Assessment of non-prescription antibiotic dispensing at community pharmacies in China with simulated clients: a mixed cross-sectional and longitudinal study

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Summary

Background Non-prescription dispensing of antibiotics at community pharmacies is a major driver of antimicrobial resistance. China has regarded curbing non-prescription sales of antibiotics at community pharmacies as an important task for tackling antibiotics resistance and planned to eliminate this practice nationwide before 2020. We aimed to quantify non-prescription dispensing of antibiotics cross-sectionally at community pharmacies in China in 2017, and longitudinally (2011–17) in a single province.

Methods A simulated client method was used to measure non-prescription antibiotic dispensing based on scenarios about paediatric diarrhoea and adult acute upper respiratory tract infection (URTI), which were presented at each pharmacy. We collected cross-sectional data for 2423 community pharmacies from 221 counties or districts in six provinces in different regions of China, in 2017. We also assessed 213 community pharmacies in Shaanxi province with a baseline survey in 2011 and subsequent follow-up surveys every 2 years until 2017. In the cross-sectional analysis, multivariate binary logistic regression with random-intercepts was used to evaluate the factors associated with non-prescription dispensing of antibiotics. We also estimated unadjusted period effects of non-prescription antibiotic dispensing using generalised estimated equations.

Findings After excluding invalid interactions within 12 community pharmacies, the study included 4822 simulated interactions within 2411 community pharmacies. Non-prescription antibiotic dispensing was observed during 1169 (48·5% [95% CI 46·5–50·5]) of 2411 diarrhoea interactions and 1690 (70·1% [68·2–71·9]) of 2411 adult URTI interactions. Non-prescription antibiotic dispensing was more prevalent in rural areas and the central and western provinces, and was negatively associated with the presence of a pharmacist on-site (odds ratio 0·66 [0·56–0·78], p<0·0001) and being part of a chain pharmacy (0·75 [0·62–0·89], p=0·0012). In Shaanxi province, significant decreases of non-prescription antibiotic dispensing occurred in paediatric cases (from 154 [72·3%] of 213 community pharmacies to 107 [50·2%], p<0·0001) and adult cases (from 204 [95·8%] to 148 [69·5%], p<0·0001) between 2011 and 2017.

Interpretation Non-prescription dispensing of antibiotics at community pharmacies was still prevalent nationwide in China in 2017, although a decrease was observed in Shaanxi Province since 2011. Multifaceted measures, including regulatory interventions, professional training, and public health education are needed.

Funding Young Talent Support Plan and High Achiever Plan of Health Science Center, Xi'an Jiaotong University, Central University Basic Research Fund, Early Career Research Start-up Plan of Xi'an Jiaotong University.

Introduction

Antimicrobial resistance is a global public health emergency.[1] The inappropriate use of antibiotics is a major driver of antimicrobial resistance,[2,3] and leads to other adverse effects, including unnecessary costs, avoidable adverse outcomes, and masking of underlying infectious processes.[3–5] Indiscriminate dispensing of antibiotics without a diagnosis and a medical prescription in community settings, which is largely associated with unnecessary use, incomplete or short treatment courses, and inappropriate dose choice,[5] is still prevalent in many parts of the world,[5] and global action is needed urgently to tackle this problem.

Most community pharmacies are conveniently located for consumers, and they play an important role to facilitate timely access of treatment in low-income settings, where access to basic primary health care is poor.[6] However, in most countries where access to basic diagnosis and treatments are generally guaranteed, non-prescription antibiotics is a major problem, because they can be sold in community pharmacies in the absence of a proven or strongly suspected bacterial infection indication. Non-prescription antibiotic dispensing at community pharmacies in many countries outside northern Europe and North America is mainly because of lax regulatory practices, unavailability of qualified pharmacists, and insufficient knowledge regarding

Research in context

Evidence before this study
We searched PubMed and Google Scholar, from database inception until Nov 1, 2018, using the terms: "simulated client" ("mystery shoppers", "standardised patients", "fake patients" or "simulated patients"), "pharmacy" ("pharmacist" or "chemist"), and "antibiotic" ("antimicrobial" or "antibacterial"), with and without the keyword "China". Only articles published in English were considered. Several studies in Asia, Africa, Central and South America, and southern Europe had used the simulated client method to assess non-prescription dispensing of antibiotics at community pharmacies. They generally showed the easy access to antibiotics without a prescription. However, evidence about temporal or geographical patterns in non-prescription antibiotics dispensing at community pharmacies are insufficient, and few studies of the factors associated with the dispensing have been reported. In China, only one study was available; it was a survey from three cities in 2015, which showed high numbers of antibiotic dispensing without a prescription. The Chinese government plans to eliminate non-prescription antibiotic sales at community pharmacies before 2020. More evidence is needed for public efforts aimed at achieving this goal.

Added value of this study
We found that non-prescription dispensing of antibiotics at community pharmacies was still prevalent nationwide in China in 2017, although a decrease was observed in Shaanxi province since 2011.

