


The Feasibility of C-Reactive Protein Point-of-Care Testing to Reduce Overuse of Antibiotics in Children with Acute Respiratory Tract Infections in Rural Kyrgyzstan: A Pilot Study

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Background: In Kyrgyzstan, the morbidity prevalence of and morbidity from acute respiratory tract infections (ARTI) in children is high. Local healthcare workers (HCW) often prescribe antibiotics that are not indicative due to a mix of professional and societal factors. It is suggested to precede with a decision on antibiotics by a point-of-care test (POCT) on the appropriateness of the treatment, eg, a measurement of C-reactive protein (CRP). CRP-guided antibiotic stewardship in children with ARTI has not previously been studied in Central Asia.

Purpose: This pilot study was conducted to examine the feasibility of the methods and procedures to be used in the upcoming randomised controlled COORDINATE clinical trial (NCT05195866) and in daily clinical practice in primary care.

Patients and methods: HCWs from three selected rural healthcare facilities were trained in the CRP POCT and in interpretation of results. Children aged 6 months to 12 years attending the primary healthcare facilities with respiratory symptoms were randomly assigned to CRP-guided management or standard care, guided by clinical findings only. Children were followed up for 14 days by scheduled telephone calls to caregivers.

Results: Eighty-one children participated in this pilot study. The CRP POCT and the trial procedures were acceptable to the target group as well as to the HCWs. Children from both groups recovered equally well, with an observed significant lower use of antibiotics in the CRP group. HCWs generally adhered to the CRP guidelines, and only once was an antibiotic prescribed despite low CRP results. No safety concerns were observed. Four parents provided wrong phone numbers impeding follow-up. We will collect all mobile phone numbers in the household for the main trial.

Conclusion: The pilot provided satisfactory results, suggesting that the COORDINATE trial of CRP POCT is effective, feasible with minor adjustments and without apparent safety concerns for the participants.

Keywords: paediatrics, family medicine, respiratory medicine, C-reactive protein, feasibility

Introduction

Acute respiratory tract infections (ARTI) are a serious problem worldwide,¹ especially in children under 5, costing the lives of almost 1 million children annually. In Central Asian countries, such as Kyrgyzstan, the prevalence and mortality from this group of diseases are disproportionately high.² ARTI are the most common cause of death among children under 5 globally,³ costing the lives of almost 1 million children annually.⁴ The annual incidence of influenza and acute

respiratory viral infection (ARVI) in Kyrgyzstan exceeds the total incidence of all other infections: their share averages 66.6% of all registered cases of infectious disease, reaching 78% in some years.^{5,6}

Healthcare workers (HCW) in primary care in Kyrgyzstan use the Integrated Management of Childhood Illness (IMCI) approach, as there are only a limited range of diagnostic methods in these often remote rural settings, eg, blood count (haemoglobin, red blood cells, and white blood cells), stethoscope, peak flow meter, and scales.⁷ In addition, the medical staff, typically represented by feldshers and family nurses, most often prescribe antibiotics unsupervised.⁸ In some cases, HCWs, regardless of educational background, may end up prescribing antibiotics that are not needed⁹ due to a mix of professional and societal factors, and patient expectations.¹⁰

A high rate of ARTI together with an overuse of antibiotics contributes to increasing antimicrobial resistance levels.¹¹ In low- and middle-income countries (LMICs), antibiotic consumption increased 114% between 2000 and 2015.¹² An analysis of the consumption of antibiotics in Kyrgyzstan showed that 46.8% of the population uses antibiotics as self-medication. The main driver for self-medication was the sale of antibiotics without a prescription.¹³ In Kyrgyzstan, patients take, on average, over two courses of antibiotics per year and harbour many misconceptions about the usefulness of and indications for antibiotics, such misconceptions are also present among HCWs.¹⁰

In this rapidly evolving landscape of antibacterial resistance, urgent actions are needed as we are moving towards a post-antibiotic era where common infections may once again become life-threatening.

One approach to reduce unnecessary antibiotic use is to assist HCWs in identifying patients who likely have a viral or self-limiting bacterial infection in order to withhold antibiotics in such patients.

