UNIVERSITY *of* York

This is a repository copy of *Protocol for a pragmatic cluster randomised controlled trial for reducing irrational antibiotic prescribing among children with upper respiratory infections in rural China*.

White Rose Research Online URL for this paper:
https://eprints.whiterose.ac.uk/id/eprint/145884/

Version: Published Version

White Rose
university consortium
Universities of Leeds, Sheffield & York

eprints@whiterose.ac.uk
https://eprints.whiterose.ac.uk/

BMJ Open

Protocol for a pragmatic cluster randomised controlled trial for reducing irrational antibiotic prescribing among children with upper respiratory infections in rural China

Guanyang Zou,[1] Xiaolin Wei,[1,2] Joseph P Hicks,[3] Yanhong Hu,[4] John Walley,[3] Jun Zeng,[5] Helen Elsey,[3] Rebecca King,[3] Zhitong Zhang,[1] Simin Deng,[1] Yuanyuan Huang,[1] Claire Blacklock,[3] Jia Yin,[4] Qiang Sun,[6] Mei Lin[5]

For numbered affiliations see end of article.

Correspondence to
Professor Xiaolin Wei;
xiaolin.wei@utoronto.ca and
Dr Mei Lin;
gxlinmei@126.com

ABSTRACT

Introduction: Irrational use of antibiotics is a serious issue within China and internationally. In 2012, the Chinese Ministry of Health issued a regulation for antibiotic prescriptions limiting them to <20% of all prescriptions for outpatients, but no operational details have been issued regarding policy implementation. This study aims to test the effectiveness of a multidimensional intervention designed to reduce the use of antibiotics among children (aged 2–14 years old) with acute upper respiratory infections in rural primary care settings in China, through changing doctors' prescribing behaviours and educating parents/caregivers.

Methods and analysis: This is a pragmatic, parallel-group, controlled, cluster-randomised superiority trial, with blinded evaluation of outcomes and data analysis, and un-blinded treatment. From two counties in Guangxi Province, 12 township hospitals will be randomised to the intervention arm and 13 to the control arm. In the control arm, the management of antibiotics prescriptions will continue through usual care via clinical consultations. In the intervention arm, a provider and patient/caregiver focused intervention will be embedded within routine primary care practice. The provider intervention includes operational guidelines, systematic training, peer review of antibiotic prescribing and provision of health education to patient caregivers. We will also provide printed educational materials and educational videos to patients' caregivers. The primary outcome is the proportion of all prescriptions issued by providers for upper respiratory infections in children aged 2–14 years old, which include at least one antibiotic.

Ethics and dissemination: The trial has received ethical approval from the Ethics Committee of Guangxi Provincial Centre for Disease Control and Prevention, China. The results will be disseminated through workshops, policy briefs, peer-reviewed publications, local and international conferences.

Trial registration number: ISRCTN14340536; Pre-results.

Strengths and limitations of this study

- We aim to test a comprehensive intervention targeting doctors and patients/caregivers, an approach shown to have the largest effect on reducing the irrational prescribing of antibiotics in rural primary care settings.
- The study is adapted to the local context and fits into the current Chinese national priority on antibiotics control.
- All the interventions are embedded within routine primary care management and practice, thus enhancing the potential scale-up of the intervention.
- The effectiveness of the pragmatic trial may be limited by various contextual factors; and this will be explored by a qualitative process evaluation.

INTRODUCTION

Irrational use of antibiotics is a serious issue within China and internationally. Worldwide, around 50% of medicines are not appropriately prescribed, dispensed or sold.[1–3] Irrational use of antibiotics not only brings high economic burdens to health systems, but also increases the risk of antibiotic resistance.[1] Acute upper respiratory infections (URIs) are very common among children; however, most are usually viral and self-limiting, with antibiotic treatment for URIs being unnecessary. For example, a systematic review has shown that antibiotic use does not shorten the duration of URIs.[4] Despite this, there is a high prevalence of antibiotics prescriptions for URIs in primary care facilities.[5] Antibiotic resistant bacteria are also frequently found in children, especially in infants and particularly in countries with less

stringent prescribing regulations in healthcare and agriculture.[6]

Overuse of antibiotics in healthcare is common in China. In 2012, the national Ministry of Health reported that the average person consumed 138 g of antibiotics per year, 10 times the rate in USA.[7] The situation is worst in rural areas where health workers receive less education and continuous medical training in practice.[8] Knowledge and awareness about antibiotic misuse and resistance is also poorer in rural communities compared to urban residents.[9] Another recent study found frequent and inappropriate use of antibiotics in primary healthcare settings in China, 78% antibiotics were prescribed for colds and 93.5% for acute bronchitis.[10] An earlier study in the primary care settings of 10 provinces in rural Western China showed that antibiotics accounted for nearly half of all prescriptions predominantly provided for URIs, while one-fourth of those receiving antibiotics were children under 10 years old.[11]

Several national policies have been issued by the Ministry of Health, including the most recent policy limiting antibiotic prescriptions to <60% of all prescriptions for inpatients and 20% for outpatients.[12] However, no operational details were provided on how to implement the policy, and no guidelines were provided on the diagnosis and treatment of childhood URIs or the related clinician training, especially for primary care doctors. In the 2009 health sector reforms, China launched the Essential Medicines List policy which was supported by the centralised procurement of essential medicines and the Zero-Markup policy. However, even after 2 years of implementation there was no significant improvement in the rational use of medicines and cost control.[13]