Implications of all the available evidence
Our findings point to the need for further public stewardship measures, not only to control non-prescription antibiotic sales, but also to improve the quality of service at community pharmacies. These findings can inform policy makers in China designing concrete strategies to achieve the 2020 goal of eliminating non-prescription antibiotic dispensing at community pharmacies, as well as other countries that have similar problems. Eliminating non-prescription antibiotic dispensing at community pharmacies will be impossible without timely multifaceted interventions, including stricter regulation, better enforcement of existing regulation, staff training, public education, and surveillance.

antibiotics among pharmacy staff.[5,7–9] Previous studies have also identified that community pharmacies are essential sources for self-determined use of these medicines.[10–13]

China is one of these countries. Despite having a prescription-only regulation on antibiotic sales, our previous observational study showed that antibiotics could be obtained without prescription at more than half of community pharmacies in urban China when common conditions, without an indication of bacterial infections, were simulated.[14] Chinese authorities are determined to change this situation. In response to China's rapid increase both in antibiotic consumption and antibiotic resistance in the past two decades,[15,16] the Chinese government issued a 5-year national action plan in 2016 to improve rational use of antibiotics and contain resistance.[17] This agenda listed curbing non-prescription sales of antibiotics at community pharmacies as a goal and planned to eliminate this problem by 2020.[17]

There are nearly 0·5 million community pharmacies across China,[18] providing both prescription-only medicines and over-the-counter products. In this study, using simulated clients based on two common medical indications in primary health care (ie, paediatric diarrhoea and adult upper respiratory tract infection [URTI]), we studied non-prescription dispensing of antibiotics at community pharmacies and evaluated the quality of pharmacy services both cross-sectionally in a sample of community pharmacies from six provinces in different regions of China in 2017 and longitudinally in a single province from 2011 to 2017.

Methods
Study design, and pharmacy and simulated clients selection
We used the simulated client method in a cross-sectional sample of 2423 community pharmacies selected from 221 county-level (rural) and district-level (urban) regions in mainland China, in 2017. Six of 31 provincial-level regions in mainland China were surveyed—namely, Shandong, Zhejiang, Henan, Hunan, Shaanxi, and Sichuan. These provinces were purposely selected to cover diverse characteristics of geographical location (eastern, central, and western China), socioeconomic status (high, middle, and low gross domestic product per capita), the density of community pharmacies, and prevalence of self-medication. More details regarding the sampling of the national cross-sectional survey are given in the appendix (pp 2–11).

We also studied 213 community pharmacies representing community pharmacies in Shaanxi province with a baseline survey in 2011 and subsequent surveys every 2 years until 2017. Shaanxi province is ranked mid-level in gross domestic product per capita among the 31 provincial regions in China[19] and is broadly representative of the typical population health condition and health system status in China.[20] More details regarding the sampling of the community pharmacy panel are given in appendix (p 12, 13).

48 medical students from Xi'an Jiaotong University were recruited as simulated clients (28 women and 20 men, aged 19–25 years; appendix pp 18, 19). Each simulated client was assigned to present the same scenario. They were grouped into fixed pairs to visit the

surveyed community pharmacies, with one who portrayed paediatric diarrhoea, and the other presenting adult URTI (ie, each pharmacy was visited twice by different simulated clients presenting different scenarios). There was an approximately 25-min interval between the two visits to each surveyed pharmacy, and the sequence of the two visits was randomly assigned (using the Excel's random number generator).

The study was approved by the Ethics Committee for Medical Research of Xi'an Jiaotong University. Given that we used the simulated client method, the committee permitted a waiver of informed consent from pharmacies.

Procedures

Two different simulated scenarios were designed—namely, paediatric diarrhoea and adult URTI, because they are the most common disease symptoms associated with antibiotics misuse in both household self-medication and primary health institution settings worldwide and in China,[11–13,21,22] and also the two most used conditions in previous studies of this type.[7,8] The visiting process, transcripts of the presentation of symptoms, and pre-determined answers to specific questions likely to be asked by pharmacy staff have been described previously,[14] and are shown in the appendix (pp 14, 15). Both the visiting process and transcripts of presentations were tested and modified in a pilot survey, outside of the study sample and before the initial survey round. Third-person scenarios[23] were used because of their suitability for China's community pharmacy settings. The simulated clients trained for the paediatric diarrhoea scenario presented as caregivers of a 5-year-old child with diarrhoea who were seeking medicines from the pharmacy. The simulated clients trained for the adult URTI scenario presented as friends of a 20-year-old male college student with URTI symptoms.

Simulated clients used three levels of demand sequentially until an antibiotic was either dispensed or refused:[24] "Can you give me some medicine to alleviate the patient's symptoms?" (level 1); "Can you give me some antibiotics?" (level 2); and "I would like some amoxicillin or cephalosporins" (level 3). This approach enabled us to assess the relative importance of inappropriate antibiotic dispensing arising from the supply side (level 1) versus the demand side (levels 2 and 3). Amoxicillin and cephalosporins were requested because they are among the most known and used (in primary health care) among the general public in China, and, hence, unlikely to cause suspicion by pharmacy staff. Our data (shown in appendix pp 20, 21) about the pattern of dispensed antibiotics under demand level 1 and 2 also confirmed this fact. After each visit, simulated clients immediately completed a data collection form out of sight of the pharmacy staff (appendix pp 16, 17).

