Point-of-care testing strategy versus usual care to safely reduce antibiotic prescribing for acute respiratory tract infections in primary care (PRUDENCE): a pragmatic, randomised controlled trial in 13 countries

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Summary

Background Point-of-care testing to guide antibiotic prescribing decisions is promoted for antibiotic stewardship. We investigated whether a point-of-care testing strategy for acute respiratory tract infections could safely reduce antibiotic prescribing in primary care.

Methods PRUDENCE was a pragmatic, randomised controlled clinical trial in 13 countries. Patients aged 1 year or older were eligible if they presented in primary care practices or long-term care facilities with symptoms of a respiratory tract infection with either cough (lasting <28 days) or sore throat (lasting <14 days) as the predominant symptom and the clinician was considering or had planned to prescribe antibiotics for them. Participants were randomly assigned to a point-of-care testing strategy plus usual care or usual care only. Before random assignment, patients could be tested for SARS-CoV-2. Participants with negative or unknown SARS-CoV-2 status were randomly assigned (1:1:1 or 1:1) according to their predominant symptom and influenza season to either a C-reactive protein (CRP) test, a group A streptococcus test, an influenza test, a group A streptococcus test plus an influenza test, or to usual care. SARS-CoV-2-positive participants were randomly assigned (1:1) to CRP testing or usual care. Randomisation was done via five modules according to predominant symptom, influenza season, and SARS-CoV-2 status and further stratified by setting (primary care or long-term care), age group, and presence of comorbidity. Varying block sizes of two and four were used for 1:1 allocations, with block sizes of three and six for 1:1:1 allocations. The coprimary outcomes were the proportion of participants prescribed antibiotics over 28 days (hypothesising superiority, with at least a 15% reduction in the point-of-care group compared with the usual care group required) and number of days to return to usual daily activities (hypothesising non-inferiority, with the lower bound of a two-sided 95% CI of the hazard ratio exceeding 0·8). The primary analysis population included all eligible, randomly assigned participants for whom data were available, regardless of intervention received, up to the point of any loss to follow-up, withdrawal, or death. The trial was registered with the ISRCTN (ISRCTN13336322) and is complete.

Findings Between Dec 15, 2021, and Jan 28, 2024, 2642 patients were randomly assigned: 1449 participants to the point-of-care testing strategy and 1193 to usual care. 2433 (92·1%) patients were in primary care (Belgium, France, Georgia, Germany, Greece, Hungary, Ireland, Poland, Spain, and the UK), and 209 (7·9%) were in long-term care facilities (Italy, Portugal, Israel, France, Ireland, and Spain). 2639 participants were included in the primary analysis (1448 [54·9%] assigned to point-of-care testing strategy, 1191 [45·1%] assigned to usual care; 1641 [62·2%] female patients and 998 [37·8%] male patients). Median follow-up was 28 days (IQR 28–28). Antibiotics were prescribed for 561 (47·1%) of 1191 participants in the usual care group and 662 (45·7%) of 1448 in the point-of-care testing group (adjusted risk difference –1·3% [95% CI –4·9 to 2·3]; p=0·47). The median number of days to return to usual daily activities was 4 days (IQR 2–8) for the point-of-care testing group and 4 days (2–7) for the usual care group, with an adjusted hazard ratio of 1·00 (95% CI 0·92 to ∞; p<0·0001). There were 42 reported serious adverse events (26 in the point-of-care testing group and 16 in the usual care group), including five deaths (three in the point-of-care testing group and two in the usual care group), all of which were assessed as being unrelated to the intervention.

Interpretation A point-of-care testing strategy for respiratory tract infection, which included testing for CRP, group A streptococcus, and influenza, did not reduce antibiotic prescribing when clinicians were considering prescribing or had planned to prescribe an antibiotic. Point-of-care testing is unlikely to be effective as a standalone solution in antimicrobial stewardship.

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Introduction

Point-of-care testing to guide antimicrobial prescribing decisions has been widely promoted as a means of reducing unnecessary antibiotic prescribing and, thus, as a key tool for limiting antimicrobial resistance.[1] More than 90% of antibiotics are prescribed in primary care, the majority for acute respiratory tract infections, which are most often viral and self-limiting and do not require antibiotic treatment. Antibiotics continue to be overprescribed for various reasons, such as diagnostic uncertainty, defensive medicine, time pressure, and to meet expectations of patients, who often overestimate the effectiveness of antibiotics for respiratory tract infections.[2,3] Overprescribing of antibiotics for respiratory tract infections is common,[3] drives antimicrobial resistance, unnecessarily exposes patients to adverse effects, and entrenches expectations about the effectiveness of antibiotics that are not supported by evidence.

Introducing point-of-care testing could optimise clinical care for patients with respiratory tract infections by enabling a more personalised approach, better targeting antibiotics for those who are most likely to benefit, and guiding non-antibiotic management for those who are unlikely to benefit.[4] Most evaluations of point-of-care tests have focused on their clinical and analytical performance rather than on improving the quality of antibiotic prescribing, patient outcomes, and the cost-effectiveness of such testing.[5] Several studies have evaluated the effect of introducing a single point-of-care test on antibiotic prescribing. Pathogen-detection point-of-care testing for group A streptococcus, used to identify aetiology, and host-response point-of-care testing for C-reactive protein (CRP), used to assess illness severity and predict treatment effect in patients with pneumonia, have reduced antibiotic prescribing in controlled trials.[4,6,7] Point-of-care testing combined with complementary strategies resulted in greater reductions in antibiotic prescribing compared with point-of-care testing alone.[8,9] However, two meta-analyses showed that rapid testing for respiratory viruses did not reduce antibiotic prescribing.[10,11] Point-of-care tests for respiratory tract infections have been widely used in countries where such testing is included in clinical guidelines and is reimbursed; however, as indicated in a study covering 18 European countries,[12] these tests are seldom used in primary care and long-term care in countries where point-of-care testing is not reimbursed. There are multifaceted barriers to widespread uptake of point-of-care testing, including uncertainty about the capacity of such tests to safely guide non-antibiotic management, falloff in use when taken up into routine care, added diagnostic and

Research in context

Evidence before this study

We searched PubMed for relevant systematic reviews of trials assessing the clinical impact of point-of-care testing to guide antimicrobial prescribing decisions for patients presenting to primary care with acute respiratory tract infections. We searched for studies published from database inception to Nov 13, 2020, without language restrictions, with the search terms ["point-of-care testing (POC)" OR "rapid PCR testing" OR "rapid molecular testing"] AND "respiratory tract infection" AND "primary care" AND "systematic review". Cochrane reviews and individual trials have found that point-of-care testing for C-reactive protein (CRP) and group A streptococcus to guide antibiotic prescribing decisions for patients presenting with a cough and sore throat, respectively, reduced antibiotic prescribing in primary care. However, the individual studies included in the reviews had mixed results and included all patients with a respiratory tract infection, regardless of clinical evaluation, illness severity, or clinicians' intentions to prescribe an antibiotic. The studies that found benefit generally used a cluster-randomised design, and larger effect sizes were found when point-of-care testing was combined with complementary intervention elements. In the past few years, more evidence has been generated that the effectiveness of point-of-care testing for respiratory tract infections should not be overestimated in antimicrobial stewardship.

