Procalcitonin and lung ultrasonography point-of-care testing to determine antibiotic prescription in patients with lower respiratory tract infection in primary care: pragmatic cluster randomised trial

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Cite this as: *BMJ* 2021;374:n2132
http://dx.doi.org/10.1136/bmj.n2132

Accepted: 23 August 2021

ABSTRACT

OBJECTIVE

To assess whether point-of care procalcitonin and lung ultrasonography can safely reduce unnecessary antibiotic treatment in patients with lower respiratory tract infections in primary care.

DESIGN

Three group, pragmatic cluster randomised controlled trial from September 2018 to March 2020.

SETTING

60 Swiss general practices.

PARTICIPANTS

One general practitioner per practice was included. General practitioners screen all patients with acute cough; patients with clinical pneumonia were included.

INTERVENTIONS

Randomisation in a 1:1:1 of general practitioners to either antibiotics guided by sequential procalcitonin and lung ultrasonography point-of-care tests (UltraPro; n=152), procalcitonin guided antibiotics (n=195), or usual care (n=122).

MAIN OUTCOMES

Primary outcome was proportion of patients in each group prescribed an antibiotic by day 28. Secondary outcomes included duration of restricted activities due to lower respiratory tract infection within 14 days.

RESULTS

60 general practitioners included 469 patients (median age 53 years (interquartile range 38-66); 278 (59%) were female). Probability of antibiotic prescription at day 28 was lower in the procalcitonin group than in the usual care group (0.40 *v* 0.70, cluster corrected difference −0.26 (95% confidence interval −0.41 to −0.10)). No significant difference was seen between UltraPro and procalcitonin groups (0.41 *v* 0.40, −0.03 (−0.17 to 0.12)). The median number of days with restricted activities by day 14 was 4 days in the procalcitonin group and 3 days in the usual care group (difference 1 day (95% confidence interval −0.23 to 2.32); hazard ratio 0.75 (95% confidence interval 0.58 to 0.97)), which did not prove non-inferiority.

CONCLUSIONS

Compared with usual care, point-of-care procalcitonin led to a 26% absolute reduction in the probability of 28 day antibiotic prescription without affecting patients' safety. Point-of-care lung ultrasonography did not further reduce antibiotic prescription, although a potential added value cannot be excluded, owing to the wide confidence intervals.

TRIAL REGISTRATION

ClinicalTrials.gov NCT03191071.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Inappropriate antibiotic prescription is common in primary care for patients with lower respiratory tract infections

Procalcitonin testing can safely reduce antibiotic prescription in patients with lower respiratory tract infections in emergency departments

Lung ultrasonography is an effective tool for detecting lung consolidation

WHAT THIS STUDY ADDS

Use of point-of-care procalcitonin led to a reduction in antibiotic prescription rates at 28 days in patients with a lower respiratory tract infection in primary care; it also led to a reduction in in the use of chest radiographs by general practitioners

Use of point-of-care lung ultrasonography in patients with a procalcitonin level of 0.25 µg/L or higher did not further reduce antibiotic prescription

Reduction of antibiotic prescription did not affect patient's clinical outcomes and satisfaction

Introduction

Lower respiratory tract infections are among the most common acute reasons for patients to consult general practitioners and often lead to inadequate prescription of antibiotics.[1-4] Despite most patients presenting to their general practitioners with lower respiratory tract infections receive an antibiotic prescription, only 5-12% of them have community acquired pneumonia, which requires antibiotic treatment.[5] The absence of specific signs and symptoms for community acquired pneumonia makes identification of these patients challenging.[6] The presence of a new infiltrate on chest radiograph confirms a definitive diagnosis of pneumonia.[6 7] However, chest radiograph is not always available in the outpatient setting,[8 9] exposes patients to radiation, and has limited diagnostic accuracy.[10]

Procalcitonin is a biomarker with a high sensitivity (92%, 95% confidence interval 86% to 95%) in differentiating bacterial infections from viral infections in acute respiratory infections.[11] Measurement of this inflammatory host biomarker is now available as a point-of-care test, making its use relevant to primary care. Several trials evaluated the use of laboratory based procalcitonin to guide antibiotic prescription in patients with acute respiratory infections in primary care and in emergency departments.[8 12-14] Inclusion of patients for whom antibiotics are not recommended and high differences in adherence to procalcitonin

guidance led to conflicting results. No evidence from pragmatic trials is available on the impact of point-of-care procalcitonin to guide antibiotic prescription in patients with lower respiratory tract infections in primary care. Point-of-care lung ultrasonography is effective in detecting lung consolidation for the diagnosis of community acquired pneumonia.[10 15 16] Its high specificity (95%, 95% confidence interval 83% to 99%)[15] could compensate for the limited specificity of procalcitonin (73%, 42% to 91%), which is particularly important in a setting with a high rate of viral infection such as general practices.[11 17] The availability of portable and affordable machines together with short training courses makes ultrasonography suitable for primary care. No evidence from randomised controlled trials is available on the impact of lung ultrasonography on antibiotic prescription.

We conducted a multicentre trial to test (1) whether point-of-care procalcitonin guided treatment would decrease unnecessary antibiotic prescriptions compared with usual care, and (2) whether an intervention combining procalcitonin with lung ultrasonography would further reduce prescription of antibiotics compared with procalcitonin only in patients consulting general practitioners for a lower respiratory tract infection.

