Implementation of point-of-care testing of C-reactive protein concentrations to improve antibiotic targeting in respiratory illness in Vietnamese primary care: a pragmatic cluster-randomised controlled trial

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Summary

Background In previous trials, point-of-care testing of C-reactive protein (CRP) concentrations safely reduced antibiotic use in non-severe acute respiratory infections in primary care. However, these trials were done in a research-oriented context with close support from research staff, which could have influenced prescribing practices. To better inform the potential for scaling up point-of-care testing of CRP in respiratory infections, we aimed to do a pragmatic trial of the intervention in a routine care setting.

Methods We did a pragmatic, cluster-randomised controlled trial at 48 commune health centres in Viet Nam between June 1, 2020, and May 12, 2021. Eligible centres served populations of more than 3000 people, handled 10–40 respiratory infections per week, had licensed prescribers on site, and maintained electronic patient databases. Centres were randomly allocated (1:1) to provide point-of-care CRP testing plus routine care or routine care only. Randomisation was stratified by district and by baseline prescription level (ie, the proportion of patients with suspected acute respiratory infections to whom antibiotics were prescribed in 2019). Eligible patients were aged 1–65 years and visiting the commune health centre for a suspected acute respiratory infection with at least one focal sign or symptom and symptoms lasting less than 7 days. The primary endpoint was the proportion of patients prescribed an antibiotic at first attendance in the intention-to-treat population. The per-protocol analysis included only people who underwent CRP testing. Secondary safety outcomes included time to resolution of symptoms and frequency of hospitalisation. This trial is registered with ClinicalTrials.gov, NCT03855215.

Findings 48 commune health centres were enrolled and randomly assigned, 24 to the intervention group (n=18 621 patients) and 24 to the control group (n=21 235). 17 345 (93·1%) patients in the intervention group were prescribed antibiotics, compared with 20 860 (98·2%) in the control group (adjusted relative risk 0·83 [95% CI 0·66–0·93]). Only 2606 (14%) of 18 621 patients in the intervention group underwent CRP testing and were included in the per-protocol analysis. When analyses were restricted to this population, larger reductions in prescribing were noted in the intervention group compared with the control group (adjusted relative risk 0·64 [95% CI 0·60–0·70]). Time to resolution of symptoms (hazard ratio 0·70 [95% CI 0·39–1·27]) and frequency of hospitalisation (nine in the intervention group *vs* 17 in the control group; adjusted relative risk 0·52 [95% CI 0·23–1·17]) did not differ between groups.

Interpretation Use of point-of-care CRP testing efficaciously reduced prescription of antibiotics in patients with non-severe acute respiratory infections in primary health care in Viet Nam without compromising patient recovery. The low uptake of CRP testing suggests that barriers to implementation and compliance need to be addressed before scale-up of the intervention.

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Introduction

Viet Nam has among the highest prevalence of antimicrobial resistance in the world.[1] Drivers of resistance are multifactorial, but human antibiotic consumption is recognised as a key contributor. Data from high-income countries[2] show that reduced antibiotic consumption reduces the prevalence of resistant bacteria at the population level, but evidence is lacking from low-income and middle-income countries (LMICs). 80–90% of human antibiotic consumption globally occurs in the community, mostly in patients with acute respiratory infections.[2–4] Interventions that could safely reduce antibiotic use in this context could have a large effect on reducing overall antibiotic consumption.

Research in context

Evidence before this study

A 2020 systematic review of 13 randomised controlled trials done around the world and published from 1995 to 2019 (n=9844) suggested that use of C-reactive protein (CRP) testing to guide antibiotic therapy reduced antibiotic use in children and adults. Meta-analyses showed that point-of-care testing of CRP concentrations significantly reduced the proportion of patients given an initial antibiotic prescription compared with routine care (38·2% *vs* 51·4%; relative risk 0·79 [95% CI 0·70–0·90; p=0·0003; I^2=76%). We searched MEDLINE and the Cochrane Library with a combination of "antibiotic", "primary care", "intervention", "respiratory tract infection", "C reactive protein" and "point-of-care" for articles published in English from database inception to Feb 24, 2023. We found three additional trials and an implementation study that had not been included in the previous systematic review. In trials in southeast Asian countries, CRP testing reduced antibiotic prescribing in primary care settings without affecting clinical outcomes. By contrast with findings from non-pragmatic randomised controlled trials done in research-oriented contexts, a pragmatic trial done at eight primary care practices in England in 2016–17 suggested that use of point-of-care CRP testing did not significantly reduce antibiotic prescribing, mainly because of poor uptake of testing—only 268 tests were done among 47 000 registered patients over 6 months, even though clinical guidance from the UK National Institute for Health and Care Excellence recommended CRP testing in people with symptoms of lower respiratory tract infection in whom clinical assessment is inconclusive. Similarly, in another pragmatic study done at nine general practices in the Netherlands, point-of-care testing of CRP influenced general practitioners to change their decision about antibiotic prescribing in patients with acute cough but did not reduce overall antibiotic prescribing in practices with low prescribing rates. However, in sensitivity analysis, the implementation of CRP testing was associated with reduced antibiotic prescription in practices with high prescribing rates. Although the introduction of point-of-care testing of CRP in three out-of-hours primary care centres in England was not associated with reductions in antibiotic prescribing, when the tests were done, they were beneficial in supporting communication around not prescribing antibiotics. All previous randomised controlled trials, except for one pragmatic cluster-randomised trial, were done in research contexts that do not reflect routine care environments. No similar trial has been done in a non-research context (ie, a pragmatic trial with little support from research staff) in a low-income or middle-income country.