C-reactive protein (CRP) is an acute inflammatory protein that increases in cases of infection or inflammation.^{14,15} It is an established biomarker for assessing inflammation and its severity in patients presenting to a healthcare facility¹⁶ and can be used as a point-of-care test (POCT) to guide antibiotic prescribing decisions.¹⁷ A Cochrane review concluded that CRP testing for ARTI in primary care reduces the number of antibiotic prescriptions with 23% without apparent safety concerns.¹⁸ There are many studies all over the world on the effectiveness and acceptability of CRP POCT testing in primary healthcare settings in LMICs,^{19–24} but few in children and none from Central Asia.

Objectives

This pilot study was conducted to examine the feasibility and possible barriers of the methods and procedures intended to be used in the upcoming randomised controlled clinical (RCT) COORDINATE trial.²⁵ We were specifically interested in understanding issues related to the study protocol, randomisation, inclusion and exclusion criteria, enrolment, implementation of the intervention, data capture, loss to follow-up and study withdrawal rate. The general feasibility was assessed through the willingness of HCWs to carry out and follow the CRP POCT algorithm.

Materials and Methods

Design

An individually randomised trial (ISCRNT No. NCT05195866) with 14 days blinded follow-up was conducted as a pilot study. HCWs from three selected healthcare centres from different villages of the Chui region in northern Kyrgyzstan were trained to perform and interpret the results of CRP POCT in the clinical assessment of children with ARTI. It was emphasized that CRP levels below 10 mg/L strongly indicated a viral or non-severe bacterial cause for the disease, making antibiotics generally unnecessary. Intermediate CRP levels ranging from 10 to 50 mg/L suggested that antibiotics might be considered. When CRP levels exceeded 50 mg/L, antibiotics were recommended. The training also covered information about CRP kinetics and scenarios where a low CRP result needed to be interpreted cautiously, such as in cases where the patient had a fever lasting less than 24 hours. The main researcher and research assistants (RA) collected data at the index consultation. Follow-up phone calls (days 3, 7, and 14) were done by another group of RAs in the general study unit in Bishkek, blinded to individuals' group allocation. Two family doctors and two nurses were trained in the family medicine centre (FMC) in Sokuluk village, two doctors and one nurse in the family physicians group (FPG) in Kyzyl-Tuu village, and one feldscher in the feldscher-obstetrics point (FOP) in Shalta village.

Study Population

All children aged 6 months to 12 years attending the selected primary care health clinics during normal business hours with symptoms of ARTI were screened for eligibility, in the two-week period November 24th to December 7th 2021. Inclusion criteria were age between 6 months and 12 years; parents/caregivers able and willing to comply with all study requirements; parents/caregivers able and willing to give informed consent; the patient had at least one of the following focal symptoms lasting for less than 2 weeks: cough, fast/difficult breathing, sore throat, shortness of breath, wheezing.²⁵ The study excluded very ill children where CRP POCT measurement would delay care, children with known immunosuppression or severe chronic disease, children with a positive SARS-CoV-2 rapid test, and children who had taken antibiotics within 24 hours before the consultation.²⁵

Data Collection

The data collection consisted of four stages:

Inclusion

Screening of patients took place in the waiting areas of the three participating medical facilities. A screening form was used to identify eligible patients according to inclusion and exclusion criteria. The screening form was in Russian (which is the official language of interethnic communication along with Kyrgyz, which is the state language in Kyrgyzstan). If the child's caregiver desired, the researcher could translate the question into Kyrgyz to help if language difficulties arose. After verbal and written information, the informed consent was signed. All included children underwent a rapid test for SARS-CoV-2. If the test was positive, the child was withdrawn from the study and managed according to the present Kyrgyz guidelines for COVID-19.

Randomisation

If the test was negative, the child was randomised to intervention or control using the SealedEnvelope™ programme.²⁶ Children allocated to the intervention had a CRP POCT done during their consultation with a HCW and the result used as guidance for initiating or withholding antibiotic treatment. The randomised children fell into two groups: the intervention group – management based on the results of the CRP test, and the control group – usual care, as in daily practice before the intervention (ie, the doctor prescribes medicines without knowledge of CRP results, but based on the clinical picture).