To obtain maximum standardisation and consistency between the simulations and maximum validity and accuracy of observations, several processes were completed before each survey. First, classroom training for the simulated clients was done by researchers. In this phase, the simulated clients were trained about the visiting process, the presentations (using transcripts), how to observe and make mental notes of the observational items during an interaction, and proper behaviour, dress, and other facts (such as, current regulation on antibiotics sales at community pharmacies in China, history and current situation of China's community pharmacy industry, the most commonly sold antibiotics in China's community pharmacies, the importance of being confident and natural, and the typical reactions of pharmacy staff in response of the simulated presentations). Second, the simulated clients rehearsed with researchers who were familiar with the clinical cases and community pharmacy settings. Third, each simulated client completed joint visits with a paired researcher at six to ten community pharmacies in Xi'an before each survey round (these visits were only used for training purpose and were done outside the sampled pharmacies). During the training visits, a researcher observed the simulated client's performance and checked the accuracy of observation and recall. Problems would be explained and training visits would continue until all mistakes had been corrected.

To identify whether the attending staff was a pharmacist or pharmacy assistant and whether the licensed pharmacist was on duty, simulated clients were trained to observe the photos of the pharmacists registered in each pharmacy that are displayed inside pharmacies and the name tags of the staff. For the few visits where it was not possible to ascertain the presence of a pharmacist by observing, simulated clients asked the staff at the end of the visits. They were also trained to accurately record the observed indicators on the summary form (appendix pp 16, 17) within 15 min after each visit. Each pair of clients had to check the indicators they observed at each pharmacy for inconsistencies and discuss to reach a consensus.

Statistical analysis

The sample size (n=400 for each survey province) was calculated based on previous estimated prevalence (unpublished data; appendix p 2) of non-prescription antibiotic dispensing at community pharmacies. Convenience sampling was done at each administrative level (provincial, prefectural, and county and district level) stratified by regional socioeconomic status and other factors to represent better the national picture.

We analysed each visited pharmacy or each interaction between the simulated client and the pharmacy staff based on diarrhoea or URTI indication. We reported the proportion with 95% CIs for non-prescription dispensing of antibiotics, the presence of a pharmacist, and other indicators of pharmacy behaviour (whether pharmacy staff asked recommended questions and gave medication advice), which reflect the quality of service. The diffe-rences in non-prescription dispensing of antibiotics across provinces and between rural and urban areas were

|	Shaanxi (n=409)	Sichuan (n=407)	Hunan (n=395)	Henan (n=400)	Zhejiang (n=400)	Shandong (n=400)	Total (n=2411)
Pharmacy characteristics							
Size (m²)							
Large (>100)	91 (22·2%)	45 (11·1%)	42 (10·6%)	51 (12·8%)	69 (17·3%)	105 (26·3%)	403 (16·7%)
Middle (50–100)	212 (51·8%)	237 (58·2%)	225 (57·0%)	268 (67·0%)	232 (58·0%)	226 (56·5%)	1400 (58·1%)
Small (<50)	106 (25·9%)	125 (30·7%)	128 (32·4%)	81 (20·3%)	99 (24·8%)	69 (17·3%)	608 (25·2%)
Type							
Independent pharmacy	176 (43·0%)	58 (14·3%)	68 (17·2%)	102 (25·5%)	133 (33·3%)	90 (22·5%)	627 (26·0%)
Chained pharmacy	233 (57·0%)	349 (85·7%)	327 (82·8%)	298 (74·5%)	267 (66·8%)	310 (77·5%)	1784 (74·0%)
Location							
Urban area	128 (31·3%)	161 (39·6%)	165 (41·8%)	170 (42·5%)	183 (45·8%)	180 (45·0%)	987 (40·9%)
Rural area	281 (68·7%)	246 (60·4%)	230 (58·2%)	230 (57·5%)	217 (54·2%)	220 (55·0%)	1424 (59·1%)
Had a licensed pharmacist on duty							
Yes	142 (34·7%)	125 (30·7%)	129 (32·7%)	112 (28·0%)	198 (49·5%)	138 (34·5%)	844 (35·0%)
No	..	..	..	..	..	..	..
Characteristics of respondent pharmacy staff in paediatric diarrhoea case							
Licensed pharmacist							
Yes	61 (14·9%)	90 (22·1%)	60 (15·2%)	47 (11·8%)	136 (34·0%)	93 (23·3%)	487 (20·2%)
No	348 (85·1%)	317 (77·9%)	335 (84·8%)	353 (88·2%)	264 (66·0%)	307 (76·7%)	1924 (79·8%)
Sex							
Male	46 (11·2%)	83 (20·4%)	29 (7·3%)	58 (14·5%)	64 (16·0%)	46 (11·5%)	326 (13·5%)
Female	363 (88·8%)	324 (79·6%)	366 (92·7%)	342 (85·5%)	336 (84·0%)	354 (88·5%)	2085 (86·5%)
Perceived age, years							
<30	47 (11·5%)	99 (24·3%)	73 (18·5%)	66 (16·5%)	76 (19·0%)	85 (21·3%)	446 (18·5%)
30–50	330 (80·7%)	267 (65·6%)	299 (75·7%)	314 (78·5%)	284 (71·0%)	273 (68·3%)	1767 (73·3%)
>50	32 (7·8%)	41 (10·1%)	23 (5·8%)	20 (5·0%)	40 (10·0%)	42 (10·5%)	198 (8·2%)
Characteristics of respondent pharmacy staff in adult URTI case							
Licensed pharmacist							
Yes	63 (15·4%)	85 (20·9%)	59 (14·9%)	38 (9·5%)	126 (31·5%)	64 (16·0%)	435 (18·0%)
No	346 (84·6%)	322 (79·1%)	336 (85·1%)	362 (90·5%)	274 (68·5%)	336 (84·0%)	1976 (82·0%)
Sex							
Male	51 (12·5%)	87 (21·4%)	33 (8·4%)	50 (12·5%)	68 (17·0%)	46 (11·5%)	335 (13·9%)
Female	358 (87·5%)	320 (78·6%)	362 (91·6%)	350 (87·5%)	332 (83·0%)	354 (88·5%)	2076 (86·1%)
Perceived age, years							
<30	57 (13·9%)	66 (16·2%)	65 (16·5%)	39 (9·8%)	69 (17·3%)	82 (20·5%)	378 (15·7%)
30–50	327 (80·0%)	314 (77·2%)	321 (81·3%)	335 (83·8%)	291 (72·8%)	301 (75·3%)	1889 (78·3%)
>50	25 (6·1%)	27 (6·6%)	9 (2·3%)	26 (6·5%)	40 (10·0%)	17 (4·3%)	144 (6·0%)