Methods

Trial design and setting

This three group, open label, pragmatic, cluster randomised superiority trial was conducted from September 2018 to March 2020, in accordance with a previously published protocol.[18] We chose a cluster design, with randomisation at the general practitioner level, to reduce contamination between groups. The trial initially recruited patients from 42 general practices in western and central-western Switzerland. Owing to slow recruitment, 18 additional practices included patients from August 2019, bringing the total of general practitioners to 60. The Swiss ethics committees of cantons Vaud and Bern approved the protocol (2017-01246). All study participants gave their written consent. An external independent monitoring board supervised the trial.

Randomisation, participants, and trial interventions

We randomly allocated practices to a study group with a 1:1:1 ratio with variable block sizes, according to a computer generated randomisation list.

General practitioners were eligible if they did not use point-of-care procalcitonin nor point-of-care lung ultrasonography for the diagnosis of pneumonia. General practitioners screened for inclusion all consecutive patients aged 18 or older presenting with an acute cough (≤21 days). General practitioners included patients with clinical pneumonia, defined as an acute cough and at least one of the following signs or symptoms: history of fever of more than 4 days, dyspnoea, tachnypnoea (>22 cycles/min), or abnormal focal lung auscultation.[2] Exclusion criteria are available in the supplementary material (table S1).

The study team trained general practitioners and medical assistants before participation in the study. Details of the curriculum are available in the supplementary material (section 3).

UltraPro group

The UltraPro algorithm combines the results of point-of-care procalcitonin with point-of-care lung ultrasonography in a sequential manner to guide antibiotic prescription. The medical assistant measured procalcitonin, using the portable BRAHMS PCT direct point-of-care test (Thermo-Fischer Scientific). This immunoassay has a measuring range of 0.22-10 µg/L and provides a quantitative result in 20 minutes using 20 µL of venous whole blood.

For any elevated concentrations of procalcitonin (≥0.25 µg/L), general practitioners did lung ultrasonography using a portable L12-4 convex transducer (Philips Lumify). The algorithm recommended prescribing antibiotics only in the presence of both an elevated procalcitonin and a lung consolidation (fig S1).

Procalcitonin group

The algorithm recommended prescribing antibiotics only in the presence of an elevated procalcitonin (≥0.25 µg/L) (fig S1). In all groups, antibiotic choice, dose, and duration were left to the discretion of the general practitioners who could also order further diagnostic tests.

Trial procedures

General practitioners recorded baseline data on patient's clinical presentation, comorbidities, and diagnostic procedures using an electronic case report form (research electronic data capture).[19] Members of the study team, blinded to study group, conducted standardised phone interviews of all participants on days 7 and 28. Participants were asked to fill a previously validated daily symptom diary until resolution of symptoms or day 28.[20] Additional details on the symptom diary are provided in the supplementary material (section 5). In case of follow-up visits, general practitioners managed their patients according to their usual practice.

Outcome measures

The primary outcome was the proportion of patients in each group prescribed an antibiotic by day 28. Secondary outcomes were antibiotic prescription at day 0 and by day 7, clinical failure by day 7 (defined as admission to hospital, death, or absence of improvement of fever and/or dyspnoea), severe adverse outcome by day 28 (defined as admission to hospital or death), duration of restricted activities due to the lower respiratory tract infection within 14 days, duration of the lower respiratory tract infection episode (based on a total symptoms score reported by patients) within 28 days, antibiotics side effects, chest radiograph at the initial consultation, follow-up medical visits for the episode of lower respiratory tract

doi: 10.1136/bmj.n2132 | BMJ 2021;374:n2132 | the bmj

infection by day 28, and patient reported satisfaction with clinical management at day 7.

Statistical analyses

For the sample size calculation, we assumed 60% of patients would receive antibiotics with usual care.[21] We calculated the sample size to assess an absolute difference in antibiotic prescriptions of at least 15% between the usual care group and the procalcitonin group (decrease from 60% to 45%) and at least 15% between the procalcitonin group and the UltraPro group (decrease from 45% to 30%) (fig S2). An expert panel agreed on a minimal 15% antibiotic reduction as the lower limit to justify eventual implementation of these interventions.

A study sample of 60 general practitioners and a mean of 10 patients per general practitioners (200 patients per group for a total of 600 participants) gives a power of 80% to detect the expected difference in antibiotic prescription with 5% level of significance, when adjusting for clustering at practice level (intracluster correlation coefficient 0.06). Additional details on the sample size calculation and the achieved power are provided in the supplementary material (section 6).

For the intention-to-treat analysis, all participants were included. Those participants lost to telephone follow-up were considered as having received antibiotics, had a clinical failure, and had a serious adverse outcome. We conducted sensitivity analyses to assess robustness to missing data, assuming missing outcome data as (1) "no antibiotics prescribed," (2) "same as day 0," or (3) "imputed outcome," and further tested the robustness of the model by introducing patient level covariates (table S3). For the per protocol analysis, we excluded patients whose general practitioners did not follow the algorithm recommendation or who did not complete telephone follow-up by 28 days. For the descriptive statistical analysis, we analysed proportions of categorical variables using χ^2 goodness of fit test; we used the Student t test for normally distributed variables or Mann-Whitney-Wilcoxon test for continuous variables with a skewed distribution. These tests did not account for clustering.

