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Title

The STOP-AB Trial protocol: Safety of discontinuing patient antibiotic treatment when physicians no longer consider it necessary.

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ABSTRACT

Introduction: Since 2011 the Spanish Society of Family Medicine has been recommending GPs to ask their patients to stop taking antibiotics when they suspect a viral infection. However, there is no evidence that discontinuing antibiotic therapy is safe. The main objective of this study is to determine whether discontinuation of antibiotic therapy when a GP no longer considers it necessary makes any difference in terms of the number of days with severe symptoms.

Methods and analysis: This is a multicentre, open-label, randomised controlled clinical trial. The study will be conducted in twenty primary care centres in Spain. We will include patients from 18 to 75 years of age with uncomplicated acute respiratory tract infections (RTIs) who have previously taken any dose of antibiotic but physicians no longer consider it necessary. The patients will be randomly assigned to the usual strategy of continuing antibiotic treatment (control group) or discontinuing antibiotic therapy (intervention group). A sample size of 215 patients per group was calculated on the basis of a reduction of one day in the duration of severe symptoms as a clinically relevant outcome. The primary outcome will be duration of severe symptoms, i.e. symptoms scored 5 or 6 by means of a symptom diary. Secondary outcomes will include: antibiotics taken, adverse events, patient satisfaction, and complications within the first 3 months. A post-trial observational study by means of a qualitative analysis is planned to be carried out after the clinical trial to know the percentage of the use of the strategy of discontinuing antibiotic treatment and the pros and cons of its use.

Ethics and dissemination: The study was approved by the Ethical Board of *Fundació Jordi Gol i Gurina* (reference number: 16/093). The findings of this trial will be disseminated through research conferences and peer-reviewed journals.

Trial registration number: NCT02900820.

Strengths and limitations of this study

- Some patients might not complete the symptom diaries. However, strategies to improve diary return rates will be implemented and non-respondents will be telephoned.
- Most patients will be diagnosed of rhinosinusitis, pharyngitis and bronchitis, limiting the inferences for patients with influenza and those with exacerbations of chronic bronchitis and mild-to-moderate COPD.
- It could be argued that the open nature of the study may cause a placebo effect favouring antibiotics. However, this effect will be minimised by the similar structured information all patients will receive about the self-limiting nature of respiratory tract infections and the advice about non-antibiotic medication use.
- Another possible limitation of this study is the fact that microbiological studies will not be taken into account. In primary care the response to treatment is mainly judged with clinical rather than microbiological criteria.
- The open design will allow us to study the perceptions of patients in a situation similarly to usual practice. The strengths of our study are its pragmatic design and that our study, as far as we know, is the first trial to assess if discontinuation of antibiotic therapy when a GP no longer considers it necessary makes any difference in terms of the number of days with severe symptoms in a randomised fashion.

BACKGROUND

Acute respiratory tract infections (RTIs) are among the most common reasons for a healthcare encounter in Western countries, accounting for about 15% of all visits [1]. Most episodes are caused by viruses, and in otherwise healthy adults these infections are typically self-limited and do not require a visit to a physician or a prescription medication. Nevertheless, many patients with uncomplicated, self-limited RTIs seek care in the primary care offices. A recent study found that 72% of the primary care visits due to an acute respiratory tract infection did not seem to require an office visit [2], subsequently increasing healthcare costs and often leading to inappropriate antibiotic prescription [3,4]. Very importantly, inappropriate overuse of antibiotic medications can be very detrimental and may lead to antibiotic resistance [5,6], which has a tremendous impact on the economy [7], and patients often experience adverse effects such as diarrhoea, thrush, nausea, urticaria, and rash, which give rise to further office visits and time off work. Despite being uncommon, patients might also experience serious complications such as anaphylaxis and *Clostridium difficile* infection [8]. In addition, medicalisation of a self-limited condition makes it more likely for patients to visit a healthcare provider the next time they have a similar episode [9].

General practitioners (GP) have always been told to continue an antibiotic regimen once the patient has initiated it in order to prevent the patient from acquiring resistant organisms. This might be true for confirmed bacterial infections. In fact, giving the right antibiotic at an adequate dose, along with good compliance with the daily regimen by the patient, i.e. taking the correct dose at the appropriate intervals, may be more important for treatment success than taking an antibiotic for a long period of time [10]. Prescribing an adequate dose of an antibiotic improves its clinical efficacy for a serious bacterial infection, with longer courses of antibiotics being associated with the greatest risk of antimicrobial resistance at both an individual and community level [11]. Some studies on carriage of antibiotic-resistant pneumococcal strains have shown that a high dose of antibiotic for a shorter duration results in less bacterial resistance than a lower dose for a longer duration [12,13]. Ideally, antibiotics should be dosed according to their pharmacokinetic and pharmacodynamic qualities to achieve the best clinical outcomes for the patient, as well as limiting the spread of antimicrobial resistance [14].

