Journal of Antimicrobial Chemotherapy

Diagnostic ability and inappropriate antibiotic prescriptions: a quasi-experimental study of primary care providers in rural China

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Background: China has one of the highest rates of antibiotic resistance. Existing studies document high rates of antibiotic prescription by primary care providers but there is little direct evidence on clinically inappropriate use of antibiotics or the drivers of antibiotic prescription.

Methods: To assess clinically inappropriate antibiotic prescriptions among rural primary care providers, we employed unannounced standardized patients (SPs) who presented three fixed disease cases, none of which indicated antibiotics. We compared antibiotic prescriptions of the same providers in interactions with SPs and matching vignettes assessing knowledge of diagnosis and treatment to assess overprescription attributable to deficits in diagnostic knowledge, therapeutic knowledge and factors that lead providers to deviate from their knowledge of best practice.

Results: Overall, antibiotics were inappropriately prescribed in 221/526 (42%) SP cases. Compared with SP interactions, prescription rates were 29% lower in matching clinical vignettes (42% versus 30%, $P < 0.0001$). Compared with vignettes assessing diagnostic and therapeutic knowledge jointly, rates were 67% lower in vignettes with the diagnosis revealed (30% versus 10%, $P < 0.0001$). Antibiotic prescription in vignettes was inversely related to measures of diagnostic process quality (completion of checklists).

Conclusions: Clinically inappropriate antibiotic prescription is common among primary care providers in rural China. While a large proportion of overprescription may be due to factors such as financial incentives tied to drug sales and perceived patient demand, our findings suggest that deficits in diagnostic knowledge are a major driver of unnecessary antibiotic prescriptions. Interventions to improve diagnostic capacity among providers in rural China are needed.

Introduction

Antimicrobial resistance (AMR) is a major threat to global public health and is driven, in part, by unnecessary antibiotic prescription.[1] As of 2010, China followed India as the second largest consumer of antibiotics globally.[2] Surveillance studies in China have also documented the fast spread of drug-resistant strains for a variety of common bacteria, making the country one of the largest contributors to AMR.[3]

Excessive prescription of antibiotics in primary care settings is a major source of antibiotic consumption.[4] Previous studies have estimated that nearly one-half of all outpatients in China, and up to 85% of patients in rural Chinese areas, are prescribed antibiotics.[4–7] Studies attempting to identify clinically inappropriate prescriptions using clinical records estimated that 61% of antibiotic prescriptions to rural outpatients were inappropriate.[5] Identifying inappropriate antibiotic prescriptions using symptoms and

diagnoses reported in patient records, however, may be complicated by inaccurate or incomplete records and diagnostic errors. Differences in disease case and patient mix across providers can further bias estimates of the determinants of overprescription.

In this study, we used direct measures of clinically inappropriate antibiotic prescriptions to document the degree of overprescription among primary care providers in rural China and to analyse the amount of overprescription attributable to deficits in provider diagnostic and therapeutic knowledge. To identify inappropriate antibiotic prescriptions, we employed unannounced standardized patients (SPs), regarded as the gold standard for the assessment of clinical practice, in a representative survey of primary care providers. We then compared the prescription practices of the same providers in treating SPs with their practices in clinical vignettes with identical disease cases, allowing us to isolate the proportion of inappropriate prescriptions due to deficits in diagnostic and therapeutic knowledge.

This study adds to the previous literature by providing direct measures of the extent of inappropriate antibiotic prescription in a representative sample of providers. Our use of a quasi-experimental approach to identify how deficits in diagnostic and therapeutic knowledge contribute to overuse also extends previous studies of antibiotic prescription practices in resource-poor settings, which have largely focused on provider incentives or knowledge of appropriate antibiotic use.[8–10] Notably, qualitative studies have highlighted the role of diagnostic uncertainty,[11] but this cause has been unexplored quantitatively in a representative sample of providers.

Methods

Ethics approval

Approvals from the institutional review boards (IRBs) of Stanford University, USA (protocol number 25904) and Sichuan University, China (protocol number K2015025) were obtained. Informed consent was obtained verbally from all providers participating in the study. To prevent influence on the study, both IRBs approved a procedure whereby providers consented to SP visits 'at some point in the next 6 months'. Consent from village and township providers was obtained as part of the facility survey ~5 weeks before SP visits. All individuals who participated as SPs were trained to protect themselves from any invasive tests or procedures.

