

35 National Health Commission of the People's Republic of China. *China health statistics yearbook*; 2022. http://www.nhc.gov.cn/mohwsbwstjxxzx/tjtjnj/202305/6ef68aac6bd14c1eb9375e01a0faa1fb.shtml. Accessed April 16, 2024.