

Tailoring antibiotic duration for respiratory tract infections in primary care: study protocol for a pragmatic randomized controlled trial (STORM).

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Abstract

Background: Combating the rise of drug-resistant organisms and minimizing side effects requires a shift in how we approach the duration of antibiotic therapy. A promising strategy involves tailoring the length of antibiotic therapy to patients' needs, allowing discontinuation once patients feel better.

Objective: We aim to assess whether shortening antibiotic therapy based on patients' recovery time is as effective as completing the full course in treating acute respiratory tract infections (RTIs).

Methods: We plan to enroll a minimum of 474 outpatients ranging from 18 to 75 years of age with clinical features of acute RTIs across Spanish health centers. Patients diagnosed with acute lower RTIs or acute rhinosinusitis, deemed by clinicians to require a β -lactam course, will be randomized to either usual care, involving a full-course antibiotic therapy based on current guidelines, or a tailored approach. In the intervention group, patients will be advised to visit the center as soon as they feel better and are afebrile for a clinical assessment and C-reactive protein rapid testing. Treatment will be discontinued if these clinical results are normal. The primary outcome will be assessment of clinical resolution at day 14, while secondary outcomes include antibiotic given and duration, adherence to the prescribed antibiotic, other therapies given, days of severe, moderate and any symptom, complications and reattendance within the first month, drug-related adverse events, absenteeism and health-related quality of life. All participants will be given a symptom diary, recording their symptoms each evening. Additionally, a cost-effectiveness study and qualitative studies involving clinicians and patients aimed at exploring the strategy's pros, cons, uptake, and satisfaction levels will be carried out.

Results: None. The final results will be published by the end of 2027.

Conclusions: We will examine whether adults who present with symptoms of RTI who are treated with antibiotic courses until they feel better are as effective as longer standard courses. It is highly important that a possible reduction in the antibiotic course as soon as the patient feels better does not compromise patients' recovery. This comprehensive approach aims to shed light on the practicality and impact of tailoring antibiotic duration in RTIs. Clinical Trial: ClinicalTrials.gov NCT06581367. Registered on August 30, 2024.

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Original Manuscript

TITLE

Tailoring antibiotic duration for respiratory tract infections in primary care: study protocol for a pragmatic randomized controlled trial (STORM).

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ABSTRACT

Background: Combating the rise of drug-resistant organisms and minimizing side effects requires a shift in how we approach the duration of antibiotic therapy. A promising strategy involves tailoring the length of antibiotic therapy to patients' needs, allowing discontinuation once patients feel better.

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Key words: Respiratory Tract Infections; Anti-Bacterial Agents; Drug Resistance, Microbial; Patient-Centered Care; Deprescriptions; Duration; Drug-Related Side Effects and Adverse Reactions.

INTRODUCTION

The judicious use of antibiotics preserves millions of lives and safeguards numerous individuals from infectious complications annually. Excessive and inappropriate antimicrobial use significantly contributes to this crisis. Research indicates a strong correlation between the consumption of antibiotics and the selection of resistant bacteria, both at societal and individual levels [1]. Primary

care is responsible for about 80% of antibiotic prescriptions, and respiratory tract infections (RTIs) account for more than half of all antibiotic prescriptions globally [2]. Given the limited development of new antibiotics, prudent antimicrobial utilization, particularly in primary care, is crucial to mitigating the spread of antimicrobial resistance. Inappropriate use of antibiotics for uncomplicated RTIs is very common worldwide. Around 50% of all general practice consultations for RTIs result in the prescription of an antibiotic, with a high variability across practices ranging from 20% to 80% [2]. In Spain, more than half of the patients with acute rhinosinusitis, acute bronchitis and sore throat seen in primary care are treated with antibiotics [3]. Most acute uncomplicated RTIs are caused by viruses and in otherwise healthy adults, these infections are typically self-limiting, and antibiotics provide no relevant benefits.

Several strategies aimed at reducing unnecessary antibiotic use have been suggested. While there have been certain local experiences of success, the reduction in unnecessary antibiotic prescribing ranges from moderate to minimal, and even null. Certain strategies prove more effective than others [4]. The effectiveness of antibiotic stewardship programs has shown considerable variability, with a less pronounced decrease in unnecessary antibiotic use in primary care compared to other settings. A recent systematic review, including six intervention studies, indicated that antimicrobial stewardship programs reduce antibiotic use among outpatients by an average of 4% [5]. As a result, primary care physicians, who are potentially the most influential professionals in tackling the issue of antimicrobial resistance, continue to show a consistently high rate of inappropriate and unnecessary antibiotic prescriptions.

Except for tuberculosis and specific upper airway infections such as otitis media and streptococcal pharyngitis, in which shorter antibiotic courses are less effective, most bacterial RTIs show equal efficacy with fewer adverse events in shorter compared to standard antibiotic courses in clinical trials. This is based on the principle of 'shorter is better,' initially conceived one decade ago [6]. Despite being recommended in guidelines for many years, standard antimicrobial therapy durations (7-10 days) are not based on controlled studies [7]. Shorter treatment durations, such as two to three days, have demonstrated to be equally effective as longer durations for lower RTIs [8,9]. Although most randomized clinical trials on this topic have been conducted in recent decades, one of the earliest trials of penicillin therapy for pneumococcal pneumonia demonstrated that when therapy was discontinued 2-3 days after clinical improvement and resolution of fever, only 5% of patients relapsed [10]. Despite this evidence, current guidelines still do not clearly support shorter

durations of antibiotic use. Consequently, many physicians do not prescribe shorter regimens, frequently defaulting to 7-day courses [11-13].

In medical schools we have been taught to advise our patients to always complete an antibiotic course once initiated. This was deemed suitable to minimize the development of antimicrobial resistance. However, this often-heard statement that to prevent antimicrobial resistance it is necessary for patients to complete the entire course, even after the resolution of symptoms, by eradicating every bacterium that could result in a future relapse, remains unproved. To the contrary, the longer patients and the environment are exposed to antibiotics, the greater the selective pressure driving antimicrobial resistance. Even short courses of antibiotics can have long-term effects causing persistence of resistant organisms lasting years and altering the normal gut microbiome and might be detrimental [14]. By shortening antibiotic duration, overall antibiotic exposure is lessened, reducing the selection pressure for multidrug-resistant organisms [15]. The cumulative evidence indicates that each day of antibiotic therapy beyond the first confers a decreasing additional benefit to clinical cure while increasing the burden of harm in the form of adverse effects, superinfections, and selection of antibiotic resistance. Specifically for pneumonia, studies have shown that longer courses of therapy result in more emergence of resistance [16,17]. This observation is consistent with what we know about natural selection [18]. Antimicrobial resistance emerges at the site of infection in only a few types of infections; moreover, resistance typically emerges off target, among colonizing flora away from the site of infection [19]. Over the last years there has been an increasing number of independent bodies, scientific academies and institutions abandoning this dogma on completing antibiotic courses [20].

The best way to contravene this historical dogma is by providing new evidence from randomized clinical trials setting a revised standard for antimicrobial therapy durations. Conventional stewardship strategies aimed at patients not requiring antibiotics do not help those who truly need them but receive excessively long treatment. However, encouraging a minimum duration of therapy might be more attainable than completely refraining from antibiotic therapy, as shown in qualitative studies [21]. In such instances, the potential harm posed by unnecessary therapy to patients without bacterial infections is considerably lower compared to adhering to standard durations, and it can prove beneficial to those with genuine bacterial infections.

It is evident that there is substantial interindividual variability in how drugs are handled, and it seems unlikely that the optimal duration of therapy is precisely the same for all patients [22].

Factors such as bacterial load, age, frailty, underlying health conditions, liver and kidney functions, and immune status vary among individuals, making it unlikely that a one-size-fits-all approach would be effective [23]. This might lead to under- or over-treating some patients [6]. This highlights the importance of individualized and patient-centered medical care, considering the unique characteristics and needs of each patient when determining the duration of therapy for RTIs. In a landmark study, a 3-day antibiotic course was as efficacious as 8 days of treatment in adults admitted to hospital with mild to moderate-severe community-acquired pneumonia who substantially improved after an initial three days of therapy, which accounted for 78.5% of the participants [8]. It would not be unreasonable to think that the percentage of patients with pneumonia who feel better after three days would be even higher in primary care.

