C reactive protein-guided prescription of antibiotics for children under 12 years with respiratory symptoms in Kyrgyzstan: protocol for a randomised controlled clinical trial with 14 days follow-up

Elvira Isaeva 1, Joakim Bloch 2,3 Anja Poulsen 3, Jørgen Kurtzhals 1,2,4 Susanne Reventlow 3,5 Volkert Siersma 3, Azamat Akylbekov 6, Talant Sooronbaev 6, Rune Munck Aabenhus 5, Jesper Kjærgaard 3

ABSTRACT

Introduction While lower respiratory tract infections are the main cause of death for children under 5 globally, only a small proportion of children with respiratory tract infections need antibiotics. Overuse of antibiotics globally is leading to increasing rates of antibiotic resistance. In Kyrgyzstan, healthcare workers regularly prescribe antibiotics when clinical uncertainty is present to err on the side of caution. Targeting antibiotic use with biomarkers of inflammation such as C reactive protein (CRP) testing at the point-of-care test (POCT) has been shown to reduce antibiotic use in general, but only few studies have been done in children and no studies exist from Central Asia. This study aims to assess whether the use of a CRP POCT can safely decrease prescription of antibiotics for children with acute respiratory symptoms in primary level healthcare centres in Kyrgyzstan. Methods and analysis Multicentre, open-label, individually randomised, controlled clinical trial with 14 days follow-up (follow-up by phone on days 3, 7 and 14) in rural lowland Chui and highland Naryn regions of Kyrgyzstan. The population are children aged 6 months to 12 years attending the primary level healthcare centres during normal business hours with acute respiratory symptoms. CRP POCT equipment will be supplied to healthcare centres, along with a short training session in CRP use, including the interpretation of results to support the clinical evaluation of the child with acute respiratory infection. The primary outcomes are the proportion of patients prescribed an antibiotic within 14 days of index consultation (superiority analysis) and days to recovery (non-inferiority analysis). Secondary outcomes are antibiotics prescribed at index consultation, reconsultations, hospital admission and vital status within 14 days. Analysis of the first primary outcome, antibiotic use, will be intention to treat using a logistic regression model. Analysis of the second primary outcome, days to recovery, will be per protocol using a linear regression model and a non-inferiority margin of 1 day.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study is the first multicentre, open-label, individually randomised controlled clinical trial in Kyrgyzstan.
⇒ The individually randomised design, as opposed to a cluster-randomised design, balances the large heterogeneity between healthcare centres and healthcare workers in Kyrgyzstan.
⇒ Violation of the randomisation protocol biases the effect towards no difference, which is particularly problematic for non-inferiority analyses.
⇒ In order to minimise lost to follow-up, this is carried out by phone, which is easier due to distance, time and financial challenges.

Ethics and dissemination The study was approved on 18 June 2021 by the Ethics Committee (ref. no. 1) of the National Centre of Maternity and Childhood Care, Bishkek, Kyrgyzstan. The results of the study regardless of the conclusion will be presented at international conferences and published in peer-reviewed scientific medical journals along with policy briefs and technical reports.

Trial registration number NCT05195866.

INTRODUCTION

Background and rationale Acute respiratory tract infections (ARTIs) are the most common causes of contact with the healthcare system and the main reason for antibiotic overuse in children at the primary care level worldwide.1–3 Antibiotic resistance is a global and ever-growing public health problem.4 Studies have demonstrated a direct link between antibiotic use and antibiotic resistance development.5 The WHO considers antimicrobial resistance a major threat to public health6 with an estimated...
1.5 million deaths attributable to antimicrobial resistance in 2019. At the same time, ARTI is the most common cause of death among children under 5 globally, costing the lives of an estimated one million children annually.