Setting and study design

This study took place in village clinics and township health centres, the two lower tiers of China's three-tiered rural health system. Village clinics and township health centres are the first point of contact with the health system for a large and increasing proportion of rural patients.[12] Consequently, they are likely to account for a substantial proportion of total antibiotic prescriptions. Although China has implemented a series of policies designed to curb excessive use of antibiotics, including establishment of a national surveillance system,[13] guidelines for the use of antibiotics in clinical settings[14] and an Essential Drug List policy,[15] available evidence suggests that overprescription remains a significant concern.[16]

This study had three objectives. First, we described the antibiotic prescription practices of primary care providers when visited by unannounced SPs. If managed correctly, none of the disease cases presented should be prescribed any antibiotics. The SP methodology offers a number of advantages over the use of facility records to study prescription practices.[17] First, SPs guarantee a high level of accuracy and completeness as they allow for direct observation of the care received by actual patients without

influencing provider behaviour. Second, SPs allow for comparison across providers because disease cases are fixed and presentation standardized. Third, data from SP interactions can be used to isolate prescription practice due to provider rather than patient behaviour. Finally, SPs allow for detailed observation of the stages of the clinical process, which are typically unobservable in clinic records.

Our second objective was to isolate the amount of inappropriate prescriptions due to deficits in provider knowledge versus other factors. By comparing prescriptions from the same providers in interactions with SPs and in vignettes designed to assess provider knowledge of the full clinical process for the same disease cases (both diagnostic and therapeutic—henceforth called 'full vignettes'), we assessed the amount of overprescription that was driven by deficits in provider knowledge and the amount that was driven by other factors such as misaligned provider incentives (for instance, due to financial incentives tied to drug sales), perceived patient demand, drug availability and lack of diagnostic equipment.

Finally, we compared prescription practices in full vignettes with prescription practices in vignettes evaluating only knowledge of appropriate treatment for a given diagnosis (henceforth called 'treatment-only vignettes'). Because prescription practice in full vignettes depends on provider knowledge of both the diagnostic process and appropriate treatment, comparing full vignettes with treatment-only vignettes isolates the amount of inappropriate prescription due to provider diagnostic uncertainty, or inability to reach the correct diagnosis, from deficits in knowledge of appropriate treatment.

Selection of facilities, data collection and study size

Facilities included in the study were from three prefectures (the administrative level below the province and above the county) in three provinces located in western, central and eastern China, respectively. Across the three regions, we randomly sampled 209 township health centres and 139 village clinics. The Supplementary Methods (available as Supplementary data at JAC Online) describe the sampling process in detail.

We conducted three separate waves of data collection with village- and township-level providers (Figure S1). Information on facility and provider characteristics was collected through a survey in June 2015. In August 2015, we conducted the SP visits. Finally, we conducted a follow-up survey in early September 2015. In this final survey, we assessed whether providers had detected any SPs and administered clinical vignettes.

SPs

All SPs included in this study were recruited from local areas and each was intensively trained to consistently and covertly present a case of pulmonary TB, viral gastroenteritis or unstable angina. The SPs were randomly assigned to facilities and, within each facility, they visited the provider following the normal procedures for any walk-in patient.

Upon presenting to the provider, SPs made an opening statement of the primary symptom(s) of the disease case (fever and cough for TB, diarrhoea for viral gastroenteritis and chest pain for angina). For the viral gastroenteritis case, SPs presented the case of a son/daughter who was not present. The SPs responded to all questions by the providers following a predetermined script, purchased all medications prescribed (which are sold by providers in China) and paid providers their fee. After each visit, the SP was debriefed using a structured questionnaire and SP responses were confirmed against a recording of the interaction taken using a concealed recording device.