The majority of studies on reducing irrational antibiotic use have been conducted in developed countries, and these have demonstrated that improving knowledge, attitudes and behaviours of healthcare providers and consumers can effectively reduce irrational antibiotic use.[14] Commonly reported interventions for improving antibiotic use in URI treatment included clinical decision support,[15–19] point-of-care testing for C-reactive protein,[20–23] clinician communication skills training,[20–22] education and feedbacks,[24] discussion and monitoring workshops,[25] governance structure change[26] and behavioural economics and social psychology.[27] A Cochrane review demonstrated that multifaceted interventions targeting both physicians and patients significantly reduced inappropriate antibiotic use in community settings;[28] whereas single interventions with parents failed to impact on antibiotic prescribing.[29–31]

Studies of irrational antibiotic prescribing in primary care settings in China are currently limited, and mainly cross-sectional surveys.[10 11] Studies involving interventions aimed at reducing the irrational prescribing of antibiotics in primary care are rare, except one study showing limited impact of a public reporting intervention for reducing antibiotics prescribing in primary care facilities.[32] Therefore, we aim to test the effectiveness of a multidimensional intervention targeting doctors' prescribing behaviours and the education of parents/caregivers which we hypothesise will reduce the irrational use of antibiotics among children with acute URIs in China's rural primary care context.

METHODS AND ANALYSIS
Design of the study

This is a parallel-group, cluster randomised controlled trial designed as a pragmatic evaluation of the superiority of a health behaviour change intervention compared with routine practice (figure 1). The study will be conducted in 25 township hospitals, with randomisation stratified by county. Randomisation is at the level of township hospitals because it would not be practical or logistically feasible to randomise individual doctors or patients/caregivers in this multidimensional intervention that involves both provider and patient/caregivers components. Study participants and doctors will not be blinded to the treatment, but measures will be taken to ensure a blinded outcome evaluation by using the 'PROBE' design.[33]

The study design broadly follows the Medical Research Council framework 'Developing and evaluating complex interventions: new guidance'.[34] Prior to the conduct of the trial, we conducted a systematic review of interventions aimed at reducing antibiotic use in children with URIs.[35] We then developed our intervention based on the results, which supported findings[28] that interventions targeting both clinicians and patients had a greater effect on reducing irrational antibiotic use than those targeting a single group. An internal pilot approach will be used to examine the feasibility and acceptability of the intervention, and the research procedures in six township hospitals. An independent trial steering committee, where lead investigators will be steering committee members, has also been set up to supervise the trial, review progress and if necessary, decide on any changes to the protocol. A data monitoring committee will not be set up given the lack of any interim analyses and very low risk to participants, but the statistician will provide any data advice to the trial steering committee, as necessary.

Setting

The trial will take place in two counties of Guangxi province, which is one of the poorest provinces in China, and is located in the southwest mountainous terrain joining Vietnam and Laos. Guangxi has a population of 48 million and contains 110 counties. In the rural areas, primary care is provided by public township hospitals and this trial will be conducted in 25 such hospitals. Each township hospital covers 20 000 to 100 000 people, and doctors in the township hospitals are responsible for acute and preventive care. Although township hospitals have inpatient treatment facilities, we only consider outpatients in this study because inpatients are likely to

Figure 1 Trial flow chart.
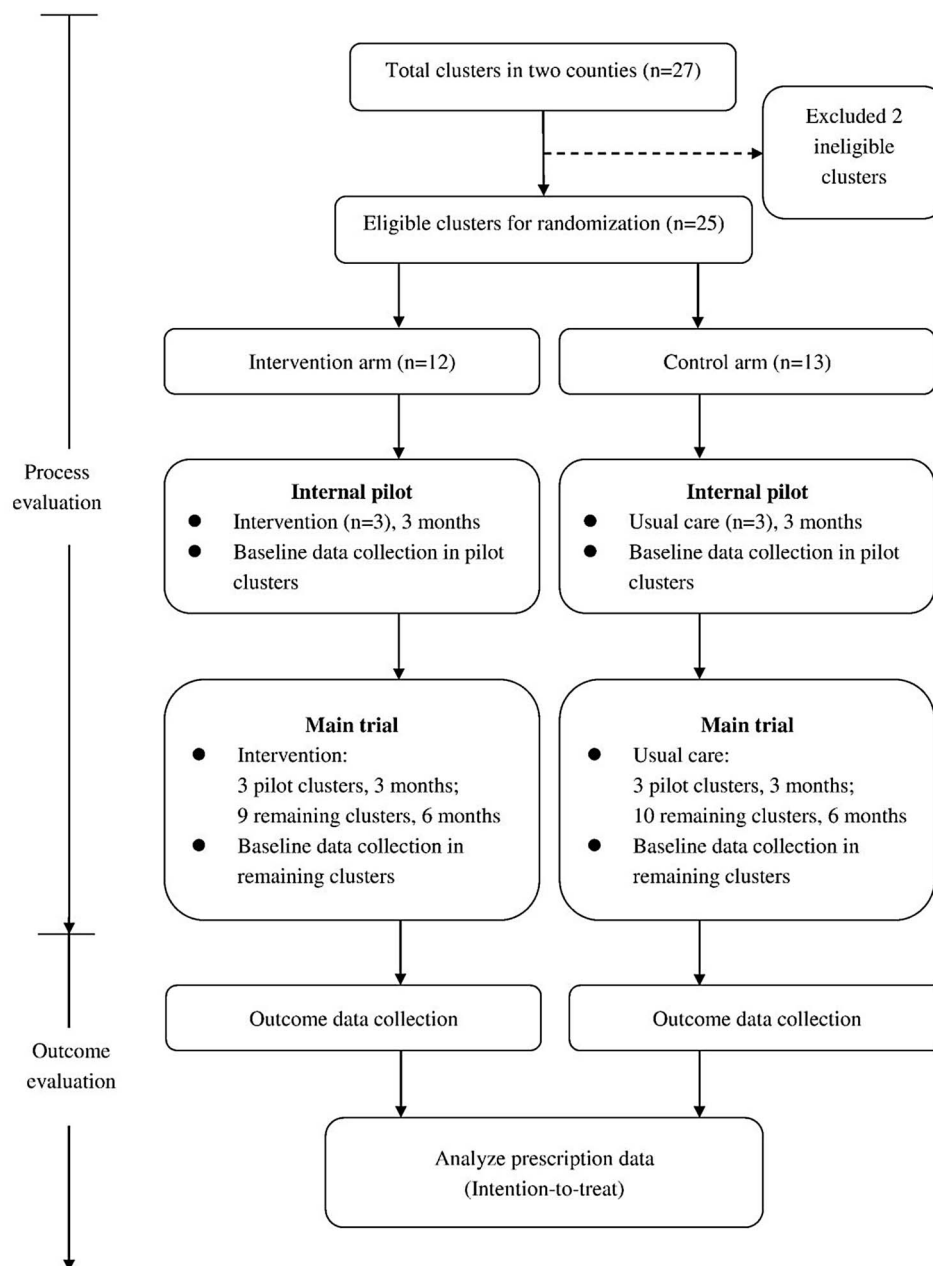
have a range of comorbidities, leading to difficulty in assessing rational prescribing for URIs. Each township hospital has 5–20 doctors. No booking system is operational in rural township hospitals. We have not included village clinics, often equipped with an upgraded community health worker, the 'village doctor', because both public and private clinics co-exist, which may confound the interventions. Rather, our intervention focuses on professionally qualified public clinicians who work as general practitioners ('doctors') in township hospitals.

