Article:
Wei, X., Zhuo, C., Hicks, J.P. et al. (2026) Effects of a comprehensive antibiotic stewardship program on antibiotic prescribing for acute respiratory infections in rural facilities: a cluster randomized trial. Nature Medicine. ISSN: 1078-8956

https://doi.org/10.1038/s41591-026-04222-y

Effect of a comprehensive antibiotic stewardship programme on antibiotic prescribing for acute respiratory infections in rural primary care facilities in China: a cluster-randomised controlled trial

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Abstract

Antimicrobial resistance is driven by inappropriate use of antibiotics for acute respiratory infections, a major challenge in primary care in low- and middle-income countries. We conducted a pragmatic, cluster-randomised controlled trial in 34 township hospitals in two rural counties of Guangdong, China, to evaluate whether a digitally enabled stewardship programme could reduce antibiotic prescribing. The intervention combined training and guidelines for doctors, concise, evidence-based guidelines embedded in the electronic medical record with point-of-care prompts, monthly prescribing peer review feedback for doctors, and patient education delivered through smartphone application. Control is usual care with no inputs. During the 12-month implementation period (March 1, 2020, to February 28, 2021), we analysed 97,239 eligible consultations for acute respiratory infections (ARIs). The primary outcome was whether a consultation resulted in any antibiotics being prescribed. This outcome was met: antibiotics were prescribed in 26% (14,521/54,799) of intervention consultations compared with 71% (30,340/42,440) of control consultations, yielding an adjusted risk difference of –39 percentage points (95% confidence interval: –47 to –29; $p<0.001$). There was no evidence of increased harm, as 30-day hospitalisation rates for respiratory illness or sepsis did not differ between groups (adjusted risk difference 0.2 percentage points; 95% confidence interval: –0.3 to 0.6). A comprehensive stewardship programme can substantially reduce inappropriate antibiotic prescribing for ARIs in rural primary care facilities in China without compromising patient safety.

Trial registration: ISRCTN96892547.

Introduction

Antimicrobial resistance (AMR) poses a significant global health challenge, leading to increasing mortality and a growing economic burden worldwide[1]. Inappropriate use of antibiotics is a major driver of AMR, with a substantial proportion of inappropriate prescribing occurring in primary care settings[2,3,4]. In particular, patients with acute respiratory infections (ARIs), including upper respiratory tract infections (URTIs) and acute bronchitis, are frequently inappropriately prescribed antibiotics, given that most of these cases are viral or self-limiting[4,5]. In a minority of cases, such as streptococcal pharyngitis or tonsillitis, where antibiotics are sometimes indicated, broad-spectrum antibiotics are often prescribed inappropriately instead of more targeted narrow-spectrum alternatives[6].

Various interventions have been implemented and evaluated to address inappropriate antibiotic use in primary care globally. Randomised trials assessing educational interventions to improve healthcare providers' knowledge and reduce patient demand for antibiotics have demonstrated a modest impact (between 5 and 21 percentage points) in reducing antibiotic prescribing rates[7-11]. Trials that integrated educational interventions with prescribing audits or feedback for healthcare providers may be more effective. However, the effects on reducing antibiotic prescribing rates vary considerably[12-16]. The use of C-reactive protein testing (CRP) at the point of care has effectively decreased antibiotic prescribing, with absolute reductions ranging from 14 to 46 percentage points[17-21], but evidence regarding feasibility and sustainability remains questionable[22]. Studies assessing decision-support tools, such

as patient decision aids and integrated clinical prediction rule systems, have reported some success[23,24] or no impact[25,26] on reducing antibiotic prescribing. Overall, the reductions in antibiotic prescribing across these studies are inconsistent, yielding modest results. Additionally, most evaluations have been conducted in high-income countries, highlighting a critical gap in research on the effectiveness and sustainability of interventions in low- and middle-income countries (LMICs). These regions face the greatest need for such interventions due to their disproportionate AMR burden stemming from frequent inappropriate antibiotic prescription/sale/use, lack of regulations, and weaker capacity to manage drug resistance[1].

China faces growing challenges from AMR due to the overuse of antibiotics in health institutions, over-the-counter purchases in pharmacies without prescriptions, and self-medication[27-30]. Since 2012, China has implemented the national AMR policy, effectively reducing inappropriate antibiotic prescribing in big hospitals. However, primary care facilities continue to report extremely high rates of antibiotic prescribing and lack effective antibiotic stewardship programmes[6], with intravenous antibiotics commonly used even for mild illnesses[30,31]. The primary reasons for the inappropriate use of antibiotics are insufficient training and monitoring, and patient demand for antibiotics[32].

We previously developed and evaluated an educational intervention for both primary care doctors and caregivers in rural Chinese primary care that reduced inappropriate antibiotic prescribing for URTIs in children by 29 percentage points[14]. Building on this, and to inform China's national policy on primary care antibiotic prescribing, we

have conducted a cluster-randomised controlled trial evaluating whether an enhanced antibiotic stewardship programme, including training and guidelines for doctors, concise, evidence-based guidelines embedded in the electronic medical record with point-of-care prompts, monthly prescribing peer review feedback for doctors, and patient education delivered through smartphone application, compared with usual care without any of the inputs, can reduce inappropriate antibiotic prescribing for ARIs among the general population in rural primary care facilities known as township hospitals[33]. Compared to our previous study, this trial incorporates digital health intervention tools, targets a broader range of ARIs, and focuses on the general population to enhance national antibiotic policies.