GPs very often visit patients with suspected viral infections, mainly of the upper and lower airways, for which antibiotic treatment makes no difference in terms of clinical outcomes.

Conversely, continuing an antibiotic regimen when this is not indicated might prompt the acquisition of resistant bugs and cause adverse events [15]. Therefore, stopping the antibiotic regimen once a previously suspected viral infection has been confirmed should be common practice. Since 2011 the Spanish Society of Family Medicine has been recommending GPs to ask their patients to stop taking antibiotics when they suspect a viral infection [16]. Despite this recommendation, GPs are reluctant and feel unsafe to discontinue an antibiotic once the patient has already started it. In fact, there is no evidence that discontinuing antibiotic therapy for these conditions is safe and studies demonstrating that this practice should be carried out are lacking. In Europe, the prescription for antibiotics differs between countries, and antibiotics are prescribed significantly more often in southern compared to northern Europe, with Spain being one of the countries with the highest consumption [17].

Discontinuing an antibiotic regimen could be carried out in the following situations:

Patients diagnosed with infectious diseases for which antibiotics are not necessary, i.e. an antibiotic course for an episode of common cold or influenza.

According to the World Health Organization, 80% of the RTIs in the community have a viral origin. Recent systematic reviews have suggested that antibiotics make no difference to the course of common cold and influenza when compared to placebo [18,19]. Despite having a viral aetiology, 2.2% of 12,373 episodes of common cold were treated with antibiotics in a large study including 340 GPs carried out in Spain [20]. This unnecessary antibiotic prescription might be mainly explained by uncertainty in the diagnosis and by GPs' perceptions regarding patient expectations for a prescription [21,22]. Data from the GRACE (Genomics to combat resistance against antibiotics in community-acquired lower respiratory tract infections in Europe) study clearly show that antibiotics are expected by 45% of the patients with lower RTIs [23].

Patients diagnosed with clinical conditions for which antibiotics might be necessary but according to the history and clinical examination the GP considers that antibiotics are not needed because of suspected viral origin or patients feel that the drug has not worked as expected and feel they need a clinical reassessment, i.e. an antibiotic regimen for a suspected rhinosinusitis.

Despite the fact that antibiotics might be required for some patients with uncomplicated acute pharyngitis, acute rhinosinusitis, and acute bronchitis, most of these infections are self-limiting and recent systematic reviews have suggested that antibiotics only slightly modify the course of most of these infections [24-27]. Even among patients with acute exacerbations of chronic obstructive pulmonary disease without purulent sputum, the benefit of antibiotics is controversial, both in the community and the hospital settings [28-30]. However, antibiotic prescription is very high in these four infectious diseases, and over 60% of adults presenting with RTIs receive an antibiotic; in addition, these antibiotics are increasingly broad-spectrum antimicrobial agents [31,32]. Even in Holland, the country with the lowest antibiotic consumption in Europe, 46% of the antibiotics prescribed for RTIs are not needed while in only 4% of the situations in which antibiotics are not prescribed they should have been recommended according to the Dutch guidelines [33].

Patients who have taken some doses of an antibiotic not prescribed by a health professional for an infectious disease for which antibiotics are not necessary, i.e. from leftovers found in the household or an antibiotic bought without prescription at the pharmacy.

The sale of antibiotics and other antimicrobial medicines without prescription remains widespread, with many countries lacking standard treatment guidelines and thereby increasing the potential for overuse of antimicrobial medicines by the public and medical professionals [34]. This practice is common outside Northern Europe and North America. The percentage of non-prescription access to antimicrobials is often underestimated, and also depends on the methodology used for making estimations. In 2016, the European Commission published a questionnaire-based study (Eurobarometer) which was carried out in 28 European countries, including 1,053 respondents in Spain. This study described that 6% of users reported to have obtained antibiotics in the previous year without prescription or stated that they used the leftovers from a previous course [35]. However, when more reliable methods are used to know how many individuals obtain antibiotics from sources other than their GPs these percentages clearly increase [36]. Self-medication with antimicrobials is also widespread, occurring among the population in the same countries where over-the-counter sale is available [37].