Added value of this study

Our pragmatic, cluster-randomised trial of point-of-care testing of CRP in patients with acute respiratory infections in primary health care in Viet Nam is, to our knowledge, the largest such trial done in a low-income or middle-income setting.
The addition of affordable CRP testing to usual care was associated with significant reductions in antibiotic prescribing in non-severe respiratory infections, especially among patients with low CRP concentrations. The 30-day frequency of referral to higher-level care centres was slightly higher in the intervention than in the control group, but this outcome could be balanced by the potential benefit of reducing antibiotic resistance. The pragmatic design of our trials means that our results should be broadly generalisable to routine practice.

Implications of all the available evidence

Our findings support previous evidence that CRP testing could be an important component of management strategies for acute respiratory infections in routine care in low-income and middle-income countries. However, low uptake in our study suggests the importance of embedding point-of-care CRP testing in a more comprehensive interventional package that also includes education, policy changes, and guideline changes at national level to combat antimicrobial resistance.

Point-of-care tests of C-reactive protein (CRP), a biomarker of inflammation, are widely used in high-income settings to guide antibiotic treatment of acute respiratory infections.[5–13] Clinical trials[10,14] in southeast Asia showed that CRP testing could safely reduce antibiotic use in patients with mild acute respiratory infections in primary care. In Viet Nam, there was a 20% absolute reduction in initial prescription of antibiotics (odds ratio [OR] 0·31 [95% CI 0·34–0·49]; p<0·0001).[14] In Thailand and Myanmar, the effect was smaller, with a 5% absolute reduction in antibiotic prescription from day 0 to day 5 among febrile patients, most of whom presented with respiratory symptoms (adjusted OR 0·80 [95% CI 0·65–0·98]; p=0·03).[10] However, these were trials in research-oriented contexts in which randomisation was done at the patient level. As a result, the same prescribers saw patients in both the intervention and control groups, introducing possible contamination and observation bias (Hawthorne effect).[15,16] Furthermore, the CRP tests used in these studies required table-top readers, potentially affecting affordability and scalability in primary care in many LMICs.

To enable policy makers to consider guideline changes and wide-scale implementation of CRP testing for suspected acute respiratory infections in primary health-care settings, a pragmatic implementation study was needed of the effect of CRP testing in routine care (ie, no research staff on site, using commercially available lateral flow tests suitable for use in low-level facilities by less skilled personnel). We aimed to assess whether introduction of point-of-care CRP tests in routine primary health care could safely reduce prescription of antibiotics for patients with acute respiratory infections.

Methods

Study design and participants

We did a pragmatic, cluster-randomised controlled trial at 48 commune health centres (CHCs) in three rural districts (Truc Ninh, Nam Truc, and Y Yen) in Nam Dinh a province in northern Viet Nam, between June 1, 2020, and May 12, 2021. In Viet Nam's public health services, CHCs are the lowest level health-care centre, and provide a range of primary health care, including preventive care for maternal and child health, curative care, and hygiene and health promotion.[17] CHCs were eligible for inclusion in the trial if they served a commune population larger than 3000 individuals, had an average of 10–40 consultations for suspected acute respiratory infections a week (verified by checking data for the previous year), had a licensed prescriber on site, and maintained an electronic database for recording patient data. Eligible patients were aged 1–65 years, had a health insurance number (to enable data linkage with the district hospital's database), and were visiting the CHC for a first consultation with an acute respiratory infection (as diagnosed by a health-care worker) with at least one focal sign or symptom and symptoms lasting less than 7 days. Focal signs and symptoms were cough, rhinitis (sneezing, nasal congestion, or runny nose), pharyngitis, shortness of breath, wheezing, chest pain, or abnormal sounds on lung auscultation (rales, rhonchi, stridor, or wheezing). Patients with severe illness necessitating urgent hospital referral were excluded. The full list of inclusion and exclusion criteria at both the CHC and patient levels has been previously published.[18]

The trial was approved by the ethics committee of the National Hospital for Tropical Diseases in Hanoi (07/HDDD-NDTW/2019) and the Oxford University Tropical Research Ethics Committee (53-18). Permission for the study was also obtained from local authorities. The need to gather written informed consent from patients (or legally authorised representatives) was waived by the ethics committees, to ensure as little disruption to routine practice as possible.

Randomisation and masking

NTTD, THN, THD, TBTL, and SL recruited centres to the trial. All patients who met inclusion criteria at each recruited centre were automatically included. Eligible CHCs were randomly assigned (1:1) to deliver either the intervention (including testing CRP concentrations in eligible patients before prescribing antibiotics, provision of guidance to health-care workers about use of the test, and displaying of posters about the test at the centre) or routine care (ie, the control group). The intervention included provision of CRP tests, health-care worker guidance, and posters about the test for both health-care workers and patients. SL oversaw randomisation and allocation of CHCs to groups. Randomisation was stratified by district and by baseline proportion of patients with cough for whom antibiotics were prescribed (ie, <85% *vs* ≥85% [85% was the mean across 48 CHCs]) in STATA (version 14), using the randtreat command, with leftover CHCs (misfits) allocated to maintain balance between strata. Because of the nature of the intervention, masking of health-care workers and participants was not possible, but data analysts were masked to allocation group until after the definitive analysis was done.