The selected disease cases are well-suited to assess the relationship between provider diagnostic ability and inappropriate antibiotic prescriptions. Both TB and viral gastroenteritis cases exhibit chief symptoms that alone may be indicative of common illnesses requiring antibiotics (persistent cough and fever for TB and diarrhoea for viral gastroenteritis); yet, upon appropriate questioning, the SP would reveal symptoms suggesting that

antibiotics should not be prescribed. For TB, these symptoms include cough duration of 2–3 weeks, fever with night sweats and loss of appetite and weight, which are consistent with a classic case of presumed TB and, according to national guidelines, should not be prescribed appropriate antibiotics until confirmation. For viral gastroenteritis, appropriate questioning would reveal symptoms of a 2-year-old child consistent with a viral infection (including watery diarrhoea without blood or mucus, no fever or vomiting and little change in behaviour). The chief complaint of the angina case, chest pain, is less likely consistent with a disease requiring antibiotics but provides insight into antibiotic prescription for less ambiguous cases.

Clinical vignettes

Full vignettes

Two–three weeks after SP visits, we administered vignettes presenting the same disease cases to the same providers. Vignettes were administered by two enumerators, one playing the role of the patient and the other providing instructions and recording the interaction. At the start, providers were asked to proceed as they would with a real patient and told that the patient would answer any questions and comply with any instructions. The enumerator playing the role of the patient then made an opening statement and providers proceeded with the interaction including diagnosis and treatment. The prescription practices observed in these full vignettes reflect providers' knowledge of both diagnosis and appropriate treatment—the two components of the clinical process.

We compared antibiotic prescriptions of providers in these vignettes, when they knew they were being observed, to their antibiotic prescriptions in unannounced SP interactions, when they did not. The difference between the two reflects the proportion of inappropriate prescriptions due to factors such as misaligned provider incentives, perceived patient demand, drug availability and unavailability of diagnostic equipment.

Treatment-only vignettes

Following these full vignettes, testing provider knowledge of both diagnosis and treatment, we tested provider knowledge of appropriate treatment only, independent of their diagnostic ability. If a provider gave an incorrect diagnosis at the end of the full vignette, they were provided the correct diagnosis for the disease case and were asked to suggest a treatment. Comparing treatments given in these treatment-only vignettes with those in full vignettes gives an estimate of the proportion of inappropriate antibiotic prescription due to deficits in diagnostic ability versus knowledge of appropriate treatment.

Outcomes

We examined two primary outcomes. First, we assessed the overall rate of antibiotic prescription. Second, we examined the rate of broad-spectrum antibiotic prescription because unnecessary broad-spectrum antibiotics may contribute more to antibiotic resistance than more-targeted therapies.[18,19] We also report antibiotic prescriptions conditional on prescription of any medicine, that is, the fraction of providers prescribing antibiotics among the group of providers prescribing any medicines. Similarly, we report the prescription of broad-spectrum antibiotics conditional on prescription of any antibiotics, as the fraction of providers prescribing broad-spectrum antibiotics among the group of providers prescribing any antibiotics.

Statistical analysis

For each of the three disease cases, we calculated the proportion and 95% CI of the primary outcomes: antibiotic prescription and broad-spectrum antibiotic prescription. We present these outcomes for the entire sample

and compare them, using logistic regression, by facility type (village clinics and township health centres).

To understand the different drivers of antibiotic prescription, we compared prescription outcomes for the SP interactions, the full vignettes and the treatment-only vignettes using logistic regression with provider individual and SP disease-case fixed effects.

Finally, we examined how outcomes are associated with the accuracy of diagnosis and percentage of checklist items completed by providers in SPs and full vignettes. To do so, we used local polynomial regression to plot the non-parametric relationship and used logistic regression to estimate correlations with and without adjusting for provider characteristics (age, gender, education, monthly salary, medical certification and training on antibiotic use) and county fixed effects. All analyses were done using Stata 14 (Stata Corporation, College Station, TX, USA).

The Supplementary Methods provide the details of sample selection, assignment of SPs to providers, SP script development, SP recruitment and training, SP detection rates, the administration of surveys and vignettes, diagnostic checklists, diagnostic standards and drug identification.