The primary analysis was a logistic regression corrected for variation at general practitioner level (generalised linear mixed effect model) to estimate the difference in the proportion of patients prescribed an antibiotic by day 28 as well as the odds ratio of antibiotic prescription between two groups. We compared binary secondary outcomes using logistic mixed effect regression. We compared safety outcomes (censored episode duration and censored duration of restricted activities) using hazard ratios derived from a frailty Cox model, and median difference estimated by Kaplan-Meier.

Patient and public involvement

Patients or the public were not involved in the design or conduct of this study. During the phone interviews on day 7, we assessed patient satisfaction regarding the consultation overall, the diagnosis, the prescribed treatment, and the amount of time spent with the general practitioner, which includes the time required to participate in research. These satisfaction outcomes were assessed using subquestions from the Visit-Specific Satisfaction Instrument, previously validated for use in French.[22]

Results

Participants

From 6 September 2018, 60 general practitioners screened 3612 patients, of whom 469 were included in the trial (UltraPro, 152/1325 (11.5%); procalcitonin, 195/1189 (16.4%); usual care, 122/1098 (11.1%)), 435 participants (93%) had complete phone follow-up (fig 1 and fig S3). Because of the SARS-CoV-2 outbreak, we stopped the trial prematurely on 10 March 2020 without knowledge of the results. Owing to logistical impediments, we did not plan to restart recruitment at a later date. The characteristics of the general practitioners and the participants were similar across the groups (table 1). Median age of the participants was 53 years (interquartile range 38-66) and 278 (59%) participants were female. We saw no significant differences in baseline characteristics, apart from chronic obstructive pulmonary disease (P=0.02), sputum production (P=0.007), fever (P=0.005), dyspnoea (P=0.04), chest pain (P<0.001), respiratory rate (P=0.02), and CRB-65 score (P=0.02).

Intervention

All patients assigned to both intervention groups received the allocated intervention. Nine patients (6%) in the UltraPro group had a procalcitonin concentration ≥0.25 µg/L, and therefore a lung ultrasonography was performed. General practitioners identified a lung infiltrate in six (67%) patients. Median duration of the lung ultrasonography was 15 minutes (interquartile range 15-20). Nineteen patients (10%) in the procalcitonin group had a procalcitonin concentration ≥0.25 µg/L. General practitioners did not use procalcitonin and lung ultrasonography in the usual care group. General practitioners adhered to the recommendation of the algorithm on antibiotic prescription in 320 patients (92%). They deviated in 15 patients (8%) in the procalcitonin group and in 12 patients (8%) in the UltraPro group.

Primary outcome

Of 469 patients included in the intention-to-treat analysis of the primary outcome, 408 (87%) contributed to the per protocol analysis (fig 1 and table S2). Compared with the usual care group, the probability of antibiotic prescription by day 28 was lower in the procalcitonin group (0.40 *v* 0.70, cluster corrected difference −0.26 (95% confidence interval −0.41 to −0.10); fig 2 and table 2). We saw no significant difference in antibiotic prescription by day 28 between the UltraPro group and procalcitonin groups (0.41 *v* 0.40, −0.03 (−0.17 to 0.12)). Compared