Procedures

Before randomisation, baseline training was provided to all participating CHCs about the role of antibiotics, antimicrobial resistance, management of acute respiratory infections, and good clinical practice for research. Additional training about the use of CRP testing was provided to health-care workers in the intervention group. Details of training content have been published previously.[18]

At all CHCs, diagnostic codes were listed by the treating health-care worker in patient electronic records for reimbursement purposes according to the tenth revision of the International Classification of Diseases. These codes were used to classify patients into different subgroups of infections (codes J00–J06 for upper respiratory tract infections, J12–J22 for lower respiratory tract infections, and J09–J11 for influenza; patients with other infections, such as unspecified chronic or acute bronchitis [J40], were also coded). Patients at all sites were provided with an information leaflet about rational use of antibiotics in acute respiratory infections, and the implications of overuse of antibiotics in terms of the development of resistance. The leaflets at intervention sites included an additional section about the role of CRP testing in guiding antibiotic prescriptions.[18]

Intervention sites were provided with Actim CRP Rapid Tests (Medix, Biochemica, Espoo, Finland). CRP testing was recommended for all eligible patients with suspected acute respiratory infections. If patients had no clinical signs of severity and CRP concentrations less than the 10 mg/L cutoff, no antibiotics were recommended (a wait-and-see approach). If CRP concentrations were between 10 mg/L and 40 mg/L in patients with no clinical signs of severity, antibiotics were unlikely to be needed but could be considered in cases of high clinical concern. Antibiotics were recommended in all patients with CRP concentrations higher than 40 mg/L according to local guidelines. The treating health-care worker decided on the basis of their clinical assessment whether or not to comply with this guidance.

The intervention was done in three phases, with enhancements introduced to address implementation challenges. In the first phase, the intervention was initiated, the CRP tests were provided, and CRP-focused training was delivered. In the second phase, screening logbooks were introduced to enable exclusion of patients who did not attend the CHC in person and could not undergo CRP testing from the per-protocol analysis, and

a refresher training session was delivered (specifically about use of CRP testing). In the third phase, CRP testing was advertised via loudspeakers at CHCs as community sensitisation to improve uptake rates. According to the Pragmatic Explanatory Continuum Indicator Summary, our trial was very pragmatic in all dimensions except the delivery domain (appendix p 1).[19]

See Online for appendix

Outcomes

The primary endpoint was initial antibiotic prescription, defined as the proportion of patients prescribed antibiotics for acute respiratory infection. Prespecified secondary endpoints included the proportion of patients in whom subsequent antibiotic use was recorded, time to resolution of symptoms, and the frequency of re-consultation at CHCs, referral to a higher-level facility, the proportion of patients visiting CHCs for all consultations who received an initial antibiotic prescription, or hospitalisation within 2 weeks of the initial consultation. The full list of secondary outcomes is in the appendix (pp 2–3). The proportion of patients receiving an antibiotic classed as being in the Watch group (according to WHO's 2019 Access, Watch, and Reserve classification[20]) was also assessed as a secondary outcome, but was not prespecified. A subgroup of patients in each group were randomly selected (irrespective of whether they underwent CRP testing) and followed up by telephone 14 days after their initial consultation for additional prespecified secondary endpoints, including the source of subsequent antibiotics taken and satisfaction with CRP testing (measured on a scale from 0 to 10, with scores of 8 or higher considered to represent satisfaction, among patients who underwent testing only).[18] Other prespecified secondary endpoints, including cost-effectiveness, usability and acceptability of CRP testing among health-care workers, and health-care workers' adherence to guidelines will be reported separately.

Statistical analysis

We estimated that with a group size of 24 CHCs (ie, 48 CHCs in total) with an average of ten consultations for suspected acute respiratory infection per facility per week (ie, around 12 480 consultations per group per year), we would be able to detect a reduction of 12–23% or more in immediate antibiotic prescription as a result of the CRP testing intervention. We estimated that 1440 telephone follow-ups at 14 days per group would enable detection of a reduction of 15–24% or more in overall antibiotic use. On the basis of findings from a previous study[6] of CRP testing in Viet Nam, in which 1% of participants were hospitalised and 0·3–0·5% re-attended their primary health-care centre, we estimated that we could detect an absolute difference in adverse outcomes of 0·7 percentage points (ie, from 1·5% to 2·2% hospitalisation or re-attendance), with 80–95% power. Our sample-size calculations were based on probabilities of 0·05 for type I errors and 0·2 for type II errors, and inter-cluster coefficients of variation of 0·15–0·30. These and other details on sample-size calculations have been published previously[18] and are in the appendix (pp 12–17).