There is substantial overlap in the clinical presentation of lower respiratory illness in young children from different causes, for example, bacterial pneumonia, viral infections and wheezing, making clinical management decisions difficult for the healthcare worker (HCW). The fear of missing a potentially treatable serious infection may prompt the HCW to prescribe ‘just in case’. Furthermore, most children in low-income and middle-income countries (LMICs) are diagnosed and treated at primary care clinics, primarily by mid-level providers with limited access to diagnostic equipment and training. To assist the HCW in clinical management under these conditions, various clinical algorithms have been developed, for example, WHO’s Integrated Management of Childhood Illness (IMCI). This approach may severely overdiagnose pneumonia resulting in substantial unnecessary use of antibiotics. Still, case fatality rates for pneumonia in children remain high in Kyrgyzstan. HCWs in Kyrgyzstan often administer antibiotics empirically, adhering to national guidelines, and sometimes based on their own experience.

Most cases of ARTI in children are viral and with the increasing coverage of pneumococcal and Haemophilus influenzae type b vaccination, an even smaller proportion of ARTIs need antibiotics. Therefore, new approaches to the management of respiratory infections in children are urgently needed.

C-reactive protein (CRP) is an acute phase reactant produced by the liver on stimulation such as tissue damage or inflammation, which can be used as a marker of serious infection. Randomised trials of using CRP point-of-care test (POCT) to guide antibiotic prescription for respiratory tract infections have been successful in lowering unnecessary antibiotic prescriptions in high-income countries and some LMIC countries. Trials of CRP POCT in children have been performed in Tanzania as part of an intervention package with a strict prescription limit of >80 mg/L CRP with a significant reduction in antibiotic prescriptions from 40% to 2%. In South-East Asia, a CRP intervention produced a smaller but significant effect (5%) in children and adults. A trial in Vietnam with both children and adults resulted in a 20 percentage point reduction of antibiotic use from 64% to 44%. A Cochrane review on the subject found that CRP POCT testing for ARTIs in general practice can reduce antibiotic use, and the intervention is unlikely to increase morbidity.

We aim to study if CRP POCT testing in primary care can safely reduce antibiotic use in children with ARTI in Kyrgyzstan.

**Objectives**
The trial will investigate if antibiotic use in children presenting with ARTI can be safely reduced by identifying children who likely require antibiotic therapy as well as children who will not likely benefit from antibiotics. This will be done by implementing CRP POCT at the primary healthcare level.

**METHODS AND ANALYSIS**

**Study design**
This is a multicentre, open-label, individually randomised, controlled clinical trial with 14 days follow-up to be conducted in low altitude Chui and high altitude Naryn regions of the Kyrgyzstan.

**Methods**
Children between 6 months and 12 years with respiratory symptoms will be screened for eligibility at the healthcare centres by a research assistant (RA) prior to routine examination by a local HCW. Children under 6 months are not included as febrile illness should be approached with alarm in this age group. Parents/caregivers of eligible children must give informed consent to participate after having received oral and written information regarding the study. On agreement to participate, children are randomised to the intervention group (CRP POCT) or control group (usual care). Case report forms (CRFs) will be filled out for all participants at the index consultation (day 1). The RA then phones the central project office and receives the participant’s allocation. Participants assigned to the intervention group will have a CRP POCT during the consultation with their HCW. Children in the control group will not have the CRP POCT test taken. Participants are randomised using the REDCap Randomisation Module.

All participants will be assessed on the 3rd, 7th and 14th day of inclusion through phone calls from the RA who is blinded to the group allocation. The study flow is shown in figure 1.

**Patient involvement**
Parents/caregivers of participants have not participated in the formulation of the research question and the design and methodology of the study. However, these parents/caregivers and their families have helped to fine-tune the study procedures and protocols through their participation in the pilot study and will play a central role in the further dissemination of information to the public, which can certainly help in poststudy dissemination.

**Study population**
All children attending the participating primary healthcare clinics during normal business hours (8:00–16:00 hours) fulfilling the following criteria.

**Inclusion criteria**
1. Between 6 months and 12 years of age accompanied by at least one parent or legal caregiver.
2. Parents/caregivers of a child are able and willing to comply with all study requirements.
3. Parents/caregivers of a child are able and willing to give informed consent.
4. The patient has at least one of the following focal symptoms lasting for less than 2 weeks: cough, fast/difficult breathing, sore throat, shortness of breath and wheezing.