Data Collection

The RA completed a case report form (CRF) for all included children during the consultation in collaboration with a HCW in their office. The CRF contained items on the child's demographics, symptoms at the time of the consultation, physical examination results, treatment prescribed, and diagnosis. In addition, at the end of the CRF there were several questions to the HCWs and the caregivers of the child about their experience of accepting and working with the CRP POCT method, which was necessary for examining the feasibility. At the conclusion of the pilot study, a dedicated feasibility survey (as part of the CRF) was administered to all HCWs involved in the research. Additionally, caregivers also provided unsolicited feedback in this survey.

Follow-Up 14 Days

Follow-up was carried out through phone calls to the caregivers. Both groups were assessed on the 3rd, 7th, and 14th day by phone calls using follow-up questionnaires including questions on recovery and symptoms as well as complications or hospitalisations.

The study procedure is shown in [Figure 1](#).

Data Analysis

This feasibility trial was not powered to detect statistically significant differences between groups. However, we analysed and calculated proportions of patient inclusion, antibiotic use, and follow-up rates to assist in optimal planning of the main trial.

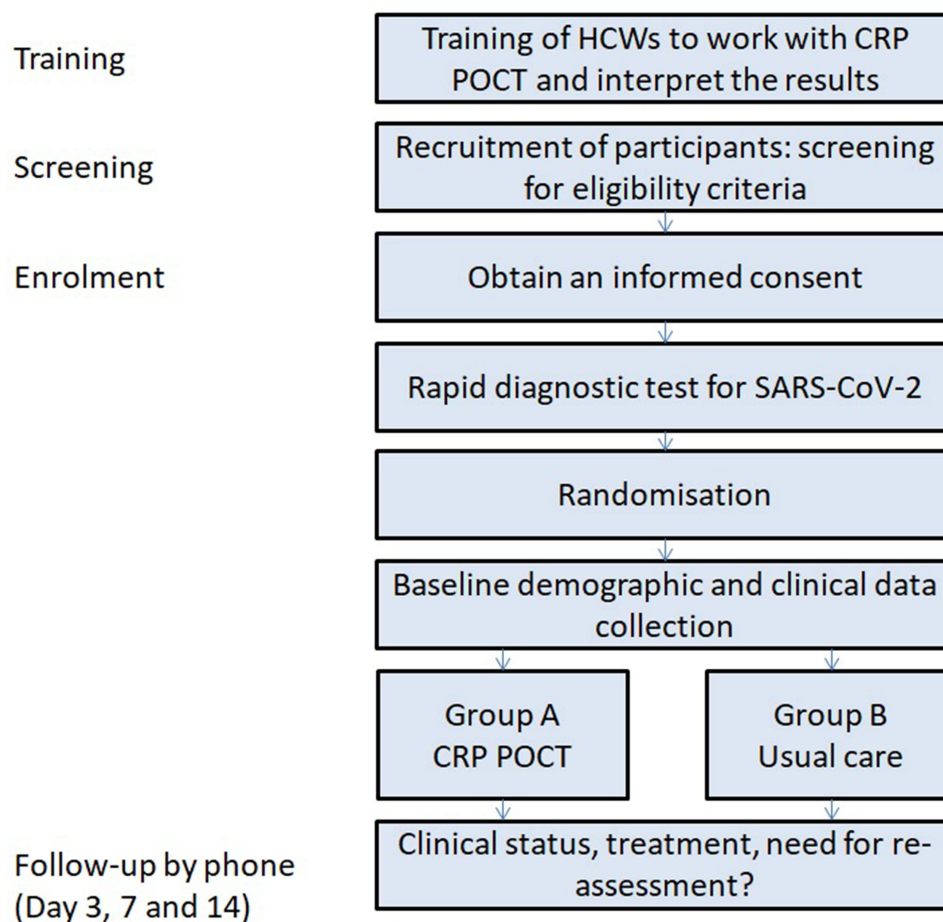


Figure 1 The study procedure. Initially, prior to data collection, HCWs at selected medical centres are trained to use the CRP machine and interpret the results, after which children are screened for eligibility. The next step is obtaining informed consent from the child's parent or caregiver, a rapid test for SARS-CoV-2, and a randomisation process. Then data is collected using the CRF, and then again on days 3, 7 and 14 by phone.