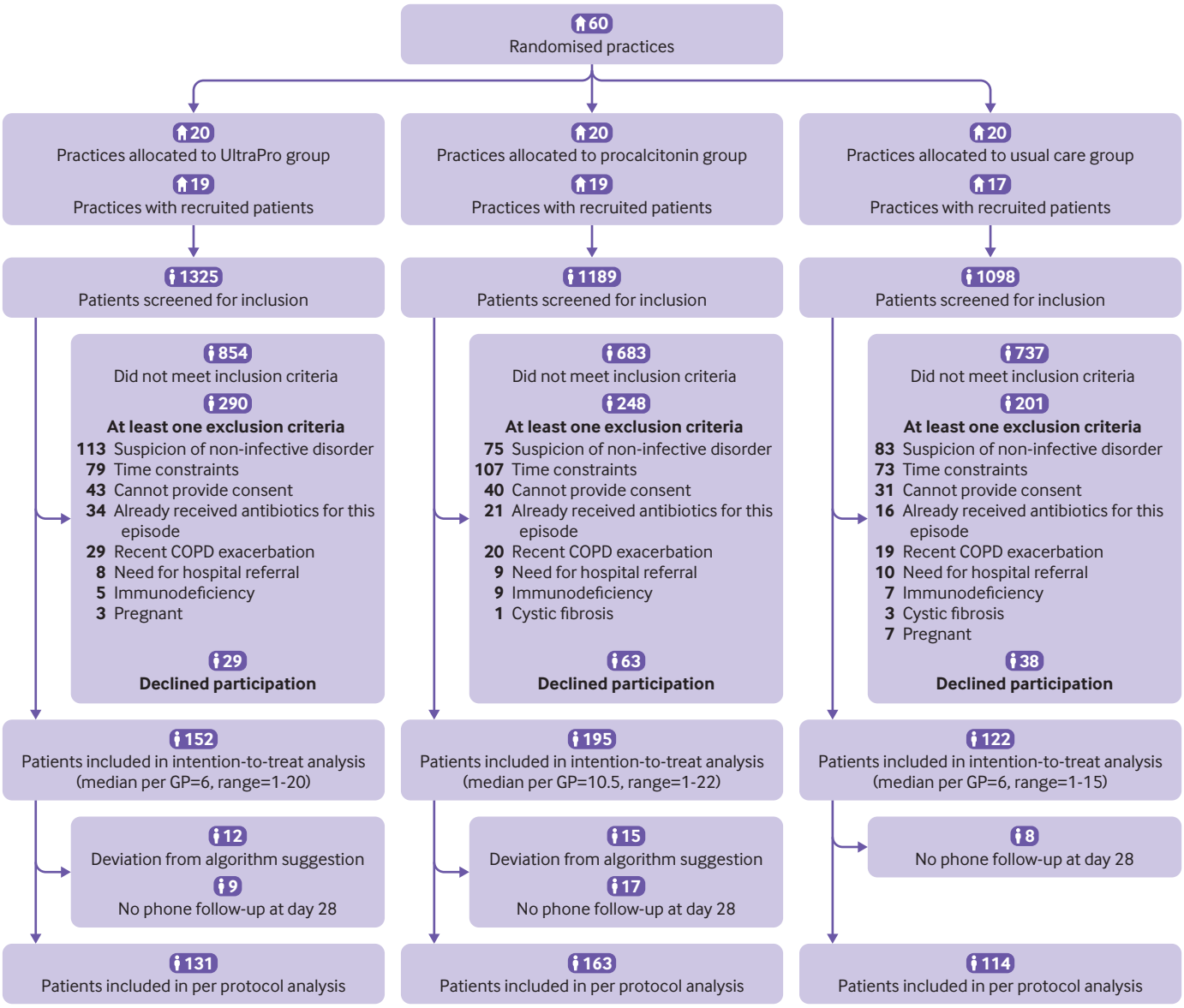

Fig 1 | Consort flowchart of trial participants. COPD=chronic obstructive pulmonary disease

with the usual care group, the odds ratio of antibiotic prescription by day 28 was 0.29 (95% confidence interval 0.13 to 0.65; intracluster coefficient 0.150) in the procalcitonin group (table 2). Compared with the procalcitonin group, the odds ratio of 28 day antibiotic prescription was 0.89 (95% 0.43 to 1.67; 0.096) in the UltraPro group (table 2).

These findings were consistent across sensitivity analyses, in the per protocol population and when adjusting the model for patient level confounding factors (table S3). However, we observed wide confidence intervals for the comparison between groups. Details of antibiotic prescriptions at day 0 are provided in the supplementary material (table S4).

Secondary outcomes

The probability of antibiotic prescription at day 0 was lower in the procalcitonin group than in the usual care group (0.18 *v* 0.57; cluster corrected difference −0.30 (95% confidence interval −0.48 to −0.14); fig 2 and table 2). We saw no significant difference between the UltraPro and procalcitonin groups (0.16 *v* 0.18, −0.02 (−0.16 to 0.12)).

The probability of antibiotic prescription by day 7 was lower in the procalcitonin group than in the usual care group (0.30 *v* 0.61; cluster corrected difference −0.24 (95% confidence interval −0.41 to −0.08); fig 2 and table 2). We saw no significant difference between the UltraPro and procalcitonin groups (0.31 *v* 0.30, −0.01 (−0.15 to 0.12)).

The characteristics of patients having received an antibiotic between days 1 and 28 despite a procalcitonin level less than 0.25 µg/L at day 0 are provided in the supplementary material (tables S5 and S6). The only factors associated with antibiotic prescription were the presence of chest pain at day 0 and a longer duration of symptoms. Nine (2%) patients were admitted to hospital by day 28. No deaths were

doi: 10.1136/bmj.n2132 | *BMJ* 2021;374:n2132 | the bmj

Table 1 | Baseline characteristics of participants, by study group. Data are number (%) unless stated otherwise

	Trial group		
	UltraPro	Procalcitonin	Usual care
General practitioners			
No	20	20	20
Female	8 (40)	8 (40)	9 (45)
Practice in French speaking region	19 (95)	15 (75)	16 (80)
>10 years' practice	8 (40)	11 (55)	10 (50)
>5 general practitioners in practice	3 (15)	6 (30)	3 (15)
Practice in urban setting	15 (75)	13 (65)	13 (65)
Radiology available in practice	10 (50)	12 (60)	13 (65)
Ultrasonography available in practice	3 (15)	6 (30)	7 (35)
Participants			
No	152	195	122
Demographic characteristics and comorbidities			
Female	87 (57)	126 (65)	65 (53)
Age (years; mean (SD))	52 (17.0)	53 (18.0)	50 (18.0)
Active smoker	26 (17)	44 (23)	31 (25)
Alcohol misuse	4 (3)	2 (1)	5 (4)
Heart failure	1 (1)	3 (2)	0
Diabetes	4 (3)	13 (7)	4 (3)
Chronic obstructive pulmonary disease	3 (2)	18 (9)	9 (7)
Asthma	20 (13)	37 (19)	13 (11)
Active malignancy	1 (1)	4 (2)	0
Presenting complaints			
Duration of cough (days; median (IQR))	6 (3-9)	7 (4-11)	6 (4-10)
Sputum production	92 (61)	148 (76)	82 (68)
History of fever	106 (70)	117 (60)	94 (77)
Duration of fever (days; median (IQR))	3 (2-5)	4 (2-5)	4 (3-5)
History of dyspnoea	108 (71)	126 (65)	68 (56)
History of chest pain	69 (45)	96 (49)	32 (26)
Clinical presentation			
Systolic blood pressure (mm Hg; median (SD))	128 (17)	130 (19)	130 (20)
Heart rate (beats/min; mean (SD))	85 (14)	84 (14)	86 (14)
Respiratory rate (cycles/min; mean (SD))	19 (4)	18 (5)	18 (5)
Temperature (°C; mean (SD))	37.0 (0.8)	37.0 (0.8)	37.0 (0.8)
SpO_2 (median (IQR))	97 (95-98)	97 (94-98)	97 (95-98)
Abnormal auscultation	60 (39)	96 (49)	64 (52)
CRB-65 score (No (%))*			
0	114 (75)	127 (65)	86 (70)
1	37 (24)	65 (33)	30 (25)
2	0	1 (1)	4 (3)
Unknown	1 (1)	2 (1)	2 (2)
DS-CRB-65 score (No (%))*			
0	87 (58)	112 (56)	62 (51)
1	28 (18)	50 (26)	27 (22)
2	3 (2)	19 (10)	5 (4)
3	0	1 (1)	2 (2)
Unknown	34 (22)	13 (7)	26 (21)

