Point-of-care C-reactive protein testing to reduce inappropriate use of antibiotics for non-severe acute respiratory infections in Vietnamese primary health care: a randomised controlled trial

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Summary

Background Inappropriate antibiotic use for acute respiratory tract infections is common in primary health care, but distinguishing serious from self-limiting infections is difficult, particularly in low-resource settings. We assessed whether C-reactive protein point-of-care testing can safely reduce antibiotic use in patients with non-severe acute respiratory tract infections in Vietnam.

Method We did a multicentre open-label randomised controlled trial in ten primary health-care centres in northern Vietnam. Patients aged 1–65 years with at least one focal and one systemic symptom of acute respiratory tract infection were assigned 1:1 to receive either C-reactive protein point-of-care testing or routine care, following which antibiotic prescribing decisions were made. Patients with severe acute respiratory tract infection were excluded. Enrolled patients were reassessed on day 3, 4, or 5, and on day 14 a structured telephone interview was done blind to the intervention. Randomised assignments were concealed from prescribers and patients but not masked as the test result was used to assist treatment decisions. The primary outcome was antibiotic use within 14 days of follow-up. All analyses were prespecified in the protocol and the statistical analysis plan. All analyses were done on the intention-to-treat population and the analysis of the primary endpoint was repeated in the per-protocol population. This trial is registered under number NCT01918579.

Findings Between March 17, 2014, and July 3, 2015, 2037 patients (1028 children and 1009 adults) were enrolled and randomised. One adult patient withdrew immediately after randomisation. 1017 patients were assigned to receive C-reactive protein point-of-care testing, and 1019 patients were assigned to receive routine care. 115 patients in the C-reactive protein point-of-care group and 72 patients in the routine care group were excluded in the intention-to-treat analysis due to missing primary endpoint. The number of patients who used antibiotics within 14 days was 581 (64%) of 902 patients in the C-reactive protein group versus 738 (78%) of 947 patients in the control group (odds ratio [OR] 0·49, 95% CI 0·40–0·61; p<0·0001). Highly significant differences were seen in both children and adults, with substantial heterogeneity of the intervention effect across the 10 sites (I^2=84%, 95% CI 66–96). 140 patients in the C-reactive protein group and 137 patients in the routine care group missed the urine test on day 3, 4, or 5. Antibiotic activity in urine on day 3, 4, or 5 was found in 267 (30%) of 877 patients in the C-reactive protein group versus 314 (36%) of 882 patients in the routine treatment group (OR 0·78, 95% CI 0·63–0·95; p=0·015). Time to resolution of symptoms was similar in both groups. Adverse events were rare, with no deaths and a total of 14 hospital admissions (six in the C-reactive protein group and eight in the control group).

Interpretation C-reactive protein point-of-care testing reduced antibiotic use for non-severe acute respiratory tract infection without compromising patients' recovery in primary health care in Vietnam. Health-care providers might have become familiar with the clinical picture of low C-reactive protein, leading to reduction in antibiotic prescribing in both groups, but this would have led to a reduction in observed effect, rather than overestimation. Qualitative analysis is needed to address differences in context in order to implement this strategy to improve rational antibiotic use for patients with acute respiratory infection in low-income and middle-income countries.

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Introduction

Worldwide, bacterial pathogens are becoming increasingly resistant to antibiotics. This problem is particularly pressing in developing countries, where the burden of infectious disease is high and availability of newer, more expensive antibiotics is low.[1]

Vietnam already has a lot of antibiotic resistance. Prevalence of penicillin resistance is 71% and erythromycin resistance is 92% for *Streptococcus pneumoniae* in Vietnam, the highest in Asia.[2] Carbapenem resistance is high in *Pseudomonas aeruginosa* (25%) and *Acinetobacter baumannii* (40%) hospital-acquired

Research in context

Evidence before this study
In a 2014 Cochrane review, Aabenhus and Jensen searched several electronic database including CENTRAL, MEDLINE, Embase, CINAHL, Web of Science, and LILACS up to January, 2014, and identified six trials (three were individual randomised controlled trials [RCTs] and three were cluster RCTs). They found that cluster RCTs of C-reactive protein (CRP) testing was mostly effective in reducing antibiotic prescription. We searched MEDLINE and the Cochrane Library for articles published with the combination of "antibiotic", "primary care", "intervention", "respiratory tract infection", "C reactive protein" and "point-of-care". We found no recent trials in addition to those already included in the Cochrane review.

