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Citation: Chen, S., Ko, W., Li, W., Xiao, R., Du, F., Zhang, J., Wu, S., Zheng, B., Zhu, N. J., Ahmad, R., et al (2025). Study protocol for evaluating delayed antibiotic prescribing to promote rational antibiotic use in primary healthcare institutions in China: a pragmatic, multicentre, open-label, clustered-randomised controlled trial. *BMJ Open*, 15(11), e106008. doi: 10.1136/bmjopen-2025-106008

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Link to published version: <https://doi.org/10.1136/bmjopen-2025-106008>

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BMJ Open Study protocol for evaluating delayed antibiotic prescribing to promote rational antibiotic use in primary healthcare institutions in China: a pragmatic, multicentre, open-label, clustered-randomised controlled trial

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To cite: Chen S, Ko W, Li W, *et al.* Study protocol for evaluating delayed antibiotic prescribing to promote rational antibiotic use in primary healthcare institutions in China: a pragmatic, multicentre, open-label, clustered-randomised controlled trial. *BMJ Open* 2025;**15**:e106008. doi:10.1136/bmjopen-2025-106008

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (<https://doi.org/10.1136/bmjopen-2025-106008>).

SC and WK are joint first authors.

Received 03 June 2025
Accepted 03 November 2025



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ABSTRACT

Introduction Delayed antibiotic prescribing (DAP) has demonstrated efficacy in reducing inappropriate antibiotic use for uncomplicated respiratory tract infections (uRTIs) in primary care across high-income countries. However, evidence regarding its effectiveness in low-income and middle-income countries remains limited. This cluster-randomised controlled trial (cRCT) aims to evaluate the effectiveness of DAP for optimising antibiotic use in primary healthcare institutions (PHIs) in China.

Methods and analysis We designed a pragmatic, multicentre, open-label, three-arm cRCT in adult patients with uRTIs. The study will involve 12 PHIs in Korla City of China. Participating institutions will be randomised at a 1:1:1 ratio to three parallel arms: (1) DAP-intervention arm, (2) Immediate antibiotic prescribing comparator arm and (3) Usual care (observational arm). The primary outcome is symptom duration. Secondary outcomes include symptom severity, antibiotic use, adverse events, patient satisfaction and patient belief regarding antibiotic efficacy.

Ethics and dissemination Ethics committee approval of this study was obtained from Peking University Institution Review Board (IRB00001052-24169). The findings will be disseminated through peer-reviewed publications and presentations at scientific conferences.

Trial registration number ChiCTR2500097330.

INTRODUCTION

Background and rationale

Antimicrobial resistance (AMR) has emerged as a critical global public health challenge, with over 1 million annual deaths directly attributable to antibiotic-resistant infections between 1990 and 2021.¹ Inappropriate antibiotic prescribing, particularly in the

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This study directly compares three antibiotic prescribing strategies (delayed antibiotic prescription, immediate antibiotic prescribing and usual care) in Chinese primary healthcare institutions.
- ⇒ The key outcomes, including symptom duration and severity, antibiotic prescription, safety outcomes, satisfaction and cognition, are systematically evaluated.
- ⇒ Due to specific geographic and socioeconomic characteristics, the sampled institutions may not be fully representative of all PHIs in China, potentially limiting the generalisability of the findings.
- ⇒ Reliance on patient self-reported data for symptom severity introduces a risk of measurement bias.

community, constitutes a major driver of this escalating crisis.² Notably, primary healthcare institutions (PHIs) account for approximately 80%–90% of all antibiotic prescriptions in the US and European countries,^{3 4} making antimicrobial stewardship interventions for this setting critical.^{5 6}

Delayed antibiotic prescribing (DAP), defined as providing prescriptions with specific instructions to delay initiation unless symptoms persist or worsen, has gained recognition as a promising antimicrobial stewardship strategy.⁷ Contemporary evidence from a Cochrane systematic review demonstrated that DAP reduced antibiotic consumption by 62% (93% vs 31%) compared with immediate prescribing, without compromising clinical safety in acute respiratory infections.⁸ A recent meta-analysis reported no change in symptom severity and lower complication rates

in respiratory tract infections (RTIs) treated with delayed antibiotics compared with immediate.⁹ DAP provides clinicians with an option to ensure treatment can be initiated when needed while reducing unnecessary antibiotic use. DAP also has potential positive downstream impact on health systems by reducing primary-care emergency visits (85.4%), scheduled visits (79%) and achieving high patient satisfaction (75.6%).¹⁰ Three large cohort studies suggested DAP significantly reduces re-consultation rates for persistent or progressive symptoms compared with immediate or non-prescription approaches.^{11–13} Given that 15%–20% of patients with initially uncomplicated presentations subsequently require follow-up consultations due to symptom evolution, DAP provides clinical safeguards for patients while enabling practitioners to reduce non-essential antibiotic exposure.¹⁴