Results

Patient disposition

All 34 eligible township hospitals agreed to participate in the trial and participated throughout the entire 12-month trial period. We informed all township hospitals of their randomised allocation on 16 December 2019 and completed all intervention training sessions by 15 January 2020. We originally planned to start implementing the intervention on 16 January but had to postpone until 1 March 2020 due to China's COVID-19 lockdown restrictions in our research sites, with the other intervention components (the enhanced electronic medical record [EMR] system and patient and/or caregiver educational materials) made available in intervention facilities from

this date. We therefore collected all outcomes and most covariates from eligible patient consultations recorded in the EMR during a 12-month endline period, when the intervention was being delivered, between 1 March 2020 and 28 February 2021 (n = 97239 eligible patient consultations). We also retrospectively collected baseline (pre-intervention) outcome data, for covariate adjustment purposes, via the EMR across a (slightly less than) 12-month baseline period between 1 January 2019 and 15 December 2019 (n = 180110 eligible patient consultations). However, while hospitalisation data were available for all patient consultations during the baseline period this data was only available until 31 December 2020, which only covered 67% (48213/71689) of patients' index eligible consultations during the endline period.

The payment information system indicated that all the prescriptions recorded were actually dispensed to patients. Of 53181 unique patients who visited any study township hospitals during the endline period just 255 (0.48%) had at least two consultations in different township hospitals where those hospitals were in different treatment groups, indicating a very low level of contamination at the patient level.

See Fig. 1 for the trial flow chart and Fig. 2 for the daily total number of eligible patient consultations occurring in each treatment group across the baseline and endline periods. On average, slightly more eligible patient consultations occurred in the intervention group but both groups showed similar trends. The large difference in the number of eligible patient consultations between baseline and endline periods in both groups was likely driven by COVID-19 policies starting in January 2020 that initially required all patients with a fever to visit designated fever clinics in Shaoguan

City rather than township hospitals. However, patients with fever who were not SARS-CoV-2 positive were then allowed to resume normal medical consultations in township hospitals. From September 2020 township hospitals were expected to implement their own fever clinics, and after September 2020 the trial would therefore also include patients who had COVID-19 as long as they met the other eligibility criteria.

Aside from the numbers of eligible patient consultations, the distribution of patient-consultation-level, family-doctor-level and facility-level characteristics was largely similar between the treatment groups across both baseline and endline periods (table 1 and Table S1).

Primary outcome

During the baseline period, the primary outcome of an whether an eligible consultation resulted in any antibiotics being prescribed was well balanced, being 83% (88828/107314) in the intervention group and 84% (61486/72796) in the control group. Across the 12-month, post-randomisation endline period the primary outcome was 26% (14521/54799) in the intervention group and 71% (30340/42440) in the control group. After adjusting for covariates, including the baseline cluster-level primary outcome (percentage), the endline, patient-consultation-level risk difference for the primary outcome was -39.2 percentage points (95% confidence interval [CI]: -47.1, -28.8; $p<0.001$; table 2).

We also estimated the unadjusted, cluster-average treatment effect for the primary outcome, which was also very similar to the patient-consultation level results (Table S2). We also illustrate the endline, cluster-level, primary outcome summary percentages for intervention-group facilities (Extended display figure 1 and Extended display figure 2), which displayed a total range of 40 percentage points (12% to 52%) but just a 17 percentage point range between the 10th and 90th quantiles (18% and 35% respectively).

Secondary outcomes

For the subgroup of eligible patient consultations where any antibiotics were prescribed, there was no clear evidence that the intervention affected any of the five antibiotic prescribing related secondary outcomes: whether those prescribed antibiotics included any 1) broad-spectrum antibiotics, 2) any fluoroquinolone antibiotics, 3) any intravenous antibiotics, 4) any antibiotics from the WHO Access group, or 5) more than one antibiotic was prescribed (table 2). There was some evidence from the covariate-adjusted analyses that the intervention may slightly increase the risk of any traditional Chinese medicines being prescribed (3.1 percentage points [95% CI: 1, 6.5; p = 0.005]) and slightly reduce the risk of any glucocorticoids being prescribed (-7.5 percentage points [95% CI: -14.2, -1.7; p = 0.013]), but this was not clearly seen in the crude analyses (table 2). There was no clear evidence from the adjusted or crude analyses that the intervention affected the mean cost of all prescribed medicines or the mean total cost of a patient consultation (table 3).

Safety

The risk of hospitalisation within 30 days increased in both groups during the trial, with an overall 1.5% risk (1827/123487) during the baseline period and a 5.9% risk (2849/48213) during the endline period (table 2 and Extended display figure 3). However, there was no clear evidence from the covariate-adjusted or crude analyses that the intervention affected the risk of hospitalisation within 30 days (table 2). The increased hospitalisations in both groups were likely attributable to greater clinical vigilance for respiratory infections during the COVID-19 pandemic period and the national policy mandating 14-day hospitalisation for patients with fever-like illnesses. For interested readers we also provide the corresponding risk ratio scale estimates for all prescribing outcomes (table S3) and the intracluster correlation coefficients for all outcomes (table S4).

Exploratory outcomes

There was no clear evidence that the intervention's effect on the primary outcome of antibiotic prescribing for ARIs varied between patient sex (self-reported), patients aged ≤14 and >14, or between the first and the second halves of the endline period (Table S5).

Sensitivity analyses

For the primary outcome we obtained similar results from the unadjusted analyses compared with the covariate-adjusted analyses (table 2).

Post-hoc analyses

A post-protocol exploratory analysis comparing the treatment effect on the primary outcome during the second, third and fourth quarters (i.e. month 4-6, 7-9 and 10-12) compared to the first quarter (i.e. month 1-3) did provide some evidence that the treatment effect may be slightly greater in the second and third quarters compared to the first quarter, but did not provide any clear evidence for any difference between the treatment effect in the fourth quarter compared to the first quarter (Table S6). See Fig. 3 for a visualisation of the raw trend in monthly mean antibiotic prescription rates per treatment group across the baseline and endline periods.