All data are n (%). URTI=upper respiratory tract infection.

Table 1: Characteristics of the visited community pharmacies in China and respondent pharmacy staff

examined using multivariate binary logistic regression, with random intercepts for each county or district adjusted for pharmacy and pharmacy staff characteristics. We also calculated the proportion of interactions resulting in different types of antibiotics under demand level 1 and 2.

We estimated unadjusted changes in non-prescription antibiotic dispensing in the longitudinal surveys in Shaanxi Province using generalised estimated equations with logit link function and binomial distribution. Sensitivity analysis of a subset of community pharmacies that were included in the panel for all rounds was done to examine the effect of loss to follow-up (appendix pp 26, 27).

To evaluate the factors associated with non-prescription antibiotic dispensing and differences in pharmacy behaviour in the 2017 cross-sectional survey data, we did multivariate binary logistic regressions with random intercepts. The random intercepts at county or district level were included to account for unmeasured region-varying factors, because the lowest level of authority within China's Drug Administration system is the county or district bureau. Analyses were done separately in diarrhoea cases (model 1), URTI cases (model 2), and pooled data of both cases (model 3). Models were further adjusted for fixed effects for simulated clients (appendix pp 28, 29). Model output was reported as odds ratios (ORs) with 95% CIs.
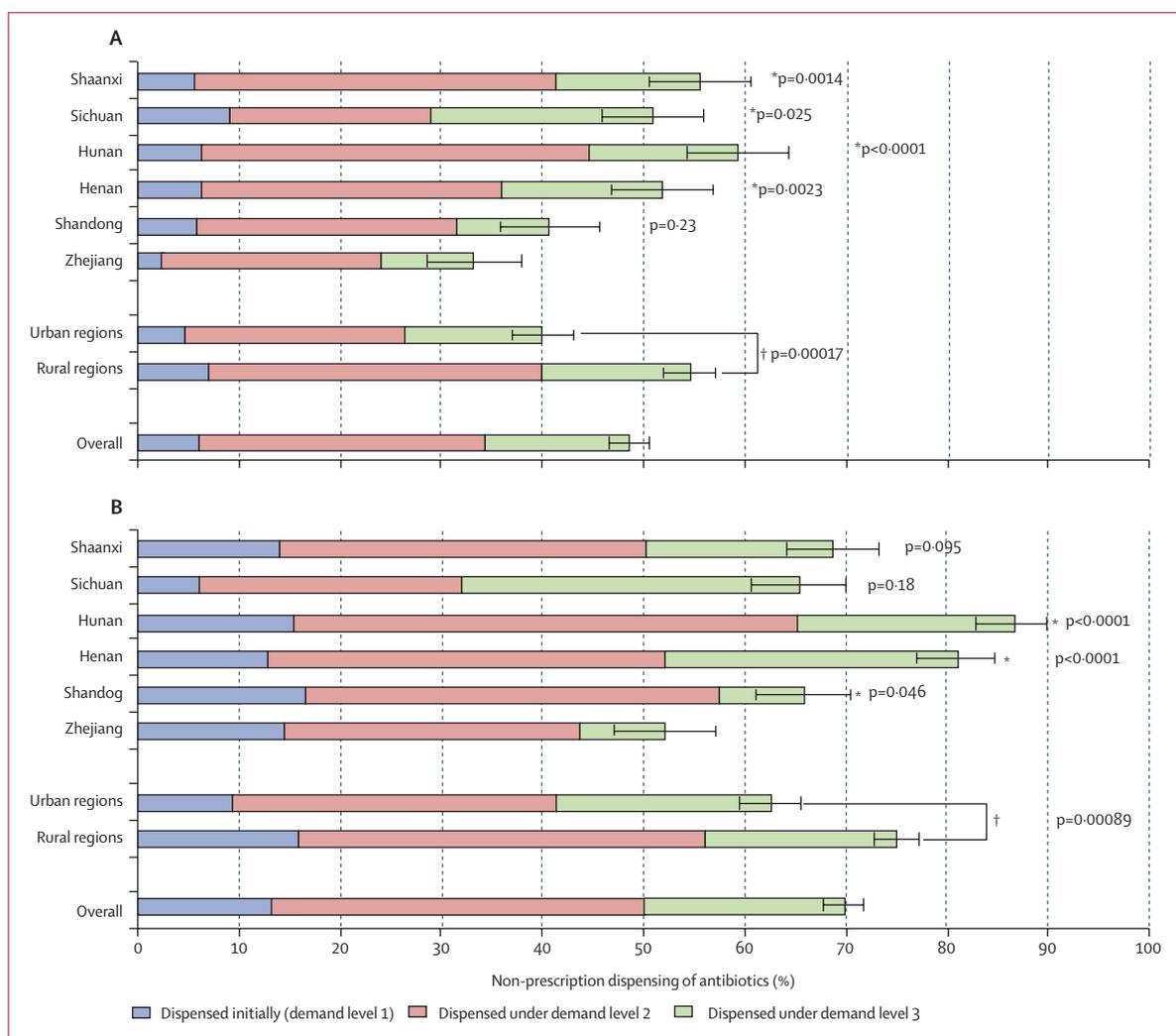
Figure 1: Non-prescription dispensing of antibiotics at community pharmacies across provinces and urban and rural areas in China in 2017
(A) Diarrhoea case. (B) URTI case. Error bars represent 95% CIs. Differences in non-prescription dispensing of antibiotics across provinces and between urban and rural areas have been analysed using the multivariate binary logistic regression with random-intercepts for each county or district and adjusted for covariates (pharmacy type, pharmacy size, whether a pharmacist was on duty, the sex and age of the attending staff, whether a separate counter for antibiotics was available, and whether a prescription-only sign was displayed). The binary dependent variable was whether antibiotics were dispensed without a prescription in an interaction. We did two separate regressions for diarrhoea and URTI, using the same model with same covariates and random-intercepts. *Statistical significance in differences between provinces (with Zhejiang province as a reference, because it had the lowest rate of non-prescription antibiotics). †Statistical significance in differences between urban and rural areas.