Added value of this study

To our knowledge, PRUDENCE is the first trial in primary care and long-term care to have investigated multiple point-of-care tests within one strategy, with relevant tests assigned on the basis of symptoms, influenza season, and SARS-CoV-2 status and with participants limited to those for whom the clinician initially intended to prescribe antibiotics. This individually randomised trial resembles routine practice. Our trial highlights the importance of carefully defining the care pathway in the intended-use population, including consideration of clinicians' clinically based prescribing decisions and their confidence in the added prognostic value of point-of-care testing.

Implications of all the available evidence

In isolation, a point-of-care testing strategy for acute respiratory tract infections is unlikely to be a sufficient solution for reducing antibiotic prescribing in primary care. Such an approach might need to be accompanied by intensive clinician training—eg, covering evidence-based antibiotic prescribing; advanced clinician–patient communication skills; interpretation of point-of-care test results; and appraisal of the evidence base that changing prescribing decisions according to the point-of-care test result is safe. The trial's findings underscore the complexity of diagnostic influences and implementation of point-of-care testing for respiratory tract infections.

prognostic value over clinical assessment in experienced hands, and cost-effectiveness.[13]

Testing every patient with a respiratory tract infection in primary care and long-term care is unlikely to be feasible, appropriate, or cost-effective. In the case of an obvious viral self-limiting infection, a point-of-care test should not be done as it would provide no added value. Nonetheless, given the high level of overprescribing of antibiotics for respiratory tract infections and high prescribing confidence,[12] testing could be useful for instances when clinicians are likely to prescribe and when patients have high expectations both of the benefit of antibiotics and of receiving them. The objective of the PRUDENCE trial was to ascertain whether a point-of-care testing strategy could reduce antibiotic prescribing in patients with a respiratory tract infection without negatively affecting patient recovery or causing complications. The point-of-care testing strategy included CRP, group A streptococcus, and influenza A and B; testing for influenza A and B was included as a confirmed viral aetiology might sway clinicians towards non-prescribing. Before random assignment, patients could be tested for SARS-CoV-2. This pragmatic, individually randomised controlled trial focused on including patients for whom the clinician was considering or had planned to prescribe an antibiotic, the most likely intended-use population for these tests.

Methods

Study design and participants

PRUDENCE was a pragmatic, multicountry, open, randomised controlled trial of a point-of-care testing strategy for respiratory tract infections versus usual care without any point-of-care testing. An individually randomised design was chosen as it has the advantage of increasing power, without the need to account for confounders introduced by an imbalance in baseline characteristics that could be introduced by cluster randomisation. A qualitative process evaluation was embedded to explore how patients and clinicians engaged with the point-of-care tests.[14] Three patient and public involvement representatives were involved in the trial (one in the Trial Management Group and two on the Data Safety and Monitoring Board); they participated in discussions around trial design and review of patient-facing materials and were informed and consulted during trial implementation.

The participating primary care practices and long-term care facilities (detailed in the appendix pp [11–12] in Belgium (ten sites), France (six), Georgia (three), Germany (seven), Greece (three), Hungary (four), Ireland (five), Israel (one), Italy (two), Poland (six), Portugal (one), Spain (five), and the UK (eight) were invited by the countries' coordinating teams. Eligibility criteria for site participation were willingness of one or more clinicians to participate, site being naive for point-of-care testing for respiratory tract infections, and availability of a fridge to store point-of-care tests. Close to the start of the trial, the six sites in France and one in Spain reported to their coordinating team that they had implemented point-of-care testing for group A streptococcus in routine care. The Trial Management Group decided that these sites could only recruit and randomly assign participants with cough as the predominant symptom.

Potential participants that were registered at participating practices or facilities were identified when they presented to their clinician with symptoms of a respiratory tract infection. Informed consent was taken after the patients had undergone a routine clinical assessment. Written versions of age-appropriate participant information sheets and participant or parent informed consent forms were presented and explained. All participants, parents or legal guardians of participants younger than 16 years, and consultees or legal guardians of participants with reduced capacity signed and dated the informed consent forms, in writing or online, before eligibility was confirmed.

Inclusion criteria for participants were age 1 year or older, presenting with symptoms of a lower respiratory tract infection with cough as the predominant symptom (lasting <28 days) or consulting with symptoms of an upper respiratory tract infection with sore throat as the predominant symptom (lasting <14 days), being considered for antibiotic treatment or with such treatment planned by the clinician (irrespective of previous treatments), and being able and willing to comply with all trial requirements. Additionally, the participant, their parent or legal guardian, or their consultee or legal guardian had to be willing and able to give informed consent. Exclusion criteria were only nasal, ear, or rhinosinusitis symptoms; any serious condition associated with being immunocompromised; being considered by a clinician to require immediate hospital admission; and being considered unable to participate because of not understanding the local language, being terminally ill, having a serious psychiatric disorder, or being deemed otherwise ineligible according to the clinician. It was not possible to systematically collect data on numbers of patients for whom the clinician did not consider antibiotic treatment, and no screening logs were implemented.

The trial was approved by the North West Liverpool Central Research Ethics Committee (reference 20/NW/0385) and thereafter in each participating country (list of ethical approvals is in the appendix [p 13]). The trial was conducted in accordance with the approved protocol (appendix pp 30–74). Substantial amendment 2 (version 3.0; July 5, 2021) allowed for SARS-CoV-2 testing before random assignment and for random assignment based on SARS-CoV-2 status (appendix pp 45, 70) and added the sample size justification (appendix pp 68–69). Substantial amendment 4 (version 4.0; Oct 19, 2023) updated the sample size justification (appendix p 69). The trial adhered to Good Clinical Practice guidelines, general data protection regulations, the UK Data Protection Act 2018, and the Declaration of Helsinki. Recruiting clinicians were paid per

See Online for appendix

included participant, with a fee in line with their time investment and EU (public) funding. The trial is registered with the ISRCTN (ISRCTN13336322; registration date Dec 11, 2020).

Randomisation and masking

Both the participants and the clinicians who enrolled and randomly assigned participants were aware of group allocation. Participants were randomly assigned via a central platform, Research Online, to receive usual care without point-of-care testing or usual care with a point-of-care testing strategy, which involved a test for CRP, group A streptococcus, influenza A and B, or a combination of group A streptococcus and influenza A and B; if allocated to group A streptococcus and influenza A and B, it was the clinician's choice to use either one of the tests or both. Random assignment was implemented via five modules according to SARS-CoV-2 status, the predominant symptom (cough or sore throat), and whether it was influenza season (yes or no; figure 1). Allocation ratios for participants with an unknown or negative SARS-CoV-2 status differed according to the predominant symptom and season (appendix p 14). For example, in influenza season, participants with cough as their predominant symptom were randomly assigned (1:1:1) to usual care, CRP test, or influenza A and B test; when it was not influenza season, they were assigned (1:1) to either usual care or CRP test. SARS-CoV-2-positive participants were randomly assigned (1:1) to usual care or CRP testing regardless of season and predominant symptom. Within each module, random assignment was further stratified by setting (primary care or long-term care), age group (1–16, 17–64, 65–79, and $\geq$80 years), and presence of any comorbidity (yes or no). Varying block sizes of two and four were used for the 1:1 allocations, and block sizes of three and six were used for the 1:1:1 allocations. Only the system administrator had access to the block composition and allocation sequence during the trial. The central trial team was masked to allocation, and the statisticians were masked to test at final analysis.