Added value of this study
All previous individual RCTs and cluster RCTs were done in European countries. No similar trial has been done in the

primary health-care setting of low-income or middle-income countries, or for children. In the lower-middle-income country setting of Vietnam we assessed whether an affordable and practical C-reactive protein point-of-care test can aid in reducing antibiotic use safely in both adult and children with non-severe acute respiratory infections.

Implications of all the available evidence
Our findings indicate that the intervention could be applied in the resource-constrained settings of low-income and middle-income countries to improve rational antibiotic use for both children and adults with non-severe acute respiratory tract infection without compromising patients' recovery and satisfaction. Considerable heterogeneity between the ten health-care stations indicates the importance of regular review of any intervention and tailoring it to specific local context.

infections.[3] Development of resistance is multifactorial but a major driver is likely to be the frequent and often injudicious use of antibiotics in people and widespread use in agriculture and aquaculture.[4] In Vietnam, most antibiotics are purchased in private pharmacies without a prescription (88% in urban regions and 91% in rural regions), mostly for cough.[5]

In the community setting, most inappropriate antibiotics are prescribed or dispensed for acute respiratory tract infections, which are often self-limiting, in primary health centres or pharmacies.[6,7] Although data concerning the drivers of prescribing in primary health care in Vietnam are scarce, one of the main reasons identified is diagnostic uncertainty.[8] Distinguishing serious from self-limiting acute respiratory tract infection is challenging, and typically relies solely upon careful history and examination. Concerns of missing a serious infection can precipitate antibiotic prescription. In low-income settings, where health infrastructure is less developed, physicians might also be concerned about patients' perceived or actual inability to access health care if their condition deteriorates. These factors can motivate overuse of antibiotics. Implementation of a rapid, affordable point-of-care test to aid diagnosis and management and reduce antibiotic use safely is therefore an attractive prospect.

C-reactive protein (CRP) is a biomarker for the presence of an inflammatory process.[9,10] Several studies in high-income countries have shown that primary health-care providers who used a point-of-care CRP test prescribed fewer antibiotics in patients with cough, without adversely affecting patient recovery.[11,12] No such trials have been done in the primary health-care setting of low-income and middle-income countries where unrestricted antimicrobial access and antibiotic resistance is highest, and different social and clinical

factors might affect its impact. Given the large number of self-limiting acute respiratory tract infections that present to primary care in Vietnam, even modest reductions would greatly decrease the absolute number of antibiotic prescriptions and thus one of the major drivers for bacterial resistance. Children in particular are frequently prescribed inappropriate antibiotics for acute respiratory tract infection, and any study should also address this important group.[7]

This study set out to assess the efficacy of CRP point-of-care testing for both children and adults presenting with non-severe acute respiratory tract infections at primary health-care centres in Vietnam to reduce inappropriate antibiotic use safely.

Methods

Study design

We did an open-label randomised controlled trial in ten selected primary health-care centres in northern Vietnam. Patients presenting with non-severe acute respiratory tract infection were randomly assigned to either CRP point-of-care testing (intervention) or routine care (control). Randomised assignments were concealed from prescribers and patients but not masked as the test result was used to assist treatment decisions.

Public health services in Vietnam are decentralised from nation to province, district and commune level. Primary health care (at the district and commune level) provides routine and urgent health care and hospital referral to the population. We aimed to include ten urban and rural primary health-care centres with a caseload of at least five acute respiratory tract infection cases per day within a 60 km radius of Hanoi. For urban centres, we invited all 20 existing regional polyclinics to participate; three did not respond, two refused to participate, and six did not meet the caseload criteria. Therefore we selected