In addition, we compared the differences in phar-macy behaviours between chain and independent pharmacies, and between pharmacies with and without a licensed pharmacist on duty. We also applied multivariate binary logistic regression with random intercepts for each county or district. Being a chain pharmacy (versus being independent pharmacy) or having a pharmacist on duty (versus a pharmacist was absent) were the exposure variables, and non-prescription dispensing of antibiotics and other indicators that reflect the high quality of pharmacy services were the outcomes (appendix pp 30, 31). To further explore these gaps in pharmacy practice, we also stratified this analysis by urban and rural areas (appendix pp 32, 33).

Analyses were done using Stata, version 14.0.

Role of the funding source

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

Results

Surveys were done in 2017, from July 3 to July 20 in Hunan; July 8 to July 23 in Sichuan; July 23 to Aug 10 in Zhejiang, Henan, and Shandong; and June 5 to Aug 31 in Shaanxi. Records of interactions within 12 community pharmacies were excluded because a suspicion by the pharmacy staff was reported by a simulated client.

1784 (74·0%) of 2411 pharmacies were chain pharmacies, and 627 (26·0%) were independent pharmacies (table 1). A pharmacist was available at 844 (35·0%) pharmacies during simulated clients' visits but this percentage varied across provinces (table 1); the attending staff was a licensed pharmacist in 487 (20·2%) of 2411 interactions based on a paediatric diarrhoea case and 435 (18·0%) of 2411 interactions based on adult URTI.

Non-prescription dispensing of antibiotics occurred in 1169 (48·5% [95% CI 46·5–50·5]; figure 1) interactions for diarrhoea case and in 1690 (70·1% [68·2–71·9]) interactions for URTI cases. We found significant differences in non-prescription dispensing across provinces and between rural and urban areas (diarrhoea 775 [54·4%; 95% CI 51·8–57·0] of 1424 community pharmacies vs 394 [39·9%; 36·8–43·1] of 987, p=0·00017; URTI 1071 [75·2%; 72·9–77·4] vs 619 [62·7%; 59·6–65·7], p=0·00089; figure 1). Antibiotics were recommended initially in only 142 (5·9% [5·0–6·9]) interactions for

diarrhoea and 321 (13·3% [12·0–14·7]) interactions for URTI; most antibiotic dispensing occurred following the simulated patients' requests: 685 (28·4% [26·6–30·3]) interactions for diarrhoea and 888 (36·8% [34·9–38·8]) interactions for URTI under demand level 2; and 342 (14·2% [12·8–15·6]) interactions of diarrhoea and 481 (20·0% [18·4–21·6]) interactions of URTI under demand level 3. The type of the antibiotics dispensed under demand level 1 and level 2 is shown in the appendix (pp 20, 21).

Non-prescription dispensing of antibiotics in Shaanxi Province has decreased continuously from 2011 to 2017 for both diarrhoea (72·3% vs 50·2%; p<0·0001) and URTI cases (95·8% vs 69·5%; p<0·0001; figure 2). A narrative timeline about the relevant policies and regulatory events and activities is shown in the appendix (pp 23–25). The results of a sensitivity analysis of a subset of community pharmacies that included all rounds of the panel in Shaanxi is shown in the appendix (pp 26, 27) and were consistent with the primary analysis.