STUDY AIMS

The main objective of the present trial is to know if discontinuation of antibiotic therapy when a GP no longer considers it necessary makes any difference in terms of the number of days with severe symptoms.

Secondary objectives:

1. Assessment of the incidence of adverse effects of medication
2. Assessment of the antibiotic consumption
3. Assessment of the satisfaction with health care and belief of the effectiveness of antibiotics by the patients included
4. Assessment of the number of complications observed within the first 3 months

METHODS AND ANALYSIS

Study design

This will be a multicentre, open-label, randomised controlled clinical trial comparing two therapy strategies for uncomplicated acute RTIs. Patients will be randomly assigned to either the usual strategy of continuing antibiotic treatment (control group) or discontinuing antibiotic therapy (intervention group). The randomisation will be stratified by condition of interest - pharyngitis, rhinosinusitis (including common cold), acute bronchitis, acute exacerbations of chronic bronchitis or mild-to-moderate chronic obstructive pulmonary disease, and influenza -. General practitioners (GP) will randomise patients centrally using an electronic online platform. An open-label study has been designed given the type of the two strategies used and considering that an effect on their beliefs is expected. Neither patients nor health professionals will be blinded.

Eligibility criteria

Any patient from 18 to 75 years of age attending the GP consultation with an uncomplicated RTI who has previously taken any dose of antibiotic due to any of the following 3 clinical scenarios and accepts to participate in the clinical trial will be included:

- Patients diagnosed with clinical conditions for which antibiotics are not necessary

- Patients diagnosed with a clinical condition for which antibiotics might be necessary but according to the history and clinical examination the GP considers that antibiotics are not needed to be taken or the patients feel that the antibiotic regimen has not worked as expected and feel they need clinical reassessment
- Patients who have taken some doses of an antibiotic (from leftovers found in the household or obtained at the pharmacy without any medical prescription) for a clinical condition for which antibiotics are not necessary

Exclusion criteria

- Subjects under 18 and over 75 years of age
- Confirmed bacterial infection
- Patients requiring hospital admission
- Severe impairment of signs (impairment of consciousness, respiratory rate > 30 respirations per minute, heart rate > 125 beats per minute, systolic blood pressure < 90 mm Hg, diastolic blood pressure < 60 mm Hg, temperature > 40°C, oxygen saturation < 92%)
- Problems to comply with treatment at home – sociopathy or psychiatric problems, drug or alcohol addiction, or within an inadequate family setting –
- Lack of tolerance to oral treatment, such as the presence of nausea and vomiting, gastrectomy, post-surgery and/or diarrhoea
- Significant comorbidity including severe renal failure, hepatic cirrhosis, severe heart failure, immunosuppression – chronic HIV infection, transplantation, neutropenic, or patients receiving immunosuppressive drugs or corticosteroids –
- Terminal disease
- Patients admitted to a long-term residence
- Difficulty to attend the programmed visits
- Refusal to participate in the study

Outcome measures

The primary outcome measure will be the duration of severe symptoms. Each symptom will be scored using a six-point Likert scale and symptoms scoring 5 or 6 will be considered as severe. We will include common symptoms such as fever, discomfort or general pain, cough, difficulty in sleeping, and changes in everyday life in all patients, and specific symptoms according to the condition (Table 1) [38].

Secondary endpoints

- Adverse events of medication, reported by the patients
- Antibiotic consumption. Patients will be asked about the antibiotic use in the two arms
- Satisfaction with health care by means a questionnaire with a Likert scale to patients
- Belief in the effectiveness of antibiotics by means a questionnaire with a Likert scale to patients
- Complications related to the RTIs will be registered during the first 3 months after randomisation. These complications will be prospectively recorded by the GPs by means of a standardised questionnaire and will be reported in a maximum of 48 hours to the study clinical coordinator, who will report to the Safety and Data Monitoring Committee, whose aim is to assess the safety of the two strategies

Sample size calculation

Excellence guidelines for treatment of RTIs include estimates of average duration of the illness (before and after seeing a doctor) of one week for acute sore throat, one and a half weeks for rhinosinusitis, including common cold, and three weeks for acute cough or bronchitis [39]. In a recent study on the effectiveness of delayed prescribing strategies carried out in Spain the mean duration of severe symptoms in uncomplicated acute RTIs including pharyngitis, rhinosinusitis, acute bronchitis, and acute exacerbation of chronic bronchitis, among patients treated immediately with antibiotics was 3.6 days (standard deviation of 3.3) [38]. Considering a reduction of one day in the duration of severe symptoms as a clinically relevant outcome, with a bilateral approximation, a sample of 215 patients per group will be able to detect this difference with an alpha error of 5% and a power of 80% (beta =0.2) and considering 20% of losses.