The main analyses were done in the intention-to-treat population, which included all eligible patients at all participating CHCs. Per-protocol analysis for the primary endpoint included only participants who underwent CRP testing. Prespecified subgroup analyses for the primary endpoint were done as for the primary analysis. For between-group comparisons, we used generalised linear models, with treatment group, age group (1–15 years *vs* 16–65 years), district, and type of acute respiratory infection as fixed effects, and health-care centre as a random effect. The main effect measures were calculated as ORs. Adjusted ORs and two-sided 95% CIs were then converted to adjusted relative risks (RRs) and risk differences.[21] Subgroup analyses were also adjusted, with age group, district, and infection type as fixed effects and health-care centre as a random effect unless the adjustment variable was part of the subgroup definition. Heterogeneity of effects between subgroups were assessed with the likelihood ratio test. We also calculated the intra-cluster correlation coefficient and assessed heterogeneity of effects between CHCs by presenting change from baseline in a forest plot. Duration of symptoms was assessed via Kaplan-Meier curves with 95% CIs. Formal comparisons between the two treatment groups were based on the Cox proportional hazards model with treatment group and age group as fixed effects and health-care centre as a Gaussian random effect (frailty).

All statistical analyses were done in R (version 3.2.2). This trial is registered with ClinicalTrials.gov, NCT03855215.

Role of the funding source

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

Results

Between Dec 1 and Dec 15, 2019, we screened 73 CHCs for eligibility, 48 of which were enrolled in the trial (figure 1). At baseline, antibiotics were prescribed in at least 76% of suspected respiratory infections at all centres (appendix p 9). The 48 CHCs included saw 153–271 patients a month before the study, with baseline antibiotic prescription rates of 97–100% for eligible patients with acute respiratory infections.

24 CHCs were randomly assigned to the CRP testing intervention and 24 to routine care (figure 1). Phase one of the intervention ran from June 1 to Sept 30, 2020, phase two from Oct 1 to Dec 31, 2020, and phase three from Jan 1 to May 12, 2021. Electronic records were available for 39 856 eligible patients: 18 621 patients in the intervention group and 21 235 patients in the routine

care group, who collectively comprised the intention-to-treat population. Patient demographic and clinical characteristics were broadly similar in both groups (table 1). Fevers were substantially more common in the intervention group than in the control group CHCs (8289 [45%] *vs* 3209 [15%]), whereas sore throats were more common in the control than in the intervention group (16 853 [79%] *vs* 11 595 [62%]); this pattern was consistent with data for the year before the study (appendix p 4). Upper acute respiratory infections were predominant in both groups (table 1). Lower acute respiratory infections (3102 [17%] *vs* 2595 [12%]) and influenza (391 [2%] *vs* 40 [<1%]) were more frequent at intervention than at control CHCs. Compared with the year before the study, the number of visits for acute respiratory infections during the study was 35% lower in the control group and 38% lower in the intervention group, perhaps due to the COVID-19 pandemic (appendix p 4).

In the intention-to-treat analysis of the primary outcome, 20 860 (98·2%) of 21 235 patients in the control group and 17 345 (93·1%) of 18 621 patients in the intervention group received an antibiotic prescription at their initial CHC visit (adjusted RR 0·83 [95% CI 0·66–0·93]; table 2; ORs are reported in the appendix pp 7–8). In the per-protocol analysis, which included 2606 patients who underwent CRP testing (14% of patients in the intervention group), 1859 (71·3%) patients received an initial antibiotic prescription (adjusted RR *vs* control 0·64 [95% CI 0·60–0·70]). The difference in prescription rates between the intervention and control group was maintained in subgroup analyses, by age group, CRP concentration, gender, the presence of fever, type of acute respiratory infection, and study period (table 2; appendix pp 7–8, 11). The largest between-group difference was for patients with CRP concentrations of less than 10 mg/L compared with the control group (650 [51·0%] of 1274 patients *vs* 20 860 [98·2%]; adjusted RR 0·45 [95% CI 0·41–0·49]). A larger reduction between the intervention group and the control group was noted among patients with upper respiratory tract infections than among those with lower respiratory tract infections (table 2). The effect of the intervention diminished over time, even after additional training and community sensitisation (table 2).

The intra-cluster correlation coefficient, which measured variation between CHCs, was 0·09 (95% CI 0·07–0·14). Because of considerable imbalance in the prevalence of fever between groups, we did a post-hoc sensitivity analysis of the primary endpoints in eight different scenarios, in which we excluded CHCs where 30–90% of patients had fever. We noted no significant difference between scenarios (appendix p 10). When we compared antibiotic prescription rates during the study with those from the preceding year, there was substantial heterogeneity in prescription reductions before and during intervention between the CHCs (I^2 98·7%

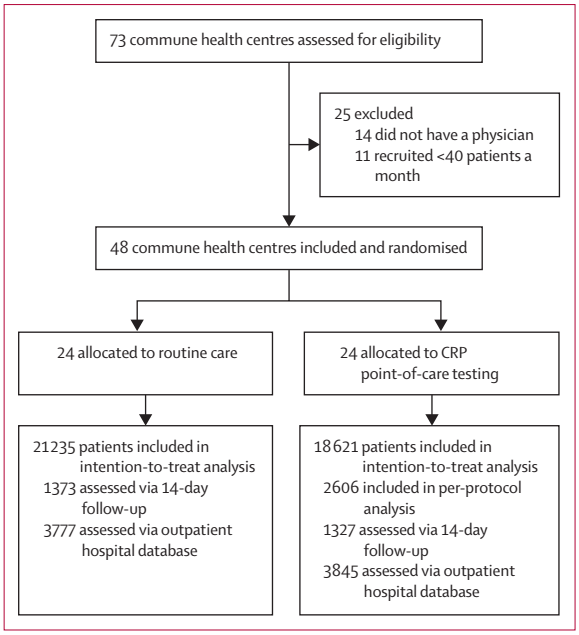

Figure 1: **Trial profile**
The intention-to-treat analysis was based on data from the commune health centres' electronic database. The per-protocol analysis included only patients who underwent point-of-case testing for CRP. CRP=C-reactive protein.

