A complex intervention to reduce antibiotic prescribing in rural China: a cluster randomised controlled trial

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Summary

Background Excessive use of antibiotics is a widespread problem. We aim to evaluate the efficacy of a multifaceted intervention for reducing antibiotic use in patients with respiratory tract infections (RTIs).

Methods In this two-arm cluster randomized controlled trial, we enrolled patients aged 18+ with symptomatic RTIs at 40 township health centers (THCs) selected from 10 counties in Anhui, China. The THCs were randomized using an online tool ('Sealed Envelope') to intervention or usual care (1:1 ratio), stratified by baseline antibiotic prescribing and with random block sizes (4 or 6). The intervention had five components: a half-day clinician training, a WeChat-based peer support group, a decision aid, a poster commitment letter and a patient leaflet. The primary outcome was whether antibiotics were prescribed at the index consultation. Secondary measures included defined daily dose (DDD), illness recovery rate, re-visits to other care-givers or retail pharmacies and incremental cost-effectiveness ratio (ICER). These measures were analyzed using generalized linear mixed modeling controlling for clustering. The study was registered as ISRCTN30652037.

Findings Between December 2021 and September 2022, 1053 patients were recruited (intervention, 21 THCs, n = 552; control, 19 THCs, n = 501), using consecutive sampling. Antibiotic prescribing rate was 55.25% and 66.67% in the intervention and control arms (Odds ratio 0.52, 95% confidence interval [CI]: 0.27, 0.98; p = 0.044). The intervention group also had lower, significant or non-significant, differences for other markers of antibiotic use: DDD (1.57 vs 2.75); prescriptions of two or more types of antibiotics (9.78% vs 11.58%); obtaining antibiotics from retail pharmacies (3.68% vs 5.78) or from other clinics (2.70% vs 4.05%). The intervention resulted in a cost reduction of 9.265 RMB (1.471 USD) per consultation episode and an ICER of –7769.98 RMB or –1233.33 USD/QALYs. The intervention did not encounter any major adverse event.

Interpretation The intervention package was effective and cost-effective in reducing antibiotics prescribing without adverse effects.

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Research in context

Evidence before this study

We searched the PubMed and the two Chinese academic databases (CNKI and CMB) for published randomized controlled trials (RCTs) on antibiotic stewardship at primary care settings before December 31, 2023. The search terms included: antibiotics, respiratory tract infection, primary care and randomized controlled trial. Although 82 RCTs were found, clinical and methodological heterogeneity limited our quantitative analysis. The interventions comprised guideline-based recommendations, clinician communication training, electronic decision support systems or models, individualized antibiotic prescribing feedback reports, delayed prescribing, point-of-care test, social norm feedback presentation, patient information leaflets and others. These interventions resulted in non to moderate effects. The effect size depends heavily on a whole range of contextual factors including: baseline rates of antibiotics prescription; incentives and guidelines/regulations with the health systems, perceptions and competence of the clinicians, socio-cultural characteristics of the patients and intervention strategies. It is well recognized that multifaceted interventions were more effective than single measures in reducing overall antibiotic prescribing. However, evidence on appropriate prescribing, adverse consequence and cost-effectiveness is insufficient.

Added value of this study

Published trials on antibiotics stewardship in China are limited thought the country is among the largest antibiotics consumers worldwide. This study aims to test a complex intervention package to contain excessive antibiotics prescribing and consumption at township health centers in an inland province of China. The package was tailored to key existing problems identified via previous studies in Anhui and China and tested effective in reducing antibiotics prescribing especially defined daily doses without adverse effects. The intervention also reduced direct medical cost incurred per consultation episode.

Implications of all the available evidence

The best evidence supports the use of multifaceted interventions incorporating proven ingredients like specific education interventions for clinicians and patients and electronic decision support etc., to reduce overall antibiotic prescribing for acute RTIs, especially in areas with relatively high prescribing rate. Future studies should better evaluate measures of appropriate prescribing, prescribing rate vs dose, adverse consequences such as hospitalization, sustainability, resource use, and the impact of potential effect modifiers.

Introduction

Excessive use of antibiotics is a widespread problem and a key driver of antimicrobial resistance.[1] Over half of antibiotics are used for humans and primary care accounts for 81% of all human antibiotic prescriptions, with the largest proportion (46%) being used for symptomatic respiratory tract infections (RTIs).[2] The rate of unnecessary or inappropriate antibiotic prescriptions for patients with RTI has been estimated to range from 36% to 68% in high income countries (HICs) and much higher in low and middle income countries (LMICs).[3–5] Excessive antibiotics use is also prevalent in China. Studies between 2009 and 2018 found that over half of all outpatients and around 70% of inpatients of hospitals in China were prescribed one or more antibiotics.[5–7] Between 70% and 90% of patients visiting township health centers (THCs) and village clinics with symptoms of RTIs were prescribed antibiotics.[8–10] In terms of person-times of health services, 72.8% were provided by primary providers (i.e., THCs and village clinics in rural areas) and about half of these services were for RTIs.[11] Unlike UK and other western countries, China does not have strict referral systems and people can get antibiotics from both medical care facilities and retail medicine shops.[8]

Since 2009, China has launched a series of initiatives to optimise antibiotics use. These include the medication audit system,[12] the special antibiotics use rectification program, the essential medicines scheme,[13] the zero-mark-up policy,[14] the antimicrobial resistance monitoring network,[15] and the 20%-limit of antibiotic prescribing for all outpatient episodes.[16] There has been a substantial reduction in the antibiotic prescription rate at county and higher-level hospitals but rates still remained as high as 82.3% and 87.8% for RTIs in THCs and village clinics.[8,17]

The persistently high rate of antibiotics prescription in China's THCs and village clinics can be attributed to reasons of three categories, i.e., clinician, patient and structural determinants. For clinicians, a large part of them (especially those working with village clinics) came from the so-called "barefoot doctors" with limited formal medical training.[18,19] Most of them are used to widespread use of antibiotics and perceive prescribing antibiotics as common practice amongst peer clinicians and a common expectation among service-seekers.[20]

They also believe that use of antibiotics: prevents potential bacterial infections and legal accusations; helps maintain good relationships with patients; and avoids treatment delay due to diagnostic uncertainty.[20] For patients, public campaigns about antibiotic use have been limited, and there is poor knowledge of antibiotic resistance and other side effects.[21] For structures, there is a generally lack of point-of-care testing. There are also pervasive incentives. For instance, although clinicians are paid partly by a fixed per-person subsidy for those with THCs and a public-service-fee for those with village clinics by the local government, their earnings are dependent on their medical care revenues to a large extent.[20] In addition, practices at primary care level are least monitored due to the large number of facilities compared with limited regulatory capacity.