In terms of the number of researchers to be included in this clinical trial, we anticipate that each researcher will include 10-12 patients in two years. Thus, we are planning to invite approximately 40 researchers from 20 different healthcare centres.

Data collection and ascertainment of visits

The patients will be randomised to one of the 2 treatment strategies. Baseline data will be collected in the clinic by the physician or with the help of the nursing staff. To standardize data collection, all of the participating healthcare professionals will be trained by the coordinating centre. The patients will receive information on the study and, if they are interested in participating, they will be provided with an informed consent form to read and sign. A maximum length of 15-20 minutes is expected for the interview and the introduction of the data. The study scheme and the visit program will be explained to the patient (Table 2).

After randomisation, information on the strategy to which they have been allocated will be given to the participants, and they will be informed as to the appropriate measures to take in case of worsening or no improvement of their condition. In addition, they will be given a diary with a validated questionnaire of symptoms for each condition, which they should complete while symptoms related to the respiratory condition are present. The degree of satisfaction or concern with different aspects of the therapy as well as the use of antibiotics will also be recorded in this diary.

Patients will be interviewed by telephone 2 or 3 days after their inclusion in the study. At this first follow-up visit, a worsening of the clinical situation of the patient will be evaluated to determine whether a change in the antibiotic treatment is necessary among patients in the intervention group or the antibiotic regimen should be continued in patients in the control group. We will provide the patients with the opportunity to ask questions and discuss any problems with diary completion. In addition, compliance and possible secondary effects of the treatment will be evaluated. The second follow-up visit will be scheduled at day 14-28 after inclusion and will depend on the infection involved at patient recruitment as established in the NICE guideline [39]. On this visit, the clinical evolution of the signs and symptoms will be evaluated and the need to change or continue the antibiotic treatment, respectively, in the case of worsening in the clinical manifestations will be determined. Symptom diaries will be collected on this visit. Participants who do not return their diary will be telephoned by the trial team in order to provide a reminder and enquire whether they need any assistance in

returning their diary or given the option of giving the information required over the phone (minimum data set). Possible secondary effects of the treatment will also be assessed. Patients will be asked to revisit again if symptoms continue or they present recurrence of the infection. On the last follow-up visit, scheduled at day 90, the recurrences or medical visits or hospital admissions due to the basal infectious disease will be reported.

Data analysis procedure

Characteristics of the study population will be described using frequencies for categorical variables and mean and standard deviation (SD) for quantitative variables. To compare the two strategies studied, we will use the Fisher's exact test for categorical variables and the t test for continuous variables. To compare the duration of symptoms across strategies, we will use the t test for continuous variables for each symptom, and a linear regression model per symptom, with symptom duration as the dependent variable, and both antibiotic consumption and symptom duration prior to the visit as the independent variables. The same approach will be performed to compare the severity of symptoms between the two strategies, but the dependent variable for each model will be symptom severity. The Chi-square test will be used to compare antibiotic consumption, satisfaction, percentage of adverse effects, and the appearance of complications between the intervention and control groups. The level of significance will be 5% (α=0.05).

Criteria for withdrawals will be the presence of a serious adverse event, an unsatisfactory therapeutic effect, protocol violation or withdrawal of informed consent. Patients will be able to choose to interrupt the medication any time during the course of the study. However, they will be followed in the same way as the other patients. Analyses will follow the intention-to-treat principle in such a way that any event in any patient will be included in the group to which the patient was randomised.

ETHICS AND DISSEMINATION

Each patient should give their written consent to participate in the study after being informed in intelligible language for him/her on the nature, scope and possible consequences of the trial. After consent is submitted, the patients will be randomised. Data confidentiality will be ensured at all times, as stated in the researcher's commitment sheet, as will compliance with

the current legislation regarding the protection of personal data. This is a clinical trial based on the outpatient setting, and neither patients nor researchers will receive any monetary compensation. From an ethical point of view, this is to certify that the objective of the study is relevant for primary care, the power of the study may be considered as reasonable, this is an original study, the risks which the participants may incur justify the study being carried out with a totally favourable benefit/risk quotient, and we ensure the external validity of the study to the primary care reality, with the inclusion and exclusion criteria clearly described. Vulnerable populations will not be participating in this study.