COPD=chronic obstructive pulmonary disease; SD=standard deviation; IQR=interquartile range.
*CRB-65 and DS-CRB-65 scores predict the severity of pneumonia and are calculated according to Kolditz et al.[23]

reported. Although confidence intervals were wide, we saw no significant differences in clinical failure by day 7 and in serious adverse outcomes by day 28 between the procalcitonin and usual care groups or between the Ultrapro and procalcitonin groups (table 2 and table S8). Table S7 details the various elements of the clinical failure composite outcome by day 7.

We saw no significant differences in antibiotic side effects within 28 days between the procalcitonin and usual care groups or between the UltraPro and procalcitonin groups (table 2). Patients in the procalcitonin group were less likely than those in the usual care group to have had a chest radiograph at day 0 (0.21 *v* 0.55; cluster corrected difference −0.33 (95% confidence interval −0.51 to −0.14); table 2 and fig S4). We saw no significant difference between the UltraPro group and the procalcitonin group (0.18 *v* 0.21; −0.11 (−0.26 to 0.05)). For patients receiving at least one follow-up visit, we saw no significant differences between the procalcitonin and usual care groups or between the UltraPro and procalcitonin groups (table 2).

The median number of days with restricted activities due to lower respiratory tract infection by day 14 was 4 days in the procalcitonin group and 3 days in the usual care group. The 95% confidence interval around the median difference (−0.23 to 2.32) included the prespecified margin (1 day), therefore non-inferiority was not proven (hazard ratio 0.75 (95% confidence interval 0.58 to 0.97; table 3). We saw no difference in the number of days with restricted activities by day 14 between the UltraPro and procalcitonin groups (4 *v* 4 days; median difference 0.0 (95% confidence interval −1.48 to 1.43); hazard ratio 1.01 (0.80 to 1.29)). The median duration of the episode by day 28 was 8 days in the procalcitonin group and 7 days in the usual care group (median difference 1.0 (−0.39 to 2.43), hazard ratio 0.81 (0.62 to 1.04)). We saw no difference in the duration of the episode by day 28 between the UltraPro and procalcitonin groups (median difference 0.0 (−1.68 to 1.74); hazard ratio 0.97 (0.76 to 1.24)).

We saw no statistical difference in the prescription of C reactive protein and white blood count at day 0 between study groups (table S9). Furthermore, no significant differences were seen in patient reported satisfaction outcomes among the UltraPro, procalcitonin, and usual care groups (table S10).

Discussion

Principal findings

Procalcitonin point-of-care guided treatment led to a statistically significant reduction of antibiotic prescription by day 28 of presentation compared with usual care in low risk patients with clinical evidence of community acquired pneumonia in primary care, with an absolute difference of 26%, without affecting patients' safety or patients' satisfaction. Point-of-care lung ultrasonography in patients with elevated procalcitonin level, according to the UltraPro algorithm, did not further reduce antibiotic prescription within 28 days when compared with treatment guided by procalcitonin only, suggesting no added benefit from its use in our algorithm. However, the wide confidence interval around this difference cannot exclude a clinically significant effect.

Because general practitioners had to perform lung ultrasonography only for instances of elevated procalcitonin, few ultrasonographies were conducted, which limited the possibility to show additional reduction in antibiotic prescription. The absence of significant differences between groups in clinical failure, serious adverse outcomes, symptom duration, and follow-up consultation rates suggests that prescribing fewer antibiotics does not affect safety. However, the wide confidence intervals observed for

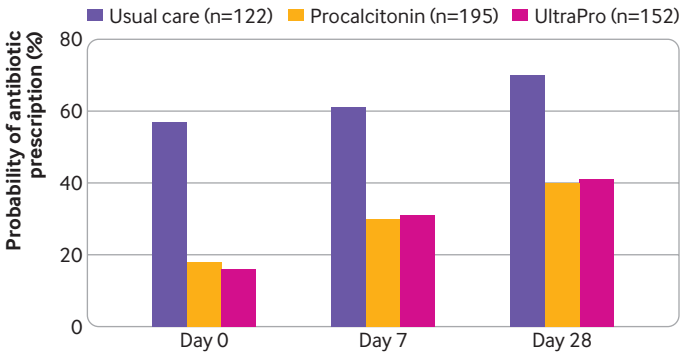

Fig 2 | Probability (%) of antibiotic prescription by days 0, 7, and 28 according to study group (usual care, procalcitonin, and UltraPro (sequential procalcitonin and lung ultrasonography point-of-care tests))

some of these secondary outcomes do not allow us to exclude large differences. The increase on 1 day in the restricted activity duration between the intervention and usual care groups suggests an effect on wellbeing, with the upper boundary of the 95% confidence interval above our prespecified non-inferiority margin. However, the confidence interval was narrow and the estimated difference remained low and likely to be not clinically relevant. A reduction in the use of chest radiographs in both intervention groups compared with the usual care group suggested that the intervention could also limit patient irradiation.