Procedures

Recruiting clinicians conducted a clinical assessment of participants before they were randomly assigned, recording the following participant information (online or on paper, with some information derived from medical records): age, sex (as registered in medical records), comorbidities, respiratory tract infection symptoms, SARS-CoV-2 test result (if applicable), illness duration and severity, suspected aetiology (viral, bacterial, or unclear), and initial prescribing likelihood (low, medium, or high at the clinician's discretion, without an imposed standardised assessment or specific guidance). Following random assignment, clinicians recorded the point-of-care test result (if applicable) and their final prescribing decision (no, immediate, or delayed antibiotic prescription, and antibiotic class). Data on race and ethnicity were not collected.

The clinician had the option to test for SARS-CoV-2 before random assignment if a participant's SARS-CoV-2 status was previously negative or unknown and onset of symptoms was within 5 days of inclusion in the trial. SARS-CoV-2 testing was done via nasal swabbing and a machine-interpreted lateral flow test, the Veritor system for Rapid Detection of SARS-CoV-2 (Beckton Dickinson; Franklin Lakes, NJ, USA; sensitivity 91·1% and specificity 99·6%). The point-of-care testing strategy could include CRP (Afinion 2 analyser; Abbott; Oslo, Norway), group A streptococcus (Veritor analyser; Beckton Dickinson; Franklin Lakes, NJ, USA; test sensitivity 96·6% and specificity 95·5%), influenza A and B testing (Veritor analyser; test sensitivity 82% and specificity 98%), or a combination of group A streptococcus and influenza A and B testing.

Usual care was at the discretion of the clinician, according to setting and national guidance, and could involve laboratory-based testing, medication prescribing, and advice with respect to rest or over-the-counter medication use, and a follow-up appointment.

Before the start of the trial, all clinicians were provided with a face-to-face training session by local network facilitators. The facilitators used a slide deck containing information on the rationale of prudent antibiotic prescribing for respiratory tract infections (not mentioning first-choice antibiotic prescribing) and the use of point-of-care tests to this end and also demonstrated tests and analysers. Additional paper and online materials on sample collection, sample processing, and test procedures (prepared by the test manufacturers) were made available. Hard-copy guidance for clinicians on how to incorporate the test result or results in clinical decision making was provided (appendix p 4).

Participants were followed up for 28 days. Participants, parents or legal guardians (for or with their child), and carers (for or with participants in a long-term care facility) were asked to complete a diary, either on paper (returned to their practice [Georgia and Greece] or posted to the country's coordinating team) or web-based, for 14 days after inclusion. The diary was used each day to record participants' return to usual daily activities (yes or no), antibiotic use (if applicable, and antibiotic name in case prescribed after the inclusion visit), use of a non-antibiotic medication for the respiratory tract infection, and severity rating of individual respiratory tract infection symptoms. Additionally, participants completed the Patient Enablement Instrument (PEI)[15] on day 0 (except for those in long-term care facilities, as residents of such facilities often do not [completely] care for themselves) and provided information on days 7 and 14 regarding health-care resource use (health-care provider contacts and hospitalisation, with details if applicable).

If diaries were not returned or not completed, participants were telephoned on day 14 (up to +3 days) to ascertain a minimum set of outcome data (ie, the day they returned to their usual daily activities, antibiotic use [if applicable], and hospitalisation). All participants were telephoned

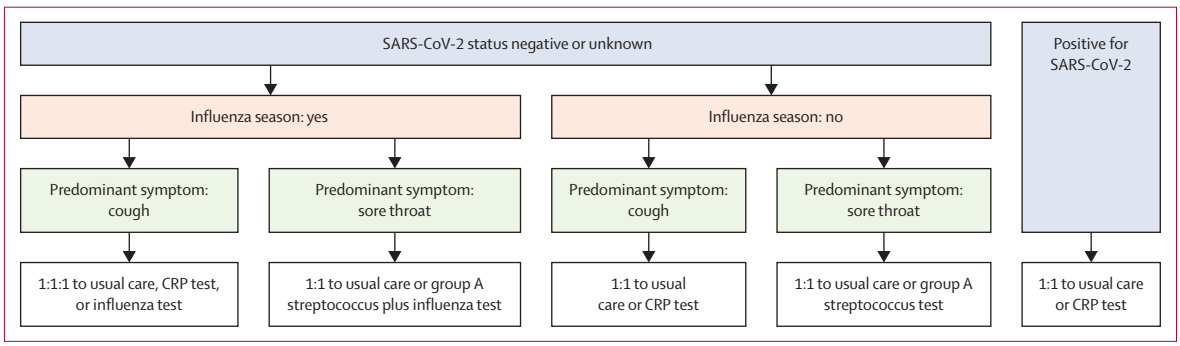


Figure 1: **Randomisation scheme**
Participants were randomly assigned to a particular test or test combination on the basis of SARS-CoV-2 status, influenza season, and predominant symptom. The white boxes indicate the randomisation options and randomisation modules, which operated within one integrated system. CRP=C-reactive protein.

on day 28 (up to + 3 days) to capture the same minimum set of outcome data.

Only serious adverse events and not adverse events were captured as the point-of-care tests were Conformité Européene-marked and used within the scope of their intended use. Serious adverse events, including deaths, were collected during the 28 days of follow-up; identified via the diary, telephone calls, and by clinicians; assessed for causality by a medically qualified sponsor's representative on the basis of information from the treating clinician or clinicians; and reviewed by the Data Safety and Monitoring Board (appendix p 2).

Data from paper forms (baseline and diary) could be entered by site personnel or a member of the country's coordinating team. Data quality was monitored regularly via a centralised approach, which could trigger monitoring a country's coordinating centre and individual sites.

Outcomes

There were two coprimary outcomes:[16] the proportion of participants prescribed at least one antibiotic course (any dose or duration) over the 28 days from inclusion and time to return to usual daily activities from inclusion (in days). Secondary outcomes were antibiotic prescription at the index consultation, with delayed or immediate prescribing and antibiotic class prescribed; antibiotic use (finished the course: yes or no); participant-reported respiratory tract infection symptoms as a moderate or major problem over days 1–14 (symptoms were rated as no problem, a minor problem, a moderate problem, or a major problem); participant-reported health-care provider contacts over the 28 days (ie, general practice, out-of-hours service, paediatrician, accident and emergency department, hospital specialist, or pharmacist); participant-reported hospitalisation; in-hospital confirmed pneumonia; non-antibiotic medication use for the respiratory tract infection over days 1–14 (inhaled medication; medication for pain or fever; cough medicine; nasal spray; lozenges or gargles; ear drops; influenza combination medicines; herbal or homeopathic medicine; and vitamins); total PEI score (obtained by adding the responses to six questions regarding patients' ability to cope and understanding of their illness, range 0–12, with higher scores indicating better coping and understanding);[15] clinician's antibiotic prescribing likelihood before random assignment; and cost data (to be reported elsewhere).