The trial has been registered with the National Institutes of Health (NIH) trial registry (NCT02900820). This protocol was presented in the last Conference of the Spanish Society of Family Medicine held in La Coruña in June 2016. A range of dissemination activities are planned at national and international conferences. We will publish the final report in an open access peer-review journal. A summary of the findings will be sent to the participating practices on completion of the STOP-AB study.

DISCUSSION

Overprescribing of antibiotics for RTIs is considerable in the Western countries. The results of this study will be applicable to patients diagnosed with clinical conditions for which antibiotics are not or might not be necessary. Few GPs in Spain ask patients to discontinue antibiotic therapy because of fear of possible worsening of symptoms and the appearance of complications even in cases of suspected viral infections. In other situations, GPs do not wish to contradict the decision made by other doctors because it might look unfair. If the results of this study do not find any difference between the two groups there will be no reason to withhold the discontinuation of an antibiotic regimen when a GP no longer considers it necessary. We believe that there is no risk – and every advantage – in stopping a course of an antibiotic immediately after a bacterial infection has been excluded or is unlikely, as Gilbert recently suggested [15]. The most obvious circumstances in which it is appropriate to stop antibiotics are when the antibiotics are initiated without certainty of what infection is being treated, if any treatable bacterial infection is present at all, and for infections that are almost always self-limiting, e.g. episodes of acute bronchitis. Patient expectation often plays a role in the decision to start antibiotic treatment in these cases.

A post-trial implementation observational clinical study is planned to be carried out after the clinical trial aimed at knowing the percentage of the use of the strategy of discontinuing antibiotic treatment by GPs, and the pros and cons of its use by means of face to face or telephone interviews to patients and GPs. These interviews will be audio recorded, transcribed and analysed using standard qualitative techniques such as framework analysis. This qualitative-based study will allow us to better identify the aspects of the physician-patient interview that should be highlighted when discontinuing an ongoing antibiotic regimen earlier than the agreed duration.

The impact of our trial is likely to be important since the evidence available in this field is still limited and adequately designed and conducted clinical trials are warranted to clarify the effectiveness of discontinuing antibiotic therapy in these cases. Similarly, the inclusion of most of the uncomplicated RTIs will increase the validity of the results. These characteristics make this study innovative and relevant to this field.

CONTRIBUTORS

CL, AM, JMC and CB were involved in the conception and design of the study. JFF, JMM, JR, IG, JA, JO, CS, JB and PR have made substantial contributions to conception and design. AM, JFF, JMM, JR, IG, JA, JO, CS, JB and PR will be involved in trial conduct and recruitment. CL drafted the manuscript and all authors read and approved the final manuscript.

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ETHICAL APPROVAL

The study was approved by the Primary Care Research and Ethics Committee of the *Jordi Gol i Gurina* Foundation, Barcelona, Spain (reference number, 16/093).

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Table 1. Symptom diary

For each symptom choose the degree of affectation in the last 24 hours, according to the following Table of codes:

Code	Explanation
0	Normal or does not upset me / does not hurt
1	Affectation is insignificant or affects me slightly / light pain
2	Mild or slightly significant affectation or affects me slightly or very little / moderate pain
3	Moderately significant affectation or affects me moderately / considerable pain
4	Significant affectation or affects me considerably / intense pain
5	Highly significant affectation or affects me highly significantly / very intense pain
6	Maximum affectation or affects me a great deal / unbearable pain

Pharyngitis: 9 symptoms were recorded daily: feeling of fever, headache, general discomfort or pain, cough, sore throat, difficulty swallowing (solids or liquids), runny nose, difficulty sleeping and difficulty with activities of daily living. Each symptom will be scored following a 0-6 scale.

Rhinosinusitis: 11 symptoms were recorded daily: feeling of fever, general discomfort or pain, headache, sudden pain in the face, pain in the face when touching, runny nose, nasal mucus colour, cough, sore throat, difficulty sleeping, and difficulty with activities of daily living. Each symptom (save for nasal mucus colour) will be scored from 0 to 6. In case of presence of nasal mucus colour, the colour will be assessed: transparent (T), light yellow clear (Y), green (V) or other (O).