	Control group (n=21 235)	Intervention group (n=18 621)
Gender		
Male	9678 (46%)	8622 (46%)
Female	11 557 (54%)	9999 (54%)
Age, years		
1–15	5835 (27%)	4901 (26%)
16–65	15 400 (73%)	13 720 (74%)
Median (IQR)	46 (14–58)	46 (14–58)
Clinical symptoms		
Fever	3209 (15%)	8289 (45%)
Cough	19 698 (93%)	16 966 (91%)
Sore throat	16 853 (79%)	11 595 (62%)
Rhinitis	2860 (13%)	2459 (13%)
Shortness of breath	735 (3%)	546 (3%)
Wheezing	197 (1%)	54 (<1%)
Chest pain	436 (2%)	326 (2%)
Abnormal auscultation	689 (3%)	355 (2%)
Type of acute respiratory infection		
Upper respiratory tract	18 244 (86%)	15 419 (83%)
Lower respiratory tract	2595 (12%)	3102 (17%)
Influenza	391 (2%)	40 (<1%)
Other	5 (<1%)	60 (<1%)
Baseline antibiotic prescription (IQR)*	99% (97–100)	99% (99–100)

Data are n (%), unless otherwise specified. *Baseline antibiotic prescription refers to the proportion of patients with suspected acute respiratory infections who received antibiotic prescriptions in 2019.

Table 1: **Baseline patient characteristics**

	Control group	Intervention group	Adjusted relative risk (95% CI)	Adjusted risk difference (95% CI)
Population				
Intention to treat	20 860/21 235 (98·2%)	17 345/18 621 (93·1%)	0·83 (0·66 to 0·93)	−7 (−8 to −6)
Per protocol*	20 860/21 235 (98·2%)	1859/2606 (71·3%)	0·64 (0·60 to 0·70)	−30 (−36 to −30)
Age group, years				
1–15	5679/5835 (97·3%)	4585/4901 (93·6%)	0·86 (0·62 to 0·97)	−14 (−36 to −3)
16–65	15 181/15 400 (98·6%)	12 760/13 720 (93·0%)	0·82 (0·66 to 0·93)	−17 (−34 to −7)
C-reactive protein concentration, mg/L*				
<10	..	650/1274 (51·0%)	0·45 (0·41 to 0·49)	−54 (−58 to −50)
10 to ≤40	..	1000/1121 (89·2%)	0·87 (0·83 to 0·89)	−13 (−16 to −10)
>40	..	209/211 (99·1%)	1·00 (0·95 to 1·02)	0 (−5 to 1)
Gender				
Female	11 357/11 557 (98·3%)	9253/9999 (92·5%)	0·83 (0·67 to 0·93)	−16 (−32 to −6)
Male	9503/9678 (98·2%)	8092/8622 (93·9%)	0·85 (0·69 to 0·94)	−15 (−31 to −6)
Febrile				
Yes	3190/3209 (99·4%)	7936/8289 (95·7%)	0·92 (0·73 to 0·98)	−9 (−26 to −2)
No	17 670/18 026 (98·0%)	9409/10 332 (91·2%)	0·81 (0·63 to 0·92)	−18 (−35 to −7)
Type of acute respiratory infection†				
Upper respiratory tract	17 949/18 244 (98·4%)	14 287/15 419 (92·7%)	0·82 (0·66 to 0·93)	−16 (−33 to −6)
Lower respiratory tract	2521/2595 (97·1%)	3001/3102 (96·7%)	0·93 (0·78 to 1·00)	−6 (−21 to 0·2)
Period				
June–September, 2020	6429/6620 (97·1%)	5824/6347 (91·8%)	0·77 (0·54 to 0·92)	−22 (−45 to −8)
October–December, 2020	6896/6991 (98·6%)	5113/5537 (92·3%)	0·82 (0·63 to 0·92)	−17 (−34 to −7)
January–May, 2021	7535/7624 (98·8%)	6408/6737 (95·1%)	0·89 (0·75 to 0·96)	−10 (−25 to −4)

Data are n/N (%), unless otherwise specified. Adjusted relative risk and risk difference (ie, the absolute percentage reduction in antibiotic prescription between the intervention and control group) were calculated based on odds ratios, which were estimated with a generalised linear model in which treatment group, age, district, and type of acute respiratory infection were fixed effects and health-care centre was a random effect. *Comparisons were against the control group from the intention-to-treat population and were adjusted by age, district, and type of acute respiratory infection (fixed effects), but health-care centre was not included as a random effect to avoid bias due to the small proportion of tested patients. †People with influenza were not included in comparisons because numbers were insufficient and there were many covariates that could have led to invalid test results.

Table 2: **Proportion of patients with suspected acute respiratory infections who were prescribed antibiotics**

[95% CI 97·5–99·1]; p<0·0001), and the pooled median treatment effect estimate was 0·97 (95% CI 0·97–0·98; appendix p 9).