Currently, DAP has been implemented in countries including the UK,¹⁵ US, Spain^{10 16} and Australia.¹⁷ It is a commitment set in the UK's National Action Plan to implement and assess DAP as a strategy to address AMR. These countries have integrated DAP into guidelines for conditions like pharyngotonsillitis and acute bronchitis, where diagnostic uncertainty exists.¹⁰ DAP has been less used in low-income and middle-income countries (LMICs), with limited evidence on its feasibility, impact on prescribing behaviour and patient outcomes. Patient self-reported outcomes following DAP were assessed in Ghana.¹⁸ While the perception and acceptability of DAP among primary care physicians have been assessed in China, evidence on its implementation is lacking.¹⁹

In China, antibiotic prescribing in PHIs remains sub-optimal. Up to 70.5% of antibiotic prescriptions in PHIs lacked clinical indication, particularly common in upper RTI.²⁰ 44.5% of the patients with acute bronchitis were treated with antibiotics, 90% of which was broad spectrum, and the overall compliance with the national prescribing guideline was 31.0%.²¹ China's second AMR National Action Plan was implemented in 2022, with interventions predominantly targeting improving antibiotic use in hospitals. Implementing stewardship in PHIs has been hampered by limited resources, despite evidence in frequent inappropriate prescribing in this setting²¹ and disproportionately affecting vulnerable populations in underdeveloped regions.²⁰ DAP could serve as a cost-effective strategy to optimise antibiotic use in primary care in China. In this research, we propose the protocol of a pragmatic, clustered randomised clinical trial (cRCT) to assess the feasibility, safety and efficacy of DAP in managing RTI in primary care in a region of Northern China characterised by a diverse population demographic and high levels of social deprivation.

Objectives

This trial aims to assess the feasibility, safety and efficacy of DAP in PHIs, by monitoring the impact of DAP on antibiotic prescribing, patient experience and clinical outcomes.

METHODS

Setting

This study will be conducted at Korla City, a mid-sized urban centre in southern Xinjiang Uyghur Autonomous Region of China, with a registered population of 477 710 and an administrative area of 7378 km² (2023 census). The city comprises 14 sub-districts, 4 towns and eight townships. Healthcare services are delivered through a network of 20 publicly funded PHIs: 7 community health centres and 13 township health centres. This trial will be conducted across 12 PHIs in Korla City, which jointly provide all outpatient care and public health services for all residents.

Eligibility

Inclusion criteria

Patients presenting to participating PHIs will be enrolled if they meet all of the following:

1. Aged ≥18 years.
2. Clinical diagnosis of acute RTIs, including:
 - Acute pharyngitis.
 - Acute sinusitis.
 - Acute bronchitis.
 - Acute exacerbation of chronic bronchitis.
 - Acute exacerbation of chronic obstructive pulmonary disease.
3. The prescribing clinician is uncertain whether an immediate antibiotic prescription is clinically necessary.

Exclusion criteria

Patients will be excluded if they meet any of the following:

1. Prior participation in DAP trials.
2. Severe systemic illness (or severe symptoms lasting for more than 2 weeks).
3. Pregnancy.
4. Symptoms or signs suggesting a complicated infection.
5. High-risk comorbidities, including heart, lung, kidney, liver or neuromuscular disease, immunosuppression.
6. Age ≥65 years with ≥2 following criteria, or age ≥80 years with ≥1 following criteria:
 - Hospital admission within preceding 12 months.
 - Insulin-dependent diabetes mellitus.
 - History of heart failure.
 - Current systemic glucocorticoid use.

Diagnosis-specific inclusion/exclusion thresholds are detailed in online supplemental file 1.

Termination/withdrawal

Criteria for trial termination or withdrawal are as follows:

1. Safety: serious adverse events (SAEs).
2. Efficacy: treatment failure requiring hospitalisation.
3. Protocol compliance: major deviations affecting outcomes.
4. Autonomy: participant-initiated withdrawal.