Discussion

Our study provides evidence about the effectiveness of antibiotic stewardship programmes within primary care settings in LMICs, where such interventions are urgently needed but under-researched[34]. Our trial showed the antibiotic stewardship programme substantially reduced antibiotic prescribing for ARIs by 39 percentage points (95% CI: -47, -29) in rural primary care township hospitals in China during the COVID-19 pandemic. We achieved a substantially higher reduction in antibiotic prescribing rates compared to a recent study conducted in rural China, which was also during the COVID-19 pandemic[11], potentially due to improved antibiotic prescribing guidelines, training for all doctors in township hospitals, and the use of the EMR system to enable doctors to self-regulate their behaviour. Our interventions were designed to be readily adopted in China to influence national policy. Compared

to physician-side interventions before the COVID-19 pandemic in Norway[12], the United States[15], the United Kingdom[35,36], and Canada[37], our intervention yielded a considerably larger effect size. A trial in Tanzania during the COVID-19 pandemic employing CRP and a digital clinical decision-making tool reported a similar effect size[21]. Previous interventions such as CRP testing may not be sustainable in the long term, as shown in trials in Vietnam[19], and Nigeria[38], because CRP is not widely available and relatively costly in LMIC primary care settings. However, any direct comparisons should be interpreted with caution due to variations in baseline antibiotic prescribing levels, intervention designs, and demographic characteristics of the study populations. For example, the baseline level of antibiotic prescribing in LMICs is commonly around 80%[4], which is substantially higher than in most high-income settings[19].

Our high baseline antibiotic prescribing rate likely contributed to allowing our intervention to achieve a large reduction in antibiotic prescribing, given that a large proportion of the ARI cases previously prescribed antibiotics were therefore likely to be mild and so doctors may have found it easier to stop prescribing antibiotics for them. Additionally, we observed no clear evidence for any changes in the risk of being prescribed broad-spectrum antibiotics, fluoroquinolones, multiple antibiotics, or intravenous antibiotics. This may be attributed to the lack of a compulsory monitoring system for these specific categories. A detailed discussion of these findings will be provided in a separate process evaluation paper.

The findings from this trial have policy implications for primary care antibiotic stewardship programmes in China. The intervention was co-designed with local health authorities and clinicians, which ensured that the antimicrobial stewardship programme was specifically tailored to address the main drivers of inappropriate antibiotic use within China's primary care settings. Additionally, the interventions were contextualised to align with the routine practices of local family doctors based on digital platform that is widely used in China. This strategic approach enhances the potential for scaling up these interventions. Furthermore, our study fills a crucial research gap by providing evidence on the effectiveness of antibiotic stewardship programmes in rural settings, which could potentially inform implementing similar interventions in similar settings.

Several strengths in our trial design and execution likely contributed to the large effect size in reducing antibiotic prescribing reported in our trial. First, our intervention is multifaceted and targets both healthcare providers and patients and/or caregivers[39]. We capitalised on the synergistic effect of engagement with multiple healthcare providers in both consultations and administrative opportunities compared with the more light-touch educational and advisory interventions in other trials[40]. Additionally, we used digital health technology (linking the EMR to a smartphone app for providers and enhancing the EMR’s prescribing system) to improve provider communication, facilitate reflection and collaboration among healthcare providers, and provide automated guidance to providers. Second, by linking EMRs from all hospitals in the prefecture, we were able to assess the safety of the intervention in

relation to the risk of increased respiratory infections or sepsis from withholding or delaying antibiotics, thereby assessing potential harms associated with reducing antibiotic prescribing.

Our study has several limitations. First, COVID-19 pandemic measures, including lockdowns, diversion of febrile patients to designated fever clinics, and mobility restrictions, delayed the trial start and reduced the overall number and composition of ARI consultations. These disruptions likely affect the generalisability of our results, as the patient population and consultation volumes during the endline period were not typical of routine practice. However, the intervention's effect remains relevant beyond the pandemic. The mechanisms by which prescribing was reduced—training, guideline integration, peer feedback, and patient education—directly target structural drivers of inappropriate antibiotic use and are not specific to COVID-related care pathways. Moreover, the control group's prescribing rate (71%) was consistent with pre-pandemic studies in rural China, indicating that inappropriate antibiotic use remained pervasive despite lower consultation volumes. As restrictions have lifted, ARI case volumes have rebounded and the same pressures for unnecessary prescribing have re-emerged, underscoring the continued policy relevance of a scalable stewardship programme. On the other hand, we have no evidence suggesting these issues differentially impacted township hospitals and patient admission in the two treatment groups, and therefore the internal validity of the trial, but we cannot of course exclude this possibility.

Second, we excluded patient consultations involving patients aged 75 or older and those with chronic conditions, based on safety considerations, as these individuals are more likely to have multiple long-term conditions and present more complex cases for which antibiotics are likely to be necessary. Township hospitals often cannot distinguish between these conditions and provide appropriate care. Therefore, findings from our trial may have limited applicability to those excluded populations.

Third, the inability to mask family doctors and their awareness of which trial group their hospital was in may have introduced a “Hawthorne effect” in the intervention group, potentially biasing the strength of the treatment effect beyond what it would be under real world conditions. However, our subgroup analysis of the treatment effect on the primary outcome during the first and second halves of the endline period showed no clear difference, and a Hawthorne effect might be expected to decline over time.

Fourth, the 30-day hospitalisation rate in the endline period was approximately three times higher compared to the baseline period, but with no evidence of any intervention-related difference between the two groups. This trend may reflect clinicians' increased vigilance regarding respiratory infections during the COVID-19 pandemic, as across China during this period all patients suspected of having COVID-19 were required to be hospitalised or quarantined for at least 14 days. Additionally, we were not able to access hospitalisation data after 1 January 2021, restricting our assessment of the patient safety indicator to only 67% of the eligible

index visits, which prevented a complete analysis of the patient safety hospitalisation outcome. However, this should not have affected the internal validity of the effect estimates for the safety outcome.