Results

Completion rates for each phase of data collection are shown in Figure S1. Out of 557 attempted SP interactions, 545 were successfully completed (132 in village clinics and 413 in township health centres). No providers were present at the time of SP visits seven times in sampled village clinics and five times in township health centres. Of the 545 completed SP interactions, matching vignettes were completed for 526. Basic facility and provider characteristics are shown in Table S1. In the analysis below, we do not attempt to impute the 2% (12/557) of missing SP interactions and 3.5% (19/545) of missing vignettes.

Antibiotic prescription to SPs

Pooling disease cases, antibiotics were inappropriately prescribed in 43% of SP interactions in village clinics and 42% of interactions in township health centres (Table 1, column 1). Combining the village clinic and township health centre samples, antibiotics were inappropriately prescribed to SPs presenting with TB symptoms in 162/253 interactions (64%, 95% CI 58%–69%) (Table S2). Of these interactions with SPs presenting the TB case, 142 (56% of all interactions, 95% CI 50%–62%) were prescribed broad-spectrum antibiotics. Antibiotics were prescribed less often in the viral gastroenteritis case (48/137 interactions; 35%, 95% CI 28%–43%) and in the angina case (17/155 interactions; 11%, 95% CI 7%–17%). Nearly all antibiotics prescribed to viral gastroenteritis and angina SPs were broad-spectrum antibiotics. Table S3 lists the classes of antibiotics prescribed for each disease case. Macrolides were most commonly prescribed for TB symptoms, aminoglycosides for viral gastroenteritis and penicillin for angina.

Comparison between SPs and full vignettes

To isolate the proportion of inappropriate prescriptions due to deficits in provider knowledge, Figure 1 and columns 1, 2 and 4 of Table 1 present prescriptions by the same providers in clinical vignettes presenting the same disease cases and compare these with the outcomes of these providers in interactions with SPs. Pooling across disease cases and facility levels, antibiotics were inappropriately prescribed in 157/526 vignettes (30%, 95% CI 26%–34%), 29% lower than in SP interactions (42% versus 30%,

Table 1. Comparison of antibiotic prescription between SPs and two types of vignette

| Characteristic | Percentage of prescriptions (95% CI) | | | P value | |
	SPs	full vignettes	treatment-only vignettes	SPs versus full vignettes[a]	full versus treatment-only vignettes
Total (n = 526)					
antibiotics prescribed	42 (38–47)	30 (26–34)	10 (8–13)	<0.0001	<0.0001
broad-spectrum antibiotics prescribed	39 (35–43)	27 (24–31)	6 (0–8)	<0.0001	<0.0001
antibiotics prescribed, if any medicines prescribed	62 (57–67)	43 (38–49)	23 (18–29)	<0.0001	<0.0001
broad-spectrum antibiotics prescribed, if antibiotics prescribed	91 (87–94)	91 (86–95)	53 (40–65)	0.4066	<0.0001
Village clinics (n = 129)					
antibiotics prescribed	43 (34–51)	35 (27–43)	15 (10–22)	0.0513	<0.0001
broad-spectrum antibiotics prescribed	40 (32–48)	33 (25–41)	10 (0–16)	0.0706	<0.0001
antibiotics prescribed, if any medicines prescribed	58 (48–67)	45 (36–55)	30 (20–42)	0.3186	<0.0001
broad-spectrum antibiotics prescribed, if antibiotics prescribed	93 (83–97)	93 (82–98)	68 (46–85)	—	<0.0001
Township health centres (n = 397)					
antibiotics prescribed	42 (38–47)	28 (24–33)	9 (7–12)	<0.0001	<0.0001
broad-spectrum antibiotics prescribed	38 (34–43)	25 (21–30)	4 (0–6)	<0.0001	<0.0001
antibiotics prescribed, if any medicines prescribed	64 (58–69)	43 (37–49)	21 (15–27)	<0.0001	<0.0001
broad-spectrum antibiotics prescribed, if antibiotics prescribed	90 (85–94)	90 (83–94)	44 (30–60)	0.3723	<0.0001

Full vignettes refer to identical disease cases presented to the same providers, administering the full clinical process (both the diagnosis and treatment). In treatment-only vignettes providers were given a diagnosis and were only required to suggest the treatment. Provider individual fixed effects and SP disease-case fixed effects were included in logistic regressions.
[a]P values are the results of logistic regressions.