Withdrawn patients will continue follow-up for intention-to-treat (ITT) analysis.

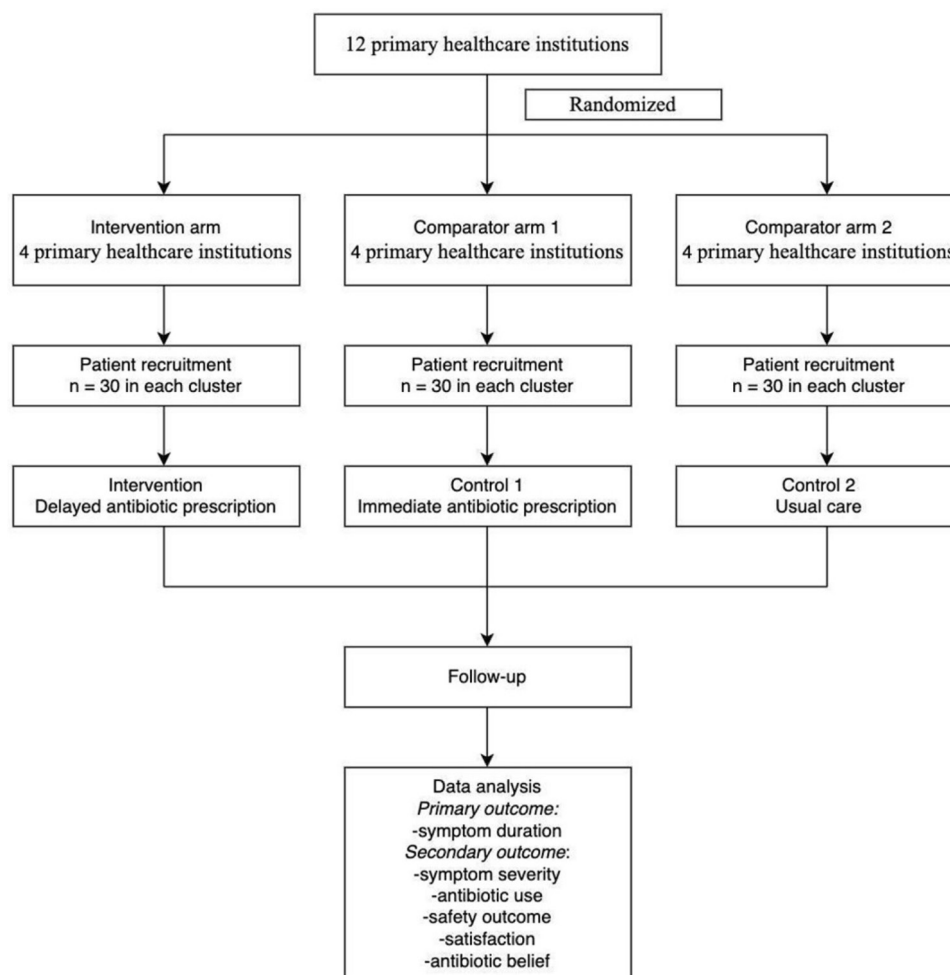


Figure 1 Trial flow chart of the study.

Trial design

Intervention

This pragmatic, open-label cRCT will randomly allocate PHIs into three arms in a 1:1:1 ratio: (1) Intervention arm: DAP, (2) Control arm: immediate antibiotic prescription (IAP) and (3) Control arm: usual care (UC) (figure 1). Eligible patients who provide written informed consent (online supplemental file 2) will be enrolled from June 2025 over a 12-month period. Antibiotic prescribing strategies will be implemented at the PHI cluster level, with individual patients receiving the intervention corresponding to the PHI group of their initial consultation (table 1).

The choice of antibiotic agent/formulary, duration and frequency will be determined by general practitioners' (GPs) clinical judgement during the first RTI consultation, while the initiation varied by arm. Any decision to prescribe antibiotics during a follow-up consultation will be based solely on the patient's clinical presentation at that time and will be independent of their original trial arm assignment.