Results

Pilot results

A total of 192 children underwent screening during the pilot study period, of which 81 children were enrolled in the study. The last follow-up phone call was conducted on 31st of December 2021. One hundred and eleven children had one or more exclusion criteria with “taken an antibiotic 24 hours before the consultation” being the most common reason ($n = 54$).

The enrolment is shown in [Figure 2](#) at three different healthcare facilities. Forty children were randomised to intervention group and 41 children to control group. Six children (4 from intervention group and 2 from control group) were referred for hospitalisation during the index consultation, after the randomisation procedure, after being examined by a HCW (by decision of a local HCW). Baseline characteristics of included children, the commonest primary complaint as stated by caregivers, HCWs clinical diagnosis, CRP values of patients from the intervention group and antibiotics prescriptions in both groups are presented in [Table 1](#).

The commonest primary complaint as stated by caregivers was cough, while an unspecified viral infection. ARVI was the most frequent diagnosis by the HCWs. The CRP guidance reduced antibiotic prescriptions markedly (17% in intervention group vs 59% in control group).

Most children had low CRP levels <10 mg/mL (29/40) and only 1/40 had a value above 50 mg/mL. In general, HCWs followed the protocol and prescribed antibiotics according to CRP levels in the intervention group. When the level of CRP <10 , almost all HCWs (97.3%) did not prescribe antibiotics; however, there was still one HCW who prescribed antibiotics despite CRP - 8.9 (1 case).

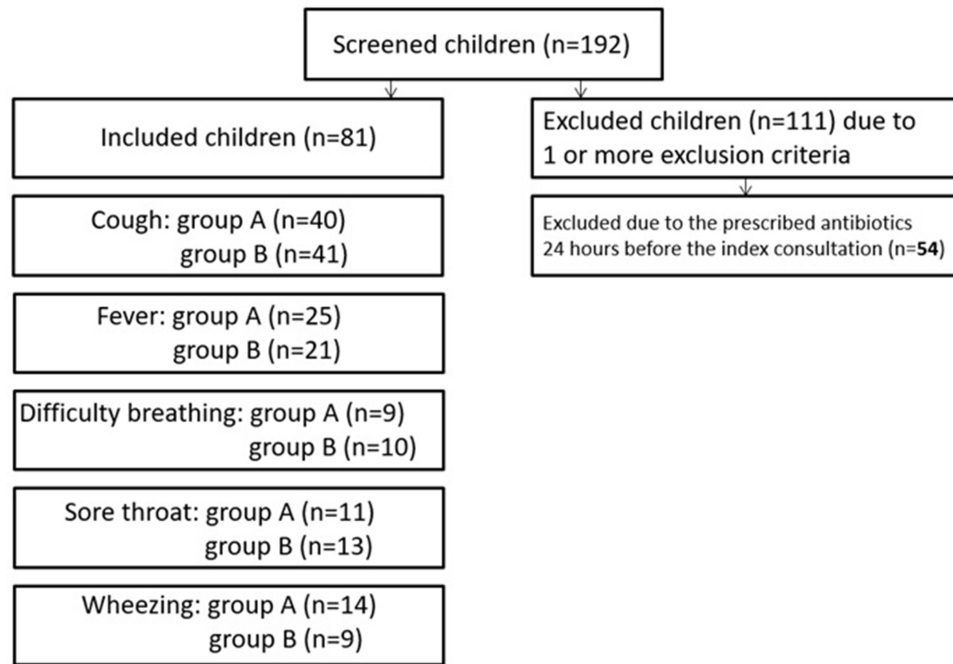


Figure 2 The enrolment tree. A total of 192 children were screened, of which 81 children were included in the study. 111 children for 1 or more criteria were excluded (of which 54 children were excluded because they took antibiotics 24 hours or less before screening). All included children had cough as the main complaint, as well as some other symptoms indicating ARTI.

Follow-up and recovery: children were considered recovered when caregivers indicated in the follow-up questionnaire that their child was feeling better, well, or excellent (see Figure 3). The majority presented with infections that recovered well during the first week of follow-up. Children from both groups recovered successfully and equally in general well-being.