In response to these challenges, we conducted an interdisciplinary mixed methods study to characterise antibiotic prescribing and dispensing patterns and drivers in rural health facilities in China.[22] Based on this and on previous work on antimicrobial stewardship in Europe and China,[23,24] we developed a complex intervention package to reduce RTI-related antibiotic prescription using the Person-Based Approach.[22] The package consisted of five ingredients (i.e., a half-day clinician training, a WeChat-based peer support mechanism, a computerized decision aid, a public commitment letter, and a patient leaflet). Complex antimicrobial stewardship interventions have been shown to be effective in similar contexts.[25,26] The package was originally designed to be tested in village clinics via a cluster randomized controlled trial during 2019 and 2021 in Anhui, China. Due to the outbreak of the COVID-19 pandemic, village clinics were temporarily prohibited from providing treatment to RTI patients in the province.[22] We finally implemented a trial in THCs aimed at primarily on assessing the effectiveness of the package in reducing antibiotic prescribing. We also aimed to evaluate the package using a number of secondary measures including the impact of reduced antibiotic use on patient illness duration and recovery, and cost-effectiveness of the intervention.

Methods

Study design and approval

The study was a parallel-group multi-centre cluster randomized controlled trial. The cluster design was selected because the health centre staff training was part of the intervention. The trial protocol was registered at ISRCTN (No. ISRCTN30652037) and further details are available in the published version at https://doi.org/10.1136/bmjopen-2020-048267. The trial implementation took place in 40 THCs in Anhui, China during December 2021 and September 2022. A baseline audit was conducted in all participating THCs to characterize the prescribing rates and service levels in each cluster and to inform the randomization. The research ethics was reviewed and approved by the Anhui Medical University Biomedical Research Committee (No. 20180259). In addition, the study underwent due diligence checks and was registered at the University of Bristol (Case No: 2020-3137).

Selection of THCs and clinicians

As specified in our protocol paper, participants were originally planned to be chosen randomly from the south, middle and north of Anhui.[22] But, after random selection of two prefectures from each of the three subareas, we were then advised, by Anhui Provincial Health Commission, not to send field data collectors forth and back across the whole province after the outbreak of COVID-19 pandemic. So, the trial had to be focused on the north of Anhui, including two prefectures and all the 10 counties. Putting together, these counties have a population of 13.186 million people and a land scape of 18,492 square kilometers. Per-capita GDP in 2023 for the two prefectures was 44700 RMB (6272USD) and 40970 RMB (5749USD) respectively.

The participant THCs and clinicians were chosen as follows: 1) all the 10 counties in the two prefectures were included; 2) 4 nonadjacent THCs were randomly selected from each county (for details, please see 3.1 of Supplement File S1); 3) informed consent was obtained from the managers of the selected THCs and each THC unable to participate was substituted by a randomly selected THC from the remaining THCs within the same county; 4) each THC enlisted one internal medicine outpatient clinician who had the largest number of RTI patients and was most influential among all the practitioners on care of RTI within the THC and willing to join the trial (i.e., to receive the evaluation and implement the intervention package in the intervention arm or practice usual care in the control arm). A THC in Anhui generally has 1 to 3 clinicians on care for RTI patients. Only the enlisted one clinician from each THC in both intervention and usuals care arms was evaluated.

Randomisation and blinding

Randomization of the site THCs proceeded in two steps. First, a baseline audit survey was conducted in the 40 site THCs, aimed at recruiting approximately 10 RIT patients from each of the participant clinicians enlisted above. Then an independent statistician with the University of Bristol performed the randomization using an online tool. The online service (Sealed Envelopes) created a stratified, blocked randomization list with THCs allocated at a 1:1 ratio, to the intervention or usual care group. The random block sizes were 4 and 6, stratified by baseline antibiotic prescribing rate (above and below median). Clinicians and patients in both the arms were concealed from the primary purpose of the study. Instead, they were told that: the study comprises

repeated observations and surveys; the observations were used to identify eligible RTI patients; while the surveys, to follow these patients for multiple time-points so as to assess the processes and effects of different self and professional care, including antibiotic use, on their disease recovery. In addition, the statisticians conducting the analysis were kept blinded from allocation until the quantitative analysis was complete.

Participant patients

All presenting patients to the participating clinicians in the 40 THCs during the trial evaluation weeks who met pre-set eligibility criteria were invited by research staff to take part in the trial (patients of all the non-participating clinicians were not considered). The inclusion criteria were any presenting patient who was: 18 years or older; clinically diagnosed with RTIs at this appointment; and able and willing to complete the planned face-to-face and telephone interviews. Written informed consent was sought from all participant clinicians and patients who were able to read and write. For illiterate patients, oral consent was audio-recorded after explanation by the field researchers of the consent letter. Written consent was also sought from designated managers of the 40 THCs.

The patient recruitment was carried out by 10 data collectors. Each of them performed "consecutive" recruitment and data collection in some 4 THCs, in a THC-by-THC way. The consecutive recruitment in a specific THC started from the day when the data collector came to the THC and each presenting patient to the participant clinician's consultation room from that day was observed for eligibility and then recruited if eligible until the pre-set goal of 30 patients had reached. Then he/she moved to another THC.

Intervention ingredients

In addition to usual care, the intervention group received an intervention package incorporating: a half-day clinician training, a WeChat-based peer support group, a decision aid (including both online & paper versions), a poster commitment letter and a patient leaflet.

The clinician training presented evidence of overuse of antibiotics in rural China and highlighted the dangers of AMR, to motivate clinicians to reduce their antibiotic prescribing. The training also reviewed the national antibiotic prescribing guidelines for RTIs, especially these do not recommend antibiotics for most of the RTIs for which clinicians currently prescribe. Other topics included: common misperceptions about antibiotic use; purpose and content of the commitment letter; use of the decision aid; and use of patient leaflet, communication strategies and tips (e.g., using the patient's words and narrative stories, asking for responses or rephrases from the patient, avoiding critics).