Overall, 1554 (64·5% [95% CI 62·5–66·4]) of 2411 respondent staff asked further details about the patient's condition after the scripted presentation of diarrhoea and 1896 (78·6% [77·0–80·3]) after the URTI case presentation (figure 3). However, inquiries about taking other medicines were done in only 234 (9·7% [8·6–11·0]) and 159 (6·6% [5·6–7·7]) of diarrhoea and URTI interactions, respectively, and about other symptoms in 439 (18·2% [16·7–19·8]) and 323 (13·4% [12·1–14·8]) of diarrhoea and URTI interactions, respectively. Consultations or advice were seldom given when non-prescription antibiotics dispensing happened. Pharmacy workers inquired about patient's drug allergy history in 188 (16·1% [14·0–18·3]) of 1169 diarrhoea interactions during which antibiotics
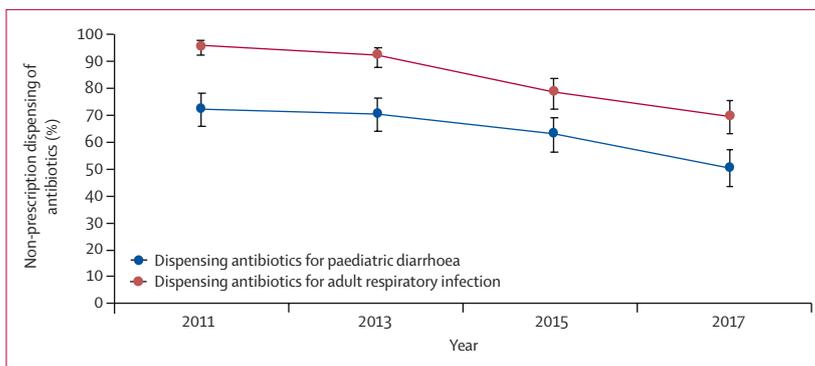

Figure 2: **Non-prescription dispensing of antibiotics at community pharmacies in Shaanxi Province (2011–17)**
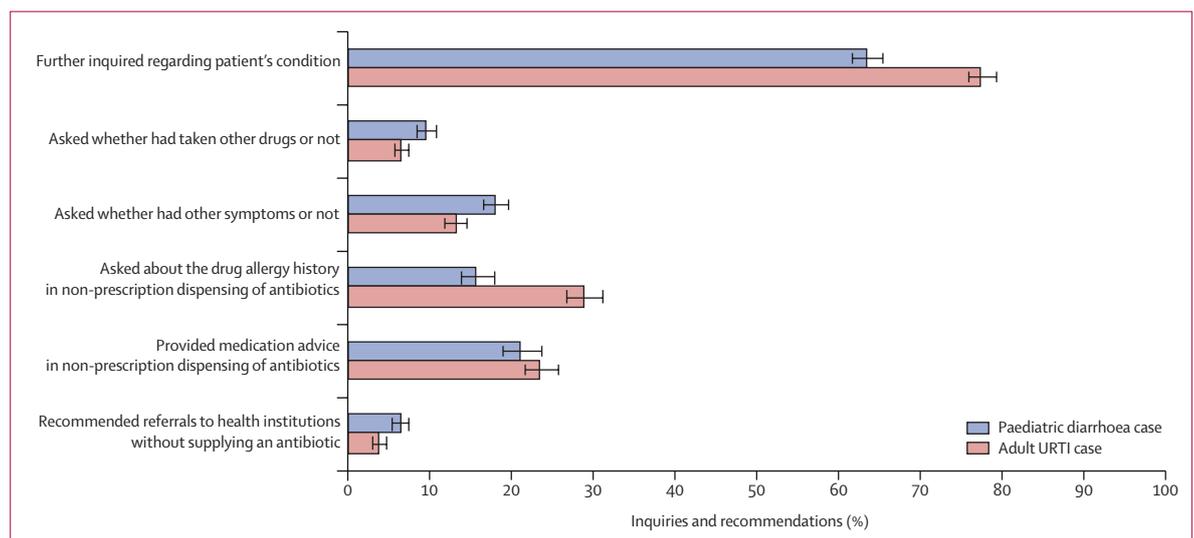Error bars represent 95% CIs. For more details see appendix (pp 22–25).

Figure 3: **Indicators assessing service quality of community pharmacies in China (2017)**
Error bars represent 95% CIs.

were dispensed and medication advice was given in 251 (21·5% [19·1–23·9]) of these interactions; for URTI interactions, the proportions were 494 (29·2% [27·1–31·5]) of 1690 and 403 (23·8% [21·8–26·0]), respectively. A referral was recommended without the non-prescription supply of antibiotics only in 156 (6·5% [5·5–7·5]) of 2411 interactions about diarrhoea and 92 (3·8% [[3·1–4·7]) of 2411 URTI interactions.

After adjusted for covariates and regional variations, and considering all cases, being a chain pharmacy (OR 0·75 [95% CI 0·62–0·89], p=0·0012), having a pharmacist on duty (0·66 [0·56–0·78], p<0·0001), and being located in urban area (0·49 [0·34–0·70], p<0·0001; table 2) were all negatively significantly associated with non-prescription dispensing of antibiotics. These findings were generally consistent for both cases,

although the negative effect of being a chain pharmacy was not significant in diarrhoea cases. Compared with paediatric diarrhoea cases, the likelihood of non-prescription antibiotic dispensing for adult URTI cases was higher (3·31 [2·88–3·81], p<0·0001). Additionally, female staff were more disposed to dispense antibiotics in paediatric cases (table 2).