$P < 0.0001$). Rates of inappropriate antibiotic prescription were 19% lower (43% versus 35%, $P = 0.0513$) for village providers and 33% lower (42% versus 28%, $P < 0.0001$) among township providers. Conditional on prescription of antibiotics, providers were equally likely to prescribe broad-spectrum antibiotics during full vignettes and SP interactions.

Comparison between full vignettes and treatment-only vignettes

Compared with full vignettes, antibiotics were prescribed 67% (from 30% to 10%, $P < 0.0001$) less often in treatment-only vignettes in which providers were given the diagnosis and were only required to suggest the treatment (Figure 1 and Table 1). Significant reductions were found in both village clinics (from 35% to 15%, $P < 0.0001$) and township health centres (from 28% to 9%, $P < 0.0001$). Conditional on prescription of any antibiotic, the use of broad-spectrum antibiotic prescriptions fell from 91% to 53% ($P < 0.0001$). Table S4 shows comparisons of antibiotic prescription between SPs and two types of vignettes, by disease.

Diagnostic ability and antibiotic prescriptions

Figure 2 shows the correlation between the two prescription outcomes and the correctness of diagnoses by providers in full vignettes. Providers who made a correct diagnosis (34% of interactions) were significantly less likely to prescribe antibiotics compared with those who made a wrong diagnosis (OR 0.08, 95% CI 0.04–0.14, $P < 0.0001$). Results are similar for the prescription of broad-spectrum antibiotics. Table S5 (row 3, columns 1–3) shows that this relationship is robust to controlling for provider characteristics as well as disease and county fixed effects.

Consistent with the correlation between antibiotic prescription and correct diagnosis, Figure 3 shows that the antibiotic prescription rate declines as providers complete more checklist items of recommended questions and examinations in SP interactions and full vignettes. The highest performing providers in terms of diagnostic process completed 60% of checklist items on average and prescribed antibiotics 10% of the time compared with the lowest performing who prescribed antibiotics 40% of the time. Regressions estimating the relationship between checklist completion and antibiotic prescription (Table S5, rows 1 and 2, columns 1–3) show an average marginal effect of −0.9 ($P < 0.0001$) in full vignettes, which remains consistent when controlling for provider characteristics and disease and county fixed effects.

Data sharing

Replication files (including data and code) are available on the Harvard Dataverse: https://doi.org/10.7910/DVN/HJMNTS.