The WeChat group was established to provide a venue for sharing and discussing experiences, problems and peer support for avoiding unnecessary antibiotic use among peer clinicians in the intervention group. Clinicians from all THCs assigned to the intervention arm were included in the WeChat support groups. They were asked to organise the first WeChat meeting within 1 month of completing the intervention training, and the second one a month later. They were provided with a guide for these two meetings (see guide in Supplement File S1) in which they were asked to discuss 2 to 5 RTI cases, focusing on the reasons for prescribing or not prescribing antibiotics and the challenges. After the first two structured meetings, they were asked to continue the WeChat Peer Support Groups with less structured asynchronous discussions.

The decision aid was developed to provide a quick guide to the national antibiotic prescribing guidelines and to facilitate the consultation procedures including production of tailored patient information leaflets where possible. Adapted from our previous project, the decision aid contains the following sections: patient eligibility criteria; patient symptoms (allowing clinicians to record what symptoms patients are suffering from); diagnosis, patient reassurance and prognosis (allowing clinicians to record their diagnosis, and provide appropriate patient reassurance and prognosis for each type of RTI patient); treatment recommendations for each type of RTI patient from Chinese National Guidelines for Treating Acute Respiratory Tract Infections; table of symptomatic treatment options for RTI patients and safety netting advice (when to come back to see the doctor).

The public commitment letter stated the clinicians' commitment to reducing the overuse of antibiotics and was displayed in areas where it would be easily seen both by patients and clinicians. It was designed to encourage the clinicians to uphold their public declaration of practicing optimal antibiotic prescribing and raise the patients' awareness of the harms of excessive antibiotics use.

The patient leaflet, designed to be taken away by the patients, gave brief accessible information covering the reasons for not prescribing antibiotics and safety-netting advice. The leaflet supports the clinician not to prescribe by giving them something to give to patients that explains the reasons for the decision, which also supports patient acceptance. The leaflet consisted of a pictural story plus eight-item question and answer about RTIs and antibiotics use addressing common misperceptions; clinicians also had the additional option of tailoring the leaflet to the specific symptoms of individual patients.[22]

In addition, all the clinicians on care of RTI in any intervention THC were provided with and taught/encouraged, by the trained clinician, to use the patient

leaflets. The commitment letters were requested to be posted in places visible to all the visiting patients.

Usual care was not constrained in any clinic - comprising existing routine procedures and management of patients with RTIs. This typically included taking a history, physical examination, laboratory tests, documenting clinical diagnosis, and prescribing treatment.

Outcome measures

The primary outcome assessed in this paper was antibiotics prescribed at the initial consultation as recorded by the clinician and provided by the THC for all enrolled patients. Secondary measures documented in the current paper included DDD of prescribed antibiotics and prescription of two or more types of antibiotics at the index consultation (collected from the THC systems) and self-report by participant questionnaires for: whether medicines or antibiotics were bought from retail pharmacies after the initial consultation; visits to other clinics for the same disease after the initial consultation; any other medicines/antibiotics obtained for this illness; patient ratings of illness recovery; quality adjusted life years (QALYs) measured by EQ-5D-5L; and resource usage and costs incurred.

In addition to the above measures, our trial protocol also included patient satisfaction and attitude, beliefs and understanding of the patient leaflet as the secondary endpoints. Besides, we performed post hoc process evaluation. These will be published separately elsewhere.

Sample size

We aimed to detect an absolute difference of 15% in antibiotic prescribing between the intervention (60%) and usual care group (75%) with 90% power and alpha 0.05, requiring 203 patient consultations for RTI in each arm. We assumed an intraclass correlation coefficient (ICC) of 0.05 based on prior research, hence a design effect of 2.45,[5,17] requiring 995 patients. Allowing for a loss to follow-up rate of 10%, we aimed to recruit 1106 participants from 40 clusters, with an average cluster size of about 30 patients per THC.

Data collection

In addition to data extracted from the THC systems, we collected patient-reported data from one face-to-face exit interview and three follow-up telephone interviews scheduled on day 7, 14 and 21 after the initial consultation. Led and supervised by two senior researchers, 10 trained graduate and college students administered the interviews. They all came from Anhui Medical University. The follow-up interviews applied only to patients who had provided their telephone number(s) during the exit interview (patients who had provided telephone numbers of their spouse, sons/daughters or other relatives were excluded). Those who reported "full recovery" during the previous interview were excluded from subsequent interviews. The interviews used structured questionnaires comprising five main areas including: patient social demographics (e.g., sex and age as indicated by the patient's ID card, education, and medical insurance); disease history before initial consultation (e.g., symptoms, days since symptom onset, self-medication); prescription of antibiotics and other medicines at the initial consultation; ratings of disease severity, and recovery; EQ-5D-5L; and service and medicine use following initial consultation. Data about the first three aspects were solicited in the exit interview. EQ-5D-5L and severity were collected at the exit and day 7 interview. Questions about illness recovery were asked at the day 7, 14 and 21 interviews, while service and medicine use following the initial consultation was documented at the day 21 interview or in earlier interviews when the patient had reported "full recovery".

Data about costs were collected using micro-costing[27] and considered mainly direct medical costs including RMB spent on registration, medicine, consultation time, clinician training, printing of patient leaflet and commitment letter. Taking the example of costing of clinician training, it proceeded in two steps. We first estimated the total cost spent on the half-day training, including rent of space, fees for the rounded trip to and from the hotel, production of training materials etc. We then divided the total training cost by estimated total number of RTI patients served by the trainee clinicians in a whole year. This was based on the assumption that the training effect can last for at least one year or can be maintained via an annual reinforcement training similar to that we had implemented. Similarly, the cost of consultation time for specific visit was estimated by multiplying the total minutes of the consultation by unit-cost (or per minute cost) of the attending clinician. Here, the total minutes was recorded by our observer; while the unit-cost was calculated as AEM/AMM. AEM stands for the clinician's annual earnings from medical care; while AMM defines the clinician's annul time (in minutes) spent on medical care.