Statistical analysis

For the first coprimary outcome, a 15% reduction in the proportion of participants in the point-of care testing group prescribed antibiotics was considered clinically meaningful and feasible. 100 participants per group (CRP, group A streptococcus, influenza, and usual care) were required for 80% power (with 133 participants per group required for 90% power) with a two-sided 0·05 significance level to detect a reduction from 90% to 75% in antibiotic prescribing during the 28 days of follow-up. For the second co-primary outcome, an exponential time to return to usual daily activities with a mean of 4 days (based on ALIC^{4}E trial data[17]) was assumed; under this assumption, a hazard ratio (HR) of 0·80 is equivalent to a mean increase of 1 day. Hence, to show an HR of no worse than 0·80 (or, equivalently, a mean increase in time to return to usual daily activities no greater than 1 day), 318 participants per group were required to provide 80% power with a two-sided significance level of 0·05. As point-of-care tests were not uniformly distributed, given the different possible combinations of tests within each cohort (figure 1), 1250 participants per season provided reasonable power estimates for the two prespecified winter seasons (appendix p 2). The sample size justification was updated (protocol version 4.0; Oct 19, 2023) on the basis of the overall proportion of prescribed antibiotics and distribution of participants with cough or sore throat in the ongoing trial; the power remained the same with the original sample size of 2500 participants (appendix p 2). The exact nominal α value was chosen to control one-sided type I error at approximately 0·025 while accounting for potential interim analyses. An interim analysis was planned for after the first winter recruitment period but was not conducted due to the delayed trial start resulting from the COVID-19 pandemic (appendix p 2). Therefore, there was no

adjustment for α spending. The point-of-care testing strategy would be considered effective if the strategy were superior to usual care on the first coprimary outcome (at least a 15% reduction with a two-sided significance level of 0·05) and non-inferior on the second coprimary outcome (the lower bound of a two-sided 95% CI of the HR exceeding 0·8).

The coprimary outcomes were prespecified to be assessed in all eligible randomly assigned participants for whom data were available, regardless of the intervention received, up to the point of any loss to follow-up, withdrawal, or death (ie, primary analysis population), as well as in only those participants who received their allocated intervention (ie, per-protocol population), as per the trial's statistical analysis plan (appendix pp 77–111). Those found to be ineligible after random assignment were excluded from the analysis. The safety analysis population consisted of all participants grouped according to the point-of-care test received. Participants without a point-of-care test result or for whom there was no information on whether they had a test result were included in the usual care group for the safety analysis. Missing data were not imputed.

The antibiotic prescribing coprimary outcome was analysed with a logit-binomial generalised linear mixed model on point-of-care testing intervention (*vs* usual care) adjusted for baseline SARS-CoV-2 status (negative and unknown, or positive), setting (primary care or long-term care), predominant symptom (cough or sore throat), influenza season (yes or no), age (in years), and comorbidities (yes or no) as fixed effects. An interaction term between predominant symptom and influenza season was included to account for some point-of-care tests only being relevant for specific combinations. Site was included in the model as a random effect to account for clustering of participants within sites. The risk difference, corresponding 95% CIs, and p values were estimated from the model.

The second coprimary outcome, time to return to usual daily activities, was analysed using a mixed-effects Cox proportional hazards regression model for the point-of-care testing intervention (*vs* usual care), adjusted for SARS-CoV-2 status, setting, predominant symptom, influenza season, age, comorbidities, an interaction between predominant symptom and influenza season as fixed effects, and site as a random effect. Year was not included in either model as there was continuous recruitment. The proportional hazards assumption was checked using log(–log) plots, and Schoenfeld residuals. In a sensitivity analysis, any covariates found to be predictive of missingness were included in the analysis models. The analyses were repeated to compare the effect of using the CRP test versus usual care and pathogen-detection point-of-care tests versus usual care (prespecified analyses).

Secondary outcomes were analysed in the primary analysis population. PEI score and health-care provider contacts were analysed using quantile regression, adjusted for the same variables as for other analyses (except the random site effect), to calculate median difference and 95% CI. Moderate or major respiratory tract infection symptoms during follow-up and hospitalisation were analysed with mixed-effects logistic regression models, adjusted for the same variables as for other analyses. Unadjusted effect estimates were calculated for outcomes assessed only in those prescribed an antibiotic, with 95% CIs. The remaining secondary outcomes, evaluated using χ^2 testing, were superiority-based and assessed at the 5% significance level.

Two post-hoc exploratory subgroup analyses were done. The first assessed the intervention effect on antibiotic prescribing over 28 days by setting (ie, primary care *vs* long-term care). The second assessed the intervention effect on antibiotic prescribing at the index consultation by initial antibiotic prescribing likelihood. For these analyses, logit-binomial generalised linear mixed models were used with the same covariates as in the primary analysis and an additional interaction term (setting by intervention for the first analysis and initial prescribing likelihood by intervention for the second analysis). Antibiotic prescribing at the index consultation in each country in the point-of-care testing and usual care groups was also summarised post hoc.

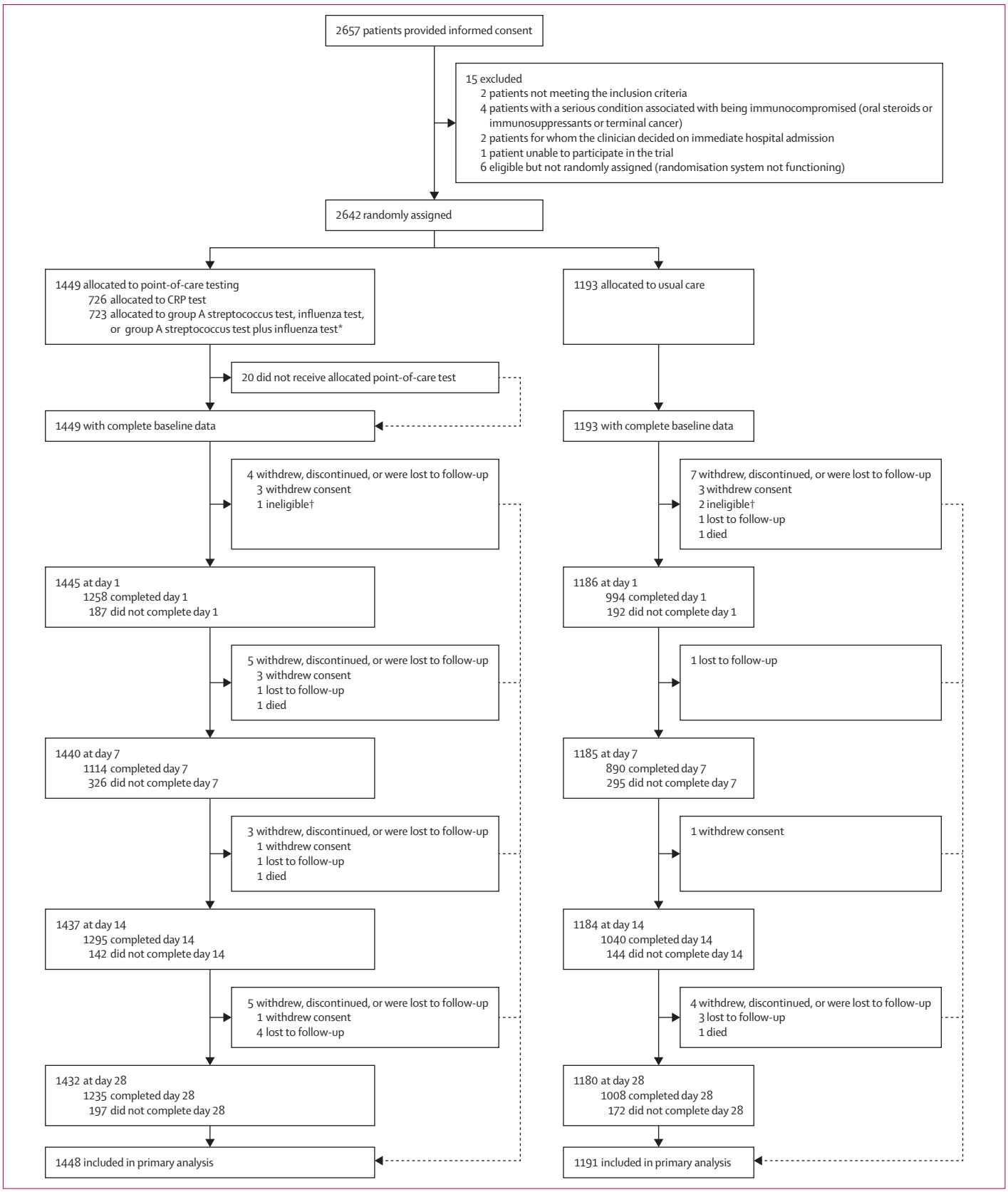
Data lock was on Feb 28, 2024. Stata version 18.5 was used for all analyses.