Discussion

To our knowledge, this study is the first to use unannounced SPs to evaluate inappropriate antibiotic prescriptions in rural China,[20,21] complementing previous studies assessing the management of
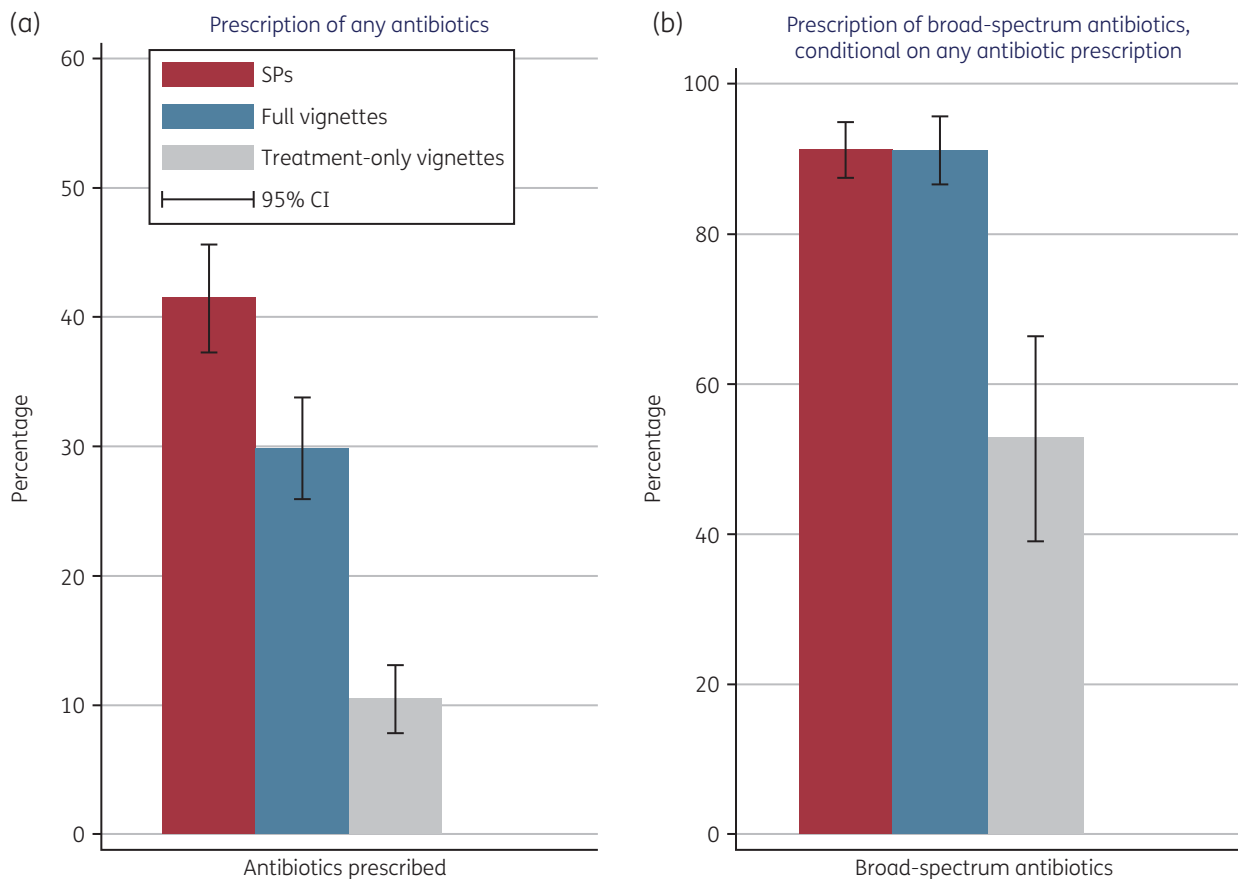
Figure 1. Antibiotic prescription in SP visits and vignettes. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

these disease cases generally. We present two key findings. First, we found that clinically inappropriate antibiotic use was common among rural providers in China. This is consistent with previous observational literature based on clinic records. Though we cannot directly compare the rates of overprescription we found with those from previous studies, our study confirms a substantial amount of overuse, including widespread reliance on broad-spectrum antibiotics.

Second, our results suggest that diagnostic uncertainty plays a major role in driving inappropriate antibiotic use. Previously, studies in China and other developing counties have focused on the role of misaligned profit-related incentives facing providers,[8,10,22] as well as therapeutic errors or provider knowledge of appropriate antibiotic use.[9,10,23] Thus, diagnostic errors may be one reason that studies conducted after the implementation of prescription-related reforms continue to find high levels of inappropriate prescribing.[24–26] We similarly found that inappropriate antibiotic prescription remains common in clinical vignettes when providers are presumably performing to the best of their knowledge. Just 29% of inappropriate antibiotic prescriptions can be attributed to a so-called 'know–do gap' between knowledge and practice as has been documented similarly in a variety of other contexts.[27,28] Conversely, we found a more substantial decrease in antibiotic prescription in vignettes where providers are given the diagnoses and asked to provide treatment, suggesting an important role of

diagnostics. Of the total amount of inappropriate antibiotic prescriptions in vignettes, we estimate that around 64% is due to deficits in diagnostic rather than therapeutic knowledge.

A proportion of antibiotic prescription may be due to providers simply misdiagnosing diseases that do not require antibiotics as ones that do; however, a more important mechanism for the relationship between diagnostic knowledge and antibiotic use could be that when providers face diagnostic uncertainty arising from deficits in diagnostic knowledge, a common response is to prescribe antibiotics.[11] In other words, antibiotics provide a stopgap in cases of diagnostic uncertainty and act as a substitute for diagnostic knowledge. Consistent with this mechanism, the results show that providers were less likely to prescribe antibiotics the more they adhered to guidelines for diagnostic process in full vignettes. Moreover, we find that, conditional on prescribing an antibiotic, providers are 42% less likely to prescribe broad-spectrum antibiotics in vignettes where they are only required to treat a given diagnosis, potentially reflecting that broad-spectrum antibiotics cover a larger range of possible disease states.