Table 1 Baseline Characteristics, Group Allocation, CRP Values, and Antibiotics Prescriptions

Baseline Characteristics	Intervention	Control
Total number of children	40	41
Age in months	μ 51.9	μ 50.9
	M 39	M 45
	IQR 66.5	IQR 46
Children sex		
Girls	21 (52.5%)	22 (53.7%)
Boys	19 (47.5%)	19 (46.3%)
The commonest primary complaint as stated by caregivers		
Cough	40 (100%)	41 (100%)
Fever	25 (62.5%)	21 (51.3%)
Difficulty breathing	9 (22.5%)	10 (24.4%)

(Continued)

Table I (Continued).

Baseline Characteristics	Intervention	Control
Clinical diagnosis at the consultation		
ARVI	16 (40%)	10 (24.4%)
Rhinopharyngitis	6 (15%)	12 (29.3%)
Tonsillitis	7 (17.5%)	5 (12.2%)
Laryngotracheitis	1 (2.5%)	6 (14.6%)
Acute bronchitis	1 (2.5%)	3 (7.3%)
Acute obstructive bronchitis	4 (10%)	2 (4.9%)
Bronchiolitis	–	1 (2.4%)
Pneumonia	4 (10%)	2 (4.9%)
ARVI + other (gastroenterocolitis)	1 (2.5%)	–
ARVI + other (lymphadenitis; stomatitis)	–	2 (4.9%)
Hospitalisation during the index consultation	4	2
CRP values of intervention group children (n)		
1.0–5.0 mg/L	25	–
5.1–10.0 mg/L	4	–
Up to 20.0 mg/L	5	–
Up to 30.0 mg/L	2	–
Up to 50.0 mg/L	3	–
>50 mg/L	1	–
Prescribing antibiotics in both groups		
Received antibiotics	6 (17%)	23 (59%)
Did not receive	30 (83.3%)	16 (41%)

In terms of the data completeness, 71 children had all baseline assessment data and all follow-up data recorded (full data); 4 children had baseline data but no follow-up data. In hospitalised children allocated to the intervention group, the CRP values were 5.5, 20, 37, and 46. But at the decision of the research team, follow-up calls were also conducted to them. Follow-up assessments were done for 95% (n = 77) of children; for 4 children a baseline assessment had been conducted, but no follow-up data were obtained as caregivers had provided wrong phone numbers.

Feasibility Results

Based on a feasibility study conducted among all HCWs involved in the study at the conclusion of the pilot project, as well as among the parents or caregivers of children participating in the study, key opinions regarding the CRP POCT method were identified. When HCWs were asked about their general feelings about the use of the test, the majority responded very positively. Regarding the question about the convenience and practicality of implementing this test in their clinical practice, a majority answered “Definitely yes”. Similarly, when asked if they would like to use CRP POCT in their future practice, the majority once again responded “Definitely yes”. Only one out of eight HCWs answered “Do not know” to all three questions.