Role of the funding source

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

Results

Between Dec 15, 2021, and Jan 28, 2024, 2642 participants were randomly assigned: 1449 to the point-of-care testing strategy and 1193 to usual care. 2433 (92·1%) patients were in primary care (Belgium, France, Georgia, Germany, Greece, Hungary, Ireland, Poland, Spain, and the UK), and 209 (7·9%) were in long-term care facilities (Italy, Portugal, Israel, France, Ireland, and Spain); recruitment varied between one and 435 participants per site. Three participants were found to be ineligible after random assignment, and so the primary analysis included 1448 participants in the point-of-care testing group and 1191 in the usual care group (figure 2). The baseline participant characteristics are shown in table 1. As anticipated, higher proportions of participants with cough as predominant symptom and participants randomly assigned in the influenza season were in the point-of-care testing group due to the 1:1:1 allocation (figure 1; appendix p 14). Baseline characteristics were similar for those receiving CRP or pathogen-detection point-of-care testing and the corresponding controls receiving usual care (appendix pp 15–17). Flow charts for participants randomly assigned to point-of-care tests for CRP or pathogen detection and the corresponding controls assigned to usual care are provided in the appendix (pp 6–7). Median follow-up was 28 days (IQR 28–28). 12 participants withdrew consent over the follow-up period (eight in the point-of-care testing group and four in the usual care group), and 11 participants were lost to follow-up (six in the point-of-care testing group and five in


2657 patients provided informed consent
15 excluded
2 patients not meeting the inclusion criteria
4 patients with a serious condition associated with being immunocompromised (oral steroids or immunosuppressants or terminal cancer)
2 patients for whom the clinician decided on immediate hospital admission
1 patient unable to participate in the trial
6 eligible but not randomly assigned (randomisation system not functioning)
2642 randomly assigned
1449 allocated to point-of-care testing
726 allocated to CRP test
723 allocated to group A streptococcus test, influenza test, or group A streptococcus test plus influenza test*
1193 allocated to usual care
20 did not receive allocated point-of-care test
1449 with complete baseline data
1193 with complete baseline data
4 withdrew, discontinued, or were lost to follow-up
3 withdrew consent
1 ineligible†
7 withdrew, discontinued, or were lost to follow-up
3 withdrew consent
2 ineligible†
1 lost to follow-up
1 died
1445 at day 1
1258 completed day 1
187 did not complete day 1
1186 at day 1
994 completed day 1
192 did not complete day 1
5 withdrew, discontinued, or were lost to follow-up
3 withdrew consent
1 lost to follow-up
1 died
1 lost to follow-up
1440 at day 7
1114 completed day 7
326 did not complete day 7
1185 at day 7
890 completed day 7
295 did not complete day 7
3 withdrew, discontinued, or were lost to follow-up
1 withdrew consent
1 lost to follow-up
1 died
1 withdrew consent
1437 at day 14
1295 completed day 14
142 did not complete day 14
1184 at day 14
1040 completed day 14
144 did not complete day 14
5 withdrew, discontinued, or were lost to follow-up
1 withdrew consent
4 lost to follow-up
4 withdrew, discontinued, or were lost to follow-up
3 lost to follow-up
1 died
1432 at day 28
1235 completed day 28
197 did not complete day 28
1180 at day 28
1008 completed day 28
172 did not complete day 28
1448 included in primary analysis
1191 included in primary analysis

	Point-of-care testing (n=1448)	Usual care (n=1191)
Age, years		
Mean (SD)	45·2 (22·0)	43·9 (21·8)
Range	1–100	1–98
Median (IQR)	45 (28 to 62)	42 (27 to 60)
Age categories, years*		
1–16	142 (9·8%)	125 (10·5%)
17–64	994 (68·6%)	826 (69·4%)
65–79	211 (14·6%)	163 (13·7%)
≥80	101 (7·0%)	77 (6·5%)
Sex		
Male	567 (39·2%)	431 (36·2%)
Female	881 (60·8%)	760 (63·8%)
Predominant symptom*		
Cough	948 (65·5%)	696 (58·4%)
Sore throat	500 (34·5%)	495 (41·6%)
SARS-CoV-2 status*		
Positive	80 (5·5%)	76 (6·4%)
Negative or unknown	1368 (94·5%)	1115 (93·6%)
Comorbidities*		
Yes	550 (38·0%)	432 (36·3%)
No	898 (62·0%)	759 (63·7%)
Setting*		
Primary care	1326 (91·6%)	1105 (92·8%)
Long-term care	122 (8·4%)	86 (7·2%)
Country		
Belgium	64 (4·4%)	54 (4·5%)
France	13 (0·9%)	13 (1·1%)
Georgia	283 (19·5%)	215 (18·1%)
Germany	100 (6·9%)	80 (6·7%)
Greece	195 (13·5%)	155 (13·0%)
Hungary	109 (7·5%)	110 (9·2%)
Ireland	135 (9·3%)	92 (7·7%)
Israel	20 (1·4%)	10 (0·8%)
Italy	55 (3·8%)	47 (3·9%)
Poland	144 (9·9%)	127 (10·7%)
Portugal	31 (2·1%)	19 (1·6%)
Spain	44 (3·0%)	41 (3·4%)
UK	255 (17·6%)	228 (19·1%)
Influenza season*		
Yes	732 (50·6%)	473 (39·7%)
No	716 (49·4%)	718 (60·3%)
Relevant comorbidity†		
Cardiovascular disease	263 (18·2%)	197 (16·5%)
Diabetes	114 (7·9%)	83 (7·0%)
Chronic respiratory condition	186 (12·8%)	148 (12·4%)
Hepatic, haematological, neurological, or neurodevelopmental condition	107 (7·4%)	62 (5·2%)
Obesity	189 (13·1%)	158 (13·3%)
(Table 1 continues in next column)		