Exclusion criteria
1. Severely ill and in need of urgent hospitalisation.
2. Terminally ill patients.
3. Patients with ear ache only.
4. Patients with known immunosuppression or severe chronic disease (HIV, hepatic disease, history of neoplastic disease, long-term systemic steroid use or similar conditions as assessed by the HCW or AI).
5. Parents/caregivers who are not able to participate in follow-up procedures (lack of telephone, etc).
6. Taken antibiotics within 24 hours before the index consultation.

Intervention
CRP POCT equipment will be supplied to the healthcare centres, along with a training session in its use. The HCW is introduced to the interpretation of CRP POCT test results in the following way: low CRP levels (<10 mg/L) indicate that with high certainty the disease is of viral or non-severe bacterial aetiology, and antibiotics are generally not needed, intermediate CRP levels (10–50 mg/L) indicate that antibiotics may be needed depending on the clinical presentation, high CRP levels (>50 mg/L) indicate inflammation and antibiotics are recommended. The training will also include information on the kinetics of CRP and cases where a low CRP may need to be interpreted cautiously, for example, a history of fever lasting less than 24 hours. CRP testing will be performed using Aidian QuickRead go CRP POCT (Aidian, Espoo, Finland). The result will be available to the HCW after approximately 3 min. In the initial phase of the data collection, the RA may assist the HCW. In the later phase, the HCW will be responsible for performing the test themselves to ensure a potential future implementation. The interpretation and decision on antibiotic prescription will be at the discretion of the HCW alone.

Study sites and participants
HCWs from 14 randomly selected healthcare centres (7 villages with healthcare centres in each region) will receive training in performing CRP tests and in interpreting their results. Villages will be selected by random draw from two containers with each the names of 30 villages in the Naryn and the Chui region, respectively, performed by a researcher not affiliated to the project.

The HCWs will mainly be from primary healthcare level (family doctors, feldshers or nurses). In many facilities, there is no doctor and patients are treated only by a feldsher. The healthcare centres are small rural primary health clinics with only the most basic equipment, for example, only very few will have equipment for basic blood count or urinalysis.

Study procedures
Eligible patients will be included in the waiting area of the healthcare centre using a brief inclusion form. When the inclusion criteria are fulfilled, the RA will follow the patient (the child and the parents/caregivers) into the examination room, where written consent will be obtained. On consent, the RA will observe the consultation and concurrently fill out the baseline CRF. After history and clinical examination, the child will undergo randomisation. Those in the intervention group will have CRP POCT carried out in the procedures room by the HCW as a finger prick test using capillary blood. Finally, the HCW decides on treatment and this decision is documented in the CRF.

The RA will complete the baseline CRF at the examination by the clinic’s HCW. Collected data are:
1. Demographic details including: sex, age, comorbidities, weight and height.
2. Duration of ARTI symptoms prior to the consultation.
3. Diagnosis of the specific ARTI and general symptoms.
4. Overall severity rating according to IMCI (HCW perception).
5. Clinical assessments and results of clinical examinations (oxygen saturation, respiratory rate, heart rate, body temperature).
6. All diagnostic tests performed or ordered.
7. Management: antibiotic, antiviral prescription, other (symptomatic) medication prescribed and advice or safety netting.
8. Referral to hospital or public health authority.
Follow-up by phone
There will be no scheduled follow-up visit at the health clinic required by the study. Parents/caregivers will receive phone calls at days 3, 7 and 14 after the index consultation to record outcomes. If parents/caregivers do not answer, then the call is repeated up to three times over the next 2 days and again at 14 days (end of study). Non-responders will keep their randomisation, and all collected data up to the time point they are no longer available to the study will be analysed. RA blinded to the patient’s group allocation will perform the follow-up phone calls. The following information will be collected over the phone:
1. Number of symptomatic days after the consultation.
2. Duration of specific symptoms.
3. General well-being of the child compared with index visit, graded on a six-category ordinal scale from ‘got worse’ to ‘excellent’.
4. Additional contacts with HCWs.
5. Any medicine bought over-the-counter or prescribed by other HCWs including the name of the drug(s).
6. Additional diagnostic testing.
7. Complications (hospitalisation, Intensive Care Unit (ICU), death).
8. Infections in their households.