Limitations

Our study has several limitations. First, we examined a limited set of disease cases and results may not be representative of other diseases. However, the selected disease cases are all common
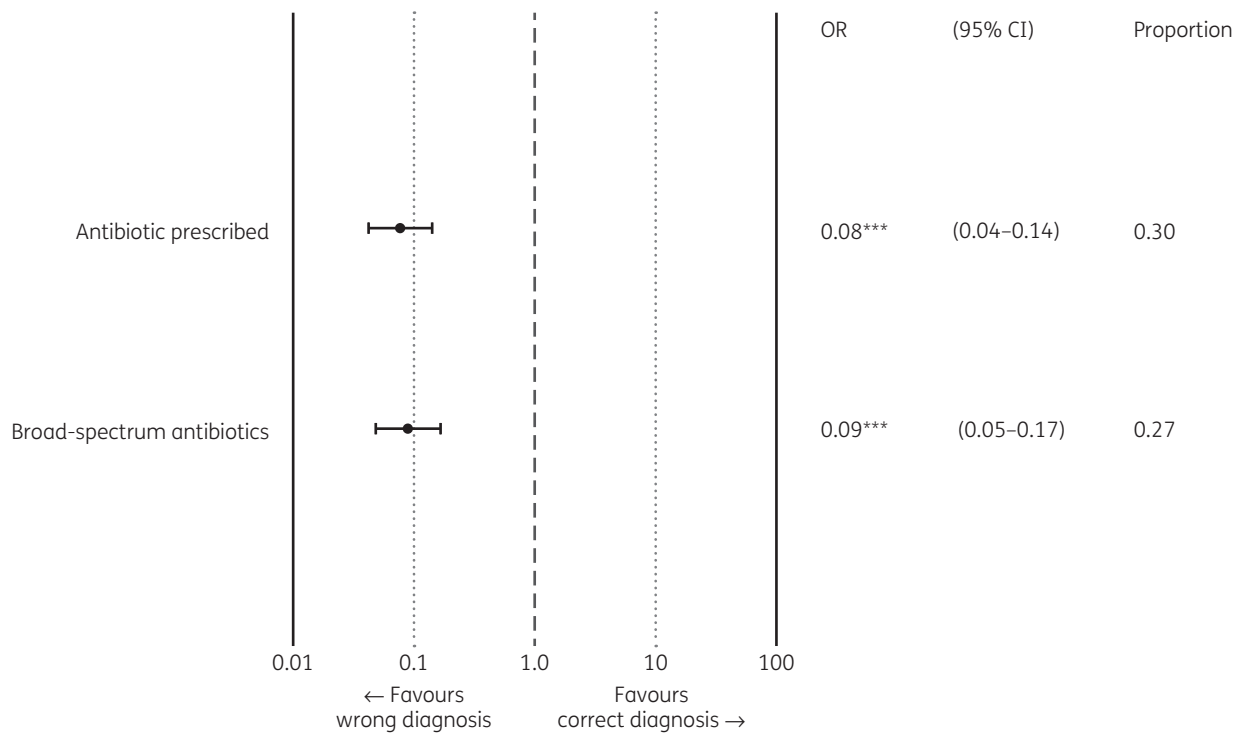
Figure 2. Correlation between antibiotic prescription and correct diagnosis in full vignettes. This figure shows the relationship between correct diagnoses and antibiotic prescriptions in vignettes. ORs were estimated using logistic regression and adjusted for SP disease-case fixed effects. ***P<0.0001.
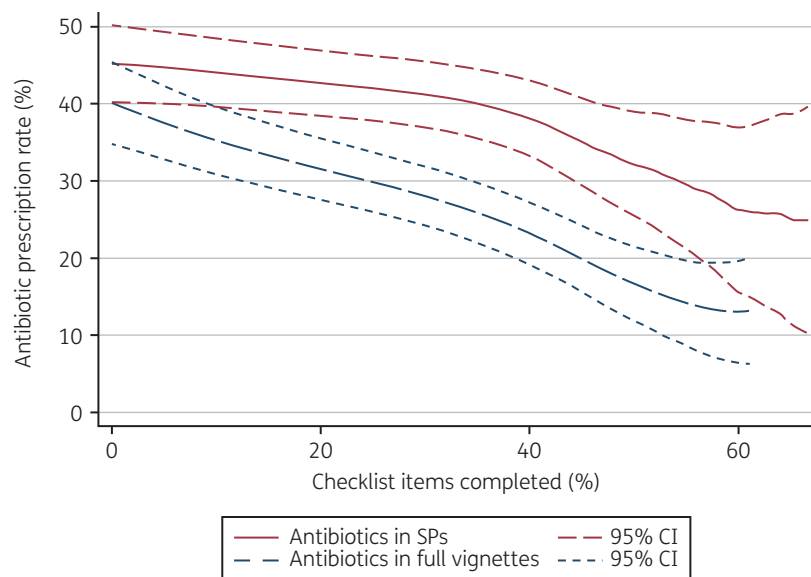