Sample size

The power calculation was conducted to detect clinically significant differences in symptom duration—the

primary outcome measure of symptom duration—across study arms. Drawing from prior trials of RTIs, we assumed a baseline symptom duration of 6 days (SD=6) for uncomplicated cases.²² Anticipated between-group differences were derived from symptom duration of 13.1 days in the DAP arm, 11.7 days in the IAP arm and 14.4 days in the UC arm.²² Using a conservative two-sided significance threshold ($\alpha=0.10$) and 70% statistical power, we accounted for an anticipated 20% loss to follow-up and an intracluster correlation coefficient of 0.02 based on regional prescription pattern studies. The design effect calculation via the Hussey and Hughes cluster-randomised trial formula indicated a requirement for 12 participating PHIs (four per arm) enrolling ≥ 30 patients each, yielding a total sample of 360 participants (120 per arm). All computations were performed using PASS 2021 (NCSS), employing mixed-effects linear regression modelling for clustered data. Prior data indicate that the 12 participating PHIs each average 2500 patient visits per month, with over 50% for RTI. Therefore, the recruitment target is considered achievable within the 12 month period.

Table 1 Antimicrobial prescribing strategies

Arm	Prescribing strategy	Clinician guidance
Intervention group (DAP)	Antibiotics are not prescribed at the first visit. Patients receive a free follow-up appointment valid from 48 hours to 14 days later. The rationale for delaying the antibiotic prescription is explained to patients. After 48 hours, they can decide whether to return for antibiotics based on symptom changes	For DAP and UC Arms: physicians will inform patients that initial symptom persistence is normal. However, if any of the following three conditions occur, patients are advised to have a follow-up consultation: (1) The symptoms continue to worsen for 3 days after the first consultation, (2) The symptoms do not start to improve after 5 days (for pharyngitis) or 10 days (for other infections) since symptom onset and (3) When patients feel it is necessary For the IAP Arm: physicians will ask the patients to complete the full antibiotic course as prescribed unless severe adverse effects occur
Control group 1 (IAP)	Antibiotics are prescribed and dispensed to the patient during the initial consultation. Patients are instructed to begin taking the medication on the same day	
Control group 2 (UC)	No antibiotics will be prescribed. Physicians may prescribe other medications for symptomatic relief as clinically appropriate	

DAP, delayed antibiotic prescription; IAP, immediate antibiotic prescribing; UC, usual care.

Allocation

PHIs will undergo cluster randomisation through a stratified, computer-generated allocation sequence implemented via a secure web-based platform (REDCap). The 12 participating institutions will be distributed equally across three parallel arms (1:1:1 ratio). Randomisation will occur at the institutional level using permuted block randomisation (block size=3), overseen by an independent trial statistician. Allocation sequences will remain concealed from site investigators until formal assignment through the platform's access-controlled interface.

Blinding

Given the behavioural nature of the prescribing interventions, this open-label design intentionally maintains unblinded status for both GPs and participants to preserve ecological validity. However, the researchers who perform data analysis will be blinded from the PHI and patient ID to ensure robustness of the analysis results.

Training of GPs

To ensure consistent, safe implementation, participating PHIs will receive standardised training prior to study initiation. The training programme was informed by findings from our previous qualitative research on facilitators (eg, profound understanding of DAP by physicians, increase in public awareness of antibiotic resistance) and barriers (eg, patient communication challenges) for DAP implementation in Chinese PHIs²¹, and co-developed with a multidisciplinary expert panel including respiratory and infectious disease physicians, a clinical pharmacist and a health psychologist. The psychologist will specifically address identified behavioural barriers through cognitive-behavioural techniques.

The core training components include

1. DAP rationale: explicitly clarifying the advantages (eg, optimising antibiotic stewardship) and operational models of DAP to mitigate misconceptions.

2. 6R's: (1) Reassurance: immediate antibiotics are unnecessary, (2) Reasons to avoid antibiotics: (effectiveness/side effects/allergy/AMR), (3) Relief: supporting paracetamol use (limit NSAIDs), (4) Providing Realistic natural history information, (5) Reinforcing the key message: ONLY use prescriptions if not STARTING to settle in the expected time and (6) Rescue (Safety-netting).

3. Evidence-based content: impacts of antimicrobial misuse on resistance and role-specific responsibilities.

GPs from the participating PHIs will be assessed at the end of the training programme using semi-structured qualitative interviews to assess their knowledge and perception in DAP, the trial process, and identify any unconscious biases which might influence patient enrolment.

GPs in the intervention arm will also receive an intervention toolkit including:

1. Communication scripts addressing common patient concerns.
2. 6R's checklist cards.
3. Eligibility criteria cards.
4. Summary of evidence-based facilitators/barriers for rapid reference.

Outcomes

The primary outcome is the **symptom duration**. It is defined as the time from the onset to the disappearance of symptoms associated with respiratory infections. A separate record entry is set for each included disease (online supplemental file 1).