Eligibility
Eligibility criteria for clusters
All doctors working in township hospitals from the two selected counties in Guangxi who agreed to participate in the study are included. We excluded the two township

hospitals located in the two county centres, as these have much better staff capacity and equipment than their peers and are close to the county general hospital. Both counties have implemented the Essential Medicine List, its treatment guidelines, and the Zero-Markup Policy since 2012.

Eligibility criteria for participants
All outpatient prescriptions for children aged between 2 and 14 years, and diagnosed with URIs during the baseline and intervention data collection period (figure 1) will be included for analysis. Children under 2 years will be excluded as they are more vulnerable to secondary bacterial infection, and exploratory work indicated that it was very difficult for doctor's to refuse antibiotics for younger children in this context. Prescriptions for

children diagnosed with pneumonia (where antibiotic prescription is appropriate) or severe diseases (eg, cancer, tuberculosis, HIV/AIDS/immunodeficiency, chronic heart diseases) or others who need long-term antibiotic treatment or prophylaxis will be excluded.

Intervention

No antibiotic should be used for self-limiting viral URIs as per the national and international guidelines. The multidimensional intervention is aimed at changing doctors' prescribing behaviours and educating parents/caregivers to reduce the irrational use of antibiotics among children with acute URIs. It is designed to fit within the policy requirements of antibiotics prescribing and routine supervision by the local health authorities.

The intervention design is informed by the Theoretical Domains Framework (TDF), an emerging method developed from a wide range of theories relevant to behavioural change. The TDF, which consists of 14 theoretical domains (groups of constructs from theories of behaviour change) has been widely used for exploring influencing factors and designing of interventions[36][37][38] in implementation research. Based on our exploratory study and systematic review, several theoretical domains from the TDF were identified as important in antibiotic prescribing, in which relevant behaviour change techniques and content of interventions were targeted (table 1).[39]

For the doctors the intervention includes: (1) operational guidelines to be distributed among township hospital doctors. The guidelines are based on Chinese antibiotics use guidelines, Integrated Management of Childhood Illness (IMCI) guidelines and the National Institute for Health and Care Excellence UK (NICE) guidelines; these focus on but are not limited to URIs. The operational guidelines cover the workflow of URI

Table 1 Multidimensional interventions designed to reduce the use of antibiotics among children

Targeted group	Theoretical domains	Behaviour change techniques, modes and content of delivery
Provider side (doctors)	1. Knowledge 2. Skills 3. Beliefs about capabilities	Techniques: information provision. Mode 1: operational guidelines. Content: URI management work flow, methods of diagnosis of URI and other common diseases among children, communication skills between clinicians and patients. Mode 2: facilitated training/workshop. Content: rational antibiotics use especially for childhood URI (using lectures, case discussions and Q&A (participatory and interactive)).
	Behaviour regulation	Techniques: monitoring and feedback. Mode: antibiotics prescribing appraisal. Contents/procedures: (1) Monthly antibiotic prescriptions collected by research team at the beginning of every month; (2) Feedback sent back to township hospital after calculating the APR by research team; (3) Antibiotics use appraisal according to APR feedback in monthly hospital staff meeting; (4) Meeting memo written down by the township coordinator; (5) Township coordinator sends the memo to trial manager.
	1. Beliefs about consequences (caregivers) 2. Knowledge (caregivers) 3. Social influence (caregivers)	Techniques: information provision and persuasive communication. Mode: health education to patient caregivers during clinical consultations. Content: specific short messages, eg., definition of antibiotic, rational antibiotic use for childhood URIs, plus simple printed educational materials.
Consumer side (parents/caregivers)	1. Beliefs about consequences (caregivers) 2. Knowledge (caregivers) 3. Social influence (caregivers)	Techniques: information provision. Mode 1: Educational messages from doctors, and educational material/leaflets. Content: explanation about antibiotics, the impacts of antibiotic resistance and rational antibiotics use for childhood URIs (using leaflets with simple words and pictures). Mode 2: educational videos played at township hospitals (5–8 min). Content: explanation about antibiotics, the situation of irrational use of antibiotics in China, and the impact of antibiotic resistance (using a local TV show).