Fifth, part of the intervention relied on unified electronic data platforms, one-time upfront costs to develop the app's embedded functionality for prescription review and communication, and human resources to establish antibiotic stewardship teams at an early stage, which might not be available in some LMICs. Adaptations are needed in these settings. However, our previous trial showed that a similar intervention can be successfully implemented using just paper-based prescriptions[14]. As the interventions are designed to be embedded into routine services, township hospitals can run antibiotic stewardship programs independently in the long run[41]. The results of a costing study will be reported separately.

Sixth, we cannot rule out that some doctors may have shifted their diagnoses to non-ARIs to justify prescribing antibiotics in the intervention group, biasing the estimated treatment effects for the primary outcome and the secondary outcomes related to antibiotic prescribing. However, we found no evidence to support this (see Fig. 1) and the very similar percentage of consultations excluded “due to non-ARIs diagnosed” in each treatment group within each trial period). Also, the composition of common ARI diagnoses was very similar between the two group during both baseline and endline periods (table 1).

Seventh, this study focused on evaluating the intervention's impact on prescribing behaviours but lacked data to assess patients' self-purchasing of antibiotics outside study facilities, which merits further investigation.

Finally, our treatment effects are average effects across the 12-month endline period, and for the primary outcome we did find some evidence that the treatment effect differed across this period. Therefore, although these differences appeared modest the intervention’s effect may well vary over shorter timescales and our data do not allow us to draw firm conclusions about longer timescales.

In conclusion, our study demonstrates that a comprehensive antibiotic stewardship programme targeting both primary healthcare providers and patients and/or caregivers can substantially reduce inappropriate antibiotic prescribing for ARIs in this context without any demonstrated safety concerns. Our intervention has the potential to be adapted into China’s national guidelines for regulating antibiotic use and to provide policy suggestions for other primary care contexts where inappropriate antibiotic prescribing is prevalent.

Acknowledgements: The authors acknowledge the support provided by the 36 township hospitals, including the 34 in the trial and two in the pilot, in Shaoguan prefecture China which were directly involved in the pilot and endline periods. We thank all patients and/or caregivers and healthcare providers who were involved in the trial. The study was funded by China Primary Health Care Foundation. The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Author Contributions Statement: XW, JPH, CZ, ZZ and NZ contributed to the study design. XW, CZ, JDW, ZZ, JZ, WG, HH contributed to guideline development, training and implementation. XW and JPH drafted the manuscript with support from ZZ and SW, while NZ, CZ, FS and AB commented on the manuscript. ZZ prepared and cleaned the data. JPH analysed the data and provided substantial scientific input in statistical methods and interpretation of results. NZ is the overall lead of the research consortium. The corresponding authors attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Competing Interests Statement: We declare no competing interests.

Table 1. Patient-consultation-level characteristics for the baseline and endline periods by treatment group

	Intervention group		Control group	
	Baseline period	**Endline period**	**Baseline period**	**Endline period**
Number of eligible patient consultations				
Overall	107314	54799	72796	42440
Nanxiong county	62462	30398	29459	17764
Lechang county	44852	24401	43337	24676
Sex[a]				
Female	49% (52941)	50% (27486)	48% (34781)	49% (20716)
Male	51% (54373)	50% (27313)	52% (38015)	51% (21724)
Age (years)	10 (41)	12 (43)	11 (41)	13 (45)
Age group				
≤14	56% (60617)	54% (29541)	57% (41383)	52% (22069)
>14	44% (46697)	46% (25258)	43% (31413)	48% (20371)
Payment method				
Insurance	67% (71919)	73% (40051)	65% (47213)	70% (29846)
OOP	33% (35395)	27% (14748)	35% (25583)	30% (12594)
5 most frequent ARI diagnoses[a]				
URTIs	77% (82902)	77% (42134)	70% (51176)	74% (31210)
Acute bronchitis	11% (12092)	9% (4914)	19% (13756)	18% (7468)
Acute pharyngitis	8% (8579)	10% (5296)	8% (5467)	8% (3289)
Acute tonsillitis	4% (3837)	4% (2143)	8% (5698)	4% (1790)
Acute otitis media	0% (486)	1% (434)	1% (381)	1% (335)

OOP = out-of-pocket. ARI = acute respiratory infection. URTIs = upper respiratory tract infections. There were no missing values for any of the variables. Data are N, % (n) or median (interquartile range). [a] Note that patients could be diagnosed with more than one diagnosis at a consultation and so the diagnosis percentages within each column can validly sum to >100%.

Table 2. Estimated treatment effects on the primary outcome and prescribing-related secondary outcomes