The appendix shows differences in pharmacy behaviours between the chain and independent pharmacies, and between pharmacies with and without a pharmacist on duty, adjusting for possible covariates, including features of pharmacy and respondent staff (pp 30, 31). Relative to independent pharmacies, chain pharmacies exhibited a higher likelihood of providing better pharmacy services. Chain pharmacies were more likely to display antibiotics in a separate counter and to display a prescription-only

	Model 1: paediatric case		Model 2: adult case		Model 3: all cases	
	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value	Odds ratio (95% CI)	p value
Pharmacy characteristics						
Type						
Independent pharmacy	1 (ref)	··	1 (ref)	··	1 (ref)	··
Chained pharmacy	0·84 (0·66–1·07)	0·16	0·61 (0·46–0·81)	0·00059	0·75 (0·62–0·89)	0·0012
Size (m²)						
Small (<50)	1 (ref)	··	1 (ref)	··	1 (ref)	··
Middle (50–100)	1·16 (0·91–1·48)	0·23	1·20 (0·89–1·62)	0·23	1·18 (0·98–1·42)	0·078
Large (>100)	1·31 (0·93–1·83)	0·12	0·84 (0·57–1·23)	0·36	1·09 (0·85–1·40)	0·49
Location						
Rural area	1 (ref)	··	1 (ref)	··	1 (ref)	··
Urban area	0·49 (0·34–0·70)	0·00012	0·46 (0·28–0·76)	0·0021	0·49 (0·34–0·70)	<0·0001
Had a licensed pharmacist on duty						
No	1 (ref)	··	1 (ref)	··	1 (ref)	··
Yes	0·61 (0·49–0·75)	<0·0001	0·69 (0·53–0·88)	0·0032	0·66 (0·56–0·78)	<0·0001
Displaying a prescription-only sign						
No	1 (ref)	··	1 (ref)	··	1 (ref)	··
Yes	0·78 (0·51–1·20)	0·26	0·81 (0·48–1·37)	0·43	0·80 (0·58–1·11)	0·18
Separate counter for antibiotics						
No	1 (ref)	··	1 (ref)	··	1 (ref)	··
Yes	0·93 (0·68–1·26)	0·63	0·98 (0·68–1·41)	0·92	0·91 (0·72–1·15)	0·43
Staff characteristics						
Sex						
Male	1 (ref)	··	1 (ref)	··	1 (ref)	··
Female	1·54 (1·15–2·07)	0·0042	1·19 (0·86–1·67)	0·29	1·35 (1·09–1·67)	0·0061
Perceived age, years						
<30	1 (ref)	··	1 (ref)	··	1 (ref)	··
30–50	1·04 (0·81–1·34)	0·77	1·07 (0·78–1·46)	0·67	1·02 (0·84–1·23)	0·88
>50	1·10 (0·73–1·66)	0·65	1·05 (0·61–1·82)	0·85	1·03 (0·75–1·42)	0·83
Simulated clinical case*						
Paediatric diarrhoea	NA	··	NA	··	1 (ref)	··
Adult upper respiratory infection	NA	··	NA	··	3·31 (2·88–3·81)	<0·0001

These data are based on 2411 observations (221 groups) for models 1 and 2, and 4822 observations for model 3. The estimated odds ratios with 95% CI were obtained from the multivariate binary logistic regressions with random-intercepts for each county or district and all the independent variables were analysed jointly in each regression model. The interclass correlation coefficient was 0·28 for model 1, 0·43 for model 2, and 0·30 for model 3. NA=not applicable. *Independent variable (ie, type of simulated clinical case) not included in regression models 1 and 2.

Table 2: Factors associated with non-prescription dispensing of antibiotics at community pharmacies in China

sign (appendix p 30). The presence of a licensed pharmacist was also associated with better pharmacy services (appendix p 31). When the analyses were stratified according to rural and urban areas, the results were generally consistent (appendix pp 32, 33). Presence of a pharmacist had relatively consistent effects in urban and rural pharmacies. The association between being a chain pharmacy and improved performance was generally stronger in urban areas.

Discussion

Using simulated clients, we measured real-world behaviours in both rural and urban community pharmacies across six provinces in China. This study extends the evidence from our previous study[14] on non-prescription dispensing of antibiotics at community pharmacies in urban China and is the first one to report trends on this practice in low-income and middle-income countries. We found that irrational over-the-counter use of antibiotics in China was still prevalent in 2017. This practice was more severe in rural areas and the central and western provinces. Moreover, broad-spectrum antibiotics accounted for a high proportion of dispensed antibiotics, and some fluoroquinolones were offered for paediatric diarrhoea (appendix p 20, 21). Several factors were associated with inappropriate antibiotic dispensing.

A 2019 meta-analysis[7] of data from 36 standardised patient or simulated client studies and two questionnaire surveys with simulated medical scenarios, including 8085 interactions within 6353 community pharmacies from 24 countries, reported non-prescription dispensing of antibiotics in 62·2% of cases (95% CI 52·8–71·6); 67% for URTI and 63% for gastroenteritis. Most previous studies of this type have been done in developing countries,[5,7,8,25] mainly in Asia, followed by Africa and Latin America,[5,7,8] and some studies have showed that indiscriminate non-prescription antibiotics dispensing is also an issue in some European countries.[24,26,27] The current study added valuable empirical knowledge on this topic.