Primary study outcomes
The primary study outcome is the proportion of included children in each study group that are prescribed an antibiotic within 14 days from the index consultation (day 1) (superiority analysis).

However, any reduction in antibiotic use must not compromise disease prognosis and the study will, therefore, include two primary outcomes. The second primary study outcome is disease prognosis measured as the number of days until recovery as stated by parents/caregivers (non-inferiority analysis).

Secondary study outcomes
1. Antibiotics prescribed at the index consultation.
2. Antiviral treatment at follow-up.
3. Reconsultation within 14 days from index consultation.
4. Hospital referral at the index consultation.
5. Hospital admission at follow-up on days 3, 7 and 14.
6. Mortality at follow-up on days 3, 7 and 14.
7. Number of patients assessed by caregivers as ‘well again (good or excellent)’ on days 3, 7 and 14.

Withdrawal of individual participants
Participants can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a participant from the study for urgent medical reasons. If any participants leave the study or are withdrawn, the reason(s) will be recorded in the CRF and all data up to the time point of study withdrawal will be included in the study.

Safety reporting
Serious adverse events (SAEs) will be collected as part of routine follow-up (from the time of consent until the end of the trial). If SAEs occur they will be assessed by the PI and presented within 1 week to a safety committee (SC) to confirm the causality classification (definitely, probably, possibly, unlikely, unrelated). As part of the study, we will collect the following outcomes at days 3, 7 and 14:
1. Death.
2. Hospitalisation after the index consultation.

Safety committee
An SC will be established and activated to assess any SAEs. The primary responsibility of the SC is to make recommendations to the PI concerning the continuation, modification or termination of the trial due to SAEs. The SC considers study-specific data as well as relevant background knowledge about the disease, test agent or patient population under study.

An SC in a framework of this study will consist of a group of paediatricians from the National Centre of Maternity and Childhood Care (NCMCC) (three senior doctors from three different departments: head of the allergology and clinical immunology department, head of the pulmonology department and one senior general paediatrician).

Data monitoring committee
Composition of the data monitoring committee (DMC): NCMCC statistician independent of the study, NCMCC lawyer, two experienced medical researchers independent of the study: one from NCMCC and the other from the National Centre of Cardiology and Internal Medicine. The main roles of the DMC are as follows: (1) to periodically review and evaluate the accumulated study data for compliance with the protocol; (2) check the correctness of the conduct and course of the study, as well as the law aspects of the study and (3) factors that may affect the outcome of the study or compromise the confidentiality of the study data (such as protocol violations, disclosure).

DATA ANALYSIS PLAN
Power calculation
As the study employs a combined superiority and non-inferiority approach based on the two related primary study outcomes, we provide two power calculations and opt for the conservative number of participants to ensure adequate sample size for answering both primary outcomes. Power calculations were performed using sample size calculators provided by Sealed Envelope.26

Superiority power calculations show that for a power of 90% to detect a 10 percentage point reduction in antibiotic use (from 55% to 45% based on previous pilot registrations in the area) at a statistical significance level of 0.05 a total of 1046 children, 523 in each both groups are necessary.

In our non-inferiority power calculation, we apply a margin of non-inferiority of 1 day (24 hours), that is,
the intervention group is allowed to have a mean time to recovery that is 1 day longer than the mean recovery time in the control group without being considered inferior. The duration of ARTI in children is approximately 7 days with an SD of 5 days. Hence, for a power of 90% and a statistical significance level of 0.05, a total of 858 children are needed.

To be able to assess both primary outcomes, we will opt for the conservative measure, that is, the superiority measure. With an expected drop-out rate of 15%, we aim to include 1204 children in total, 602 in each group.