Secondary outcomes are symptom severity, antibiotic use, safety outcomes, satisfaction and cognition.

Symptom severity: a 5-point Likert scale is used to classify symptom severity from mild to severe (ranging from 1='no pain/discomfort', to 5='extreme pain/discomfort') except for shortness of breath and/or difficulty breathing. For shortness of breath and/or difficulty

breathing, the severity is assessed with reference to the modified Medical Research Council scale, which categorises symptoms into six levels, from 1='I never get breathless', to 6='I am too breathless to leave the house or I am breathless when dressing' (online supplemental file 1).

Antibiotic prescription: the antibiotic prescription rate will be calculated as the proportion of enrolled patients who used antibiotics during the trial by asking patients whether they used antibiotics in follow-up, determined by dividing the number of patients who used antibiotics by the total number of enrolled patients.

Safety outcomes: infection-related complications and unscheduled healthcare encounters within 30 days will be recorded. Physicians in PHIs will prospectively document these complications using standardised questionnaires and report them to the trial coordinator within a maximum of 48 hours.

Satisfaction: a 6-point Likert scale is used to classify patient satisfaction with the prescribing strategy from low to high (ranging from 1='completely dissatisfied', to 6='extremely satisfied').

Belief in antibiotics: a 6-point Likert scale is used to classify patient beliefs on antibiotic efficacy from low to high (ranging from 1='completely ineffective', to 6='extremely effective').

Health economic outcomes

Direct medical costs

1. Facility-level: outpatient registration fees and costs associated with physician consultation time during RTI-related medical visits.
2. Medication: costs of antibiotics and non-antibiotics medication during RTI-related medical visits.

Direct non-medical costs

1. Patient expenditures: travel expenses incurred by patients for RTI-related medical visits.

Indirect costs

1. Productivity loss: costs attributable to work absenteeism resulting from time spent on RTI-related medical visits.

RTI-related medical visits refer to consultations during the initial consultation and 30-day follow-up period for RTIs, related adverse reactions and complications.

Patient follow-up

During the initial consultation of any enrolled patient, the GP will document the patients' demographic information, comorbidity profile and other relevant conditions.

Symptom duration and severity will be obtained by telephone follow-up with patients on day 3 and 30 after enrolment, and patients will continue to be monitored by telephone on day 5, 7, 10, 15 and 22 if they report persistent symptoms during previous telephone calls. The results of each patient's follow-up visit will be recorded on a standardised form.

Antibiotic use, safety outcomes, satisfaction, cognition and cost data will be collected by standard questionnaires

via telephone follow-up. Satisfaction, cognition and cost data will only be collected on day 30 (table 2).

Data collection

Antibiotic prescribing

Data on antibiotic prescribing will be extracted from both electronic and paper-based routine records for all infection-related consultations at

1. Baseline period: 6 months preceding intervention commencement.
2. Post-trial period: 6 months following trial completion.

A standardised data extraction instrument will capture: presenting symptoms and diagnoses, antibiotic agent/formulary, prescribed dose, duration and frequency. Dual independent review by trained clinical auditors will ensure data fidelity, with discrepancies resolved through consensus meetings moderated by the lead principal investigator (PI).

GP consultation process

Physicians will prospectively document patient encounters using phone-based electronic case report forms (eCRFs) (DingTing) with automated validation rules. Physicians will be trained on software utilisation and informed consent administration to ensure protocol adherence. During the 15min initial enrolment consultation, clinicians will:

1. Disclose trial objectives and cluster randomisation design.
2. Provide antibiotic strategy-specific guidance.
3. Administer written informed consent with witness verification.
4. Inform follow-up actions and emergency protocols in case symptoms worsen.

Signed consent documents will be securely archived, with scanned copies integrated into the trial's master database.

Patient clinical outcomes

Standardised telephone-administered surveys will be conducted by trained outcomes assessors at two predefined intervals:

1. Primary follow-up (Day 3 post-consultation): comprehensive symptom progression assessment using validated form.
2. Final evaluation (Day 30): patient satisfaction with the prescribing strategy and beliefs about antibiotic efficacy.
3. Adaptive extensions: patients reporting unresolved symptoms will trigger enhanced monitoring through serial contacts on Day 5, 7, 10, 15 and 22 until the patient reports a full recovery.