	Point-of-care testing (n=1448)	Usual care (n=1191)
(Continued from previous column)		
Influenza vaccination in the past year		
Yes	450 (31·1%)	345 (29·0%)
No	961 (66·4%)	822 (69·0%)
Unknown	37 (2·6%)	24 (2·0%)
COVID-19 vaccination in the past year		
Yes	765 (52·8%)	591 (49·6%)
No	650 (44·9%)	580 (48·7%)
Unknown	33 (2·3%)	20 (1·7%)
COVID-19 vaccination doses		
None	683 (47·2%)	600 (50·4%)
First dose	20 (1·4%)	14 (1·2%)
Second dose	188 (13·0%)	144 (12·1%)
Third dose	557 (38·5%)	433 (36·4%)
Pneumococcal vaccination in past 5 years		
Yes	191 (13·2%)	151 (12·7%)
No	1189 (82·1%)	983 (82·5%)
Unknown	68 (4·7%)	57 (4·8%)
Smoking		
Yes	273 (18·9%)	213 (17·9%)
No	1161 (80·2%)	966 (81·1%)
Unknown	14 (1·0%)	12 (1·0%)
Signs and symptoms†		
Ear pain	141 (9·7%)	130 (10·9%)
Rhinitis	574 (39·6%)	489 (41·1%)
Sore throat and/or difficulty swallowing	870 (60·1%)	770 (64·7%)
Cough	1173 (81·0%)	908 (76·2%)
General symptoms	1065 (73·5%)	899 (75·5%)
Number of days with respiratory tract infection symptoms (before index consultation)		
Mean (SD)	6·0 (4·3)	6·0 (4·5)
Range	1–28	1–28
Median (IQR)	5 (3 to 7)	5 (3 to 7)
Overall illness severity (clinician-rated)		
Mild	722 (49·9%)	609 (51·1%)
Moderate	689 (47·6%)	551 (46·3%)
Severe	37 (2·6%)	31 (2·6%)
Suspected aetiology by clinician		
Viral	631 (43·6%)	507 (42·6%)
Bacterial	423 (29·2%)	340 (28·5%)
Uncertain	394 (27·2%)	344 (28·9%)
Initial antibiotic-prescribing likelihood		
Low likelihood	755 (52·1%)	619 (52·0%)
Medium likelihood	412 (28·5%)	340 (28·5%)
High likelihood	281 (19·4%)	232 (19·5%)

Data are n (%) unless otherwise specified. Percentages were computed with numbers of participants with a response available as the denominator. *Stratification factors. †Not mutually exclusive.

Table 1: **Baseline characteristics of primary analysis population**

Figure 2: **Participant flow diagram**
Baseline information was collected by the clinician at the index consultation, and follow-up data were collected via daily diaries and telephone calls for 28 days after the index consultation. *For participants randomly assigned to group A streptococcus plus influenza point-of-care testing, it was the clinician's decision to use either one of the tests or both. †Excluded from primary analysis population.

the usual care group; figure 2). Details on data completeness are in the appendix (p 18).

No notable differences between groups were found in antibiotic prescribing. Of the 1448 participants in the

	Point-of-care testing (n=1448)	Usual care (n=1191)	Treatment effect (95% CI)*	p value†
Coprimary outcomes				
Antibiotic prescription				
Yes	662 (45·7%)	561 (47·1%)	−1·3% (−4·9 to 2·3)‡	0·47
No	786 (54·3%)	629 (52·9%)	..	..
Missing	0	1	..	..
Time to return to usual daily activities, days				
Median (IQR)	4·0 (2·0 to 8·0)	4·0 (2·0 to 7·0)	1·00 (0·92 to ∞)§	<0·0001
Missing	82	87	..	..
Returned to usual daily activities				
Yes	1314 (95·7%)	1066 (96·2%)	..	..
No	59 (4·3%)	42 (3·8%)	..	..
Missing	75	83	..	..
Secondary outcomes				
Antibiotic class			..	0·96¶
Tetracycline	30/662 (4·5%)	27/561 (4·8%)	..	..
Narrow-spectrum penicillin	85/662 (12·8%)	82/561 (14·6%)	..	..
Broad-spectrum penicillin	169/662 (25·5%)	142/561 (25·3%)	..	..
Co-amoxiclav	112/662 (16·9%)	85/561 (15·2%)	..	..
Macrolide	159/662 (24·0%)	134/561 (23·9%)	..	..
Quinolone	22/662 (3·3%)	23/561 (4·1%)	..	..
Cephalosporin	78/662 (11·8%)	63/561 (11·2%)	..	..
Other	7/662 (1·1%)	5/561 (0·9%)	..	..
Antibiotic prescribing at index consultation				
Yes	638 (44·1%)	534 (44·9%)	−0·63% (−4·20 to 2·93)	0·73
No	810 (55·9%)	656 (55·1%)	..	..
Missing	0	1	..	..
Delayed or immediate prescribing at index consultation				
Delayed	119/638 (18·7%)	116/534 (21·7%)	−3·07% (−7·69 to 1·55)	0·19
Immediate	519/638 (81·3%)	418/534 (78·3%)	..	..
Antibiotic use				
Finished course	524/662 (79·2%)	426/561 (75·9%)	3·22% (−1·48 to 7·92)	0·18
Did not finish course	138/662 (20·8%)	135/561 (24·1%)	..	..
Any respiratory tract infection symptom rated as moderate or major				
Yes	1206 (94·1%)	940 (93·3%)	0·79% (−1·01 to 2·59)‖	0·39
No	75 (5·9%)	68 (6·7%)	..	..
Missing	167	183	..	..
Patient-reported health-care provider contact				
Median (IQR)	1·0 (0·0 to 3·0)	1·0 (0·0 to 3·0)	−0·05 (−0·24 to 0·14)**	0·60
Range	0·0 to 21·0	0·0 to 23·0	..	..
Missing	106	100	..	..
Hospitalisation				
Yes	13 (1·0%)	9 (0·8%)	0·11% (−0·68 to 0·91)‖	0·78
Pneumonia confirmed	4 (30·8%)	2 (22·2%)		
No pneumonia confirmed††	9 (69·2%)	7 (77·8%)		
No	1307 (99·0%)	1057 (99·2%)	..	..
Missing	128	125	..	..
Non-antibiotic medication use				
Yes	1191 (92·6%)	943 (92·8%)	..	0·85¶
No	95 (7·4%)	73 (7·2%)	..	..
Missing	162	175	..	..

(Table 2 continues on next page)

	Point-of-care testing (n=1448)	Usual care (n=1191)	Treatment effect (95% CI)*	p value†
(Continued from previous page)				
Patient Enablement Instrument score‡‡				
Median (IQR)	6·0 (3·0 to 8·0)	6·0 (2·0 to 7·0)	0·00 (–0·32 to 0·32)**	>0·99
Range	0·0 to 12·0	0·0 to 12·0	..	..
Missing	213	215	..	..

Data are n, n (%), or n/N (%), unless otherwise specified. *Point-of-care testing versus usual care; treatment effect is adjusted risk difference unless otherwise indicated. †Level of statistical significance (two-sided test) was 0·05 for the antibiotic prescription superiority outcome and secondary outcomes; level of statistical significance (one-sided test) was 0·025 for return to usual daily activities (non-inferiority outcome). ‡A risk difference less than 0 indicates reduced antibiotic prescribing with point-of-care testing. There was one missing value in the usual care group; percentages were computed with 1190 as the denominator. §Treatment effect is hazard ratio. 11 participants (seven in the point-of-care testing group and four in the usual care group) had a time to return to usual daily activities of 0 days and were not included in the model; 169 participants (82 in the point-of-care testing group and 87 in the usual care group) were missing the days to return to usual daily activities outcome. ¶χ^2 test. ||A risk difference less than 0 indicates fewer patients with moderate or major symptoms with point-of-care testing. **Treatment effect is adjusted median difference; a median difference less than 0 indicates fewer health-care provider contacts with point-of-care testing. ††Either x-ray not done or x-ray done and no pneumonia visible. ‡‡Patient Enablement Instrument questionnaire was only completed by participants recruited from primary care (n=1326 in point-of-care testing group and n=1105 in the usual care group).