Our findings raise concerns about whether China can achieve its 2020 national goal to end non-prescription antibiotic sales. Most drugs in China are dispensed in health-care institutions,[28] and the accessibility and affordability of primary health care has improved since China's health reform initiated in 2009.[29,30] Therefore, we consider that ending non-prescription dispensing of antibiotics at community pharmacies would not pose a considerable risk for people's timely access to essential medications. However, considering the large number of community pharmacies, the heterogeneity within China's health-care system, the for-profit nature of pharmacies, and patient expectations about receiving antibiotics, eliminating non-prescription antibiotic dispensing in China will be difficult. We found that non-prescription antibiotic dispensing has been decreasing continuously since 2011, in Shaanxi. This decrease might be due to a

series of national-level and provincial-level policies, particularly since 2014 (appendix pp 23–25), and an increasing perception about rational use of antibiotics among pharmacy staff. However, whether Shaanxi's experience is generalisable to other regions in China is unclear.

Besides non-prescription dispensing of antibiotics, our study showed a considerable service quality gap—ie, the essentially recommended questions and advice that should be asked or given according to good pharmacy practice were missing in a large proportion of our simulated visits—at China's community pharmacies. The inadequacy of community pharmacy performance in low-income and middle-income countries has been a long-standing problem.[31,32] Fewer pharmacy workers in our study asked recommended questions and gave appropriate advice than in previous studies.[7] However, pharmacy personnel's responses to third person-based scenarios might differ from the response to standardised patients, which could account for the difference. Our childhood diarrhoea case allows a direct comparison with other simulated clients studies done in Ethiopia and India;[33,34] we found similar levels of recommendations and advice.[33,34]

A 2016 review[32] of six studies on the effects of public stewardship on private pharmacy practices in low-income and middle-income countries showed that regulation and training can enhance private pharmacy's adherence to recommended practice. Both are important for China's community pharmacies. Insufficient knowledge among pharmacy staff, and discrepancies between knowledge and actual behaviour,[31,35] are the key determinants of poor performance in private pharmacies in low-income and middle-income countries. There are several possible remedies. First, further reinforcement of regulations is needed. Most antibiotics have been restricted to prescription-only use in China since 2004, and further regulatory measures have been introduced more recently, and punitive mechanisms for offenders have been enhanced.[36] Additional short-term policies to address non-prescription dispensing of antibiotics could include introducing heavier penalties and enhancing the frequency of pharmacy inspections. In the long-term, surveillance systems capable of tracking medicine sales at every community pharmacy are warranted.

Second, face-to-face educational outreach, training workshops, and persuasive printed materials can enhance the quality of services at private pharmacies in developing countries.[31,32] Further studies exploring the innovative design, effectiveness, and cost-effectiveness of these types of educational interventions in China are needed. Mobile phones and the internet should be explored as ways of delivering educational information to pharmacists and other pharmacy staff.

We found that chain pharmacies was associated with less non-prescription antibiotic dispensing and better practice, in line with findings from India published in

2017.[37] As chains and franchises become increasingly common, their effect on service quality should be studied further.

We found that the presence of licensed pharmacists was also associated with fewer non-prescription sales and better performance, showing their importance to community pharmacies. Our previous study of urban pharmacies in China[14] noted that only 15% had a pharmacist present, versus 35% in the present study, despite regulatory measures.[36] A lack of pharmacists in community pharmacies is also a problem in other low-income and middle-income countries.[8,31] If community pharmacies are to be regarded as more than informal providers in the health system,[31] pharmacists will be indispensable. Attracting and retaining qualified pharmacists in community pharmacies is still challenging.

Most antibiotics dispensed occurred following the simulated clients' explicit requests for antibiotics (demand level 2 and 3). This result is in line with the previous finding that patients' expectations for antibiotics increase antibiotic prescribing.[38–40] This finding points to the need for educational interventions, such as media campaigns and displaying persuasive printed materials in community pharmacies, to improve understanding about antibiotics among the general public.

Our study had some limitations. First, the simulated client method derives data according to specific standardised scenarios; hence, caution is needed in generalising our results to other conditions. Second, the study was not designed to identify more detailed provider characteristics associated with pharmacy practices, such as knowledge, educational attainment, and employment status. Third, although simulated clients were trained to achieve a uniform presentation and random assignment was used, differences in simulated clients' may have existed. However, the inclusion of fixed effects had little effect on estimated coefficients of the differences between chain and independent pharmacies, and between those with and without a licensed pharmacist (appendix pp 28, 29). We did find a small protective effect of simulated clients' fixed effects in rural areas, which implies that some simulated clients might be more confident in the rural pharmacies, which in turn might have facilitated dispensation of antibiotics. Nonetheless, this effect does not change the conclusion that rural pharmacies' performance was worse. Fourth, as an observational study, we did not explore the effect of possible interventions. Non-prescribed dispensing of antibiotics fell over time in Shaanxi following national and local policy changes; however, a causal relationship could not be established. Last, our sample was drawn from six selected provinces, and we did not sample in proportion to population size or include a design effect for multistage sampling in the sample size calculation, which has resulted in an over-representation of pharmacies from smaller prefecture-level regions and smaller provinces in the overall sample. This limitation reduces the representativeness of our results for the included regions and China as a whole.

Our findings highlight the urgency for policy makers to develop multifaceted approaches to stewardship of antibiotic use in retail settings, including stricter regulation, enforcement of both the prescription-only policy and pharmacist-on-duty rules, pharmacy staff training, and public education, and also the establishment of a systematic electronic network to monitor changes in the practice over time.

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