Strengths and limitations

We chose a cluster randomised trial design to ensure the feasibility of the trial from a logistical aspect, which is crucial in primary care, and to avoid contamination

Table 2 | Effect of procalcitonin versus usual care, and of UltraPro versus procalcitonin on primary outcome and binary secondary outcomes in the intention-to-treat population. P values pertain to odds ratios

			Group comparison (procalcitonin v usual care; UltraPro v procalcitonin)			
Outcome measure and trial group	No of patients	Observed (No (%))	Estimated difference corrected for cluster size (95% CI)	Unadjusted odds ratio (95% CI)	P value	Intracluster coefficient
Primary outcome measure						
Antibiotic prescription by day 28						
Usual care	122	86 (70)	—	—	—	—
Procalcitonin	195	78 (40)	−0.26 (−0.41 to −0.10)	0.29 (0.13 to 0.65)	0.001	0.150
Procalcitonin	195	78 (40)	—	—	—	—
UltraPro	152	62 (41)	−0.03 (−0.17 to 0.12)	0.89 (0.43 to 1.67)	0.71	0.096
Secondary outcome measures						
Antibiotic prescription at day 0						
Usual care	122	69 (57)	—	—	—	—
Procalcitonin	195	35 (18)	−0.30 (−0.48 to −0.14)	0.17 (0.05 to 0.50)	0.001	0.312
Procalcitonin	195	35 (18)	—	—	—	—
UltraPro	152	25 (16)	−0.02 (-0.16 to 0.12)	0.85 (0.38 to 1.89)	0.68	0.132
Antibiotic prescription by day 7						
Usual care	122	75 (61)	—	—	—	—
Procalcitonin	195	58 (30)	−0.24 (−0.41 to −0.08)	0.29 (0.12 to 0.72)	0.004	0.212
Procalcitonin	195	58 (30)	—	—	—	—
UltraPro	152	47 (31)	−0.01 (−0.15 to 0.12)	0.94 (0.44 to 1.83)	0.86	0.101
Clinical failure by day 7						
Usual care	122	52 (43)	—	—	—	—
Procalcitonin	195	84 (43)	0.01 (−0.14 to 0.15)	1.04 (0.51 to 2.02)	0.90	0.097
Procalcitonin	195	84 (43)	—	—	—	—
UltraPro	152	67 (44)	0.02 (−0.12 to 0.15)	1.08 (0.61 to 2.04)	0.80	0.068
Serious adverse outcome by day 28						
Usual care	122	10 (8)	—	—	—	—
Procalcitonin	195	20 (10)	0.03 (−0.06 to 0.10)	1.40 (0.56 to 4.25)	0.49	0.097
Procalcitonin	195	20 (10)	—	—	—	—
UltraPro	152	11 (7)	−0.03 (−0.09 to 0.03)	0.68 (0.30 to 1.44)	0.32	0.176
Any side effects from antibiotics by day 28						
Usual care	122	38 (31)	—	—	—	—
Procalcitonin	195	41 (21)	−0.10 (−0.21 to 0.02)	0.60 (0.31 to 1.16)	0.11	0.061
Procalcitonin	195	41 (21)	—	—	—	—
UltraPro	152	30 (20)	−0.02 (−0.11 to 0.08)	0.90 (0.48 to 1.68)	0.73	0.051
Chest radiograph (performed at day 0)						
Usual care	122	67 (55)	—	—	—	—
Procalcitonin	195	40 (21)	−0.33 (−0.51 to −0.14)	0.13 (0.04 to 0.44)	<0.001	0.390
Procalcitonin	195	40 (21)	—	—	—	—
UltraPro	152	27 (18)	−0.11 (−0.26 to 0.05)	0.32 (0.06 to 1.66)	0.18	0.509
At least one follow-up visit (days 1 to 28)						
Usual care	122	33 (27)	—	—	—	—
Procalcitonin	195	53 (27)	0.01 (−0.13 to 0.16)	1.10 (0.49 to 2.56)	0.81	0.152
Procalcitonin	195	53 (27)	—	—	—	—
UltraPro	152	43 (28)	0.00 (−0.10 to 0.11)	1.01 (0.6 to 1.7)	0.96	0.021

Table 3 | Effect of study group comparisons (procalcitonin *v* usual care; UltraPro *v* procalcitonin) on censored duration of limited activities due to lower respiratory tract infection by day 14 and censored duration of episode by day 28. Analysis accounted for the cluster effect via a frailty term. No evidence of non-proportionality was detected by Gramsch and Therneau's test. P values pertain to hazard ratios