Table 2: **Trial outcomes**

point-of-care testing group, 662 (45·7%) were prescribed an antibiotic between the index consultation and 28 days of follow-up, as were 561 (47·1%) of the 1191 participants assigned to usual care (unadjusted risk difference –1·4% [95% CI –5·3 to 2·4]; p=0·47; adjusted risk difference –1·3% [–4·9 to 2·3]; p=0·47; table 2). Similar results were seen in a per-protocol analysis (adjusted risk difference –1·3% [–4·9 to 2·3]; p=0·47; appendix p 19).

The median time from random assignment to return to usual daily activities was 4 days (IQR 2–8) for the point-of-care testing group and 4 days (2–7) for the usual care group, with an unadjusted HR of 0·98 (95% CI 0·91 to ∞; p<0·0001) and an adjusted HR of 1·00 (0·92 to ∞; p<0·0001), meeting the non-inferiority criteria (figure 3). The per-protocol analysis (appendix pp 8, 19) and a sensitivity analysis using a model that included six additional factors found to be predictive of missingness (appendix p 21) showed similar results.

There was no evidence of a difference in the proportions of participants prescribed an antibiotic in the CRP point-of-care test group and usual care group (appendix p 22) or between those in the pathogen-detection point-of-care test group and usual care group (appendix p 23). Random assignment to either point-of-care tests for CRP or pathogen-detection was non-inferior in terms of days to return to usual daily activities compared with usual care (appendix pp 9, 10).

No significant differences between the point-of-care testing and usual care groups were found in terms of antibiotic-related outcomes (antibiotic prescribing and immediate *vs* delayed prescribing at the index consultation, antibiotic class prescribed, and completion of the antibiotic course) or patient-reported outcomes (proportion of participants reporting individual respiratory tract infection symptoms as a moderate or major problem during follow-up, health-care provider contacts, use of non-antibiotic medications, hospitalisations, and PEI score; table 2; appendix p 24). Hospitalisation (n=22) was reported by 13 participants in the point-of-care testing group and nine in the usual care group, and hospital-confirmed pneumonia (n=6) was reported by four participants in the point-of-care testing group and two in the usual care group. There were 42 serious adverse events, including five deaths (three in the point-of-care testing group and two in the usual care group; causes of death were sepsis, cardiac arrest, COVID-19, heart failure, and cancer), which were all assessed as being unrelated to the intervention (appendix pp 25–26).

Three post-hoc analyses were done. Descriptive antibiotic prescribing proportions by country for the point-of-care testing and usual care groups are shown in the appendix (pp 27–28). When split by setting, the adjusted risk difference was –1·4% (95% CI –5·1 to 2·4) for primary care and 9·9% (–1·2 to 21·0) for long-term care (appendix p 29). Before each participant was randomly assigned, clinicians rated their initial likelihood of antibiotic prescribing on the basis of their clinical assessment (table 1). This likelihood considerably modified the effect of the point-of-care testing strategy. When clinicians indicated a low likelihood of prescribing antibiotics, antibiotic prescribing at the index consultation was higher in the point-of-care testing group than in the usual care group, whereas when clinicians indicated a medium or high likelihood, antibiotic prescribing was lower in the point-of-care testing group than in the usual care group (appendix p 29).

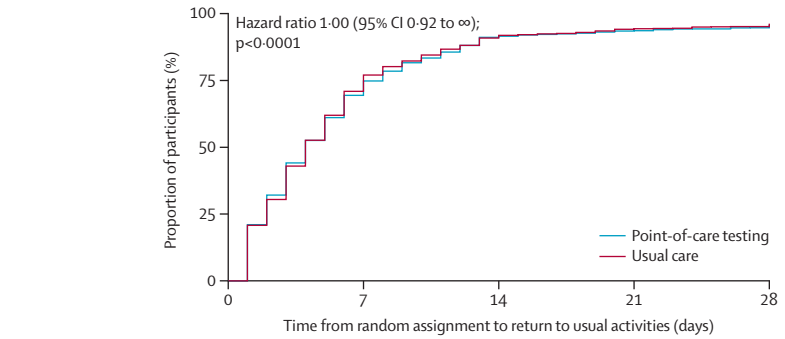
Discussion

This 13-country trial, PRUDENCE, including patients in primary care or long-term care being managed with symptoms of an acute respiratory tract infection, found that adding a point-of-care testing strategy that included either CRP, group A streptococcus, influenza A and B, or group A streptococcus plus influenza A and B did not reduce antibiotic prescribing overall or affect patient recovery. To our knowledge, PRUDENCE is the first trial to have investigated a point-of-care testing strategy that tailored the test (or combination of tests) to the symptom, influenza season, and SARS-CoV-2 status for patients for whom the

clinician was considering or planning to prescribe antibiotics. Results from the trial's qualitative process evaluation also showed that point-of-care testing as a standalone solution is often not enough to change the initial prescribing decision. The non-prescribing implications of the tests were overridden, particularly when test results conflicted with clinicians' experiential knowledge—correct or not—and when clinicians doubted the test accuracy.[14] Therefore, the effect of point-of-care testing is influenced by clinicians' initial intentions, interpretations, and context, highlighting the complexity of implementing diagnostic strategies in real-world practice.[18]

There is conflicting evidence regarding the effects of point-of-care testing for respiratory tract infections on antibiotic prescribing. Systematic reviews and individual trials have found that point-of-care testing for CRP and group A streptococcus in patients consulting with a cough and sore throat reduced antibiotic prescribing in primary and long-term care.[4,6–8,19,20] However, individual trials and a systematic review found that point-of-care testing did not meaningfully decrease antibiotic prescribing.[10,21,22] Moreover, according to Dutch national data, there was no decrease in antibiotic prescribing after point-of-care testing was included in management guidelines.[23] The differences between these findings could relate to study design effects, varying inclusion criteria, country, and setting. The pooled effect estimates from trials that randomly assigned clinicians or practices (clusters) to intervention or not[8,20] found larger effect sizes than trials that randomly assigned participants,[6] as was done in PRUDENCE. We only included patients for whom the clinician was considering or had planned to prescribe antibiotics, whereas in most other trials, all those with symptoms of a respiratory tract infection were eligible, with less clear-cut thresholds for eligibility. Furthermore, perceptions of risk and legal consequences might have changed, resulting in increased defensive medicine with more antibiotic prescribing. Finally, the diverse countries that participated in PRUDENCE levelled out any country-specific intervention effect. Exploratory analyses are planned to assess how the point-of-care test results, alongside initial prescribing likelihood, clinical findings, and patient characteristics (sex, age, and presence of comorbidities), influenced the final antibiotic prescribing decisions. These planned analyses will further contextualise the trial findings and will be reported separately.