Eligible participants include all outpatient prescriptions for children, aged between 2 and 14 years, diagnosed with URIs.
Intervention package for doctors includes: operational guidelines, training, peer-review meetings, consultation (with educational leaflets); and for parents/caregivers includes: messages from doctors, educational leaflets and videos.
Usual care refers to healthcare as per routine practice at discretion of individual doctors.
Baseline data: 3 months before intervention; outcome data: the past 3 months of the intervention.
URIs, upper respiratory infections.

management, methods of diagnosis of URIs and other common diseases among children, and communication skills between doctors and patients; (2) training workshops in which all the doctors in township hospitals will be trained on the rational use of antibiotics, especially for childhood URIs, through participatory and interactive lectures, case discussions, and question and answer sessions. These two components address the theoretical domains of knowledge, skills and beliefs about capabilities of rational prescribing, using the technique of information provision; (3) a monthly peer review of rational use of antibiotics where antibiotics prescriptions are collected and reviewed by the research team at the beginning of each month. The research team calculates the antibiotic prescription rate (APR) for childhood URIs and gives the feedback to the township hospitals. Peer review of antibiotics use are then conducted based on the APR feedback in the monthly hospital staff meeting. The project coordinator in the township hospitals will communicate the results of the peer review back to the research team. This component addresses the theoretical domain of behaviour regulation among doctors by using the techniques of monitoring and feedback; and (4) health education to caregivers where concise messages are given by doctors to the caregivers whose children have URIs during the clinical consultations, along with simple printed educational materials that include explanations about antibiotics and rational use of antibiotics for childhood URIs. This component addresses the theoretical domains of beliefs about consequences (specifically of not being given antibiotics), knowledge and social influence of antibiotics use among caregivers/parents, and uses the techniques of information giving and persuasive communication.

On the caregivers' side, the intervention includes: (1) health education messages from the doctor and printed educational materials/leaflets (with simple words and pictures) for distribution among caregivers whose children have URIs during the clinical consultation. These mainly cover explanations about antibiotics, the impacts of antibiotic resistance and rational use of antibiotics for childhood URIs; and (2) educational videos that are played on a loop in the waiting areas of township hospitals (5–8 min). The content mainly includes explanations about antibiotics, the situation of irrational use of antibiotics in China, and the impacts of antibiotic resistance (using a local TV show). This component also addresses the theoretical domains of beliefs about consequences (specifically of not being given antibiotics), knowledge and social influence of antibiotics use among caregivers/parents and uses the technique of information giving.

Usual care

In the control arm, doctors will be allowed to continue prescribing antibiotics according to current national guidelines and existing practices. In these conventional clinical consultations treatment is provided according to

existing knowledge; antibiotics are given at the individual clinician's discretion, and no systematic health education is provided to patients. This is, therefore, a pragmatic comparator reflecting typical routine practice, which allows for useful comparison of the intervention to the existing situation.

Outcomes

The primary outcome is the APR for childhood URIs, and will be measured for each township hospital based on all prescriptions for URIs in outpatients aged between 2 and 14 years that were issued between the start of the intervention's implementation and 6-month follow-up. Based on these prescriptions, the APR is defined as the proportion of outpatients aged between 2 and 14 years who have been diagnosed with a URI and after clinical consultation, prescribed at least one antibiotic as a result of the diagnosis. This primary outcome is selected because it should reflect the integrated effect of the behavioural change in both doctors and patients/caregivers. A reduction in the APR will be a clinically beneficial outcome demonstrating increased rational prescribing of antibiotics, as most self-limiting URIs are caused by viral infection that do not require antibiotics. This measurement is reliable and feasible in the primary care setting where prescriptions are well preserved either electronically or in paper files.

The secondary outcomes are all based on data extracted from the same prescriptions as described for the primary outcome:

1. The multiple antibiotic prescription rate: the proportion of prescriptions for childhood URIs that include two or more antibiotics.
2. The broad-spectrum antibiotic prescription rate: the proportion of prescriptions for childhood URIs that include at least one broad-spectrum antibiotic.
3. The quinolones prescription rate: the proportion of prescriptions for childhood URIs that include at least one quinolone.
4. The mean cost of childhood URI prescriptions.

These secondary outcomes relate to other commonly observed practices in routine primary care that cause great concern for their potential to promote drug-resistance, while misuse of quinolones may also contribute to the increasing identification of extensively drug-resistant tuberculosis.[40]

Sample size

Based on our exploratory study, the current APR is ~50% and this is, therefore, assumed for the usual care arm. Based on a conservative estimate from our systematic review, we expect our intervention to lead to at least a 25% relative reduction in the antibiotic prescription rate within township hospitals.[35] Consequently, to detect a 25% or greater reduction in the APR (ie, an absolute reduction to 37.5% APR or less) with 90% power, by using two-sided testing at the 5% significant level, assuming a harmonic mean cluster size of 200 and a between

cluster coefficient of variation of 0.15 (based on exploratory and pilot work), we estimate that we require 9 township hospitals per arm.[41] Allowing for stratified randomisation and a 10% loss of data, due to lost and illegible prescriptions, this requires a total of 24 township hospitals. As there are 25 eligible township hospitals within the two counties, it was decided to include all 25.