Health economic outcomes

Data of the following dimensions will be collected:

1. Direct medical costs (obtained by physician self-report and PHI billing system).
 - Facility-level: consultations, diagnostics, prescriptions.

Table 2 Participant timeline

	Study period							
	Enrolment and allocation and intervention				Follow-up			
Time point	t ₀	t ₁	t ₂	t ₃	t ₄	t ₅	t ₆	t ₇
Day	0	3	5	7	10	15	22	30
Enrolment:								
Eligibility screen	X							
Informed consent	X							
Allocation	X							
Demographic data	X							
Medical history	X							
Interventions:								
Delayed antibiotic prescription	X							
Immediate antibiotic prescription	X							
No antibiotic prescription	X							
Assessments:								
Symptom duration and severity	X	X	X	X	X	X	X	X
Antibiotic use	X	X	X	X	X	X	X	X
Infection-related complications		X	X	X	X	X	X	X
Unscheduled healthcare		X	X	X	X	X	X	X
Belief in the efficacy of antibiotics								X
Satisfaction with prescription strategy								X
Medication costs	X	X	X	X	X	X	X	X
Related-adverse reactions		X	X	X	X	X	X	X
Complications costs								X
Transportation costs								X
Lost productivity costs								X

- Medication: antibiotics and other medications.
- 2. Direct non-medical costs (obtained by patient self-report questionnaire).
 - Patient expenditures: transportation, caregiving.
- 3. Indirect costs (obtained by patient self-report questionnaire and National Statistical Yearbook).
 - Productivity loss: human capital approach calculation.

Data management

Demographic, diagnostic and medication data will be systematically collected using standardised eCRFs. The data entry process will be conducted by PHI staff with all data fields being anonymised at source. The research team will solely access de-identified datasets.

Statistical methods

Missing data will be handled using multiple imputation, and the primary analysis will be based on the imputed dataset. Analyses will be conducted using STATA/MP V.18.0 (StataCorp) on an ITT basis. The threshold for statistical significance will be set at a two-tailed p value

<0.05. Baseline demographic and clinical characteristics will be compared across arms using Kruskal-Wallis tests (continuous variables) and χ^2 tests (categorical variables). Clinically meaningful imbalances (standardised difference >0.1) will be addressed through multivariable-adjusted models. Between-group differences will be assessed through pairwise Mann-Whitney U tests. Descriptive statistics will be used to summarise baseline data. Continuous variables will be presented as mean $\pm$ SD for normally distributed data or median and IQR for non-normally distributed data. Categorical variables will be presented as frequencies and percentages (n, %).

Primary outcome analysis

Symptom duration will be analysed via negative binomial regression with robust variance estimators, incorporating the following covariates:

1. Prescribing strategy (DAP/IAP/UC).
2. Index diagnosis (ICD-11 categories).
3. Age, smoking status, comorbidities (Charlson Index).
4. Cluster-level random intercepts.

Results will be reported as incidence rate ratios with 95% CIs.

Secondary outcomes

Symptom severity: symptom severity will be analysed using ordinal logistic regression. The proportional odds assumption will be formally tested.

Categorical outcomes (eg, antibiotic use): multilevel modified Poisson regression for relative risk estimation.

Economic evaluation

A societal perspective cost-minimisation analysis will be conducted if clinical non-inferiority is established (symptom duration ≤ 1 day between arms). Uncertainty will be assessed through deterministic sensitivity analyses ($\pm 20\%$ parameter variation) and threshold analyses.

Data monitoring

Comprised of a pharmacoepidemiologist, clinical pharmacist, biostatistician and public health ethicist, the data review and management committee will periodically audit dataset completeness and fidelity against source documents, and validate adherence to pre-registered statistical analysis plans.

Data availability statement

Patient-level data will not be publicly shared due to legal and regulatory requirements. This study's statistical results will be disseminated through peer-reviewed publications and academic conferences.

Requests for data sharing should be directed to the corresponding author of this study. On formal agreement, the de-identified datasets used to generate the reported statistical results may be shared.

Harms

All AEs and SAEs will be proactively monitored, documented and managed throughout the study. The site PI is responsible for ensuring that any AE/SAE is medically managed appropriately. All SAEs, regardless of their perceived relationship to the study intervention, will be reported by the PI to the Peking University Institution Review Board within 24 hours of awareness, in accordance with regulatory requirements.