In cases of a self-limiting infection or when a non-bacterial infection is suspected, our initial objective is either to refrain from initiating antibiotic therapy or stopping it. Unless the infection is deemed potentially serious, when dealing with patients who have a prescription with a fixed antibiotic duration, they should be informed that if their symptoms resolve before completing the antibiotic course, they can stop the treatment [21]. In fact, one third of the patients already do that by themselves. Studies using medication event monitoring systems reveal that in real-life scenarios, only one-third of patients adhere to the prescribed antibiotic course [24]. In potentially serious RTIs, general practitioners (GP) may advise reassessment for clinical examination and/or point-of-care testing, such as C-reactive protein (CRP) rapid testing, before discontinuing the antibiotic therapy. Convincing physicians to refrain from prescribing antibiotics proves to be a greater challenge than persuading them to prescribe for a shorter duration, provided it is supported by evidence, as professionals demand clear and unambiguous evidence that this strategy is beneficial and safe [25]. Although the potential to tailor the duration of therapy for patients with RTIs based on such a strategy has never specifically been evaluated, it is highly likely that antibiotic exposure could be reduced in the near future with the emergence of new evidence.

It is hard to convince doctors not to prescribe antibiotics at all when they are in doubt or in the face of patient expectations. The limited to moderate impact in reducing unnecessary antibiotic use in primary care observed in antimicrobial stewardship programs necessitates the exploration of new strategies [26]. Studies focused on reducing unnecessary antibiotic prescribing and on tailoring antibiotic therapy, dose, and length of therapy to patients' needs, present a promising strategy. This can be encouraged based on randomized clinical trials indicating that patients most often recover

within three days. In the end, we are not treating RTIs, we are treating patients with RTIs. Therefore, we intend to initiate a pragmatic randomized clinical trial focused on assessing the effectiveness of customizing the duration of antibiotics according to the individual requirements of the patients.

METHODS

Study Design

This is the protocol for a pragmatic, randomized non-inferiority trial with a two-group parallel design. The unit of randomization is the patient, and the allocation ratio between the control and intervention groups is 1:1. This protocol follows the Standard Protocol Items: Recommendations for Interventional Trials, 2013 statement [27].

Objectives

The primary aim of the STORM trial is to assess whether the clinical resolution on day 14 for adults presenting with symptoms of an acute lower respiratory tract infection (RTI) or acute rhinosinusitis in general practice is non-inferior in the intervention group (stopping the antibiotic course as soon as patients feel better and clinical assessment is within the normal range) compared to the control group (patients completing standard antibiotic courses).

Secondary objectives:

- 1) Evaluate the antibiotic prescribed at the index visit and the planned and actual duration in the two groups
- 2) Evaluate the adherence to the prescribed antibiotic in the two groups
- 3) Evaluate the duration of symptoms in the two groups: a) duration of severe symptoms, b) duration of moderate symptoms, c) total resolution of symptoms
- 4) Evaluate the utilization of antibiotics others than the study medication and other symptomatic therapies within the first 4 weeks in the two groups
- 5) Determine the number of re-attendances to any doctor regarding the infection within the first 4 weeks in the two groups
- 6) Determine the number of complications related to the infection within the first 4 weeks, such as visits to emergency departments, hospital admissions, in the two groups
- 7) Determine the number of adverse events in the two groups
- 8) Estimate the incremental cost per patient achieving successful clinical efficacy (within-trial cost-effectiveness analysis) and the incremental cost per quality-adjusted life year (long-term cost-effectiveness analysis)

effectiveness analysis) in the two groups

- 9) Determine the number of days of work absenteeism due to the infectious disease in the two groups
- 10) Determine the improvement in health-related quality of life in the two groups
- 11) Assess the percentage of patients assigned to the intervention group who feel better who comply with the criteria for stopping the antibiotic therapy in the two groups

We hypothesize that patients with ages ranging from 18 to 75 who are allocated to the intervention group and are asked to discontinue antibiotic therapy as soon as they feel better and afebrile, their clinical stability criteria are normal (systolic blood pressure >90 mm Hg, axillary temperature <37°C, respiratory rate <20 breaths/minute, and oxygen saturation >92%) and CRP falls within normal range will have a similar overall clinical efficacy at day 14 and will not present a higher re-consultation rate compared to those allocated to the control group. We expect a lower number of drug-associated adverse events in the intervention group.

Eligibility Criteria

We will prospectively recruit adult patients with acute cough as the predominant symptom which the clinician believes to be a bacterial acute lower RTI or also an acute bacterial rhinosinusitis, for whom GPs deem β -lactam therapy is necessary. All patients who agree to participate will provide a signed informed consent and will be informed about the nature of this study. The participating GP will prescribe an antibiotic, and the patient will be later randomized. Patients in the intervention group will be asked to return to the center as soon as they feel better and afebrile for an assessment of the clinical stability criteria and CRP measurement. To be eligible for the study, patients must fulfil all the inclusion criteria:

1. Age ranging from 18 to 75 years of age
2. Either:
 - a) Acute lower RTI: defined as acute cough (new or worsening of a previous cough present for 21 days or less) as the predominant symptom, accompanied by at least one other lower respiratory tract symptom—such as sputum production, dyspnea, wheezing, and/or chest discomfort/pain—with no alternative explanation, as stated by the European Society for Clinical Microbiology and Infectious Diseases [28]. It is presumed to have a bacterial cause, such as community-acquired pneumonia, acute bronchitis, or acute exacerbations of chronic obstructive pulmonary disease (COPD), according to the clinician's judgment; or

- b) Acute bacterial rhinosinusitis: which is defined as the presence of purulent nasal discharge (anterior, posterior, or both), accompanied by nasal obstruction, facial pain, pressure, or fullness, or both, lasting less than four weeks, as stated by the American Academy of Otolaryngology-Head and Neck Surgery Foundation [29], and which the clinician believes to have a bacterial cause

3. GPs deem β -lactam therapy for at least seven days is necessary

The presence of any of the following exclusion criteria leads to patient exclusion from the study:

1. RTIs different from a lower RTI or acute rhinosinusitis
2. The doctor decides not to give an antibiotic for this RTI
3. Patients with suspected septicemia (quick SOFA: respiratory rate ≥ 22 breaths/minute, systolic blood pressure < 100 mm Hg or altered mental status with a Glasgow score < 5) ≥ 2
4. Patients with pneumonia and a CRB-65 (confusion, respiratory rate ≥ 30 breaths/minute, blood pressure $< 90/60$ mm Hg, or age > 65 yr.) ≥ 1
5. Patients with very severe COPD ($FEV_1 < 30\%$)
6. Patients with COPD who have taken four or more antibiotic courses in the previous year, presence of significant bronchiectasis, and/or isolation of *Pseudomonas* in a previous sputum culture
7. Patients with reported allergy to β -lactams
8. Patients who have taken an antibiotic in the previous two weeks
9. A working diagnosis of a non-infective disorder, such as heart failure, pulmonary embolus, esophageal reflux
10. Immunocompromised patients, such as HIV infection, patients taking immunosuppressive treatment, antineoplastic therapy, or systemic corticosteroids
11. Currently participating in another clinical trial
12. Previously participated in the STORM study
13. Active neoplasia
14. Terminal illness
15. Institutionalized patient
16. Inability/unable to understand and/or take part in the clinical trial

GPs will be informed about managing acute RTIs with β -lactam therapy, following the specific RTIs outlined in this study and the latest Spanish primary care guidelines [30,31] (Table 1). The guidelines

recommend the use of seven-day antibiotic durations. Doctors participating in this study will be provided with a summary of the current local guidelines, including indications for when to treat. However, the final decision on antibiotic prescriptions will be at the discretion of the GP. The trial is pragmatic, aiming to mirror the real-life practices of doctors in Spain. According to a recent study conducted in Barcelona in 2023, approximately 80% of all prescriptions for amoxicillin and amoxicillin-clavulanate in primary care corresponded to box sizes of 30 pills, representing a ten-day duration, while the remainder were 20-pill boxes [32]. Considering that this clinical trial is pragmatic, we will consider a minimal duration of seven days.