Statistical analysis

The data analysis centered on the primary and secondary outcomes specified above, using an intention to treat basis regardless of adherence to allocated groups.

The primary analysis used a generalized linear mixed model (GLMM) framework with a logit link and a random effect for clinics, allowing for the clustering of participants within clinics. Results were reported as odds ratios with 95% confidence intervals. The analysis of secondary outcomes also used GLMM with a logit link for binary outcomes (e.g., prescription of 2 or more types of antibiotics, buying medicines from retail pharmacies after initial consultation, visits to other clinics for the same disease after initial consultation); or a Gaussian link for ordinary or continuous outcomes

(e.g., illness recovery rating on day 7, 14 and 21 after initial consultation, EQ-5D-5L rating on day 7 after initial consultation). All models controlled for clustering and patients' age, sex, illness duration, and disease severity rating and all primary and secondary outcome measures on day 0 or baseline (specified in the Statistical Analysis Plan (SAP)). All covariates (e.g., patients' age, sex, disease severity rating on day 0 and illness duration prior to the consultation) were treated as fixed effects and the cluster level variables (THC) was treated as a random effect, allowing the model to correctly account for the clustering of participants within THCs.

We compared the cost and effectiveness of the service in the intervention and usual care arms from mainly patients' or payer's point of view. Bootstrapping was used in generating the average total cost for the two arms. The effectiveness was measured in terms of disease recovery and severity ratings and gains in QALYs derived from EQ-5D-5L ratings using published formula,[28] and incremental cost-effectiveness ratio (ICER) defined as: (total cost in the intervention arm - total cost in the control arm)/(summed QALYs in the intervention arm - summed QALYs in the control arm).

Two-sided t tests were used to estimate the statistical power of the differences in the costs and effectiveness between the intervention and usual care groups. See Supplement S2 for the SAP.

Adverse event monitoring and report

The study engaged two researchers and two THC clinicians on care of RTI patients to track, manage and document adverse events.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Recruitment and ascertainment

The trial was implemented in 4 stages (Fig. 1). First, a total of 40 THCs were determined from two rounds of random selection and recruitment. Second, a baseline audit survey was carried out which covered all the 40 THCs and recruited 769 RTI patients. Third, the 40 THCs were randomly assigned to control (n = 19) and intervention (n = 21) groups by an independent statistician based on the audit survey. Fourth, a set of evaluation surveys were conducted, after 10-months of implementation of the 5-ingredient package in the intervention arm and usual care only in the control condition, which recruited 1053 subjects in total, with 552 and 501 from the intervention and usual care groups respectively. Recruitment was 48 and 99 patients short of planned recruitment in the intervention and control arms respectively. This was because patient recruitment in some THCs turned out to be exceptionally slow due to occasional occurrence of COVID-19 cases. The final response rates to the exit survey and interviews on day 7, 14, and 21 were 99.10%, 94.84%, 69.29%, and 65.84% for the intervention group and 96.2%, 89.60%, 63.58%, and 59.54% for the usual care group. No major adverse event was reported.

Characteristics of THCs and clinicians

As shown in Supplement File S2, the 40 township health centers had a median of 6768 annual RTI outpatient visits, 67.5 beds, and 15.5 clinicians. All the centers had hematology and radiology laboratories, and 29 (72.5%) had computed tomography capabilities. The participating clinicians comprised 35 (87.5%) males and 5 (12.5%) females, and only 52.5% (21/40) of them had an undergraduate college education in medicine. They aged 44.0 ± 8.0 years on average and had 22.1 ± 7.7 years of experience as practicing clinicians. The 40 THCs had an overall prescribing rate of 67.2% (517/769) for patients presenting with RTIs at the baseline audit survey.

Description of patients

The characteristics of patients recruited are presented in Table 1, with balanced sexes, the majority (70.94% or 747/1053) aged over 40 years, and illiterate patients accounting for 28.96% (305/1053). Over 90% (948/1053) of the patients had rural residency and medical insurance. The time interval between onset of RTIs and the first primary care visits ranged from 0 to 15 days, with a median being of 3 days. The most frequently reported symptom was cough (72.74% or 766/1053 of the patients). The rate of prescription of antibiotics was estimated as 55.25% (or 305/552) vs 66.67% (or 334/501) in the intervention and usual care conditions. While the defined daily dose (DDD) between the two groups were calculated as 5.317 ± 3.127 vs 6.016 ± 3.064, 1.049 ± 0.536 vs 1.264 ± 0.741 and 2.831 ± 2.900 vs 4.112 ± 3.651 for oral, subcutaneous/intravenous and all antibiotics respectively. The largest composition of prescribed antibiotics by WHO AWaRe was watch (62.00% in intervention and 52.00% in usual care group), followed by access (37.28% vs 46.43%). QALYs as derived from the EQ-5D-5L ratings (please see Supplement File S2) were 0.90 in the two arms.

Modeling of outcome measures

Table 2 summarizes the statistics from our GLMM of the primary and secondary measures. Antibiotic prescribing rates were estimated as 55.25% (305/552) and 66.67% (334/501) in the intervention and usual care groups respectively. The likelihood of being prescribed antibiotics was reduced in the intervention arm by 48% (odds ratio 0.52, 95% confidence interval [CI]: 0.27, 0.98; p = 0.044). The intervention group also scored lower than the usual care group for the other measures of antibiotic prescribing, with a lower rate of