Auditing

An independent monitor, delegated by the study sponsor, will conduct site monitoring visits periodically throughout the trial. These audits will involve source data verification to ensure that the data reported in the eCRFs are accurate, complete and verifiable from source documents. The monitor will also assess protocol compliance and adherence to Good Clinical Practice guidelines. Any discrepancies or findings will be documented, and corrective and preventive action plans will be implemented.

Patient and public involvement

No patients or members of the public were involved in the design, conduct, or reporting of this research. The study

results will be disseminated to the academic community through peer-reviewed publications.

ETHICS AND DISSEMINATION

Research ethics approval

Ethics committee approval of this study was obtained from Peking University Institution Review Board (IRB00001052-24169).

Protocol amendments

In the event that challenges arise during the trial, such as insufficient recruitment due to strict eligibility criteria or consistent protocol deviations observed during monitoring, an amendment to the protocol may be warranted. Any such revisions will be formally documented and submitted to the Peking University Institution Review Board for approval prior to implementation.

Consent or assent

The informed consent process will be conducted by trained physicians at participating PHIs. Prospective participants will receive a detailed explanation of the study's purpose, procedures, potential risks and benefits. They will be given adequate time to ask questions and consider participation. Written informed consent must be obtained from each participant before any trial-related procedures are performed. A signed copy of the consent form will be provided to the participant, and the original will be retained in the site's study records.

Confidentiality

Participant data will be de-identified and assigned a unique numerical identifier on entry into the trial database. All electronic trial data, including the master database, statistical code and analysis outputs, will be stored securely. All data will be stored on an independent server with account access control and can only be used on designated, offline computers by authorised research personnel.

Access to data

The findings of this study will be disseminated through peer-reviewed publication in a scientific journal. The final, de-identified dataset will not be made publicly available to protect participant confidentiality. However, reasonable requests for data access from qualified researchers can be directed to the corresponding author. Each request will be evaluated by the study steering committee based on its scientific merit and adherence to ethical principles.

Ancillary and post-trial care

Patients eligible for this study present with mild, uncomplicated RTIs that do not initially necessitate antibiotic therapy. While these conditions are generally self-limiting, potential risks include symptom progression or secondary bacterial complications. To mitigate these risks, clinicians will prescribe guideline-aligned symptomatic treatments and provide structured patient education on

recognising key indicators of clinical deterioration and stepwise responses. The structured telephone follow-up is designed to monitor patient recovery and facilitate early detection of any complications.

DISCUSSION

Over the past two decades, China has made significant progress in addressing AMR by implementing stewardship. Nevertheless, healthcare resources remain disproportionately concentrated in tertiary and secondary healthcare institutions, leaving primary healthcare infrastructure under-resourced and struggling with substantial inappropriate antimicrobial prescribing practices.

International evidence establishes DAP as an effective stewardship tool requiring minimal additional resources, showing particular promise for resource-constrained PHIs. However, its implementation in LMICs remains underexplored, with limited evidence regarding contextual adaptation and long-term effectiveness. Therefore, this study aims to systematically evaluate DAP's clinical and behavioural impacts within China's primary care setting.

While there is a rich body of research comparing DAP against immediate antibiotics, the evidence regarding whether DAP is superior to no antibiotics at all remains unclear. There are concerns that DAP ultimately might still expose patients to the risk of adverse effects, including AMR and drug toxicity, due to unnecessary use of antibiotics.¹¹ While some studies suggested that missing or delaying antibiotic treatment might lead to patient deterioration.²³ Therefore, long-term monitoring of patient outcomes at the population level is necessary.

This study has a few limitations. First, although we employ cluster randomisation across 12 representative PHIs in Xinjiang Uyghur Autonomous Region, geographic and socioeconomic particularities may limit generalisability to coastal metropolitan settings. Second, the reliance on patient self-reported symptom severity indices introduces potential measurement biases. Third, this cRCT carries a risk of selection bias, particularly in patient-level data. To mitigate this risk, we will separate geographical clusters and implement standardised provider training. In data analysis, we will use mixed-effects models to account for cluster and individual effects and adopt an ITT analysis to further reduce bias.

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manuscript for the protocol. NJZ, RA and PL refined the study protocol. FD, JZ and SW assisted in the development and implementation of the study. BZ, XG and LS will supervise the study. WL and RX will contribute to the statistical design and analysis of data. All authors critically reviewed and approved the final manuscript. HW is the guarantor.

Funding This study was supported by the National Natural Science Foundation - General Programme (Number: 72374009).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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