		Outcome summary values[a]		Percentage point difference (95% CI); p-value[b]	
Outcome	**Trial period**	**Intervention group**	**Control group**	**Adjusted**	**Crude**
Primary outcome					
One/more antibiotic(s) prescribed[c]	Baseline	83% (88828/107314)	84% (61486/72796)		
	Endline	26% (14521/54799)	71% (30340/42440)	-39.2 (-47.1, -28.8); <0.001	-43.7 (-51.7, -32.6); <0.001
Secondary outcomes relating to all eligible patient consultations where antibiotics where prescribed[d]					
One/more broad-spectrum AB prescribed	Baseline	53% (47310/88828)	56% (34521/61486)		
	Endline	52% (7599/14521)	52% (15897/30340)	0 (-16, 24.9); 0.59	
One/more fluoroquinolone AB prescribed	Baseline	4% (3417/88828)	3% (1808/61486)		
	Endline	4% (631/14521)	3% (927/30340)	-0.7 (-5.8, 3.4); 0.623	
Multiple ABs prescribed	Baseline	42% (37423/88828)	34% (20860/61486)		
	Endline	25% (3695/14521)	27% (8077/30340)	-4.7 (-15.8, 15.7); 0.718	
One/more intravenous AB prescribed	Baseline	49% (43865/88828)	44% (26857/61486)		
	Endline	45% (6463/14521)	36% (11034/30340)	-5.1 (-16.6, 18.3); 0.949	
One/more WHO Access AB prescribed	Baseline	61% (54373/88828)	62% (38103/61486)		
	Endline	65% (9415/14521)	64% (19417/30340)	-0.4 (-18.9, 20); 0.819	
Secondary outcomes relating to all eligible patient consultations[e]					
One/more TCMs prescribed	Baseline	88% (93963/107314)	91% (66322/72796)		
	Endline	90% (49252/54799)	89% (37658/42440)	3.1 (1, 6.5); 0.005	1.3 (-2.8, 5); 0.522
One/more glucocorticoids prescribed	Baseline	28% (29556/107314)	20% (14519/72796)		
	Endline	10% (5524/54799)	14% (6067/42440)	-7.5 (-14.2, -1.7); 0.013	-4.8 (-12.8, 2.8); 0.218
Safety outcome					
Hospitalisation within 30 days[f]	Baseline	1.7% (1247/74313)	1.2% (580/49174)		
	Endline	6.2% (1717/27858)	5.6% (1132/20355)	0.2 (-0.3, 0.6); 0.429	0.5 (-0.8, 1.6); 0.512

AB = antibiotic. WHO Access AB = any antibiotic from the *World Health Organization AWaRe (Access, Watch, Reserve) antibiotic book* antibiotic "access" list. TCM = Traditional Chinese Medicine. [a] Values are % (n/N) with N also being the sample size analysed for each treatment effect estimate. [b] Treatment effects are endline intervention minus control risk differences presented on the percentage point scale. 95% confidence intervals were computed via the bias-corrected and accelerated bootstrapping approach, with resampling at the cluster level to account for the multi-level clustering in the data, with two-tailed p-values computed by inverting those confidence intervals. Results are not adjusted for multiple testing. [c] Binary indicator of whether an eligible patient consultation that resulted in a diagnosis of an ARI resulted in a prescription containing any antibiotics vs not. [d] Binary indicator of whether an eligible patient consultation that resulted in a diagnosis of an ARI and a prescription containing any antibiotics included any antibiotics of the type indicated vs any other type. The treatment effects for these outcomes are restricted to the model-predicted subgroup of eligible patient consultations that would have generated a prescription containing any antibiotics irrespective of their treatment allocation. [e] Binary indicator of whether an eligible patient consultation that resulted in a diagnosis of an ARI resulted in a prescription containing any of the medication type indicated vs not. [f] Binary indicator of whether a patient was hospitalised for any respiratory infection or sepsis in any hospital in the Shaoguan Prefecture within 30 days of having had an eligible consultation at a trial township hospital vs not.

Table 3. Estimated treatment effects on consultation-related cost outcomes

		Outcome summary values[a]		Mean difference (95% CI); p-value[b]	
Outcome[c]	**Trial period**	**Intervention group**	**Control group**	**Adjusted**	**Crude**
Total cost of all prescribed medications	Baseline	31.4 (24.6; 107314)	36.4 (30.6; 72796)		
	Endline	29.6 (25.2; 54799)	36 (31.6; 42440)	-0.8 (-5.7, 5.7); 0.807	-3.4 (-13.5, 2); 0.524
Total cost of all prescribed medications, any tests & the consultation fee	Baseline	49.5 (29.3; 107314)	53.4 (32.8; 72796)		
	Endline	46.3 (31.5; 54799)	52.4 (35.8; 42440)	-2.3 (-6.7, 4.5); 0.507	-5.5 (-16.1, 1.5); 0.144

[a] Values are mean (SD; N) with N also being the sample size analysed for each treatment effect estimate. [b] Treatment effects are endline intervention minus control mean differences. 95% confidence intervals were computed via the bias-corrected and accelerated bootstrapping approach, with resampling at the cluster level to account for the multi-level clustering in the data, with two-tailed p-values computed by inverting those confidence intervals. Results are not adjusted for multiple testing. [c] All costs are in Chinese renminbi with units of yuan and relate to the total cost at each eligible patient consultation for the items indicated.

Figure legends

Fig. 1 CONSORT trial flow diagram.

† Baseline period = January 1 to December 15, 2019, endline period = March 1, 2020 to February 28, 2021.

§ To be eligible a patient consultation had to result in a diagnosis of one or more of the following acute respiratory infections: acute upper respiratory tract infections of multiple and unspecified sites, acute nasopharyngitis (common cold), acute pharyngitis, acute tonsillitis, acute bronchitis, acute sinusitis, acute otitis media, streptococcal pharyngitis, and streptococcal tonsillitis.

‡ To be eligible a patient consultation had to involve a patient aged 0-75.

¶ To be eligible a patient consultation must not result in a diagnosis of any chronic conditions including asthma, chronic obstructive pulmonary disease, non-infective or non-acute disorders (e.g. cystic fibrosis, pulmonary embolus, heart failure, oesophageal reflux and/or allergies), non-respiratory infections (e.g. cutaneous infections, urinary tract infections, trauma-related infections, bacterial enteritis and/or cellulitis/abscess), immunological deficiencies, tuberculosis, or any form of cancer.

** We used the electronic medical record system to track whether a patient was hospitalised for any respiratory infection or sepsis in any hospital in the Shaoguan Prefecture within 30 days of having had an eligible index consultation at a trial township hospital. However, hospitalisation data were only available for the period between January 1, 2019 to 31 December, 2020. Thus, we secured hospitalisation

data for the full baseline period (January 1 to December 15, 2019) but only 9 months of the endline period (March 1 to December 1, 2020).