Analysis of baseline variables
An unadjusted comparison will be done between baseline variables of the intervention and non-intervention group using $\chi^2$ tests for categorical variables and t-tests for continuous variables. Baseline variables to be compared include age, sex, comorbidities, number of siblings, smoking in household, study site and specialty of HCW.

Analysis of outcomes
For binary outcomes, including the first primary outcome, the comparison between the two randomised groups is done with an OR from a multivariable logistic regression model. Alongside this comparison, an absolute risk difference is estimated from a multivariable linear regression model. For continuously valued outcomes, including the second primary outcome, the comparison will be done in a multivariable linear regression model. All models account for clustering of subjects within healthcare centres through the method of generalised estimating equations. All comparisons will be done both unadjusted and adjusted for sex, age, and clinical status. All comparisons are done intention to treat (ITT), and the second primary outcome, a non-inferiority comparison, is also done per protocol in that all subjects who violated the randomisation will be omitted from the analysis.

The statistical analyses will be performed after data from the last follow-up have been entered. Data will be stored in a REDCap database.24

Timeline
The study is planned to start inclusion of patients in October 2022. We aim to reach our desired sample size within 3–6 months.

Ethics and dissemination
Ethics
The Ethical Committee of the NCMCC of the Kyrgyz Republic has approved the Study Protocol (Ref: no. 1. Date: 18 June 2021). The study participants are children living in the Kyrgyz Republic, who are covered by the protection of citizens of the Kyrgyz Republic. The trial will comply fully with all regulatory authorities and will be executed in accordance with Good Clinical Practice. Children in the CRP POCT arm are subjected to a finger prick causing minor transient pain.

Public disclosure and dissemination plan
The results of the study, negative as well as positive outcomes, will be presented at international conferences and published in peer-reviewed scientific medical journals. It is planned to write policy briefs and technical reports. Oral presentations are also intended at local scientific and medical conferences and symposiums with the participation of invited representatives of the government, the media, primary HCWs, medical workers of various specialties, administration and teachers of medical universities and colleges and other interested parties.

Author affiliations
1Department of Allergology, National Centre of Maternity and Childhood Care, Bishkek, Kyrgyzstan
2Department of Clinical Microbiology, Rigshospitalet, Copenhagen, Denmark
3Department of Paediatrics and Adolescent Medicine, Rigshospitalet, Copenhagen, Denmark
4Department of Immunology and Microbiology, University of Copenhagen, Copenhagen, Denmark
5The Research Unit for General Practice and Section of General Practice, Department of Public Health, University of Copenhagen, Copenhagen, Denmark
6Department of Pulmonology, National Centre of Cardiology and Internal Medicine named after academician Mirsaid Mirrakhimov, Bishkek, Kyrgyzstan

Contributors EI is a main author and coordinator of the paper. JB worked on the methodology, writing—review and editing. AP is responsible for a conceptualisation, writing—review and editing, and also funding acquisition. JK is responsible for the methodology, writing—review and editing. SR is responsible for writing—review and editing, and also resources. VS wrote the statistical analysis plan and revised the draft paper. AA helped with a technical support and a literature review. TS is responsible for a conceptualisation, writing—review and editing, and also project administration. RMA is responsible for a conceptualisation and the methodology; writing—original draft, review and editing, and also supervision. JEk is responsible for a conceptualisation and methodology; writing—review and editing; supervision; project administration and also funding acquisition.

Funding This research was funded by the International Centre for Antimicrobial Resistance Solutions (ICARS) (grant number 100008) Copenhagen, Denmark and Global Health Unit, Department of Paediatrics and Adolescent Health, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iDs
Elvira Isaeva http://orcid.org/0000-0002-4165-5156
Jørgen Kurtzhals http://orcid.org/0000-0003-2760-8713
Susanne Reventlow http://orcid.org/0000-0002-4990-142X
Azamat Akylbekov http://orcid.org/0000-0001-5761-399X

REFERENCES


Sproston NP, Ashworth JJ. Role of C-reactive protein at sites of inflammation and infection. *Front Immunol* 2018;9:754.