	No of patients	Median duration (days)	Group comparison (procalcitonin v usual care, and UltraPro v procalcitonin)	
			Duration difference (days; 95% CI)	Hazard ratio (95% CI)
Duration of limited activities by day 14				
Usual care	102	3	—	—
Procalcitonin	159	4	1.0 (−0.23 to 2.32)	0.75 (0.58 to 0.97)
Procalcitonin	159	4	—	—
UltraPro	129	4	0.0 (−1.48 to 1.43)	1.01 (0.80 to 1.29)
Duration of symptoms by day 28				
Usual care	102	7	—	—
Procalcitonin	159	8	1.0 (−0.39 to 2.43)	0.81 (0.62 to 1.04)
Procalcitonin	159	8	—	—
UltraPro	129	8	0.0 (−1.68 to 1.74)	0.97 (0.76 to 1.24)

between study arms. Contamination is important in trials carried out in general practices where individual patients are treated by the same physician, which might dilute or even negate the intervention impact. Indeed, the interventions target patient management at the general practitioner level. Although the cluster design introduces the possibility of recruitment bias after randomisation (because a different number of patients and patients with different characteristics might be included after the intervention has been allocated[24]), it is the only study design that avoids contamination across groups that would arise from using randomisation at the individual level.

No substantial differences were seen in the characteristics of general practitioners. However, we observed a different screening and recruitment rate between study arms with a lower rate in the usual care group, as well as some differences in the baseline characteristics of participants suggesting the presence of a recruitment bias. The prevalence of chronic obstructive pulmonary disease and sputum production as well as low severity disease (CRB-65 severity score of 0) were lower in the UltraPro group. Prevalence of anamnestic fever was higher and of chest pain was lower in the usual care group. To account for these differences, we included potentials confounders (relevant patient level covariates) in a sensitivity analysis of the statistical model. Furthermore, to minimise selection bias, general practitioners screened consecutive patients attending care for a cough and included patients based on stringent, reproducible, and objective criteria. They included only patients with clinical pneumonia who, according to guidelines and not to physician opinion, might benefit from antibiotics.[2] Although our study had a recruitment bias, our findings were robust and the differences in the baseline characteristics of participants have little relevance from a clinical viewpoint, suggesting its effect on our results was minor.

We observed a low proportion of included patients among all screened patients, raising the question of the generalisability of our results. This low proportion is due to our stringent inclusion criteria of clinical pneumonia, which excluded patients who do not need antibiotics based on clinical criteria alone according to guidelines. Only 22% (588/2674) of excluded patients were prescribed an antibiotic at the initial consultation, while this proportion rose to 57% (69/122) in the usual care group at day 0, suggesting that we selected the appropriate target population.

Although we conducted a pragmatic study, general practitioners adhered to the algorithm's recommendations at inclusion at a high rate (92%; 320/347), suggesting that they integrated the intervention in their practice even with minimal training.

Our primary outcome was antibiotic prescription by day 28 rather than antibiotic prescription at day 0, which shows that the effect of our intervention persisted over time. However, antibiotic prescription more than doubled in the intervention groups between days 1 and 28. Baseline characteristics of patients, including clinical severity, and of general practitioners were similar between patients who did and did not receive antibiotics during follow-up despite a low procalcitonin value at baseline. Patients who received antibiotics during follow-up presented a longer duration of symptoms, suggesting that antibiotic prescription during follow-up was not related to patients' clinical severity, but rather to persisting symptoms. These data highlight the importance to inform patients and providers about the expected duration of an acute respiratory tract infection. Additional interventions during follow-up or improved information at first consultation might also further reduce antibiotic prescription.

This clinical trial evaluated lung ultrasonography for the management of lower respiratory tract infections, and we did not show any benefit from its use in low risk patients with clinical community acquired pneumonia and procalcitonin values ≥0.25 µg/L. General practitioners only performed lung ultrasonography in patients with elevated procalcitonin, which saved their time while managing the patients, a strategy that was considered easier to implement at a larger scale if proven successful. However, we only observed elevated levels of procalcitonin in 6% (9/152) of patients in the UltraPro group, which suggests limited additional room for reducing antibiotic prescription using sequential tests after procalcitonin use at first consultation. Whether lung ultrasonography might be useful as the first diagnostic test, in parallel to procalcitonin or in a higher risk population with clinical pneumonia, is not assessed in this study.

Owing to the first epidemic wave of SARS-CoV-2 in Switzerland, we had to stop the trial prematurely because we did not consider it feasible to continue recruiting participants under these exceptional circumstances. However, we did not identify any SARS-CoV-2 infection in trial participants.[25] We, therefore, did not reach our target sample size. Nevertheless, with over than 100 patients in each group, the comparison between procalcitonin and usual care yielded significant results. Owing to the nature of the

UltraPro algorithm (lung ultrasonography performed only in patients with elevated procalcitonin) and to the low prevalence elevated procalcitonin in this setting, we do not expect that the UltraPro algorithm could reduce antibiotic prescription sufficiently to have a public health impact, compared with procalcitonin only, even with a much higher sample size. However, with the wide confidence intervals when comparing the UltraPro group to the procalcitonin group, we cannot formally exclude a potential added value of this intervention.

General practitioners' participation on a voluntary basis led to a possible inclusion bias. Indeed, we expected these general practitioners to have lower rates of inadequate antibiotic prescription. Therefore, we could have underestimated the impact of our intervention. Over-prescription of antibiotics in primary care is a concern in Switzerland, albeit a lesser one than in other European countries. The daily defined dose per 1000 inhabitants per day in Switzerland is 9.1 versus 18.4 in countries participating in the European Surveillance of Antimicrobial Consumption Network surveillance study.[26] We hypothesise that if the intervention is efficacious in a setting with low prescription rates, its impact would probably be robust in settings with high prescription rates.