Fig. 2 Daily total number of eligible patient consultations per treatment group.

Daily total number of eligible consultations per treatment group across the baseline (1/1/19 to 15/12/19) and endline (1/3/2020 to 28/2/2021) periods. The dotted vertical lines indicate 1) the end of the baseline period and the start of the enforced suspension period due to the COVID-19 pandemic (15/12/19) and 2) the end of suspension period and the start of the endline period (28/2/2021)

Fig. 3 Antibiotic prescribing rate by month (actual timeline) and treatment group.

Percentage of eligible patient consultations where any antibiotics were prescribed per month and treatment group across the baseline (1/1/19 to 15/12/19) and endline (1/3/2020 to 28/2/2021) periods. Suspended period = the enforced suspension period due to the COVID-19 pandemic.

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Methods

Study design

We conducted a pragmatic, parallel-arm, cluster-randomised, controlled, superiority trial to compare our antibiotic stewardship intervention against usual care within 34 township hospitals, across a 12-month endline (post-implementation) period. Our unit of observation and analysis was the patient consultation, and we used routine health system data on all eligible patient consultations during the endline period.

Our trial clusters consisted of a township hospital, including all the primary care doctors working in the township hospital, plus all eligible patients in the catchment area. We chose a cluster-randomised design as elements of the intervention are delivered at the level of the township hospital and cannot be removed once delivered. We report the trial results here following the Consolidated Standards of Reporting Trials reporting guidelines for cluster trials (see Supplementary CONSORT checklists).

Settings

The study was conducted in two counties, Nanxiong and Lechang (1 million population in total), within Shaoguan Prefecture in Guangdong Province, China. Shaoguan has a median per capita GDP of US$8,000, representing a low-income setting in China and globally. Most residents are enrolled in the urban-rural resident medical insurance scheme, which covers 60%-70% of healthcare expenses at township hospitals including consultation fees, medication costs, and diagnostic

tests, with an annual reimbursement cap of 300 RMB. Primary care in rural China is mainly provided by primary care doctors in township hospitals, known as family doctors, and village doctors.

Township hospitals provide most of the care for common acute illnesses. Family doctors can practice in township hospitals and prescribe antibiotics after either obtaining their Junior Medical College Diploma, which involves 3 years of medical education after high school in a medical institute, or a Bachelor of Medicine, which is equivalent to an MBBS and involves five years of medical education after high school. The current national guidelines on antibiotic use available to family doctors are in a 340-page document written by physicians from teaching hospitals and are not user-friendly[42]. The consultation time available in township hospitals is usually 5 to 10 minutes.

Village doctors are community healthcare workers who are managed by township hospitals and have received basic medical training equivalent to a secondary school level. Village doctors are not allowed to prescribe antibiotics, but we included them in our training workshops because our previous work found that they may sell small amounts of self-purchased antibiotics, which could increase patients' demand for antibiotics when they visit township hospitals[32].

In Shaoguan, China, all patients who seek medical care at township hospitals are registered in the EMR system. According to EMR data from the study township hospitals, all outpatient consultations for respiratory infections at the study township

hospitals resulted in a prescription, often including a Traditional Chinese Medicine, antibiotics or symptomatic medication. This is due to the cultural expectation among patients of needing to receive some medication after a consultation (typically at least a traditional Chinese medicine) to feel adequately treated. This is also reflected in our process evaluation work (to be published later).

Eligibility criteria

Our pragmatic eligibility criteria for clusters only required that township hospitals had to have functioning and extractable EMR systems to allow data collection. All township hospitals in our research area used a unified prescription system connected throughout the province, capturing information on all consultations and prescriptions in primary care practice. We therefore included all township hospitals within our study area, other than the two where we conducted our pilot study.

Our eligibility criteria for eligible patient consultations required that patients were aged 0-75, were given a primary diagnosis of any ARI by a family doctor and were issued a prescription. The eligible ARI diagnoses were URTIs of multiple and unspecified sites, nasopharyngitis, pharyngitis, tonsillitis, bronchitis, sinusitis, otitis media, streptococcal pharyngitis/tonsillitis, and were based on the International Classification of Disease 10th Revision (ICD-10). Many township hospitals lacked the capacity to differentiate between viral and bacterial infections. As a result, all the above diagnoses were included. Patients were ineligible if they were diagnosed with a non-ARI, pneumonia (as it is often severe and clinically challenging), or any chronic

conditions including asthma, chronic obstructive pulmonary disease (COPD), any non-infective or non-acute disorders, non-respiratory infections, immunological deficiencies, tuberculosis, or any form of cancer. Since less than 7% and 3% of asthma[43] and COPD[44] cases are diagnosed and treated in China, we excluded asthma and COPD exacerbations in practice. Pneumonia, asthma, or COPD exacerbation is always treated in hospitals at the county level or above. Sex of patients was recorded in the electronic medical record system by self-report at the time of registration. Both males and females were eligible, and sex was prespecified as a covariate in the statistical analysis plan.

Trial registration, randomisation and masking

Our trial was registered at ISRCTN on 18 August 2019 before the trial randomisation, which was conducted on 16 December 2019 by the statistician (JPH), who randomly assigned all clusters to the intervention or control groups in a 1:1 ratio, stratified by county and masked to cluster identities. Given there were 17 clusters per county, one county received a 9:8 allocation ratio and the other a 8:9 ratio. A computer program was written to randomly allocate each county to one of the allocation ratios, enumerate all possible cluster allocations for each county, and then choose one allocation for each county for the trial. Patients were not informed about the trial, but due to the nature of the interventions it was not possible to mask the doctors. We employed the PROBE design to mask data extractors and the data analysts[45].