Figure 3. Association between antibiotic prescription and diagnostic checklist completion. This figure shows the non-parametric relationship between antibiotic prescriptions and checklist completion in SP and vignette interactions. These were estimated using local polynomial regressions with a bandwidth of 0.135 and were not adjusted for additional characteristics. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

problems in rural China and span a range of disease types relevant for antibiotic prescribing.[29–31] Second, we studied how providers prescribe to SPs presenting fixed cases and do not test the effects of varying patient behaviour.[8] Third, though our study sample is not nationally representative, we included three geographically diverse regions (western, central and eastern China) and a rigorous sampling methodology within each selected prefecture. Fourth, some bias may have resulted from missing SP and vignette

interactions. The amount of bias, however, is likely to be limited given the small number of missing observations (2% in SP interactions and 3.6% in vignettes). A bounding analysis (assuming that none or all missing observations would have prescribed antibiotics if observed) suggests that the maximum influence on antibiotic prescriptions in SP and vignette interactions for the full sample would be −1 to 1 and −1 to 2 percentage points, respectively.

Finally, it is important to note that our study does not test how resolving uncertainty affects actual prescription behaviour. Our findings are nevertheless consistent with a recent study that found pharmacists in urban India were substantially less likely to prescribe antibiotics to patients presenting symptoms of TB when patients presented with a laboratory report showing microbiological confirmation of TB.[17]

Implications for research and policy

A key implication of the results of this study is that only training providers on the appropriate use of antibiotics is unlikely to have a substantial impact on the overuse of antibiotics in rural primary care settings. Of the substantial amount of overuse observed in the treatment of SPs, our results imply that a relatively small proportion of this (24% of inappropriate prescriptions, pooling diseases) is plausibly due to providers being unaware that antibiotics are inappropriate for a given disease case. Moreover, given low levels of diagnostic ability, encouraging the judicious use of antibiotics could be harmful to patients if antibiotics are not prescribed when needed.[32]

A more promising approach could be interventions that aim to increase the diagnostic ability of providers. Without further evidence, however, it is difficult to say whether interventions targeting only diagnostic knowledge would translate into reductions in overprescription. It is possible, for instance, that even with increased diagnostic knowledge, misuse is unaffected due to misaligned provider incentives or because providers use antibiotics as a 'labour-saving' technology, substituting antibiotics for their own effort. Experimental studies are needed to test the effect of interventions targeting the different factors highlighted here.

In summary, this study found that clinically inappropriate prescription of antibiotics is substantial among primary care providers in rural China. While a large proportion of overprescription may be due to factors such as financial incentives tied to drug sales and perceived patient demand, a larger proportion appears to be driven by deficits in diagnostic knowledge. Results suggest that interventions only training providers on the risks of AMR and appropriate antibiotic use are likely to be ineffective. However, interventions to improve general diagnostic ability among grassroots providers in rural China could significantly reduce inappropriate antibiotic prescription to patients.

Acknowledgements

Funding

Transparency declarations

None to declare.

Supplementary data

Supplementary Methods, Figure S1 and Tables S1 to S5 are available as Supplementary data at *JAC* Online.

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