Randomisation

A total of 25 township hospitals were eligible for the trial, with 14 in Rong County and 11 in Liujiang County. Randomisation was stratified by county to avoid any imbalances in allocation between counties, given the potentially important variation in outcomes between counties. Within each county, randomisation was further restricted to two subsets of all possible allocation ratios. In Rong County, randomisation was restricted to those allocations resulting in equal numbers of township hospitals in each arm; in Liujiang County, the randomisation was restricted to those allocations resulting in township hospital treatment: control arm allocation ratio of 5:6. This was chosen to ensure as equal an allocation ratio as possible, while minimising the logistical cost from treatment arm hospitals. After all 25 hospitals were randomised, within Rong County, 6 hospitals (3 from each arm) were further randomly selected to become the internal pilot clusters. The remaining 19 township hospitals (8 in Rong County and 11 in Liujiang County) will, therefore, participate in the main trial, along with the 6 hospitals involved in the internal pilot. Therefore, overall the 25 hospitals were allocated in a treatment: control allocation ratio of 12:13. Randomisation was conducted by the study statistician (JPH) using a computer program written in R (V.3.2.0) (Team. RDC. R: A Language and Environment for Statistical Computing. Available online at http://www.R-project.org/: Vienna, Austria: the R Foundation for Statistical Computing, 2011).[41]

Internal pilot process

The internal pilot study aims to assess recruitment rates and the extent to which the intervention is delivered within township hospitals; it will also contribute outcome data to the main trial. The six township hospitals in the pilot study will be recruited and followed-up for 3 months, and the decision as to whether to continue with the full trial will then be taken based on two key criteria: (1) sufficient levels of recruitment (number of prescriptions sufficient to achieve minimum sample size required); (2) feasibility of implementing the intervention (at least 50% of clinicians trained and 50% using the guidelines at the end of the 3 months after the intervention). If these criteria are met, the internal pilot hospitals and their outcome data will then become part of the main trial, and will be followed up for a further 3 months. The remaining 19 hospitals will have been recruited and if the trial is proven to be feasible via the pilot, these hospitals will be enrolled into the study and followed-up for 6 months (in other words, data collection in the pilot and main trial hospitals will finish at different times).

Data collection and management

To evaluate the primary and secondary outcomes, 200 prescriptions for childhood URIs will be randomly selected in each township hospital during the 3 months before the implementation of the intervention to provide baseline data, and during the fourth to the sixth month after randomisation. Prescription data will be obtained from electronic records where available, or alternatively photographic copies will be taken of patients' paper prescriptions. Data collected from electronic or photographic records will then be entered into a password-protected SPSS database (V.20.0, IBM Corp Armonk, New York, USA). Information collected will include the township hospital, the date of the prescription, the patient's age, symptoms, diagnosis, prescribed medicines, related treatment, related laboratory tests, treatment payment, and insurance status.

Data analysis

Analysis of outcomes

The statistical analyses are described in full detail in the accompanying statistical analysis plan (see online Supplementary info 1) and are, therefore, only outlined in brief here. No interim analyses are planned, and all outcomes will be analysed following data collection. All analyses will be on the intention-to-treat (ITT) population, defined as all outpatient-prescriptions issued in township hospitals for URIs in children aged 2–14 years, regardless of the compliance of township hospitals, doctors and parents/caregivers to the intervention. Descriptive statistics will be calculated and presented, and formal inference will be based on hypothesis testing with statistical significance assessed at the 5% level.

The crude effect of the intervention on outcomes will be analysed using methods appropriate for cRCTs where there are small numbers of clusters per arm.[41] For the primary and secondary outcomes involving proportions, data at the township hospital level will be used to calculate weighted risk ratios and their 95% CIs (accounting for between-hospital variance and stratification), and formal hypothesis testing with stratified t-tests will be conducted. If the data are strongly skewed, a logarithmic transformation will first be applied. The same methods will be used to analyse the data on the average cost of childhood URI prescriptions, but based on the weighted mean difference in the outcome between treatment arms.

To adjust for important covariates, including individual and contextual factors, a two-stage process will be carried out.[41] This will involve fitting either logistic or normal regression models (for the proportion or average cost of prescription outcomes, respectively) to individual-level outcome data with all covariates of interest (including stratum) included, apart from the treatment effect. Township-hospital specific covariate-adjusted ratio or

difference residuals will then be calculated for proportion or average cost of prescription outcomes, respectively. Using the methods described above, the hospital-specific residuals will then be used in place of raw hospital-level outcome data to calculate covariate-adjusted weighted risk ratios/the weighted mean difference (as appropriate) and their 95% CIs, and to conduct stratified t-tests. All data will be analysed using STATA V.12.1 (SE) (STATA Corporation, College Station, Texas, USA).

Subgroup analyses

Planned subgroup analyses will be conducted on outcomes to determine whether there is any significant heterogeneity in treatment effects occurring between important groups such as across patients of different genders and ages, and between hospitals of different sizes. For each outcome, the cluster-level residuals described above will be regressed on stratum, treatment group, the subgroup variable and all their possible two-way interactions. F-tests will be used to determine whether there are any significant interactions between treatment group and subgroups.

Process evaluation

A qualitative process evaluation[41] will be conducted at 6 months into the intervention in selected clusters from the intervention and control arms (in the control arm to understand the implementation process of existing guidelines by clinicians, ie, usual practice). The process evaluation aims to describe the health system and service delivery context in which the intervention was delivered; explore whether or not the intervention is delivered as intended, both at the cluster level (training) and the individual level (provider delivery); and understand mechanisms of impact both at the provider level and caregiver level. The methods, which will also be informed by the TDF,[36–38] will include document review (eg, meeting minutes), observation of training sessions and consultations and qualitative interviews.

In each county we will select one control cluster. After 3 months of implementation we will review prescription rates in intervention clusters. If all intervention clusters are performing in a similar way (ie, very good, medium, poor), then we will select one intervention cluster from each county. However, if intervention clusters are performing very differently, then we will need to select two intervention clusters from each county (high and low performers) to understand cluster level factors. In each township hospital selected we will interview doctors, the hospital director, and the pharmacist. We will also conduct a focus group discussion with caregivers. A sampling frame will be developed and participants will be purposively selected for inclusion from the selected sites.