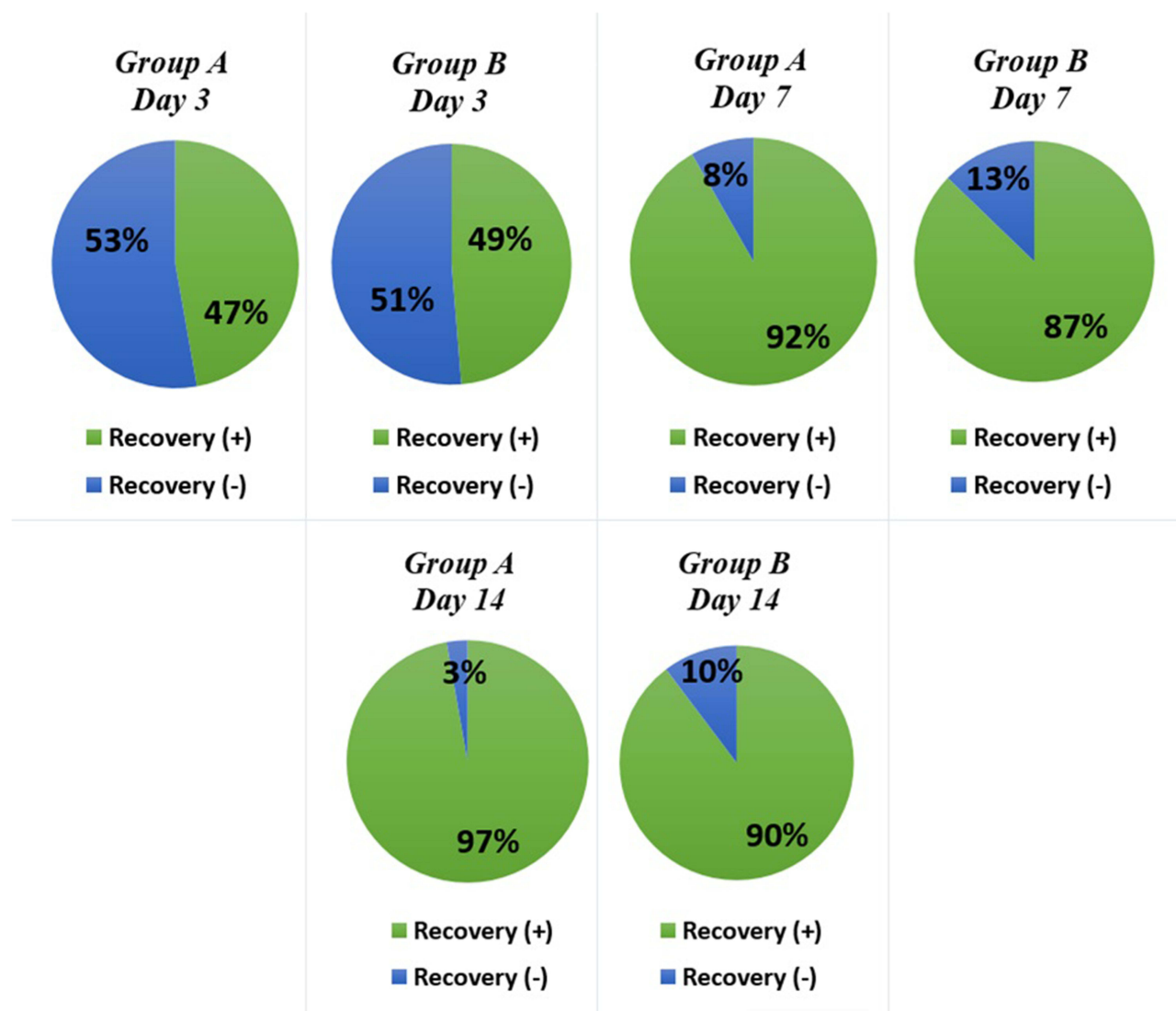


Figure 3 Percentage of children in both groups who were considered recovered by their caregivers. In intervention group, on Day 3, according to parents or caregivers, 47% of children recovered, on Day 7–92%, and finally on Day 14–97%. In control group, parents or caregivers reported recovery on Day 3–49%, Day 7–87% and Day 14–90%.

Regarding the survey for parents and caregivers, there were only two questions: how they reacted to the use of CRP POCT to diagnose their children in general, and whether they consider it acceptable to use this test to diagnose children. The vast majority of responses were positive.

Discussion

Feasibility Findings

HCWs viewed CRP as a simple and quick aid in diagnosis, and normal CRP levels were a strong argument for them to refrain from prescribing antibiotics. Local HCWs fully supported the introduction of this method into routine clinical practice based on their first experience with it and were positive about its use in the future. As for the attitude of caregivers to the CRP POCT method in relation to their children, their high willingness to accept this method in the daily clinical practice of health workers was noted, suggesting a high acceptability of this method could be expected in the main trial. With regard to their attitude towards the participation of their children in the study, in general, no incidents and opposition were noticed. A qualitative study in Lebanon on children's participation in clinical trials found that Lebanese caregivers have similar perceptions and attitudes towards children's participation in clinical trials as those reported in

industrialised countries.²⁷ One qualitative study targeting the acceptability of the test among general practitioners reported that CRP POCT was acceptable to clinicians who believed in its usefulness and that CRP POCT, when used as an adjunct to clinical assessment, could be used to support efforts to counselling patients and improving decisions about prescribing antibiotics for ARTI.²⁸

The logistics of data collection worked as expected in the pilot. The completeness of data collection at the stage of follow-up calls was high. Four caregivers provided incorrect or no longer serviced phone numbers, leading to loss of follow-up. There are five mobile phone operators in Kyrgyzstan,²⁹ and many people have SIM cards from different operators; it may be wise to collect all phone numbers from the child's caregiver and household. We estimate that the research model is quite suitable for a larger sample size in the main trial and will likely improve data completeness.