Eligible participants will be informed about the STORM trial and provided with an information leaflet and a consent form from the GP. The GP will ensure that the patient understands the purpose of the project, potential benefits, risks, and procedures involved. The GP will emphasize that participation is voluntary and that the patient can decline to participate or withdraw from the project at any time without consequences. The patient is informed that consent to participate will give the primary investigator, sponsor, and controlling authorities access to obtain information in the patient's medical records, including the electronic records, to obtain information about the patient's health conditions. The GP will check patients against the eligibility criteria stated above and invite patients to participate if they fulfil all the inclusion criteria and none of the exclusion criteria. Patients who agree to participate will be asked to provide written consent, which will be obtained by the GP. Informed consent will be obtained prior to the collection of participant data. Participants will be informed about the storage and use of their data.

Interventions

Patients assigned to usual care will be given a full course of the first-line antibiotic course as recommended by the updated local guidelines [30,31]: amoxicillin 750 mg three times daily (t.i.d.) for seven days for acute rhinosinusitis, 1,000 mg t.i.d. for seven days for suspected pneumonia (with clavulanate if the patient is older than 65 years), and amoxicillin/clavulanate 875 mg/125 mg t.i.d. for seven days for suspected acute exacerbations of COPD (Table 1). Nonetheless, this guideline is designed to serve as a reference for making informed and improved choices in prescribing. The decision to prescribe an antibiotic is solely at the discretion of the participating doctor. The trial is pragmatic, thus mirroring the real-life practices of doctors in Spain. Doctors may also prescribe antibiotics for longer regimens, such as ten-day durations, as shown in recent studies [32]. The decision to prescribe an antibiotic will always be made before randomizing the patient.

Patients in the intervention group will be treated accordingly following the same recommendations as patients assigned to the control group, but they will be asked to return as soon as they feel better and are afebrile.

When deciding whether to discontinue the antibiotic course after a patient feels better during a consultation, the participating professionals must assess three key areas:

1. Overall improvement in the patient's symptoms.
2. Evaluate the vital signs, confirming that all are within the normal range and that the following clinical criteria are met: temperature $<37^{\circ}\text{C}$, blood pressure $>90/60$ mm Hg, pulse <100 beats/min, respiratory rate <20 breaths/min, and oxygen saturation $>92\%$.
3. Assess the CRP value and interpret the results according to the provided table based on current recommendations [33].

Patients who meet all these criteria will be asked to discontinue treatment. On the contrary, patients who do not meet these criteria will be advised to extend their antibiotic course by an additional two days if they experience improvement in their condition. Otherwise, they will be instructed to undergo new reassessment.

CRP point-of-care testing training program

An on-the-spot one-hour training workshop in the different centers will take place before the inception of the study with explanation of the clinical guidelines and how to perform CRP rapid testing. Participating professionals will be informed about the updated recommendations on how to interpret the CRP values and the evidence-based management, and this interpretation will depend on the day the patient feels better [33,34] (Table 2). The tests will be carried out with Affinion 2 CRP test (Abbott Diagnostics, United States). Professionals will practice using the device during a run-in period two weeks before the study starts.

Criteria for discontinuing or modifying allocated interventions

Due to the short intervention period after index consultation, the allocated intervention may only be discontinued for a given trial participant by the GP due to an unexpected event, hindering the GP from conducting or completing the allocated intervention, e.g. acute worsening of the participant's condition during index consultation, after consent has been given and allocation has been revealed. Moreover, the study may be discontinued for a given trial participant upon participant request or by withdrawal of informed consent. The data collected before the discontinuation or withdrawal of consent will be retained and used in the analyses; however, no further data will be obtained from

the participant.

Strategies to improve adherence to interventions

Monthly meetings with the coordinators of the different centers will be carried out during the performance of the randomized clinical trial. Each center will have a centralized mobile phone for the study, through which patients will contact when they feel well to be directly scheduled at the center as soon as possible to assess the discontinuation of the antibiotic.

Relevant concomitant care permitted or prohibited during the trial

Treatments taken on a chronic basis will be permitted, such as inhaled corticosteroids, beta-agonists, anticholinergics, symptomatic treatments, and medications for other concomitant diagnoses, as all these treatments must be distributed evenly between the two groups. Patients taking immunosuppressive treatment, antineoplastic therapy, systemic corticosteroids, or antibiotics in the previous two weeks will be excluded.

Outcomes

Primary efficacy endpoint

The primary outcome is the percentage of patients achieving clinical resolution, defined as the disappearance of fever and either the disappearance or improvement in overall condition, such that no additional antimicrobial treatment is necessary. Any other clinical outcome that does not meet the definition is considered treatment failure. The time point for evaluation is on day 14 through a phone call.

Secondary efficacy endpoints

1) Outcomes collected from the RTI symptom diaries:

Participants will use a validated self-reported RTI symptom diary, utilized in previous studies by the research team [35]. Each symptom will be graded on a 7-point Likert scale (0=not affected; 1=very little problem; 2=slight problem; 3=moderately bad; 4=bad; 5=very bad; 6=as bad as it could be). Symptoms recorded include cough, phlegm, shortness of breath, wheeze, blocked/runny nose, spontaneous facial pain, facial pain on touch, chest pain, sensation of fever (high temperature), muscle aching, headache, disturbed sleep, feeling generally unwell, and interference with normal activities/work. Participants will rate symptoms for 14 days and return the diary upon completion (electronically or paper-based). It will document daily antibiotic doses and other therapies. For patients who do not return diaries, a short form asking about how many days antibiotics were actually taken, whether antibiotics have been taken after being discontinued by their doctors, and

details of duration and severity of symptoms will be completed by a telephone call to the patient at day 14.

- 1.1) Duration of antibiotic therapy, in days, defined as the number of days until discontinuing treatment in both groups (mean/median)
- 1.2) Utilization of antibiotics others than the study medication and other symptomatic therapies within the first two weeks (mean/median)
- 1.3) Duration of severe symptoms, in days, defined as the number of days until the last day the patient scores 5 in any of the symptoms (mean/median)
- 1.4) Duration of moderate symptoms, in days, defined as the number of days until the last day the patient scores 3 in any of the symptoms (mean/median)
- 1.5) Total resolution of symptoms, in days, defined as the number of days until the last day the patient scores 0 in all the symptoms (mean/median)
- 1.6) The duration of antibiotic therapy, in days, defined as the number of patients discontinuing treatment in both groups and what day they discontinue recorded will also be checked via electronic medical records

Outcomes 1.1 to 1.6 from the RTI symptom diary will be calculated for each participant every day from day 0 until day 14 or when the participant has scored 0 for every item, whichever comes first.

- 2) Outcomes collected from electronic case report forms (e-CRFs), when available, and from follow-up phone calls, which will be cross-checked with the patients' electronic clinical records:
 - 2.1) Type of antibiotic prescribed and the planned duration
 - 2.2) Number of re-attendances to any doctor for new or worsening symptoms regarding the infection, within 28 days after the index consultation
 - 2.3) Number of complications related to the infection within 28 days after the index consultation, such as visits to emergency departments and/or hospital admissions regarding the RTI
 - 2.4) Number of days of work absenteeism due to the infectious disease, within 28 days after the index consultation
 - 2.5) Difference in health-related quality of life on days 14 and 28, compared to baseline, measured using the 5-level EQ-5D version-Quality of Life instrument (EQ-5D-5L) [36]
 - 2.6) Drug-associated adverse events related to the antibiotic and antibiotics changed within the first 14 days
- 3) Other outcomes

3.1) Percentage of patients assigned to the intervention group who feel better who comply with the criteria for stopping the antibiotic therapy, based on the information collected during the visit to the center

Participant timeline

A flow chart of patients is described in Fig. 1. To ensure a standardized and uniform inclusion process, the principal investigator and a senior project manager will inform all participating healthcare professionals on the inclusion procedures for the study. Eligible participants will be identified as they present to general practice. Once the GP identifies the patient as eligible for the study and a first-line antibiotic with a β -lactam is warranted, all the information about the study will be provided, and informed consent will be signed. A diagram of the enrollment, allocation, intervention, and follow-up of the participants is shown in Fig. 2.