Qualitative data will be recorded if the participants agree to use audio recording. The audio files will be transcribed as soon as possible, and any audio files recorded by mobile recording devices will be immediately deleted once they have been transcribed.

Analysis of process evaluation

Qualitative data will be analysed as soon as possible after it has been collected. The analysis will feed into subsequent interviews and if new issues emerge, these can be followed up in subsequent interviews. Data will be audio recorded and transcribed. Nvivo V.10 (QSR International Pty Ltd) will be used to manage the data. The data will be analysed using a simple thematic approach.[43] Quality of reporting the qualitative study will be ensured by adhering to the Consolidated Criteria for Reporting Qualitative Research (COREQ).[44]

DISCUSSION

Our study is one of the first trials to address irrational antibiotic prescribing in the primary care context in China. The study is of great significance given the high levels of antibiotic resistance among children, particularly in developing countries with less stringent antibiotic prescribing regulations.[6] Our study will contribute to the currently limited number of studies addressing irrational antibiotic prescribing in the primary care context of rural China, and should be made more widely applicable to similar contexts. In China, most studies have focused on either clinicians or patients. We, therefore, aim to test a comprehensive intervention targeting both clinicians and patients, an approach shown to have the largest effect[28] in rural primary care settings.

The evidence-based and user-friendly guideline on rational antibiotic prescribing is developed to address the current lack of operational guidelines for primary care practices. However, simple dissemination of guidelines alone has had limited effects on health worker performance,[45 46] including in ambulatory care settings.[28] Considering the insufficient medical training received by rural primary care doctors compared to their urban peers in China,[8] we aim to improve their knowledge through continued professional training in rational antibiotic prescribing. Peer review of antibiotics prescribing is also planned at monthly hospital staff meetings to monitor fidelity to the intervention, and enhance the knowledge of doctors. Antibiotics are culturally accepted in rural China as the first response to self-limiting viral URIs. Thus, educating the caregivers through primary care doctors is challenging but essential.[47] We have designed an iterative and participatory training process, with an emphasis on improving the communication and educational skills of primary care doctors interacting with elders. Our study will be conducted in poor rural areas where many caregivers are grandparents as many of the young generation have temporally migrated to cities for employment. We have, thus, tailored the educational materials to be more easily understood by people with less education. By improving caregivers' knowledge,

the intervention is expected to reduce patient demand for antibiotic prescribing in URIs.

The study fits into the current national priority on antibiotics control in China. However, major control efforts have currently focused on referral hospitals rather than the primary care level, especially in rural areas. The study will thus help to shape the policies and regulations regarding antibiotic use, especially under primary care settings.[12] Multiple interventions have proved effective in improving the rational use of antibiotics. However, some interventions, such as point-of-care tests, are not feasible in primary care settings in poor rural areas of China. In this trial, all the interventions are embedded within the routine primary care management and practice. Thus, additional work and costs that would otherwise have been added to primary care will be reduced, enhancing the replicability of the intervention.

Normalisation process theory (NPT)[48 49] provides a useful lens for understanding the processes that affect the implementation, embedding and integration of rational antibiotic prescribing into healthcare systems. However, our main aim for the process evaluation[42] is to understand the barriers and facilitators which are embedded within the context, the implementation and mechanisms of impact, and determine which mechanisms affect behaviour change outcomes. We also aim to understand how to overcome implementation challenges and scale up the intervention. For instance, the uncertain effect of the zero-markup policy on reducing medicine use may suggest influences beyond providers and patients such as those of pharmaceutical companies.

In this study, we use the APR as the outcome rather than other clinical and laboratory measures, such as the positive rate of the extended-spectrum β-lactamases, since we want to focus on provider behaviour; more complex patient outcomes will be difficult to interpret in the face of many confounding factors. Trials of reducing antibiotic prescriptions for acute respiratory infections are not uncommon in high-income countries.[17 20 24 27] Given that few relevant interventions exist in low-to-middle income countries, and different studies have focused on different populations, comparisons with other studies need to be cautious. Misdiagnosis (either over-diagnosis or under-diagnosis) of URIs may happen, which would bias the APR and could even have a negative impact on treatment. However, this bias will be minimised as diagnosis and treatment in both arms is based on Chinese antibiotics use guidelines and IMCI guidelines.

Outputs will include an operational guideline on the rational use of antibiotics for URIs among children, and training modules and other materials that may be scaled up in Guangxi and other western provinces. These materials also have the potential to be adapted to other low-income and middle-income country contexts. We, therefore, believe that this trial will greatly contribute to improving the prescribing behaviour of doctors in the rural primary care context in China, and other developing countries.

Ethics and dissemination

The results will be disseminated through policy briefs, workshops, peer-reviewed publications, and local and international conferences.

There have been no modifications to the protocol which may impact on the conduct of the study, potential benefit and safety of the patients, including changes in the objectives, design, population, sample sizes, procedures or significant administrative aspects of the study. Any amendment in the future will seek prior approval from the Ethics Committees.

No consent form will be provided for prescription review. Guangxi CDC will seek agreement from each hospital under study. It will be pointed out that we will use the patients' information only for research purposes, and thus ensure the confidentiality of the patients. Personal identifying information, such as names and national ID, would be deleted before data is inputed into our research files. Each prescription will be assigned a unique study identification number. For the provider interviews, we will permit verbal consent to be given by providers, if requested, for interviews so as to protect people working in bureaucratic health systems, and to obtain as much objective information as much. Regarding the patient/caregiver focus groups, written informed consent will be obtained from each participant (verbal consent from the illiterate parents/caregivers). Information sheets will be provided and/or explained for both providers (see online supplementary info 2) and caregivers (see online supplementary info 3).