1373 patients in the control group and 1327 patients in the intervention group were randomly followed up by telephone 14 days after their initial consultation. Subsequent antibiotic use among patients without an initial prescription was higher in the control group than in the intervention group (190 [13·8%] *vs* 117 [8·8%]; adjusted RR 0·64 [95% CI 0·51–0·79]; table 3). Among these 307 patients who reported subsequent antibiotic use within 14 days, the source of antibiotics was recorded in 289 cases. The most frequent source was private pharmacies or drug stores (160 [88%] of 181 patients in the control group *vs* 82 [76%] of 108 in the intervention group), followed by private hospitals or clinics (14 [8%] *vs* 19 [18%]) and public facilities (two [2%] *vs* four [4%]). The remaining participants were given antibiotics by their friends or relatives.

Among all patients registered at study CHCs, the proportion receiving an initial antibiotic prescription in any consultation (ie, not only those related to acute respiratory infection) did not differ significantly between intervention and control CHCs (62 303 [73·6%] of 84 693 *vs* 67 403 [67·4%] of 99 995; adjusted relative risk 1·07 [0·93–1·19]). Similarly, the proportion of all patients who attended CHCs for non-routine visits (excluding those routinely attending for chronic diseases, such as hypertension, diabetes, chronic obstructive pulmonary disorder, etc) receiving an initial antibiotic prescription did not differ significantly between intervention and control CHCs (table 3). Among study participants, the proportion who received a Watch-group antibiotic, re-attended the CHC within 30 days, or were referred to a higher-level health facility was significantly higher in the intervention group than in the control group (table 3).

Time to resolution of symptoms was similar in both groups, with a median symptom duration of 5 days in the control group and 5 days (IQR 4–6) in the intervention group (hazard ratio 0·70; 95% CI 0·39–1·27; figure 2).

Adverse events, defined as hospitalisation within 2 weeks of the initial consultation, were rare. We identified 26 hospitalisations: seven cases verified from 1531 follow-up telephone interviews and 19 cases from in-patient provincial and district hospital databases. The

	Control group	Intervention group	Adjusted relative risk (95% CI)	Adjusted risk difference (95% CI)
Subsequent antibiotic use within 14 days*	190/1373 (13·8%)	117/1327 (8·8%)	0·64 (0·51 to 0·79)	−5 (−7 to −3)
Proportion of all patients initially prescribed antibiotics	67 403/99 995 (67·4%)	62 303/84 693 (73·6%)	1·07 (0·93 to 1·19)	4 (−6 to 13)
Proportion of all patients attending CHCs for non-routine visits initially prescribed antibiotics	62 671/93 240 (67·2%)	58 439/78 029 (74·9%)	1·07 (0·89 to 1·21)	4 (−7 to 14)
Proportion of patients with acute respiratory infections prescribed Watch Group antibiotics†	890/21 235 (4·2%)	836/18 621 (4·5%)	1·12 (1·02 to 1·24)	1 (0 to 1)
Days to resolution of symptoms	5 (3–5)	5 (4–6)	0·70 (0·39 to 1·27)‡	
Re-attendance at commune health centre	3421/21 235 (16·1%)	3813/18 621 (20·5%)	1·18 (1·13 to 1·23)	3 (2 to 3)
Referral	3777/21 235 (17·8%)	3845/18 621 (20·6%)	1·16 (1·11 to 1·22)	3 (2 to 4)§
Hospitalisation¶	17/3777 (0·5%)	9/3845 (0·2%)	0·52 (0·23 to 1·17)	..
Satisfaction score‖	NA	9 (7–10)	..	..

Data are n/N (%) or median (IQR) unless otherwise specified. Adjusted relative risk and risk difference (ie, the absolute percentage reduction in antibiotic prescription between the intervention and control group) were calculated on the basis of odds ratios, which were estimated with a generalised linear model in which treatment group, age, district, and type of acute respiratory infection were fixed effects and health-care centre was a random effect. Comparisons were based on data from 14-day follow-up data, commune health centre data, and hospital data. NA=not applicable. *Measured via telephone follow-up. †Not a prespecified outcome, but analysed in the same way as the primary endpoint. ‡This is a hazard ratio calculated with a Cox regression model adjusted for age group and random site effect. §Unadjusted. ¶Serious adverse events were based on district and provincial hospital inpatient datasets. ‖Satisfaction with point-of-care testing of C-reactive protein was measured among patients in the intervention group only.

Table 3: **Summary of secondary endpoints**

proportion of hospitalisations did not differ significantly between groups (table 3).

The median satisfaction score among participants who underwent CRP testing was 9 (IQR 7–10). Of the 2606 participants whose CRP levels were measured, 1274 (49%) had concentrations less than 10 mg/L, 1121 (43%) had concentrations between 10 and 40 mg/L, and 211 (8%) had CRP concentrations higher than 40 mg/L. 650 (51%) patients with CRP concentrations less than 10 mg/L received an initial antibiotic prescription (ie, non-compliance). The frequency of non-compliance was similar across age groups (appendix p 5). Among 1006 participants who underwent CRP testing and had fever, 337 (34%) had CRP concentrations less than 10 mg/L, 518 (51%) had CRP concentrations of 10–40 mg/L, and 151 (15%) had CRP concentrations higher than 40 mg/L. Among 312 participants who underwent CRP testing and had lower respiratory tract infections, 178 (57%) had CRP concentrations less than 10 mg/L, 122 (39%) had concentrations of 10–40 mg/L, and 12 (4%) had concentrations higher than 40 mg/L (appendix p 6).