Patient data will be collected at four specific time points for patients assigned to the control group and five for those allocated to the intervention:

- Day 0 [inclusion date at the center]: Patients meeting the inclusion criteria will be invited to join the study by their GP. After obtaining informed consent, patients will be randomized into either the control group (receiving a full course of β -lactam therapy for at least seven days) or the intervention group (instructed to return for assessment upon feeling better and being afebrile). The GPs will complete a case report form on day 0 (inclusion day), recording details such as age, inclusion and exclusion criteria, symptoms, date of symptom onset, comorbidities, concomitant medication, quality-of-life questionnaire (EQ-5D-5L instrument), randomization, assigned group, and details of the antibiotic administered. Patients will also be provided with a symptom diary (online or paper-based)
- From day 1 until the last day of the antibiotic regimen duration [at the center, only for patients assigned to the intervention group]: For patients assigned to intervention, they will be asked to return to the center for clinical reassessment and CRP rapid testing by the professional. Each center will organize ways to make it easy for patients to reach out and schedule an appointment as soon as they feel better (e.g., phone number, web-based page, etc.). To decide whether to discontinue the antibiotic course when the patient reports feeling better during the consultation, three types of assessment are needed: 1. Overall improvement in the patient's symptoms; 2. Signal signs are in normal range (temperature $<37^{\circ}\text{C}$; blood pressure $>90/60$ mm Hg; pulse < 100 beats/minute; respiratory rate <20 breaths/minute, and oxygen saturation

>92%), and 3. CRP value is lower than the pre-specified values depending on the day of the visit.

All this information will be recorded in the e-CRF (Table 2)

- Day 3±1 [phone call, only for patients assigned to the intervention group]: A reminder phone call for all patients assigned to the intervention group will be made on this day. They will be asked how they feel and reminded to reach out to the center as soon as they feel better for a discontinuation assessment
- Day 14 [phone call]: The main clinical efficacy outcome and some secondary outcomes, including clinical progression of signs and symptoms, compliance with the study treatment, EQ-5D-5L instrument, adverse reactions, any complications, re-attendance visits, changes in the assigned treatment or concomitant medication, including the use of antibiotics other than the study medication, will be assessed. Patients will be asked to return their diaries
- Day 28 [phone call]: Patients will be contacted for information on the number of re-consultations, complications, and the quality-of-life (EQ-5D-5L) instrument

Sample size

We assumed 85% clinical recovery in the group assigned to the full antibiotic course based on some studies. Considering a power of 80%, a level of significance of 5%, one sidedness non-inferiority margin of 10%, which gave a sample size of 402 patients. Assuming that the primary outcome could not be evaluated in 15% of patients, 474 needed to be included in the study (237 in the control group and 237 in the intervention group).

Recruitment

A total of 474 eligible patients will be enrolled by doctors in 25 primary care centers throughout Spain. The study is planned to run from October 2025 to April 2027, including two winter periods (last patient recruited in March 2027). A tight follow-up on the process and different strategies will be implemented, and if needed: 1) other professionals in the existing centers will be invited to participate in the study; 2) we can extend the recruitment period by an additional two months, until May 2027 (last follow-up in June 2027); and/or 3) other sites will be opened to increase the candidates to enter the study. Monthly meetings will be held with the coordinators at the different centers to maintain recruitment and enrolment active during the inclusion period.

Assignment of interventions: allocation

Sequence generation: Patients fulfilling the inclusion criteria will be asked to participate in the trial. All patients who agree to participate and provide signed informed consent will receive an increasing

sequential patient number and be randomly assigned to one of the two treatment groups in a 1:1 ratio stratified per main diagnosis, one for acute rhinosinusitis and another one for lower RTI.

Concealment mechanism: Since this study is open-label to patients and investigators, randomization will be based on investigator-blinded blocks of randomly varying size to protect against potential predictability of treatment assignments. Blocks will be small to decrease the potential for mid-block inequality.

Implementation: The allocation sequences will be prepared by one remote independent researcher who is available for generating more allocation sequences.

Assignment of interventions: blinding

Owing to the type of intervention, participants and GPs are not blinded to group allocation. It is also difficult for the principal investigator and members of the research team involved in obtaining and/or analyzing the data (outcome assessors and data analysts) to be blinded to group allocation, as patients allocated to the intervention group have more visits scheduled.

Data collection and management

Plans for assessment and collection of outcomes: All the data is collected via e-CRFs and surveys through Research Electronic Data Capture (REDCap®), which is a secure online data collection platform for building and managing online databases and surveys [37].

Collection of baseline characteristics of GPs: The baseline characteristics of the participating GPs are collected through email correspondence and registered in REDCap® by the principal investigator. The following information will be obtained: age, sex, region of Spain, type of primary health clinic, seniority as a GP, experience with randomized clinical trials, experience with research on RTIs, comfort with stopping antibiotic courses, and baseline antibiotic prescribing.

Collection of the participant data: We will collect health and personal data from the patients included in the study via REDCap®, where the researchers will register basal data and evolution of the illness and via a patient diary completed by the patient himself. Regarding to patient's diary we will also create an online symptoms diary to make it available for all patients recruited. All patients will be able to choose between the online or paper version of the symptom diary. Patients will be informed about the type of data that will be collected and about their rights when being informed about the study and will sign a consent form consenting on the use of their data. No data will be collected before the patient signs the consent form. As soon as the patient has signed the consent form, they will be given a study code and will be identified by the study code in all the study

material. The relationship between his identity and the study code will be kept in the healthcare center and will only be available to those that need it to fulfil their duties. Data collected in this pragmatic study is considered codified data. IDIAPJGol has license to use REDCap© and the data is collected and held in IDIAPJGol servers, which comply with the European and national requirements. Data controller will be the institution (IDIAPJGol) for the study related data and the healthcare institution for the health data collected to manage the patient in clinical practice. There will not be any transfer of data. Only the investigator team will have access to study datasets and always with codified information to preserve the confidentiality of the participants involved. All the recruiting investigators will have access to REDCap© platform to collect the data, each of them with their own specific credentials and they will only have access to the patients recruited in their own setting. We will follow the FAIR (Findable, Accessible, Interoperable and Reusable) principles: all datasets and publications will be identifiable by using a “Digital Object Identifier (DOI)” and we will share the data (as far as possible) in the Zenodo platform. We will publish the results in Open Access journals and wherever possible the data will be shared without delay following the Creative Commons License with Attribution (CC-BY) or the “No Rights Reserved” (CC0). Data will be saved and shared using standardized formats (.txt, .csv, .pdf,...).

Ethical aspects and Data Protection

The main study will be reviewed by the Spanish Agency of Drugs and Health Products and ethical committee for approval. No study procedures will start before obtaining the appropriate approval. We will follow the legislation on data protection (EU 2016/679) and its national implementation (LOPD 3/2018 of 5 Dec on the protection of personal data and guarantee of digital rights).

Plans to promote participant retention and complete follow-up

The loss of follow-up data obtained from medical records and shared medication records is expected to be minimal. Outcome data from medical records be collected for all participants, except those who are discontinued by the GP or who have withdrawn informed consent before day 28. We expect some participants to be lost to follow-up in the RTI symptom diary, as we anticipate that some participants will fail to complete the electronic diary or will fail to submit the paper version to the GP. For those who do not return the diaries, participants will be contacted by phone on day 14 to gather information on antibiotic usage, adherence, and symptom duration details.