Intervention procedures

The full details of the intervention procedures are available in Table S7 (and reported in our protocol[33]). Based on the existing Chinese guidelines on antibiotic use in clinical care[42], the World Health Organization's (WHO) toolkit for AMR programmes[46] and the UK's guidelines on antibiotic use for self-limiting respiratory infections[47], we previously developed a comprehensive but concise (20 page) set of guidelines for family doctors on treating ARIs, with a focus on appropriate antibiotic use. In each township hospital we first conducted a half-day training workshop, where we guided township hospitals on how to create an antibiotic stewardship team. During these sessions, we also trained all family doctors, pharmacists and village doctors, using case discussions, role plays, and question-and-answer sessions, on how to apply the guidelines[14], which we provided to them in printed form and through access to a custom (WeChat-based) smartphone app. We also trained doctors on how to communicate with patients and caregivers to educate them about appropriate antibiotic use and manage their demand for antibiotics. Township hospitals also provided leaflets and ran videos in their public areas providing information for patients and/or caregivers on appropriate antibiotic practices, and following consultations patients and/or caregivers were given access to a QR code to access information on appropriate antibiotic practices through a public WeChat account (patient information was blinded for privacy). We also improved the electronic prescription system in the EMR system to include pop-up information during consultations to remind family doctors when to request laboratory tests and to

provide recommendations on when antibiotics may be required or not and, if so, which antibiotics.

Following the training, in each township hospital the antibiotic stewardship team (as instructed) implemented antibiotic peer-review meetings with all the family doctors in their township hospital within their facility's routine monthly management meetings. Before each meeting, prescription data were automatically extracted from the EMR via a pre-designed program and presented on the app to inform family doctors about their monthly antibiotic prescription rate for ARIs compared to the average rate for their township hospital. If their prescription rate exceeded the average among all doctors, they were asked to explain why to the stewardship team using the app. The research team also conducted monthly supervisory visits to the intervention group township hospitals during the endline period to ensure compliance, gather feedback, address questions, and collaborate with the antibiotic stewardship team on issues and solutions.

Control procedures

In the control group, family doctors treated patients with ARIs using existing clinical practices. We did not incorporate any elements from the antibiotic stewardship program implemented in the intervention group, such as the app or EMR system enhancements. Although routine monthly management meetings took place in the control group township hospitals, we did not intentionally modify how they operated.

Pilot work

Prior to the trial we piloted the interventions in two township hospitals for three months, with the results meeting our pre-determined continuation criteria: the number of prescriptions met the minimum requirement, and over 80% of family doctors received the training and used the intervention guidelines[33].

Outcome measures

The primary outcome was a binary measure of whether an eligible patient consultation where any ARIs were diagnosed resulted in any antibiotics being prescribed by the doctor. Given that most ARIs are viral and do not benefit from antibiotics, we chose this widely used outcome as a proxy to measure unnecessary antibiotic prescribing[48].

We also collected a range of secondary outcomes related to prescribing different classes of antibiotics and other medicines. Among those eligible patient consultations where any ARIs were diagnosed and where any antibiotics were prescribed we measured, as binary indicators, whether those antibiotic(s) prescribed included 1) any broad-spectrum antibiotics (quinolones, amoxicillin-clavulanate, second- and third-generation cephalosporins, and azithromycin and clarithromycin)[49], 2) any fluoroquinolone antibiotics, 3) any antibiotics delivered by intravenous injection, 4) any antibiotics in the Access group of the WHO's 2019 Essential Medicine List classification (antibiotics from the Reserve group are not allowed to be prescribed in township hospitals)[50], or 5) whether two or more antibiotics were prescribed. We also collected secondary outcomes to evaluate whether the intervention affected the risk

of being prescribed other key medicines. Among all eligible patient consultations where any ARIs were diagnosed we also measured, as binary indicators, whether the patient was prescribed any 6) traditional Chinese medicines or 7) glucocorticoids. We also collected secondary outcomes to evaluate the possible financial effects on patients. Among all eligible patient consultations where any ARIs were diagnosed we measured 8) the total cost of all prescribed medicines and 9) the total cost to the patient for the consultation, including all prescribed medicines, any tests, and the consultation fee, reported in Chinese renminbi.

To evaluate the safety of the intervention, we investigated whether it increased the risk of patients developing serious infections, possibly due to withholding or delaying the prescription of antibiotics. We assessed this risk using a binary indicator of whether a patient was hospitalised for any respiratory infection or sepsis (in any hospital at any level) in the Shaoguan Prefecture within 30 days following an eligible consultation at a township hospital where any ARIs were diagnosed (with any eligible consultations occurring within 30 days following that consultation being ignored).

We reported all these trial outcomes as outlined in our protocol. Outcomes regarding the process evaluation, costing study and long-term follow-up study will be reported separately elsewhere.

Data collection

Prescriptions from all eligible patient consultations were exported from the EMRs of all participating township hospitals. As these prescriptions are anonymised our ethics

committee agreed we did not need to seek patient consent. Using the EMR, we collected comprehensive prescription information as well as information on key patient and family doctor characteristics. For all prescriptions we encrypted and de-identified all personally identifiable information prior to extraction (an encrypted unique number was autogenerated for each patient at the data source for analysis purpose), and collected information on age, sex, date of visit, diagnoses, medicines prescribed, costs and payment method. For all family doctors we also collected information on age, sex, years' experience, and education level, which was linked to each prescription via unique prescriber IDs. We also collected information regarding hospitalisations for the safety outcome. We matched hospitalisation data to the township hospital EMR prescription database at the data source using an encrypted unique identifier.

Sample size calculation

For our primary outcome, based on previous data[14], we assumed a control group antibiotic prescribing rate of 80% and an intra-cluster correlation coefficient of 0.14 in the intervention group and 0.09 in the control group. Using all 34 eligible township hospitals in the two study counties[14], to detect a reduction of 15 percentage points or greater with 80% power, via a two-tailed hypothesis test at a 5% significance level (accounting for the stratified randomisation design), required at least 500 eligible prescriptions per township hospital, which our pilot work suggested was feasible for our endline period[33].