Pilot Study Findings

The pilot study showed that we could enrol roughly half of the screened patients; 81 children were enrolled in approximately two weeks (data collection in fields were conducted in period from 24th of November to 7th of December and the last follow-up phone call was conducted on 31st of December). In the upcoming main study, we plan to enrol 1204 children at 14 primary healthcare centres. According to the archival data of local medical institutions, the largest number of children with respiratory syndromes is observed in winter (December to March). It follows that the main study should also be done in winter to get the most patients in the least amount of time. The second finding is that children in the CRP POCT group were prescribed less antibiotics (17% as opposed to 59% in the control group). Given the small sample size of the pilot, the estimate must be interpreted with caution. Regardless, the finding is in line with a published meta-analysis summarising current data from 13 studies on the association between CRP POCT testing and antibiotic prescribing for ARTIs in general practice. CRP POCT testing has been found to significantly reduce antibiotic prescribing at the initial consultation.³⁰ This may generally speak in favour of confirming the effectiveness of this method, especially in conditions of low resources, when there are no other methods of laboratory or instrumental diagnostics at hand.^{30–36}

In terms of the primary outcomes, the recovery based on caregivers' phone responses on Days 3, 7, and 14, overall recovery was similar in both groups. Naturally, we take into account that caregivers are not clinicians to assess the clinical or laboratory recovery of children, but they seem to do well in reporting subjective or objective indicators of recovery (general well-being of the child, body temperature, cough, shortness of breath, runny nose, etc).³⁷

It is worth paying attention to the fact that in both groups (A and B) a large proportion of the diagnosis of ARVI was made (40% in intervention group and 24.4% in control group, as well as laryngotracheitis 29.3% in control group, which can also be attributed to the manifestation of ARVI). That is, clinicians were aware that they diagnosed an infection of predominantly viral nature, but prescribed an antibiotic nevertheless. It is interesting that pneumonia was not particularly common and that most diagnoses recorded would normally not warrant antibiotic therapy. The low levels of CRP measured in the pilot support the notion that most cases of ARVI were likely self-limiting viral infections. These preliminary pilot data suggest that local HCWs are not entirely sure about the correctness of prescribing antibiotics for children with ARVI, highlighting the need for education and practical tools to assist in a more rational antibiotic use for children with ARVI. Furthermore, the study is likely safe to conduct in children, as no adverse events occurred during the pilot period.

Conclusion

This study was a pilot model before running a full-scale RCT. The pilot provided satisfactory results regarding both the effectiveness of the CRP algorithm as the CRP intervention group was prescribed markedly less antibiotic treatments as well as the feasibility of the study set up and associated procedures. Important issues to consider in the upcoming main trial include logistics and follow-up data from caregivers. Overall, we found both caregivers HCW to be interested in and comply with study requirements.

Abbreviations

ARTI, Acute respiratory tract infections; ARVI, Acute respiratory viral infections; COVID-19, coronavirus disease 2019; CRF, clinical report form; CRP, C-reactive protein; FMC, family medicine centre; FOP, feldscher-obstetrics point; FPG,

family physicians group; HCW, healthcare workers; IMCI, integrated management of childhood illness; ISCRNT, international standard randomised controlled trial number; KAP, knowledge, attitudes and practices; LMIC, low- and middle-income countries; POCT, point-of-care test; RCT, randomised controlled clinical trial; SARS-CoV-2, severe acute respiratory syndrome-related coronavirus 2.

Ethics

The Ethical Committee of the National Centre of Maternity and Childhood Care of the Kyrgyzstan has approved the Study Protocol (Ref. no. 1. Date: 18/06/2021). The study participants are children living in the Kyrgyzstan, who are covered by the protection of citizens of the Kyrgyzstan. 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.

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Disclosure

The authors report no conflicts of interest in this work.

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