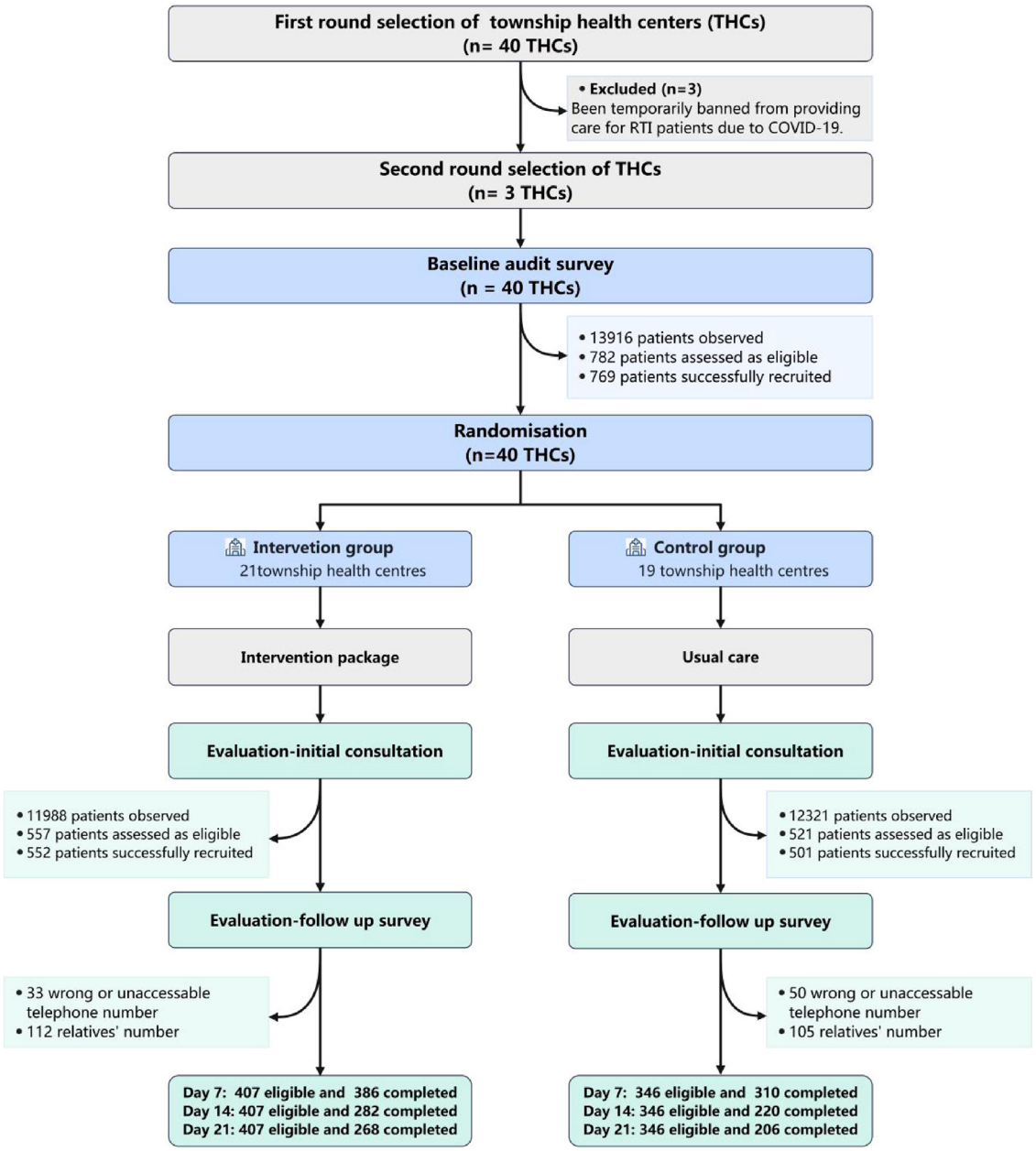

Fig. 1: **Trial flowchart** (Note: the second-round selection was used to identify substitutes for the 3 THCs being temporarily banned from seeing RTI patients due to COVID-19; the unequal number (21 vs 19) of THCs originated from the independent randomization and the research team did not know the allocation until a very late stage; whether a patient had "completed" a follow-up survey was defined by whether he/she had responded over 90% of the survey questions).

prescribing for two or more types of antibiotics (9.78% or 54/552 vs 11.58% or 58/501); lower rate of purchasing antibiotics from retail pharmacies after initial consultation (3.68% or 15/407 vs 5.78% or 20/346); and lower rate of obtaining antibiotics from other clinics after the initial consultation respectively (2.70% or 11/407 vs 4.05% or 14/346). However, none of these differences were statistically significant. Illness recovery favoured the intervention group at day 14, but the mean difference was small (–0.10, 95% CI –0.20, 0.00; p = 0.044), which may not be clinically meaningful. Sex exerted no statistically significant influence on the intervention (odds ratio 1.012, 95% CI 0.27, 0.986, 1.002; p = 0.935).

Characteristics	Control (N = 501)	Intervention (N = 552)
Female, *n (%)*	281 (56.09)	271 (49.09)
Age, *mean ± SD*	51.88 ± 17.46	52.86 ± 19.16
Education years, *mean ± SD*	5.33 ± 4.57	5.62 ± 4.64
Rural residency, *n (%)*	460 (91.82)	510 (92.39)
Medical insurance		
NCMS, *n (%)*	479 (95.61)	529 (95.83)
Others, *n (%)*	22 (4.39)	23 (4172)
Days after onset of illness, *mean ± SD*	4.74 ± 3.64	4.53 ± 3.60
Disease severity rating, *mean ± SD*	1.33 ± 1.56	1.53 ± 1.56
Number of reported symptoms	2.97 ± 1.45	3.03 ± 1.49
Nasal symptoms, *n (%)*	159 (31.74)	220 (39.86)
Coughing symptoms, *n (%)*	367 (73.25)	399 (72.28)
Throat symptoms, *n (%)*	332 (66.27)	347 (62.86)
Breathing symptoms, *n (%)*	204 (40.72)	206 (37.32)
Pain, *n (%)*	116 (23.15)	151 (27.36)
Others, *n (%)*	255 (50.90)	301 (54.53)
Rate of antibiotics prescribing		
One type of antibiotics, *n (%)*	276 (55.09)	251 (45.47)
Two or more antibiotics, *n (%)*	58 (11.58)	54 (9.78)
Any antibiotics, *n (%)*	334 (66.67)	305 (55.25)
Amount of prescribed antibiotics in defined daily dose		
DDD of oral antibiotics, *mean ± SD*	6.016 (3.064)	5.317 (3.127)
DDD of subcutaneous/intravenous antibiotics, *mean ± SD*	1.264 (0.741)	1.049 (0.536)
DDD of all antibiotics, *mean ± SD*	4.112 (3.651)	2.831 (2.900)
Composition of prescribed antibiotics by WHO AWaRe		
Access, *n (%)*	169 (46.43)	129 (37.28)
Watch, *n (%)*	192 (53.00)	216 (62.00)
Reserve, *n (%)*	3 (0.82)	1 (0.29)
Utility of EQ-5D-5L states, *mean ± SD*	0.90 ± 0.01	0.90 ± 0.01