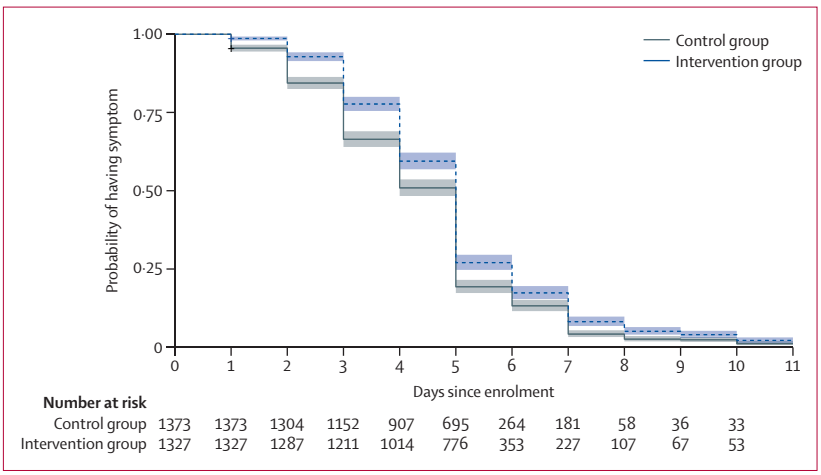

Figure 2: **Kaplan-Meier curve of time to resolution of symptoms, by treatment group**
Shaded regions represent 95% CIs.

Discussion

In this pragmatic, cluster-randomised controlled trial, we showed that use of point-of-care testing for CRP concentrations in people with suspected acute respiratory infections reduced initial antibiotic prescribing in primary health-care centres in Viet Nam without compromising clinical recovery. The study, which included nearly 40 000 participants, is, to our knowledge, the biggest trial done so far in LMICs to support the efficacy of CRP testing in routine practice to inform potential wide-scale implementation. Our pragmatic trial design strengthens the applicability and generalisability of our trial results to routine practice.

The overall absolute reduction in the proportion of people prescribed antibiotics in the intervention versus the control group was small, compared with the effect of CRP testing reported in previous cluster-randomised trials[5,8,10,11,22] in high-income countries and LMICs, in which between-group reductions ranged from 4·5% to 28·8%. However, for various reasons, only a small proportion of the intervention group received the intervention in our trial. Larger reductions were noted in people who received the CRP test compared with the control group, particularly in participants with CRP concentrations of less than 10 mg/L. The effect of the intervention was thus probably diluted by low uptake of point-of-care CRP testing, with only 14% of eligible patients being tested. However, this uptake is higher than that reported in a pragmatic trial[23] in a high-income setting where, despite point-of-care CRP testing being recommended by the National Institute for Health and Care Excellence in people with suspected acute respiratory infections, only 268 (0·6%) tests were done

among 46 000 registered patients in primary care centres across England.[23] Partly because of low uptake and test usage, CRP testing in primary care centres in high-income settings was not associated with a reduction in antibiotic prescribing.[23] However, when testing was done, it supported communication around not prescribing antibiotics.[12]

Another implementation study[24] in primary care in the Netherlands showed that, in settings where antibiotic prescribing was low, point-of-care CRP testing did not reduce overall antibiotic prescription.[24] However, in a post-hoc sensitivity analysis, implementation of testing was associated with reduced antibiotic prescription in practices with higher prescribing proportions.

Factors associated with the low uptake of the intervention in our trial will be reported separately. However, briefly, many patients were treated remotely (partly because of the COVID-19 pandemic) and therefore could not be tested, patients often expected to be prescribed an antibiotic, and many were unsure about taking the test. These findings emphasise that different settings with country-specific health systems and cultural features are likely to have different barriers that need to be identified and addressed with appropriate interventions to achieve optimal effectiveness in uptake of any new diagnostic strategy.

Systematic reviews[25–28] have identified four clinician-targeted interventions that efficaciously decreased antibiotic prescribing for acute respiratory infections in primary care (mainly in high-income countries): delayed prescribing, rapid point-of-care testing of CRP, rapid point-of-care testing of procalcitonin, and shared decision making. However, intervention uptake was a major limitation on population effects across all the interventions compared. Evidence from a systematic review[29] also supports the efficacy of educational interventions to reduce antibiotic prescribing. The largest effect identified was for a training and educational intervention targeting both prescribers and caregivers in Chinese primary care, which was associated with an absolute reduction in total antibiotic prescribing of 29% (95% CI –42 to –16) compared with usual care, although use of broad-spectrum antibiotics increased.[30,31] None of the trials in the included reviews reported on management costs for the treatment of acute respiratory infections or associated complications, which means that there is a paucity of evidence about the cost-effectiveness of interventions.[28] We plan to separately report a detailed economic assessment of this trial incorporating primary cost data.

Most participants in the trial presented with mild upper respiratory tract infections, probably caused by viruses, but even people with bacterial upper respiratory tract infections might not benefit from antibiotic treatment.[32] Furthermore, given its low specificity, CRP is not of high diagnostic value in the identification of patients with acute respiratory infections caused by bacteria. However, against a backdrop of near-universal antibiotic prescribing, CRP testing could provide assurance to most patients with low CRP concentrations (and their doctors) that antibiotics can be safely withheld. In the long-term, changes in national policy and guidelines could help to shift attitudes to antibiotic prescribing so that CRP testing would not have to be so heavily relied upon.