The applicability of the findings is enhanced by our multicountry approach, recruitment of sufficient participants to meet the target sample size, validity of 95% of point-of-care test results, and analyses at the level of individuals rather than clinicians. Given the broad inclusion criteria, we consider the trial population to be representative of community patients consulting a clinician for respiratory tract infections. Our pragmatic trial reflects situations in which clinicians are first introduced to point-of-care testing (self-purchase). The process evaluation conducted alongside the trial further informs the interpretation of results.[14]



Point-of-care testing					
Number at risk (censored)	1366 (0)	343 (3)	115 (3)	87 (3)	56 (3)
Number returned to usual activities	7	1027	1255	1283	1314
Usual care					
Number at risk (censored)	1104 (0)	254 (0)	89 (1)	62 (1)	41 (1)
Number returned to usual activities	4	854	1018	1045	1066

Figure 3: **Time to return to usual daily activities over 28 days for the point-of-care testing group versus usual care group**

11 participants (seven in the point-of-care testing group and four in the usual care group) had a time to return to usual daily activities of 0 days and were not included in the model; 169 participants (82 in the point-of-care testing group and 87 in the usual care group) had the outcome missing. Numbers at risk, censored, and returned to usual activities for each consecutive day from day 0 to day 28 are provided in the appendix (p 20).

Some limitations need to be acknowledged. Trial implementation was delayed by the COVID-19 pandemic; however, this delay allowed us to incorporate SARS-CoV-2 status into the point-of-care testing strategy and include CRP testing for SARS-CoV-2-positive patients. Participants were included on the basis of clinicians' intention to prescribe an antibiotic, whereby the intervention was expected to have the greatest benefit. Consequently, no historical data were available for this specific patient group at the time of sample size calculation. Antibiotic prescribing was higher in our trial than in studies that included all patients presenting with a respiratory tract infection[12] but lower than anticipated when the sample size was calculated. Moreover, rating of initial prescribing likelihood was based on clinicians' individual assessment of the patient and was, therefore, inevitably subjective. As a result, a heterogeneous patient group was included, with variation in prescribing thresholds at the clinician level. We did not include complementary strategies, such as clinician or patient education, as part of the intervention. A form of contamination might have arisen from randomly assigning individuals. Experience gained by clinicians from testing those randomly assigned to point-of-care testing might have contributed to changes in evaluating and managing patients assigned to usual care;[24] however, the trial design did not enable us to evaluate whether clinicians used the testing experiences in their routine care. The appropriateness of antibiotic prescribing was not assessed. However, the finding that patient recovery was neither superior nor inferior in the point-of-care testing group compared with the usual care group indicated that point-of-care testing did not increase prescribing or lead to inappropriately reduced

prescribing for those likely to benefit. We do not consider the Hawthorne effect (ie, behaviour change caused by awareness of being observed) to be responsible for differences, as it would also have applied to previous studies and, in the trial, would have applied equally to those assigned to point-of-care testing and to usual care. We acknowledge that as an outcome, return to usual daily activities is more applicable for patients in primary care than for those in long-term care.

The trial findings raise three relevant questions. The first regards the selection of patients who should undergo point-of-care testing. We previously found that clinicians are generally confident about their decision to prescribe antibiotics in patients with respiratory tract infections.[12] Given the high prescribing rates for indications with a clinician-suspected viral aetiology, this confidence in patients needing antibiotics might not always be justified. In these cases, point-of-care testing could provide the opportunity to re-appraise intentions and decrease antibiotic prescribing. However, the trial showed increased antibiotic prescribing after point-of-care testing when the initial likelihood of prescribing was low. Presumably, an unexpected point-of-care test result that carried an implication of antibiotic benefit (eg, a CRP test result slightly higher than 20 mg/L or a positive group A streptococcus test without consideration of the possibility that the patient might be a carrier and without the knowledge that not every group A streptococcus throat infection benefits from antibiotics) influenced the clinicians towards prescribing. Some initial high-likelihood prescribing decisions were converted to non-prescribing, indicating that point-of-care testing could be of added value for this particular patient group. However, the small decrease in antibiotic prescribing could be accounted for by the low amount of evidence to support that prescribing in line with the test result is sufficiently safe, with clinicians being unconvinced that a positive influenza test excludes other pathogens, feeling uncomfortable with CRP cutoff values, or struggling to address patient expectations about antibiotics.[25,26] The point-of-care tests alone might, therefore, not be sufficient for clinicians to confidently override their clinical assessment. A further question is how point-of-care testing could be implemented into routine care. Point-of-care testing as part of antibiotic stewardship might provide better value when supported by complementary approaches—eg, clinician training on evidence-based prescribing, guideline-advocated first-choice antibiotics for respiratory tract infections, and advanced communication skills, or management strategies to clearly identify the place of testing in care pathways and systematically add in clear safety-netting advice.[8,9,20,27] Research-generated evidence evaluating the safety of following point-of-care test results should support the implementation of these tests. The final question regards how to view massive point-of-care testing for respiratory tract infections in some countries. Large scale, real-world implementation studies should use national dispensing data to evaluate trends in antibiotic use and examine the appropriate use of point-of-care tests, cost-effectiveness, trends in complications, and health-care seeking behaviour. Moreover, point-of-care testing has been shown to increase health-care attendance by patients expecting to be tested.[28] Underuse as well as overuse of point-of-care testing has been linked to increased inappropriate antibiotic prescribing.[29]

In conclusion, a point-of-care testing strategy for respiratory tract infections that included testing for CRP, group A streptococcus, and influenza did not reduce antibiotic prescribing when clinicians were considering or had planned to prescribe an antibiotic. The findings from the trial and its process evaluation highlight the complexity of implementing point-of-care testing in routine care and the need for complementary strategies to more effectively address the multiple clinical and non-clinical drivers of antibiotic overprescribing. Given the increasing availability and promotion of point-of-care testing platforms, future research should better define the intended-use population, the niche in care pathways, and additional behavioural components that should be included in any roll-out of this complex intervention.

Contributors

CCB and AWvdV were co-chief investigators. CCB, JM, SM, AWvdV, and L-MY directly accessed and verified the trial data and take responsibility for the integrity of the data and accuracy of the data analysis. CCB, AWvdV, HG, and L-MY decided to publish the paper. CCB, AWvdV, SE, AZ, BRS, LM-Y, and HG contributed to trial design. EH, EB, FM, SC, GNH, PJT, ET, SA, ST-C, and MW helped with planning the trial and coordinating internationally. SC, MA, FB, JD, AG-S, BK, AK, CL, LM, LR, and AV implemented the trial in practices and facilities in their countries. SM, JM, MS, BRS, and L-MY contributed to trial simulations and statistical analysis. CCB, AWvdV, SC, JM, SM, and L-MY drafted the manuscript. All authors had full access to the data, reviewed the manuscript, and accept responsibility for the decision to submit for publication.

Declaration of interests

AWvdV is a member of the Global Respiratory Infection Partnership (with an educational grant from Reckitt Benckiser), SE is an employee of Abbott Rapid Diagnostics, AZ is an employee of Beckton Dickinson, and BRS reports grant support for statistical consulting paid to their previous employer Berry Consultants (Austin, TX, USA). All other authors declare no competing interests.

Data sharing

On publication, de-identified individual participant data with data dictionary will be shared with qualifying researchers who submit a proposal (a.w.vandervelden@umcutrecht.nl; christopher.butler@phc.ox.ac.uk) with a valuable research question for assessment by a committee formed from the PRUDENCE Trial Management Group, including senior statistical and clinical representation.

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