Note: SD stands for standard deviation and DDD for defined daily dose; utility or quality adjusted life years were derived using patient-reported EQ-5D-5L states and the formula by Delvin N and colleagues.[28]

Table 1: **Characteristics of participating patients recruited via exit interview.**

Cost and effectiveness

Table 3 compares the costs and effectiveness per RTI episode by day 7 after the initial consultation between the intervention and usual care conditions. The average direct cost for the usual care of a RTI episode was estimated as 42.755 RMB (9.637 USD). Compared with the usual care condition, the intervention group had a reduced cost of 9.265 RMB (1.471 USD) per episode. More specifically, the intervention incurred 1.078 RMB or 0.171 USD for intervention procedures (e.g., clinicians training, printing of patient leaflet) and 0.144 RMB or 0.023 USD on longer consultation and peer support time, yet saved 10.360 RMB or 1.644 USD on medications. The differences in relief in severity and recovery ratings and QALY gains were non-significant (p = 0.142, 0.52 and 0.801 respectively).

Incremental cost-effectiveness ratios

Fig. 2 displays scatterplots using incremental cost as the y-axis and incremental QALYs, relief in severity ratings, recovery ratings and antibiotics prescription rates as the x-axis respectively. As shown by the red or brown points, only 10 out of 1000 rounds of bootstrapping of 50% of the samples resulted in positive incremental costs (cost in the intervention minus cost in the usual care arm). Similarly, positive incremental QALYs, relief in severity ratings and recovery ratings via the bootstrapping accounted for 70.00%, 92.00% and 96.70% respectively. While the likelihood of encountering negative incremental antibiotic prescription was as high as 98.90%. The per QALY incremental cost-effectiveness ratio (ICER) was estimated as –7769.98 RMB (or 1233.32 USD). Only 2 out of the 1000 bootstrap computation resulted in ICERs over 89358 RMB (or 14183.81 USD) per QALY. Here, 89358 RMB stands for China's per-capita gross domestic productivity in 2023.

Discussion

Principal findings

In this cluster randomized controlled trial that evaluated the efficacy of a five-component intervention, the antibiotic prescribing rate and amount for RTI patients was significantly lower in the intervention group compared with usual care without any significant deterioration in symptom duration or patient satisfaction. The intervention group also had gains in short-term QALYs and slightly quicker recovery. RTI patients in the intervention arm also benefitted from reduced direct medical costs and less consumption of prescribed antibiotics.

Comparison with other studies

A variety of trials have been implemented in reducing antibiotics use in outpatients worldwide. Approaches tested in these trials include medical audit, social norm feedback presentation, guideline-based recommendations, electronic decision support systems, patient information leaflets, delayed prescribing, clinician communication training. Most published trials have been done in HICs (high income countries), with attempts to reduce antibiotic overuse in low- and middle-income countries (LMICs) being scarce.[23,25,26] Published trials on antibiotics stewardship in China are also limited. Among these, Shen and colleagues implemented a cluster randomized trial involving 24 village clinics in Anhui using online just in time feedback[17]; Wei and colleagues conducted a 6-month-trial targeting children aged 2–14 years in two counties of Guangxi, using clinician guidelines and training, monthly prescribing feedback, peer-review meetings, and brief child caregiver education[23]; Chang and collaborators carried out two related trials in Guizhou, using real-time pop-up warning message for inappropriate antibiotic

prescriptions, feedback of antibiotic prescription rate and ranking, and distribution of educational manuals.[29]

Our trial builds upon published efforts in general format but differs in specific tactics. Similar training, guideline reminders and peer discussion elements have formed part of most previous successful antimicrobial stewardship interventions.[25,26,30] By comparison, patient leaflets given out by clinicians are a less common element in previous complex antimicrobial stewardship interventions in LMIC contexts.[25] Perhaps, the most important feature with our trial is guideline-oriented tailoring. The goal of our intervention is to promote compliance with national guidelines for treating RTIs (rather than simply reducing antibiotics use). While our multifaceted approaches are geared toward this end by targeting real world obstacles or problems. Before the current trial, we had carried out a series of qualitative and quantitative studies on pathways of antibiotic use in Anhui, China.[8,17,20] Our clinician training, commitment letter, patient leaflet etc., are all tailored to the existing misperceptions and incompetencies identified via these studies coupled with multi-rounds of thinking aloud and refinement involving local clinicians and patients. Our intervention also characterizes complex yet pragmatic. Although our intervention involves 5 ingredients, the training materials, commitment letter, patient leaflet etc., are all easily applicable at very low costs.

The effect size of our trial falls in the middle of published results which varied greatly. Most trials in HICs were tested with marginal to moderate effects.[31] While trials in LMICs documented apparently greater reduction in antibiotic use.[23,25] The trials in China resulted in 13%–40% of absolute reduction in antibiotics prescription. The varied effect size has been attributed to a variety of factors. In addition to HICs vs LMICs, it may be dependent on baseline infection and prescription rates, intervention strategies, and age groups of patients. There are indications that multifaceted interventions, including two or more components targeting both clinicians and patients, were more effective than simple ones.[32] Antibiotics use for children and for patients in areas with relatively low baseline antibiotic prescribing rates was less sensitive to the interventions.[33] The effect size of the current trial is relatively smaller than the previous trials in China cited above, which may be partly due to lower baseline antibiotics prescription rates in the current trial.[34] The outbreak of COVID-19 may have also played a role to some extent. The current trial was implemented in a time when a series of strict restrictions to contain the pandemic were being gradually relaxed. There are indications that restrictions for controlling COVID-19 also reduced antibiotic prescribing.[34]