Physical hard copies of study data materials will be stored securely in a locked cabinet, separate from the data of other studies. The photographed prescriptions will be deleted as soon as possible following information extraction. For the qualitative data, only the researchers conducting the study will know the names of participants, and have access to the responses from individual participants.

Only the principal investigators (XW and ML) will be given access to the cleaned data sets. Project data sets will be stored electronically by the China Global Health Research and Development, and all data sets will be password protected.

We will disseminate the main findings to provincial and national CDC and authorities, our Communicable Disease—Health Service Delivery (COMDIS-HSD) Research Programme Consortium country partners in South Asia and Africa, and relevant international stakeholders. We will publish the findings in national and international journals, and present these at national and international conferences.

The protocol adheres to the recommendations provided by the SPIRIT 2013.[50] All items from the WHO Trial Registration Data Set are available in online supplementary info 4.

Author affiliations
[1]China Global Health Research and Development, Shenzhen, China
[2]Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada
[3]Nuffield Centre for International Health and Development, University of Leeds, Leeds, UK
[4]School of Public Health and Primary Care, Chinese University of Hong Kong, Hong Kong, China
[5]Guangxi Autonomous Region Centre for Disease Control and Prevention, Nanning, China
[6]Centre for Health Management and Policy, Shandong University, Jinan, China

REFERENCES

1. WHO. Promoting Rational Use of Medicines: Core Components - WHO Policy Perspectives on Medicines, No. 005, September 2002. Geneva: World Health Organization, 2002. http://apps.who.int/medicinedocs/en/d/Jh3011e/
2. WHO. Medicines use in primary care in developing and transitional countries: Fact book summarizing results from studies reported between 1990 and 2006. 2009. Geneva: World Health Organization. http://www.who.int/medicines/publications/primary_care_8April09.pdf
3. Sabaté E. *Adherence to long-term therapies. Evidence for action*. World Health Organization, 2003.
4. Alves Galvao MG, Rocha Crispino Santos MA, Alves da Cunha AJ. Antibiotics for preventing suppurative complications from undifferentiated acute respiratory infections in children under five years of age. *Cochrane Database Syst Rev* 2014;(2):Cd007880.
5. Andrews T, Thompson M, Buckley DI, et al. Interventions to influence consulting and antibiotic use for acute respiratory tract infections in children: a systematic review and meta-analysis. *PLoS ONE* 2012;7:e30334.
6. Ilic K, Jakovljevic E, Skodric-Trifunovic V. Social-economic factors and irrational antibiotic use as reasons for antibiotic resistance of bacteria causing common childhood infections in primary healthcare. *Eur J Pediatr* 2012;171:767–77.
7. Li Y. China's misuse of antibiotics should be curbed. *BMJ* 2014;348: g1083.
8. Anand S, Fan VY, Zhang J, et al. China's human resources for health: quantity, quality, and distribution. *Lancet* 2008;372:1774–81.
9. Gu J, Zhao J, Huang Y, et al. Use of antibiotics by urban and rural residents in Heilongjiang Province, China: cross-sectional study. *Trop Med Int Health* 2015;20:1815–182211.
10. Wang J, Wang P, Wang X, et al. Use and prescription of antibiotics in primary health care settings in China. *JAMA Intern Med* 2014;174:1914–20.
11. Dong L, Yan H, Wang D. Antibiotic prescribing patterns in village health clinics across 10 provinces of Western China. *J Antimicrob Chemother* 2008;62:410–15.
12. Xiao Y, Li L. Legislation of clinical antibiotic use in China. *Lancet Infect Dis* 2013;13:189–91.
13. Mao W, Vu H, Xie Z, et al. Systematic review on irrational use of medicines in China and Vietnam. *PLoS ONE* 2015;10: e0117710.
14. Harbarth S, Albrich W, Brun-Buisson C. Outpatient antibiotic use and prevalence of antibiotic-resistant pneumococci in France and Germany: a sociocultural perspective. *Emerging Infect Dis* 2002;8:1460–7.
15. Mainous AG III, Lambourne CA, Nietert PJ. Impact of a clinical decision support system on antibiotic prescribing for acute respiratory infections in primary care: quasi-experimental trial. *J Am Med Inform Assoc* 2013;20:317–24.
16. Litvin CB, Ornstein SM, Wessell AM, et al. Use of an electronic health record clinical decision support tool to improve antibiotic prescribing for acute respiratory infections: the ABX-TRIP study. *J Gen Intern Med* 2013;28:810–16.
17. Gonzales R, Anderer T, McCulloch CE, et al. A cluster randomized trial of decision support strategies for reducing antibiotic use in acute bronchitis. *JAMA Intern Med* 2013;173:267–73.
18. Litvin CB, Ornstein SM, Wessell AM, et al. Adoption of a clinical decision support system to promote judicious use of antibiotics for acute respiratory infections in primary care. *Int J Med Inform* 2012;81:521–6.
19. Hingorani R, Mahmood M, Alweis R. Improving antibiotic adherence in treatment of acute upper respiratory infections: a quality improvement process. *J Community Hosp Intern Med Perspect* 2015;5:27472.
20. Little P, Stuart B, Francis N, et al. Effects of internet-based training on antibiotic prescribing rates for acute respiratory-tract infections: a multinational, cluster, randomised, factorial, controlled trial. *Lancet* 2013;382:1175–82.
21. Cals JW, de Bock L, Beckers PJ, et al. Enhanced communication skills and C-reactive protein point-of-care testing for respiratory tract infection: 3.5-year follow-up of a cluster randomized trial. *Ann Fam Med* 2013;11:157–64.
22. Altiner A, Berner R, Diener A, et al. Converting habits of antibiotic prescribing for respiratory tract infections in German primary care—the cluster-randomized controlled CHANGE-2 trial. *BMC Fam Pract* 2012;13:124.
23. Price EL, Mackenzie TD, Metlay JP, et al. A computerized education module improves patient knowledge and attitudes about appropriate antibiotic use for acute respiratory tract infections. *Patient Educ Couns* 2011;85:493–8.
24. Pettersson E, Vernby A, Molstad S, et al. Can a multifaceted educational intervention targeting both nurses and physicians change the prescribing of antibiotics to nursing home residents? A cluster randomized controlled trial. *J Antimicrob Chemother* 2011;66:2659–66.
25. Ruvinsky S, Monaco A, Perez G, et al. Effectiveness of a program to improve antibiotic use in children hospitalized in a children's tertiary care facility in Argentina. *Arch Argent Pediatr* 2014;112: 124–31.
26. Liang X, Xia T, Zhang X, et al. Governance structure reform and antibiotics prescription in community health centres in Shenzhen, China. *Fam Pract* 2014;31:311–18.
27. Persell SD, Friedberg MW, Meeker D, et al. Use of behavioral economics and social psychology to improve treatment of acute respiratory infections (BEARI): rationale and design of a cluster randomized controlled trial [1RC4AG039115-01]—study protocol and baseline practice and provider characteristics. *BMC Infect Dis* 2013;13:290.
28. Arnold Sandra R, Straus Sharon E. Interventions to improve antibiotic prescribing practices in ambulatory care. *Cochrane Database Syst Rev* 2005;(4):CD003539.
29. Huang SS, Rifas-Shiman SL, Kleinman K, et al. Parental knowledge about antibiotic use: results of a cluster-randomized, multicommunity intervention. *Pediatrics* 2007;119:698–706.
30. Taylor JA, Kwan-Gett TS, McMahon EM Jr. Effectiveness of a parental educational intervention in reducing antibiotic use in children: a randomized controlled trial. *Pediatr Infect Dis J* 2005;24:489–93.