Statistical methods

Statistical methods for primary and secondary outcomes: The characteristics of the study

population will be described using frequencies for categorical variables and mean and standard deviation for quantitative variables. To compare the clinical efficacy between the two strategies, we will analyze the difference in the proportion of recovered patients in each arm on day 14. Efficacy evaluation will be primarily based on intention-to-treat analysis in such a way that any event in any patient will be included in the group to which the patient was randomized, and per protocol analysis will be used as a secondary analysis. For all analyses the level of significance will be $p < 0.05$.

Interim analyses: No interim analysis is planned.

Methods for additional analyses (e.g. subgroup analyses): We will conduct subgroup analyses of the primary outcome of participants with lower RTIs, and for acute rhinosinusitis.

Cost-effectiveness analyses

We will estimate the cost-effectiveness of tailoring antibiotic duration therapy for the 'within-trial' period (28 days) and over the expected lifetime of patients (lifetime/long-run model).

In the within-trial analysis, cost-effectiveness will be measured by the incremental cost per patient achieving successful clinical efficacy. In this analysis, effectiveness will be calculated using the primary endpoint of the study. Costs considered will include antibiotic prescription costs according to the duration of treatment, other drug costs, re-consultations in primary and secondary care (including hospitalizations), and costs associated with adverse events. Data on healthcare resource use and duration will be taken from the patients' diaries, from the collected information in the e-CRF and at the follow-up phone calls at day 14 and 28, and from a review of patients' medical notes. Unit cost data will be taken primarily from national sources published by the Spanish Ministry of Health. The incremental cost-effectiveness ratio will be calculated by dividing the estimated difference in costs by the estimated differences in effects observed between the intervention and control groups. Nonparametric methods to calculate confidence intervals around the incremental cost-effectiveness ratio based on bootstrapped estimates of the mean cost and effect differences will be used.

The intervention under evaluation in this study is likely to have an impact beyond the trial period. To capture these potential effects, we will extrapolate the results to an extended time horizon, i.e., considering the remaining life expectancy of the patients. In this analysis, we will complement data from the trial with relevant data from the published literature to estimate the incremental cost per quality adjusted-life year (QALY) gained. Health-related quality of life data collected during the trial using the EQ-5D-5L questionnaire at baseline, at 14 and 28 days will be used as inputs to estimate

baseline QALY values for these patient group. A decision-analytical model synthesizing all relevant information will be used to estimate the differences in lifetime QALYs and lifetime healthcare costs of a cohort of patients under the tailored duration strategy versus the standard of care strategy.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data

Analyses will be performed as intention to treat (pragmatic trial) and also per protocol. The primary analysis population will comprise all participants, irrespective of follow-up.

Data will be examined for missing values and outliers. Measures of central tendency and dispersion for continuous study parameters will be portrayed. Extreme or unexpected values will be examined individually for authenticity and data discrepancies addressed where appropriate.

Plans to give access to the full protocol, participant-level data, and statistical code

The full protocol, statistical code, and e-CRF templates designed for the study will be available upon request once the report has been published. Participant-level data will not be available.

RESULTS

Recruitment of patients will start in October 2025 and will be stopped in April 2027. The current protocol is version 3 of 2 March 2020.

DISCUSSION

The limited to moderate impact in reducing unnecessary antibiotic use in primary care observed in antimicrobial stewardship programs necessitates the exploration of new strategies aimed at reducing patients' exposure to unnecessary courses [26]. This highlights the need for exploring new strategies to minimize patients' exposure to unnecessary antibiotic courses. Convincing doctors, especially general practitioners, not to prescribe antibiotics when uncertain or under patient pressure is challenging. Despite the widespread practice, standard durations for common infections lack support from clinical studies [7]. However, recent randomized clinical trials, conducted mainly in the last two decades, show that ending antibiotic courses by day 2-3 for most RTIs is effective and safe, similar to early studies on short-term antibiotic courses for uncomplicated urinary tract infections carried out twenty years ago [38]. We believe healthcare professionals should encourage patients to stop antibiotic treatment promptly after symptom resolution unless a serious infection is suspected. In our clinical trial these potential serious infections are clearly excluded. Continuing

antibiotics beyond symptom resolution does not appear to prevent or reduce antimicrobial resistance. Conversely, reducing the duration of courses has been shown to curb the spread of antimicrobial resistance in pneumonia. It is essential to move away from strict, predetermined durations and adopt a patient-centered approach by customizing antibiotic courses to meet each patient's individual needs. The key challenge involves identifying when exactly antibiotics can be safely stopped based on symptoms to minimize chances of relapse. We currently lack evidence on how pathogen burden is associated with symptoms experienced by patients with RTIs.

STORM's main focus on primary care settings makes it directly applicable to the daily practice of GPs who frequently encounter patients with uncomplicated RTIs. Infectious diseases represent one third of all GP consultations, with over half of these visits attributed to RTIs [39]. This indicates that RTIs are among the most prevalent conditions encountered by GPs in their clinical practice. It acknowledges the challenges faced by healthcare professionals, particularly GPs, in resisting patient pressure and uncertainty when deciding whether to prescribe antibiotics. By advocating for a patient-centered approach to antibiotic prescribing, the proposal provides practical guidance for healthcare providers to tailor treatment regimens according to individual patient needs and clinical circumstances [40]. STORM draws upon recent clinical trials conducted over the past two decades, suggesting that the findings are based on contemporary evidence and thus likely applicable to current clinical practice.

To the best of our knowledge, there has not been any study in primary care exploring the feasibility and efficacy of stopping the antibiotic course once the clinical signs of the patient are normal and the CRP level is low. Furthermore, a randomized clinical trial has never been conducted to assess the effectiveness and safety of this crucial strategy in combating antimicrobial resistance and drug-related adverse events. Primary health centers are the first contact point for patients with RTI symptoms, reason for why we will conduct the study in this setting. This will constitute the first clinical trial aimed at answering whether it is safe to shorten and tailor the antibiotic therapy duration to the needs of the patients. This study does not pursue the medicalization of tailoring the antibiotic course by requiring patients assigned to the intervention group to return for a clinical reassessment and CRP testing; however, this is the first trial of its kind. We aim to determine the efficacy and safety of this strategy. If tailoring antibiotic courses for RTIs proves to be as effective and safe as completing the entire course, further studies will investigate the necessity of the reassessment visit.

Limitations

This is a pragmatic clinical trial evaluating the efficacy of different antibiotic therapy durations for acute RTIs, and therefore masking techniques are not used. One limitation of this study is that a percentage of self-limiting viral infections will be included. While antibiotics are not the recommended treatment, they are still frequently prescribed for most RTIs worldwide [3]. However, all participants will receive a summary of the updated current guidelines, which discourage the use of antibiotics for most patients with uncomplicated acute bronchitis and acute exacerbations without purulent sputum, leaving the decision to the clinician in this pragmatic approach. Nevertheless, we believe that the percentage of 'viral self-limiting infections' included in this randomized clinical trial will be much lower than what is typically observed under normal conditions, as GPs will be informed about the appropriate indications for therapy and will have this information available before deciding whether to prescribe a β -lactam to the participant.

Both the primary and some of the secondary objectives of the study are based on information provided by the patients themselves. Regarding the CRP rapid testing, we are aware that high CRP levels can signal systemic inflammation in conditions like inflammatory disorders, not just infections, there is limited research on how CRP changes day by day in RTIs. Although levels above 100 mg/L might reflect the natural progression, we set conservative thresholds for this initial trial on shortening treatments as patients improve. Another limitation is that a patient can feel better on Saturday or Sunday and most health centers are closed these days. In that case, patients will attend the center on the following Monday.

Another limitation is defining 'feeling better' in a way that allows for clear, actionable guidance, which both clinicians and patients seek [21,41]. The concept of 'feeling better' is likely to differ depending on the individual, the type of infection, and the specific symptoms involved. It might refer to a reduction in certain symptoms or a complete resolution of some or all symptoms. For instance, fever might be a more reliable indicator for discontinuing antibiotics compared to a lingering cough, which may persist without significantly affecting daily life. A clear, practical definition of when antibiotics should be stopped is essential to enable clinicians to provide precise and consistent advice. We decided to rely on the normalization of vital signs, along with a reduction in inflammatory markers, in our study using CRP rapid testing.