In addition to antibiotics prescribing rate, our trial also documented promising findings regarding the secondary measures. Of these, the DDD between the two arms merits particular mentioning. Although antibiotic prescribing rate in the usual care was only 11.07% higher than that in the intervention group (being 66.77% vs 55.25%), per patient DDD for the former was 1.74 times that of the latter (being 2.75 vs 1.57). DDD was seldom calculated in published trials. Our finding suggests that: a) antibiotic prescribing rate may underestimate the effect size of interventions; b) DDD may be more amenable for change; and c) targeting DDD or both DDD and prescribing rate may prove to be more effective. Another point worth noting concerns the cost-effectiveness of our trial, including the reduced service and antibiotic seeking from other sources, improved recovery and severity rating, and better QALYs. These findings should help resolve the often-raised concerns that: if patients are not prescribed with antibiotics, they may resort to alternative sources; if clinicians are asked to reduce antibiotic prescription, they may use other medicine in compensation; reduced antibiotic use may delay patients' recovery and/or affect

Outcomes	Control	Intervention	Adjusted OR/Adjusted mean difference[a] (95% CI)	p value
Prescription of any antibiotics at initial consultation, *n (%)*	334 (66.67)	305 (55.25)	0.52 (0.27, 0.98)	0.044
Prescription of two or more types of antibiotics, *n (%)*	58 (11.58)	54 (9.78)	0.71 (0.30,1.71)	0.445
Buying medicines from retail pharmacies after initial consultation, *n (%)*	44 (12.72)	33 (8.11)	0.62 (0.36,1.10)	0.100
Buying antibiotics from retail pharmacies after initial consultation, *n (%)*	20 (5.78)	15 (3.68)	0.61 (0.30,1.24)	0.173
Visits to other clinics for the same disease after initial consultation, *n (%)*	30 (8.67)	32 (7.86)	0.90 (0.50,1.60)	0.712
Medicine(s) obtained from other clinics after initial consultation, *n (%)*	30 (8.67)	27 (6.63)	0.79 (0.39,1.60)	0.513
Antibiotics obtained from other clinics after initial consultation, *n (%)*	14 (4.05)	11 (2.70)	0.67 (0.21,2.13)	0.501
Summed ratings of service process at exit survey *(the higher the better), Mean (SD)*	2.07 (1.16)	2.34 (1.67)	0.04 (−0.22, 0.29)	0.769
Illness recovery rating on day 7 following initial consultation *(the lower the better), mean (SD)*	1.59 (0.79)	1.49 (0.74)	−0.12 (−0.24, 0.00)	0.051
Illness recovery rating on day 14 following initial consultation *(the lower the better), mean (SD)*	1.34 (0.59)	1.23 (0.45)	−0.10 (−0.20, 0.00)	0.044
Illness recovery rating on day 21 following initial consultation *(the lower the better), mean (SD)*	1.04 (0.29)	1.01 (0.12)	−0.03 (−0.07, 0.00)	0.079
Utility of EQ-5D-5L states on day 7 following initial consultation, *mean (SD)*	0.97 (0.00)	0.97 (0.00)	−0.00 (−0.01, 0.01)	0.955

[a]Model controlled for the baseline value of the outcome (including utility of EQ-5D-5L states on day 0), age, sex, illness severity on day 0 and illness duration prior to the consultation at the patient level. The random effect of the GLMM is THC.

Table 2: **Generalized linear mixed modeling of the primary and secondary measures.**

Cost/Effect	Intervention (a)	Usual care (b)	Diff a and b	p
Cost per episode of RTI (*yuan*, RMB)				
Outpatient registration	8.000	8.000	0.000	1.000
Medicine and other products, median (IQR)	32.990 (55.110)	43.355 (62.870)	−10.360	0.011
Consultation time, mean (SD)	6.617 (2.971)	6.494 (3.062)	0.127	0.640
Printing of patient leaflet	1.000	0.000	1.000	<0.001
Clinician training	0.076	0.000	0.076	<0.001
Printing of commitment letter	0.002	0.000	0.002	<0.001
Peer support	0.017	0.000	0.017	<0.001
Sub-total, median (IQR)	33.490 (54.990)	42.755 (63.900)	−9.265	0.049
Effectiveness measures on day 7				
Relief in severity rating, mean (SD)	1.091 (0.088)	0.898 (0.100)	0.192	0.142
Recovery rating, mean (SD)	2.520 (0.726)	2.407 (0.798)	0.113	0.052
Gains in QALYs, mean (SD)	0.061 (0.235)	0.057 (0.223)	0.004	0.801

Note: SD stands for standard deviation; a relief in severity rating was derived using a patient's severity rating on day 7 minus his/her severity rating on day 0 of the initial consultation. Similar approach applied to gains in QALYs; the p values were estimated using t-test for measures with normal distributions as indicated with mean (SD) or Mann-Whiteney U test for measures with non-normal distributions as indicated with mean (median).

Table 3: **Costs on day 0 and effects by day 7 of initial consultation.**

their health.[20] It is worth noting that sex was not linked with the intervention effects.

Strengths and limitations

Strengths of the study include robust development of the intervention, rigorous data collection, and inclusion of important secondary measures. The intervention was easily applicable and tailored to key existing problems identified via the team's previous studies in Anhui and China including the research on drivers of antibiotics use in the same settings.[8] The study not only sent researchers to all THCs sites to observe the clinician-patient encounters, but also performed multiple time-point telephone interviews of eligible patients. Although there was lower coverage from the telephone interviews on day 7, 14 and 21, observation was maintained for all the clinical consultations over 2–4 weeks and response rates for the post-consultation exit survey which collected all data for computing the primary measure were very high, being 99.1% and 96.2% for the intervention and usual care arms respectively. In addition to the primary measure, the study analyzed DDD, illness