Statistical analysis

We fully described our statistical analyses, including any changes from the protocol, in our statistical analysis plan and only provide key details here. We computed standard summary statistics to describe our sample at both the patient-consultation level and cluster level by treatment group and data collection period, and we computed standard summary statistics to summarise all outcomes at the patient-consultation level by treatment group and data collection period. We estimated the causal effect of the intervention on all outcomes at the patient-consultation level[51], and in our statistical analysis plan we fully defined all treatment effects in terms of estimands, following the *ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials*[52].

We estimated the average treatment effect on the primary outcome as the intervention minus control risk difference, using marginal effects methods[53] applied to a generalised linear model with Bernoulli errors and a logit link, and computed the corresponding 95% confidence intervals using the bias-corrected and accelerated bootstrapping approach, with resampling at the cluster level to account for the multi-level clustering in the data[54]. We computed the corresponding two-tailed p-value by inverting those confidence intervals[55]. For our primary analysis we adjusted our estimate for a range of pre-randomisation covariates to increase precision[56]. These were chosen for their assumed prognostic relationship with the outcome: the sampling strata (county), the baseline cluster-level mean of the outcome, the baseline cluster-level number of eligible patient consultations, the patient's age, age^2,

sex, payment method (out-of-pocket/insurance), and diagnosis (upper respiratory tract infection/acute bronchitis/acute pharyngitis/acute tonsillitis/acute otitis media/acute sinusitis, acute nasopharyngitis, streptococcal pharyngitis or streptococcal tonsillitis), and the family doctor's sex, age, age^2 and education level (bachelor of medicine/junior medical college diploma/ high school diploma). As a sensitivity analysis, we also computed a corresponding crude estimate that only adjusted for the sampling strata. For this treatment effect, under the estimand framework we followed a treatment policy approach to dealing with any intercurrent (post-randomisation) events, which is analogous to an intention-to-treat approach, by analysing all outcomes according to the original randomisation of township hospitals, irrespective of any non-compliance at any level. As per our statistical analysis plan, we also estimated whether there was any effect modification of the intervention's effect on the primary outcome by patient sex, patient age (≤14 vs >14), or between the first and the second halves of the endline period.

We used the same approach as for our primary outcome to estimate treatment effects on our outcomes measuring prescribing of traditional Chinese medicines and glucocorticoids, and a similar approach for our outcomes measuring costs (but using generalised linear models with gamma errors and log links to estimate mean differences, given the non-negative, right-skewed data)[57]. However, our secondary outcomes relate to prescribing of specific classes of antibiotics only applied to the subgroup of eligible patient consultations where antibiotics had been prescribed. As prescription occurs post-randomisation this is likely to induce selection bias[58]. For

these outcomes we therefore computed treatment effects as risk differences using a regression-based approach designed to adjust for this likely bias[59]. This approach took a principal stratum strategy to dealing with the intercurrent event of antibiotic prescription and estimated the treatment effect among the principal stratum of patients who would be predicted to receive antibiotics for their ARI irrespective of their treatment allocation. For these outcomes we necessarily only computed adjusted estimates.

We also computed corresponding treatment effect estimates for all binary outcomes on the risk ratio scale to complement the risk difference measures. We did not correct our secondary outcome analyses or primary outcome subgroup analyses for multiple testing, which should be considered exploratory. There were no missing data. We used R statistical software version 3.6.1 for our sample size and randomisation computations and version 4.4.1 for our data analyses.

Ethics and Inclusion Statement

This study was designed and implemented in close collaboration with local investigators, health authorities, and frontline clinicians in Guangdong, China. All authors contributed substantially to study conception, design, data collection, analysis, and interpretation. Decisions on authorship and order reflect the International Committee of Medical Journal Editors (ICMJE) criteria and were made transparently, ensuring fair recognition of contributions from both local and international partners. The study fostered equitable collaboration by engaging local

research staff in protocol development, training, and capacity building in pragmatic trial methodology and data analysis. The intervention was co-developed with input from local health authorities, township-level physicians and patients to ensure cultural and contextual appropriateness.

Ethics approval

The study obtained ethical approval from the Ethics Committee of the First Affiliated Hospital of Guangzhou Medical University, China (2019-53) and the University of Toronto Office of Research Ethics, Canada (38265). Since we only used anonymised routine patient prescription data, our ethical committees agreed that no individual patient consent was required. This collaborative and inclusive approach is consistent with Nature Medicine's policies on equitable authorship and ethics in global health research.

Data Availability

Anonymised patient-level data underlying the results of this study are held at the Guangzhou Institute of Respiratory Health. Data will be made available for non-commercial research purposes to qualified investigators upon submission of a data access application, which must include a brief study protocol and a signed data use agreement compliant with China's Public Data Safety Law. Applications should be sent to the corresponding author (Prof. Nanshan Zhong, nanshan@vip.163.com) and will be reviewed by the institutional data access committee. Decisions on access will

be provided within two months of application as approvals are required from both academic institute and Shaoguan Health Bureau to ensure compliance with current legal and regulatory requirements. Approved applicants will be granted secure access to the data repository for a time-limited period.

Code Availability

The statistical code used for the analyses in this study is available for non-commercial research purposes upon submission of a request to the first author (Prof. Xiaolin Wei, xiaolin.wei@utoronto.ca) and the chief biostatistician (Dr. Joseph Hicks, J.P.Hicks@leeds.ac.uk). Applicants must provide a brief description of the intended use and agree to a code-sharing agreement. Requests will be reviewed within two weeks, and approved applicants will be provided with the relevant R scripts via a secure repository.

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