As with any randomized clinical trial, the STORM study faces some challenges. One potential difficulty is recruiting enough patients with acute RTIs who are willing to participate. Despite this

moderate risk, the study is planned to run from October 2025 to April 2027, covering two winter periods, with the last patient recruited by March 2027. To ensure recruitment success, tight follow-up processes and various strategies will be implemented. These strategies may include inviting other professionals from existing centers to participate, extending the recruitment period by an additional two months if needed, and, if necessary, opening recruitment at additional sites to increase the pool of candidates.

Professionals will follow up all patients assigned to the intervention group on day 3 for assessment of the clinical condition and as reminder of reaching out to the center as they feel better. Professionals will be trained on how to explain the study's objectives and the importance of adhering to the study procedures. For patients who do not return their symptom diaries, a short form will be completed via a phone call on day 14, asking about the number of days they took antibiotics, other therapies, and details regarding the duration and severity of their symptoms.

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To all the clinicians who will be participating in the study.

DATA AVAILABILITY

The data sets generated or analyzed during this study are available from the corresponding author on reasonable request.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The protocol has also been submitted to the Spanish Agency of Drugs and Health Products and Hospital de Sant Pau Independent Ethics Committee, Barcelona, for approval.

AUTHORS' CONTRIBUTIONS

All authors contributed to the study design. R.Mor. and C.L. conceived the study. A.M., A.G.S. M.M. and C.L. obtained funding. A.G.S. and C.I.J are involved in the acquisition of data, R.Mor., A.G.S., R. Mon. and L.V.T. are responsible for the analysis of data. R.Mon is responsible for the software used in the work. C.L. wrote the first draft of the protocol. All authors critically revised the protocol, made substantial contributions and approved the final version of the protocol to be submitted for publication. The corresponding author has the final responsibility for the decision to submit for publication.

CONFLICTS OF INTEREST

Dr Miravittles has received speaker fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, Bial,

GlaxoSmithKline, Menarini, Kamada, Takeda, Zambon, CSL Behring, Specialty Therapeutics, Janssen, Grifols, Zambon, Tabuk Pharmaceuticals, Glenmark Pharmaceuticals, Sanofi/Regeneron and Novartis, consulting fees from AstraZeneca, Atriva Therapeutics, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, CSL Behring, Inhibrx, Ferrer, Menarini, Mereo Biopharma, Spin Therapeutics, Specialty Therapeutics, GondolaBio, Palobiofarma SL, Takeda, Novartis, Beam therapeutics, Novo Nordisk, Sanofi/Regeneron, Zambon, Zentiva and Grifols, research grants from Grifols, participation on a Data Safety Monitoring Board from Mereo, and support for attending meetings from Boehringer Ingelheim, Menarini, Chiesi, Bial, CSL Behring, and Grifols. The other authors declare no competing interests.

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PROTOCOL VERSION

Version 3.0, 3 April 2025

ABBREVIATIONS

COPD: Chronic obstructive pulmonary disease

CRP: C-reactive protein

e-CRF: Electronic case report form

EQ-5D-5L: 5-level EQ-5D version-Quality of Life instrument

GP: General practitioner

QALY: Quality Adjusted-Life Year

REDCap©: Research Electronic Data Capture

RTI: Respiratory tract infections

REFERENCES

1. Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ*. 2010;340:c2096. [doi: 10.1136/bmj.c2096] [Medline: 20483949]
2. Gulliford MC, Dregan A, Moore MV, Ashworth M, van Staa T, McCann G, et al. Continued high rates of antibiotic prescribing to adults with respiratory tract infection: survey of 568 UK general

- practices. *BMJ Open*. 2014;4(10):e006245. [doi: 10.1136/bmjopen-2014-006245] [Medline: 25348424]
3. Llor C, Cots JM, Hernández S, Ortega J, Arranz J, Monedero MJ, et al; Happy Audit Study Group. Effectiveness of two types of intervention on antibiotic prescribing in respiratory tract infections in Primary Care in Spain. Happy Audit Study. *Aten Primaria*. 2014;46(9):492–500. [doi: 10.1016/j.aprim.2014.02.006] [Medline: 24768657]
 4. Dyar OJ, Beović B, Vlahović-Palčevski V, Verheij T, Pulcini C; on behalf of ESGAP (the ESCMID [European Society of Clinical Microbiology and Infectious Diseases] Study Group for Antibiotic Policies). How can we improve antibiotic prescribing in primary care? *Expert Rev Anti Infect Ther*. 2016;14(4):403–413. [doi: 10.1586/14787210.2016.1151353] [Medline: 26853235]
 5. Zay Ya K, Win PTN, Bielicki J, Lambiris M, Fink G. Association between antimicrobial stewardship programs and antibiotic use globally: A systematic review and meta-analysis. *JAMA Netw Open*. 2023;6:e2253806.
 6. Spellberg B. The maturing antibiotic mantra: “shorter is still better.” *J Hosp Med*. 2018;13(5):361–362. [doi: 10.12788/jhm.2904] [Medline: 29370317]
 7. Hanretty AM, Gallagher JC. Shortened courses of antibiotics for bacterial infections: A systematic review of randomized controlled trials. *Pharmacotherapy*. 2018;38(6):674–687. [doi: 10.1002/phar.2118] [Medline: 29679383]
 8. el Moussaoui R, de Borgie CA, van den Broek P, Hustinx WN, Bresser P, van den Berk GEL, et al. Effectiveness of discontinuing antibiotic treatment after three days versus eight days in mild to moderate-severe community acquired pneumonia: randomised, double blind study. *BMJ*. 2006;332(7554):1355. [doi: 10.1136/bmj.332.7554.1355] [Medline: 16763247]
 9. Messous S, Trabelsi I, Ali KBH, Abdelghani A, Daya YB, Razgallah R, et al. Two-day versus seven-day course of levofloxacin in acute COPD exacerbation: a randomized controlled trial. *Ther Adv Respir Dis*. 2022;16:17534666221099729. [doi: 10.1177/17534666221099729] [Medline: 35657073]
 10. Meads M, Harris HW, Finland M, Wilcox C. Treatment of pneumococcal pneumonia with penicillin. *N Engl J Med*. 1945;232(26):747–755. [doi: 10.1056/NEJM194506282322601]
 11. Lee RA, Centor RM, Humphrey LL, Jokela JA, Andrews R, Qaseem A, et al. Appropriate use of short course antibiotics in common infections: best practice advice from the American college of physicians. *Ann Intern Med*. 2021;174(6):822–827. [doi: 10.7326/M20-7355] [Medline: 34011111]

33819054]

12. Pouwels KB, Hopkins S, Llewelyn MJ, Walker AS, McNulty CA, Robotham JV. Duration of antibiotic treatment for common infections in English primary care: cross sectional analysis and comparison with guidelines. *BMJ*. 2019;364:l440. [doi: 10.1136/bmj.l440] [Medline: 30814052]
13. Llor C, Hansen MP, Lykkegaard J, Olsen J, Lindberg BH, Rebnord IK, et al. Duration of antibiotic treatment for respiratory tract infections in primary care. *JAC Antimicrob Resist*. 2025;7(1):dlaf028. [doi: 10.1093/jacamr/dlaf028] [Medline: 40008154]
14. Nixon MS, Vendelø MT. General practitioners' decisions about discontinuation of medication: an explorative study. *J Health Organ Manag*. 2016;30(4):565e80. [doi: 10.1108/JHOM-01-2015-0011] [Medline: 27296879]
15. Jernberg C, Löfmark S, Edlund C, Jansson JK. Long-term ecological impacts of antibiotic administration on the human intestinal microbiota. *ISME J*. 2007;1(1):56–66. [doi: 10.1038/ismej.2007.3] [Medline: 18043614]
16. Chastre J, Wolff M, Fagon JY, Chevret S, Thomas F, Wermert D, et al. PneumA Trial Group Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. *JAMA*. 2003;290(19):2588–2598. [doi: 10.1001/jama.290.19.2588] [Medline:]
17. Singh N, Rogers P, Atwood CW, Wagener MM, Yu VL. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit: a proposed solution for indiscriminate antibiotic prescription. *Am J Respir Crit Care Med*. 2000;162(2 pt 1):505–11. [doi:] [Medline:]
18. Spellberg B, Bartlett JG, Gilbert DN. The future of antibiotics and resistance. *N Engl J Med*. 2013;368:299–302. [doi:] [Medline: 14625336]
19. Russo TA, Spellberg B, Johnson JR. Important complexities of the antivirulence target paradigm: a novel ostensibly resistance-avoiding approach for treating infections. *J Infect Dis*. 2016;213(6):901–903. [doi: 10.1093/infdis/jiv533] [Medline: 26563238]
20. Huttner B, Saam M, Moja L, Mah K, Sprenger M, Harbarth S, et al. How to improve antibiotic awareness campaigns: findings of a WHO global survey. *BMJ Glob Health*. 2019;4(3):e001239. [doi: 10.1136/bmjgh-2018-001239] [Medline: 31179029]
21. Moragas A, Uguet P, Cots JM, Boada A, Bjerrum L, Llor C. Perception and views about individualising antibiotic duration for respiratory tract infections when patients feel better. A qualitative study with primary care professionals. *BMJ Open*. 2024;14(2):e080131. [doi:

- 10.1136/bmjopen-2023-080131] [Medline: 38316598]
22. Moser C, Lerche CJ, Thomsen K, Hartvig T, Schierbeck J, Jensen PØ, et al. Antibiotic therapy as personalized medicine – general considerations and complicating factors. *APMIS*. 2019;127(5):361–371. [doi: 10.1111/apm.12951] [Medline: 30983040]
23. Palin V, Welfare W, Ashcroft DM, van Staa TP. Shorter and longer courses of antibiotics for common infections and the association with reductions of infection-related complications including hospital admissions. *Clin Infect Dis*. 2021;73(10):1805–1812. [doi: 10.1093/cid/ciab159] [Medline: 33623985]
24. Llor C, Hernández S, Bayona C, Moragas A, Sierra N, Hernández M, et al. A study of adherence to antibiotic treatment in ambulatory respiratory infections. *Int J Infect Dis*. 2013;17(3):e168–72. [doi: 10.1016/j.ijid.2012.09.012] [Medline: 23116609]
25. Spellberg B, Rice LB. The shorter is better movement: past, present, future. *Clin Microbiol Infect*. 2023;29(2):141–142. [doi: 10.1016/j.cmi.2022.04.005] [Medline: 35436612]
26. Llor C, Frimodt-Møller N, Miravittles M, Kahlmeter G, Bjerrum L. Optimising antibiotic exposure by customising the duration of treatment for respiratory tract infections based on patient needs in primary care. *EClinicalMedicine*. 2024;74:102723. [doi: 10.1016/j.eclinm.2024.102723] [Medline: 39070175]
27. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med*. 2013;158(3):200–207. [doi: 10.7326/0003-4819-158-3-201302050-00583] [Medline: 23295957]
28. Woodhead M, Blasi F, Ewig S, Garau J, Huchon G, Ieven M, et al; Joint Taskforce of the European Respiratory Society and European Society for Clinical Microbiology and Infectious Diseases. Guidelines for the management of adult lower respiratory tract infections--summary. *Clin Microbiol Infect*. 2011;17(Suppl 6):1-24. [doi: 10.1111/j.1469-0691.2011.03602.x] [Medline: 21951384]
29. Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, Brook I, Kumar KA, Kramper M, et al. Clinical practice guideline (update): Adult Sinusitis Executive Summary. *Otolaryngol Head Neck Surg*. 2015;152(4):598-609. [doi: 10.1177/0194599815574247] [Medline: 25833927]
30. Patología infecciosa. (eds.) Martín Zurro A, Cano Pérez JF, Gené Badia J, Atención Primaria, Principios, organización y métodos en Medicina de Familia, Barcelona: Elsevier España, 2024; pp. 856–92.

31. Plan Nacional Resistencia Antibióticos (PRAN). Guía terapéutica antimicrobiana del SNS (salud humana). 2024. URL: <https://www.resistenciaantibioticos.es/es/guia-terapeutica-antimicrobiana-del-sns-salud-humana> [accessed 2025-04-03]
32. Llor C, Rodríguez-Bernuz C, Troncoso-Mariño A. Antibiotic use in Barcelona in 2023 in primary care and the potential reduction by adjusting box sizes to current guidelines. *Rev Esp Quimioter.* 2024;37(6):504–508. [doi: 10.37201/req/054.2024] [Medline: 39348221]
33. Melbye H, Hvidsten D, Holm A, Nordbø SA, Brox J. The course of C-reactive protein response in untreated upper respiratory tract infection. *Br J Gen Pract.* 2004;54(506):653–658. [Medline: 15353049]
34. Van Hecke O, Bjerrum L, Gentile I, Hopstaken R, Melbye H, Plate A, et al. Guidance on C-reactive protein point-of-care testing and complementary strategies to improve antibiotic prescribing for adults with lower respiratory tract infections in primary care. *Front Med (Lausanne).* 2023;10:1166742. [doi: 10.3389/fmed.2023.1166742] [Medline: 37324137]
35. Little P, Stuart B, Francis N, Douglas E, Tonkin-Crine S, Anthierens S, et al. Effects of internet-based training on antibiotic prescribing rates for acute respiratory-tract infections: a multinational, cluster, randomised, factorial, controlled trial. *Lancet.* 2013;382(9899):1175–1182. [doi: 10.1016/S0140-6736(13)60994-0] [Medline: 23915885]
36. 5-level EQ-5D version-QoL instrument, EQ-5D-5L, EuroQol. URL: <https://euroqol.org/information-and-support/euroqol-instruments/eq-5d-5l/> [accessed 2025-04-03]
37. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) – A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform.* 2009;42(2):377–381. [doi: 10.1016/j.jbi.2008.08.010] [Medline: 18929686]
38. Giacomini E, Perrone V, Alessandrini D, Paoli D, Nappi C, Esposti LD. Evidence of antibiotic resistance from population-based studies: A narrative review. *Infect Drug Resist.* 2021;14:849–848. [doi: 10.2147/IDR.S289741] [Medline: 33688220]
39. Kontopantelis E, Panagioti M, Farragher T, Munford LA, Parisi R, Planner C. Consultation patterns and frequent attenders in UK primary care from 2000 to 2019: a retrospective cohort analysis of consultation events across 845 general practices. *BMJ Open.* 2021;11(12):e054666. [doi: 10.1136/bmjopen-2021-054666] [Medline: 34930742]

40. Staszewska A, Zaki P, Lee J. Computerized Decision Aids for Shared Decision Making in Serious Illness: Systematic Review. *JMIR Med Inform.* 2017;5(4):e36. [doi: 10.2196/medinform.6405] [PMID: 28986341]
41. Borek AJ, Edwards G, Santillo M, Wanat M, Glogowska M, Butler CC, et al. Re-examining advice to complete antibiotic courses: a qualitative study with clinicians and patients. *BJGP Open.* 2023;7(2):BJGPO.2022.0170. [doi: 10.3399/BJGPO.2022.0170] [Medline: 36720563]



Table 1. Guidelines for prescribing antibiotics for respiratory tract infections in primary care in non- β lactam-allergic patients in Spain, based on the updated recommendation [30,31]_(to be

performed by the GP).

Diagnosis	When is it appropriate to prescribe antibiotics?	First choice antibiotic
Acute rhinosinusitis ¹	Do not administer, unless there are signs and symptoms that do not improve within 10 days, severe symptoms from day 3, or worsening of symptoms from day 5	Amoxicillin and clavulanate 875-125 mg/8 h/7 d or penicillin V 1,000 mg/8 h/7 d
Lower respiratory tract infection (non-COPD) ²	In acute bronchitis, antibiotics should not be given, except in specific situations. Always treat in pneumonia	Amoxicillin 1,000 mg/8 h/7 d or penicillin V 1.000 mg/8 h/7 d. Amoxicillin and clavulanate 875-125 mg/8 h/7 d if age >65 yr.
COPD exacerbation ³	Only if there is sputum purulence and in all very severe or very severe COPD exacerbations	Amoxicillin and clavulanate 875-125 mg/8 h/7 d

¹Refer to the hospital if persistent temp. >39°C, periorbital oedema, intense headache, neurological focal signs, signs of meningeal irritation, impaired consciousness, suspicion of orbital infection, or diplopia.