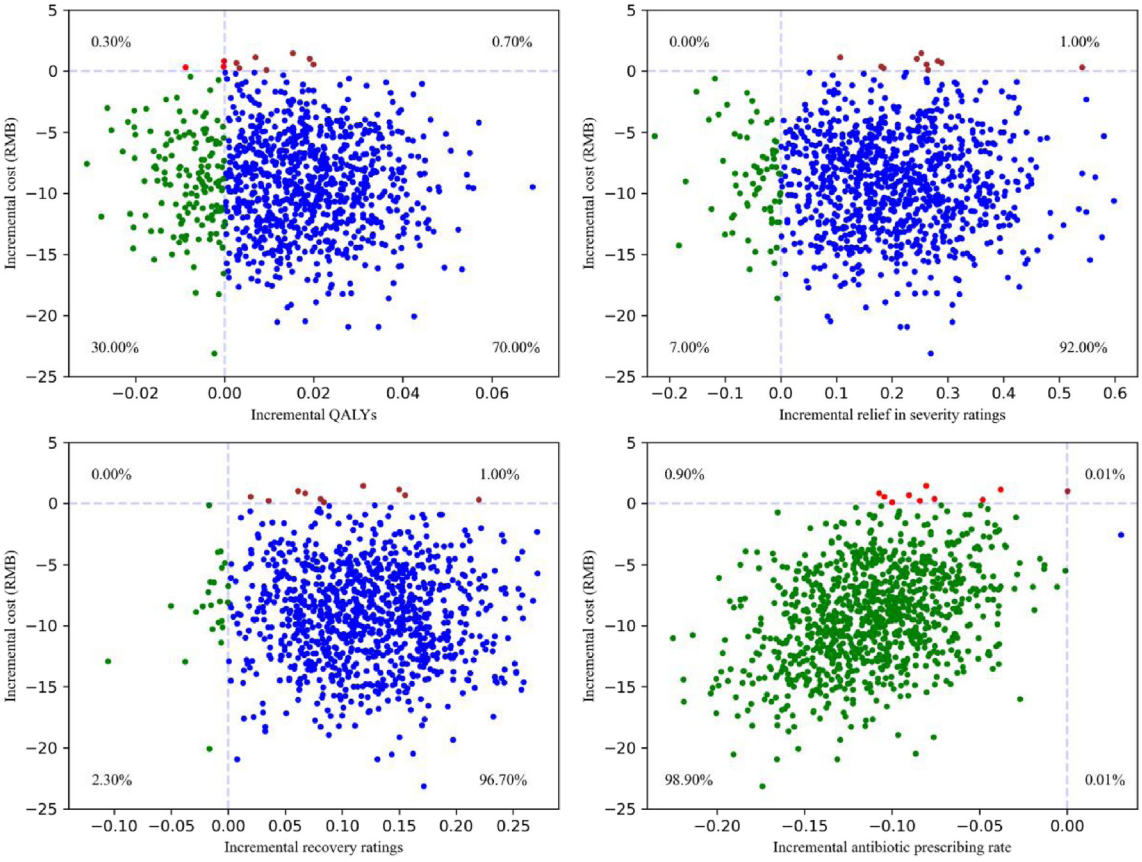

Fig. 2: **Scatterplot of incremental cost and effectiveness** (Note: a total of 1000 rounds of bootstrapping were performed to obtain samples for calculating the mean cost and effectiveness measures; Each bootstrapping randomly selected of 50% of the samples; an incremental measure was derived by the mean value of the measure of the sample from the intervention arm minus that from the usual care arm).

recovery, visit to other clinics and purchases of antibiotics from retail medicine shops. These secondary measures are of particular relevance to the China context which lacks primary care registration and referral systems and patients are free to choose sources of care.

The study also has limitations. First, being a complex intervention, the two-arm trial confirmed only the overall efficacy of the package as a whole but was unable to distinguish the effects of specific ingredients. Second, the cost-effectiveness analysis was incomplete. The costs taken into account were limited to direct medical costs. Direct non-medical costs (e.g., transportation expenses to and from the clinics) and indirect costs (e.g., loss of earnings from disease-related absenteeism) were not considered, though it is reasonable to assume that these costs are compatible between the two arms as far as RTI is concerned. Third, the trial used only partial blinding, and clinicians and patients may have changed their behavior due to awareness of their participation in the study. Forth, the primary measure was based on electronic records, and readers may raise data quality concerns. Yet, there are indications that the routinely collected records about antibiotic use by THC clinicians in Anhui are fairly reliable.[35] In addition: the non-participant observation may have had some effects on clinicians' practice, though this applied to both arms; the study had not considered comorbidity though it was seldom mentioned during our observed interactions between the clinicians and RTI patients; the follow-up surveys after the initial consultation were conducted only on the patients who provided a telephone number during the exit interview. Finally, the antibiotic prescribing rate in the intervention arm was still relatively high despite the complex intervention and further efforts for improvement are needed.

Implications for clinical practice and future research

The trial indicates that the intervention package can effectively address the high antibiotics prescribing rate in community health facilities in China. The reduction in antibiotic prescribing was not followed by delay in illness recovery or elevated service and medication use from other sources, but reduced direct medical costs for both the patients and public insurer. These findings merit incorporation of the package into the essential healthcare covered by the existing public insurance system, with training included in the continuing education of practicing primary care givers. The findings also call for further research efforts to monitor the effectiveness of policies implementing the intervention in routine care for RTI patients.

Conclusions

The complex intervention is effective and cost-effective in reducing antibiotic prescribing and merits being incorporated into routine care for RTI patients in THCs of China. There is also a need for further studies incorporating the intervention package with China's existing public medical insurance schemes and use, in particular, the savings from the package as incentives to leverage compliance and sustainability of the intervention.

Contributors

XRS and BS verified the data and had access to the raw data. Data analysis and paper drafting were conducted jointly by XRS and BS. The implementation of the study and data collection were carried out by RL, ECC and JC, and supervised by all authors. The protocol was developed with contributions from CC, TZ, WC, IO, XH, and LY. The intervention development was led by CC & LY with contributions from TZ, WC, HL, PL, XH, IO, DW, XRS, JC, RL and ECC. Additionally, XH played a crucial role in training the doctors. GY was responsible for designing and overseeing the economic analysis. The study was conceptualized and supervised by DW, along with CC, HL, and PL. HL and DW were responsible for funding acquisition. DW and HL had final responsibility for the decision to submit for publication.

Data sharing statement

Individual participant data that underly the results reported in this article, after de-identification (text, tables, figures, and appendices) will be shared. The study protocol and statistical analysis plan will be available. The data will become available beginning 3 months and ending 5 years following article publication. The data will be shared with researchers who provide a methodologically sound proposal. Proposals should be directed to wangdebin@ahmu.edu.cn and H.Lambert@bristol.ac.uk. To gain access, data requestors will need to sign a data access agreement. Requests for clarification of specific issues related to the current publication will be considered by the steering committee as long as provision of such data does not interfere with future publications by the research team.

Declaration of interests

None declared.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.lanwpc.2024.101236.

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