In high-income settings, a combined intervention of CRP testing and enhanced communication training (risk ratio 0·38 [95% CI 0·25–0·55]) was associated with a greater reduction in antibiotic prescribing than either intervention alone in people with acute respiratory infections (0·53 [0·36–0·74] for testing alone and 0·68 [0·50–0·89] for enhanced communication alone).[8] A 2019 study[33] of the use of antibiotics in primary care in the same Vietnamese province that our study was done in showed poor knowledge of, and inaccurate perceptions about, the use of antibiotics, with staff having had little post-basic training and education. Thus, in addition to improved diagnostics, education and training interventions are needed to improve antibiotic stewardship in this community. In late 2023, WHO will launch the Antibiotic Handbook, which will provide diagnosis and treatment guidance for 35 common infections in primary care and hospitals, with particular focus on LMICs. Embedding a CRP intervention within a more comprehensive antimicrobial stewardship intervention based on this guidance could be a promising way to reduce unnecessary antibiotic prescribing in primary care while preventing overuse of CRP testing in low-risk populations.

Follow-up by telephone and review of hospital medical records in a subset of patients provided important information about the safety of CRP testing in routine care. The risk of re-attendance at CHCs was slightly higher in the intervention than in the control group, as was the risk of hospital referral (although absolute differences between groups were small and there was no difference in hospitalisation risk). Similarly, previous trials[10,14,34] showed no differences in the frequency of recovery, serious adverse events, or patient satisfaction after the introduction of CRP testing in both high-income countries and LMICs. In only one trial[8] did hospital admissions increase after the introduction of CRP-guided treatment. However, hospitalisation was rare and concerns about this risk should be balanced against the benefits of reducing inappropriate antibiotic use on a large scale.[8] In our trial, we found no difference between the two groups in subsequent antibiotic use (mostly accessed through private pharmacies) within 14 days. This finding was similar to those of another randomised controlled trial[14] in Viet Nam, suggesting the need for complementary community-based interventions to tackle antibiotic demand.

Our trial has several limitations. First, the pragmatic trial design inevitably involved trade-offs, such as our

ability to establish whether the intervention was always used as intended. Notably, we were unable to exclude patients included in the electronic database who did not attend CHCs in person. Anecdotally, we learned that non-attendance was common, perhaps more so in the context of the COVID-19 pandemic, although no community SARS-CoV-2-positive cases were detected in the study area during implementation. Without close supervision, the documentation in study logbooks (introduced from October, 2020) was inconsistent across CHCs, making the denominator unreliable for the per-protocol analysis. Because patients treated remotely could not be tested, the uptake rate of the intervention was low, which diluted the intervention effect. Second, although we trained health-care workers at study outset about the value and use of point-of-care CRP testing, uptake was low. In response we introduced further enhanced training focusing on CRP testing and community sensitisation. Previous studies[8,31,35,36] have successfully used educational approaches to improve awareness among health-care workers (of clinical guidelines, appropriate prescribing practices, and the importance of communication) and reduce inappropriate antibiotic prescribing. A more detailed process assessment based on a theoretical framework to better understand the contextual reasons associated with high antibiotic prescribing and low uptake of CRP testing will be reported separately. Third, a higher prevalence of fever and lower respiratory tract infections was noted in the intervention arm compared with the control arm, which raised concerns about between-group comparisons and might have influenced the intervention's effect. However, this symptom pattern was consistent with that in the year preceding the study, and we think this imbalance was related to practical documentation differences rather than epidemiological differences between groups. Fourth, the Actim test we used in this trial might be less accurate than other more expensive CRP tests, with moderate agreement for low CRP concentration categories. As a result, we noted a lower proportion of patients with CRP concentrations less than 10 mg/L than in a previous trial[14] done in a similar context.[14] This limitation could also have led to a reduction in the intervention effect. Roughly half the participants with low CRP concentrations still received antibiotic prescriptions, suggesting further improvements are required. Reasons associated with non-compliance will be further investigated and reported in our future process assessment paper. Finally, the study was run during the early phases of the COVID-19 pandemic, and the number of visits and antibiotic prescribing patterns for acute respiratory infections might have been affected by this context.

Our results show that, although point-of-care testing of CRP concentrations can safely and efficaciously reduce antibiotic prescribing in patients with acute respiratory infections, the low uptake of the intervention suggests that scale-up needs to consider barriers to wider implementation and address them by changing the policy landscape for diagnostic testing. Furthermore, given the small population effect achieved in the study, further work investigating the potential for a more comprehensive antimicrobial stewardship intervention combining education and CRP testing in this population is needed.

Contributors

YL, SL, and SD conceived the study and were responsible for the funding application. YL, RCG, SD, SL, NTTD, and HRvD designed the study. NTP, DNT, and HTC were responsible for local institutional review board approval, getting permission from local authorities, and training sites. NTTD and THN were responsible for coordinating study activities across sites under the supervision of HRvD and SL. Data analysis was led by TVDV. NTTD drafted the Article, with contributions from all authors. All authors approved the final version, and had full access to all study data. NTTD and TVDV accessed and verified all study data. NTTD had final responsibility to submit for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Data might be made available according to the data-sharing policies of our local partners. Requests for data should be addressed to the corresponding author.

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