²Refer to the hospital if oxygen saturation <92%, significant alterations in chest X-ray, difficulties in complying with treatment at home, decompensation of underlying illness, lack of tolerance to oral treatment, immunosuppression, or CRB65 ≥1. Refer to the hospital if CRB65 >1 (confusion, respiratory rate ≥30 breaths/min, systolic blood pressure <90 mm Hg or diastolic blood pressure <60 mm Hg, age >65 years).

³Impaired consciousness, cyanosis, respiratory rate ≥30 breaths/min, severe dyspnea, oxygen therapy, inability to stay at home, or oxygen saturation <92%. COPD patients with FEV₁ <30% are excluded from this study.

VERY IMPORTANT:

The decision to prescribe an antibiotic is solely at the discretion of the participating GP. Regardless of whether the patient is assigned to the control or intervention group, the antibiotic should be the same, and the decision is always made before randomizing the patient. Refer to the provided guideline for recommended β -lactam therapy in various RTIs and instances when prescription is recommended. This guideline is designed to serve as a reference for making informed and improved

choices in prescribing. Consider antibiotic prescription in situations not covered by this guideline and feel free to choose different durations, doses, or antibiotics if you believe it is the best option for your patient. Only patients treated with β -lactams can participate in the trial. After prescribing the antibiotic, explaining the study to the patient, and obtaining informed consent, proceed to randomize the patient. Instruct patients in the intervention group to return for a clinical reassessment and CRP rapid testing as soon as they feel better.



Table 2. C-reactive protein rapid testing value interpretation [33,34]

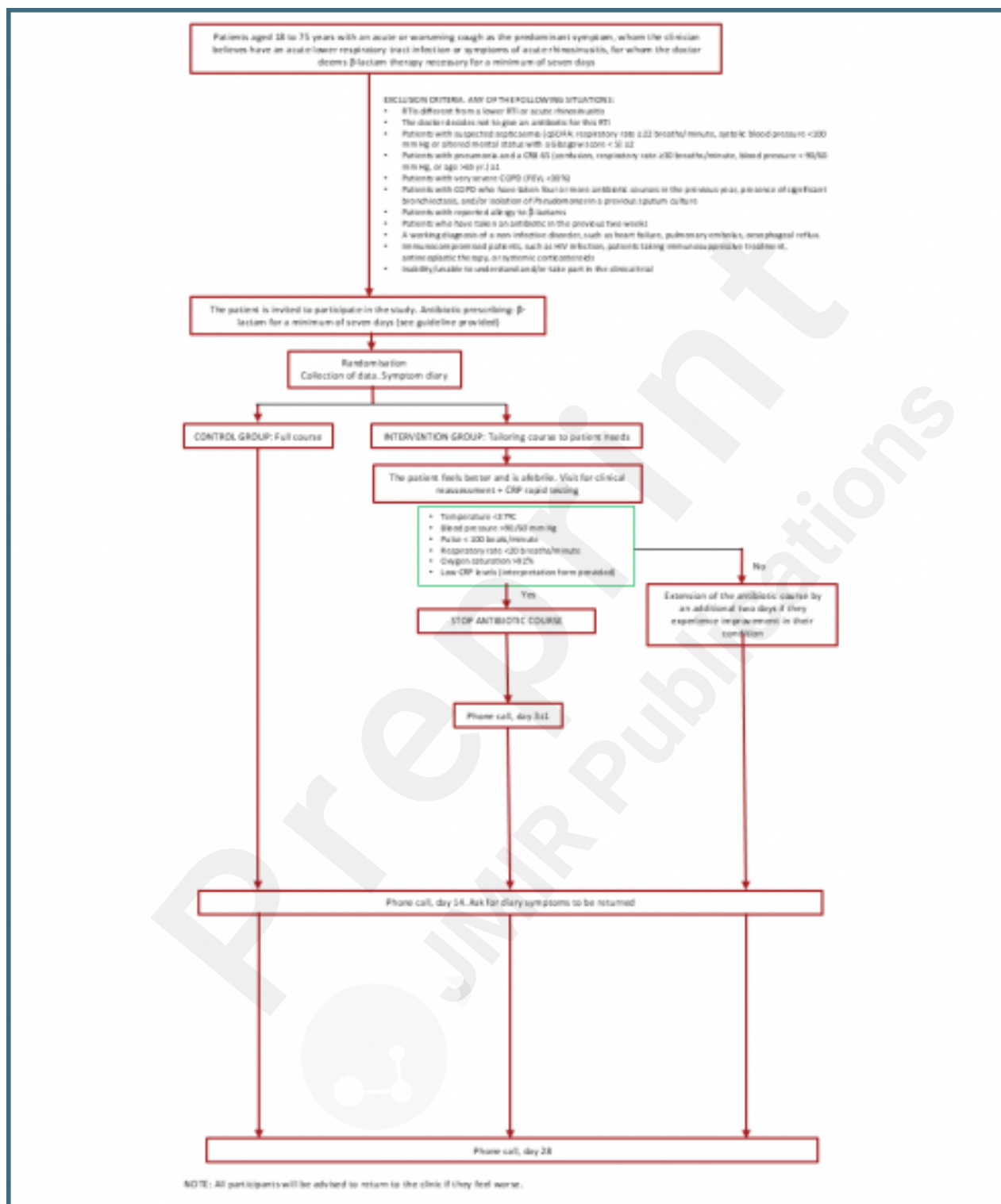
CRP value	Observations	Decision to stop the antibiotic course
<40 mg/l	Self-limiting infection, significant improvement, or cure	It is safe to stop the course of antibiotics.
40-100 mg/l	Consider other risk factors, age, signs, comorbidity and symptoms of the infection	It is safe to stop the course of antibiotics if the patient returns before day 5. Generally, it is safe to stop the course of antibiotics, unless there are significant comorbidities or advanced age, if the patient returns on day 5 or later. Do not stop the course in patients with COPD.
>100 mg/l	Reassess the patient. The doctor should reexamine the patient with RTI	Do not stop the course of antibiotics.

COPD=chronic obstructive pulmonary disease; CRP=C-reactive protein rapid; RTI=Respiratory tract infection

Supplementary Files

Figures

Study flowchart of the clinical trial.



Ascertainment of visits for the clinical trial.

Visits	V1	V2	V3	V4	V5
Type of visit	Face to face visit		Phone call		
Day	Day 0 (baseline visit)	From day 1* (interv.)	Day 3 (± 1 day)	Day 14	Day 28
Medical history	X	X			
Standard physical examination	X	X			
Eligibility criteria	X				
Informed consent	X				
Prescription of the antibiotic	X				
Randomization	X				
EQ-5D-5L questionnaire	X			X	X
Hand-out of the symptom diary	X				
C-reactive protein rapid testing		X			
Decision to stop antibiotic course		X			
Collection of the symptom diary		X		X	
Assessment of the clinical efficacy			X	X	
Assessment of the drug adherence		X	X	X	
Monitoring of adverse events			X	X	X
Complications, re-attendance			X	X	X

CRP=C-reactive protein rapid testing; EQ-5D-5L= 5-level EQ-5D version-Quality of Life instrument.

*As soon as the patient feels better, only for patients in the intervention group.

Multimedia Appendixes

Funded and reviewed by an independent body.

URL: <http://asset.jmir.pub/assets/120344eaaa9b92f48d5dcd8e50e6cfcb.pdf>



CONSORT (or other) checklists

SPIRIT Checklist.

URL: <http://asset.jmir.pub/assets/7ff2c41cd1ac72e84bd86bebe5543165.pdf>