31. Wheeler JG, Fair M, Simpson PM, *et al*. Impact of a waiting room videotape message on parent attitudes toward pediatric antibiotic use. *Pediatrics* 2001;108:591–6.
32. Yang L, Liu C, Wang L, *et al*. Public reporting improves antibiotic prescribing for upper respiratory tract infections in primary care: a matched-pair cluster-randomized trial in China. *Health Res Policy Syst* 2014;12:61.
33. Hansson L, Hedner T, Dahlf B. Prospective Randomized Open Blinded End-point (PROBE) Study: a novel design for intervention trials. *Blood Press* 1992;1:113–19.
34. Medical Research Council. Medical Research Council (MRC) framework Developing and evaluating complex interventions: new guidance. http://wwwmrcacuk/documents/pdf/complex-interventions-guidance/
35. Hu Y, Walley J, Chou R, *et al*. Interventions to reduce childhood antibiotic prescribing for upper respiratory infections: systematic review and meta-analysis. *J Epidemiol Community Health. In press*.
36. Cane J, O'Connor D, Michie S. Validation of the theoretical domains framework for use in behaviour change and implementation research. *Implement Sci* 2012;7:37.
37. French SD, Green SE, O'Connor DA, *et al*. Developing theory-informed behaviour change interventions to implement evidence into practice: a systematic approach using the Theoretical Domains Framework. *Implement Sci* 2012;7:38.
38. Tavender EJ, Bosch M, Gruen RL, *et al*. Understanding practice: the factors that influence management of mild traumatic brain injury in the emergency department-a qualitative study using the Theoretical Domains Framework. *Implement Sci* 2014;9:8.
39. Michie S, Johnston M, Francis J, *et al*. From theory to intervention: mapping theoretically derived behavioural determinants to behaviour change techniques. *Appl Psychol* 2008;57:660–80.
40. Chan ED, Strand MJ, Iseman MD. Multidrug-resistant tuberculosis (TB) resistant to fluoroquinolones and streptomycin but susceptible to second-line injection therapy has a better prognosis than extensively drug-resistant TB. *Clin Infect Dis* 2009;48:e50–2.
41. Hayes RJ, Moulton LH. *Cluster randomised trials*. CRC Press, 2009.
42. Moore GF, Audrey S, Barker M, *et al*. Process evaluation of complex interventions: Medical Research Council guidance. *BMJ* 2015;350: h1258.
43. Patton M. *Qualitative research and evaluation methods: integrating theory and practice*. 4th edn: SAGE, 2015.
44. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *Int J Qual Health Care* 2007;19:349.
45. Giguere A, Legare F, Grimshaw J, *et al*. Printed educational materials: effects on professional practice and healthcare outcomes. *Cochrane Database Syst Rev* 2012;(10):Cd004398.
46. Rowe AK, de Savigny D, Lanata CF, *et al*. How can we achieve and maintain high-quality performance of health workers in low-resource settings? *Lancet* 2005;366:1026–35.
47. Yu M, Zhao G, Stalsby Lundborg C, *et al*. Knowledge, attitudes, and practices of parents in rural China on the use of antibiotics in children: a cross-sectional study. *BMC Infect Dis* 2014;14:112.
48. Finch TL, Rapley T, Girling M, *et al*. Improving the normalization of complex interventions: measure development based on normalization process theory (NoMAD): study protocol. *Implement Sci* 2013;8:43.
49. McEvoy R, Ballini L, Maltoni S, *et al*. A qualitative systematic review of studies using the normalization process theory to research implementation processes. *Implement Sci* 2014;9:2.
50. Chan AW, Tetzlaff JM, Gøtzsche PC, *et al*. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. *BMJ* 2013;346:e7586.