Owing to the pragmatic nature of the study and to the intervention, we conducted an open label study. This design could modify practitioners' or patients' behaviour—for example, the number of follow-up consultations when antibiotics were not prescribed or a subjective slower improvement of symptoms in patients who did not receive any antibiotics. However, this open label design better mimics real world settings.

Comparison with other studies

Although procalcitonin guided treatment led to a reduction of antibiotic prescription for acute respiratory infections in two randomised control trials in primary care, few participants had a lower respiratory tract infection preventing recommendation in this patient group.[8 14] Furthermore, inclusion criteria were non-reproducible, which makes application of study findings difficult in another setting. Two randomised controlled trials tested procalcitonin guided treatment in patients with lower respiratory tract infections in the emergency department, and showed conflicting results on antibiotic prescription, mainly due to physician's adherence to the guidance and to the patient population.[12 13]

Policy implications

The evidence from our trial expands the knowledge on the impact of procalcitonin guided treatment in patients with lower respiratory tract infections to primary care. Procalcitonin is now available at the point of care, which makes the implementation of its use in primary care scalable. The pragmatic design of our study also supports the feasibility of implementation. However, further analyses regarding the acceptability of the intervention by general practitioners and cost effectiveness ratio of the intervention are warranted to consider large scale implementation. The external validation of our findings in settings with different epidemiology or during outbreaks, such as SARS-CoV-2, needs confirmation.

Conclusions

The evidence from this trial suggests that using point-of-care procalcitonin for patients with lower respiratory tract infection in primary care reduces antibiotic use without prejudicing patients' clinical recovery and satisfaction. However, we could not show any added benefit from the use of lung ultrasonography to manage these patients, when used for those with an elevated procalcitonin level.

We thank all the patients who accepted to participate and make this study possible; all general practitioners (Allain-Pons Béatrice, Anex Frédéric, Antonini-Revaz Sylvie, Babic Ivana, Baraschi Constantin, Barbanneau-Sadoun Marie-Pierre, Barrois Dallière Olivia, Berdah Daniel, Bielinski Rainer, Blanc Louis, Blanc Müller Muriel, Brändle Carolina, Buff Evelyn, Collipal Tatiana, Cosandey-Tissot Marjorie, Darioli-Pignat Delphine, Dermigny Emilie, Draeyer Juerg, Fumeaux Christophe, Fuzat Laurent, Gennheimer Carl, Gropetti Gwenaël, Grunder Rolf, Hottinger Michaël, Hulliger Stéphane, Huynh Thanh-Liem, Jahns Maximilian, Jaunin-Stalder Nicole, Junod Michel, Keravec Erwan, Klay Michaël, Lombardo Patrick, Maire Ponci Céline, Marbouh Samira, Mayor Vladimir, Miéville Anne, Minnig Adrian, Montaru Rozain Corrine, Morel Abram, Mosimann Madeleine, Neumann Nicolas, Ochs Nicolas, Oppliger Séverine, Pasche Olivier, Paul Sophie, Persoz Christophe, Pierrisnard Marie-Amélie, Potin Mathieu, Rigamonti Véronique, Ronga Alexandre, Sagez Julien, Schwed François, Sibai Karim, Sierro Bard Fabienne, Steiner Anne-Sylvie, Vonnez Jean-Luc, Zahui Angenor, Zaugg Thomas, Zundel Rolf, Zundel-Maurhofer Doris) who enrolled patients in this study; all medical assistants who helped the general practices with the enrolment of patients and the measurement of procalcitonin; Cattaneo Nadia, Delaloye Martin, Ghidoni Céline, Legay Constance, and Vesin Timothée who helped us with patient follow-up; and Hodel Pascale who helped with training general practitioners in canton Bern.

Contributors: LL and NB-B contributed to the study conception, study design, study performance, study management, data analysis, data interpretation, and manuscript writing. AK, IL, NS, and VD contributed to the study conception, study design, study performance, data interpretation, and critical review of the manuscript. J-YM contributed to the study training, data interpretation, and critical review of the manuscript. YM contributed to the study design, data interpretation, and critical review of the manuscript. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. LL had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. LL is study guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding: This work was supported in part by the Swiss National Science Foundation (grant 407240_167133) and by an academic award of the Leenaards Foundation (to NB-B). The funders had no role in considering the study design or in the collection, analysis, interpretation of data, writing of the report, or decision to submit the article for publication. Brahms GmbH, the manufacturer of the BRAHMS PCT direct point-of-care test, supported the study in providing the BRAHMS direct Reader, BRAHMS PCT direct tests, and quality controls free of charge. Brahms GmbH had no other role in the trial.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: support from the Swiss National Science Foundation and the Leenaards Foundation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Data sharing: All relevant data are available via the Zenodo repository (10.5281/zenodo.4032527).

Ethical approval: The Swiss ethics committees of cantons Vaud and Bern approved the protocol (2017-01246). All study participants gave their written consent. An external independent monitoring board supervised the trial. We attest that we have obtained appropriate permissions and paid any required fees for use of copyright protected materials.

The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Dissemination to participants and related patient and public communities: Results of the research will be disseminated by the Swiss Society of General Internal Medicine and the Swiss Society for Infectious Diseases who will have key roles in the implementation of the results. There are no plans to disseminate the results of the research to study participants. Study results will be shared with the public via press release, social media, and conference presentations.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Web appendix: Supplementary material