Acute bronchitis: 9 symptoms were recorded daily: feeling of fever, general discomfort or pain, cough, expectoration or phlegm (mucus when coughing), shortness of breath (suffocation, fatigue), pain when breathing (chest pain), chest breath sounds, difficulty sleeping and difficulty with activities of daily living. Each symptom (save for expectoration

or phlegm) will be scored from 0 to 6. In case of expectoration or phlegm, their colour will be assessed: transparent (T), light yellow clear (Y), green (V) or other (O).

Exacerbation of chronic bronchitis or mild to moderate chronic obstructive pulmonary disease: 9 symptoms were recorded daily: feeling of fever, general discomfort or pain, cough, expectoration or phlegm (mucus when coughing), shortness of breath (suffocation, fatigue), pain when breathing (chest pain), chest breath sounds, difficulty sleeping and difficulty with daily life activities. Each symptom (except for expectoration or phlegm) will be scored from 0 to 6. In case of expectoration or phlegm, their colour will be assessed: transparent (T), light yellow clear (Y), green (V) or other (O).

Influenza: 15 symptoms were recorded daily: feeling of fever, runny nose, sore throat, headache, cough, shortness of breath (suffocation, fatigue), muscle pain, sweat or chills, diarrhoea, nausea or vomits, abdominal pain, dizziness, general discomfort or pain, difficulty sleeping, and difficulty with activities of daily living. Each symptom will be scored from 0 to 6.

Table 2. Visit schedule during the clinical trial

	Visit 1 Day 0	Visit 2* Day 2-3	Visit 3 Day 14-28**	Visit 4* Day 90
Medical history and physical examination	x		x	
Informed consent form	x			
Randomisation	x			
Giving out of symptom diaries	x			
Evaluation of clinical evolution		x	x	
Assessment of adverse events		x	x	
Collection of symptom diaries			x	
Reporting of recurrences, medical visits or hospital admissions due to the basal infection		x	x	x

*Phone call

**Depending on the infection (14 days for influenza and sore throat; 28 days for acute bronchitis, acute rhinosinusitis, and acute exacerbations of chronic bronchitis or mild-to-moderate chronic obstructive pulmonary disease). A further visit should be scheduled if symptoms persist on visit 3.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	___1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	___3,12_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____
Protocol version	3	Date and version identifier	____cover letter__
Funding	4	Sources and types of financial, material, and other support	____13_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	____1,13_____
	5b	Name and contact information for the trial sponsor	___14_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	____14_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	____N/A_____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-7
	6b	Explanation for choice of comparators	5-7
Objectives	7	Specific objectives or hypotheses	8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8,9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-11
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	11
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10,11
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10,11,table 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	9,10
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	10,11
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10,11

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10,11
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10,11
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	11
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	3,13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	8
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Not applicable
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	14
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	11,12
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

The STOP-AB Trial protocol: Efficacy and safety of discontinuing patient antibiotic treatment when physicians no longer consider it necessary.

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Title

The STOP-AB trial protocol: Efficacy and safety of discontinuing patient antibiotic treatment when physicians no longer consider it necessary.

Authors

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ABSTRACT

Introduction: Since 2011 the Spanish Society of Family Medicine has recommended general practitioners (GPs) to ask their patients to stop taking antibiotics when they suspect a viral infection. However, this practice is seldom used because there is no evidence that discontinuing antibiotic therapy is safe. The main objective of this study is to determine whether discontinuation of antibiotic therapy when a GP no longer considers it necessary makes any difference in terms of the number of days with severe symptoms.

Methods and analysis: This is a multicentre, open-label, randomised controlled clinical trial. The study will be conducted in ten primary care centres in Spain. We will include patients from 18 to 75 years of age with uncomplicated acute respiratory tract infections – acute rhinosinusitis, acute sore throat, influenza, or acute bronchitis – who have previously taken any dose of antibiotic for less than 3 days, but physicians no longer consider it necessary. The patients will be randomly assigned to the usual strategy of continuing antibiotic treatment or to discontinuing antibiotic therapy. A sample size of 240 patients per group was calculated on the basis of a reduction of one day in the duration of severe symptoms being a clinically relevant outcome. The primary outcome will be duration of severe symptoms, i.e. symptoms scored 5 or 6 by means of validated symptom diaries. Secondary outcomes will include: antibiotics taken, adverse events, patient satisfaction, and complications within the first 3 months.

Ethics and dissemination: The study was approved by the Ethical Board of *Fundació Jordi Gol i Gurina* (reference number: 16/093). The findings of this trial will be disseminated through research conferences and peer-reviewed journals.

Trial registration number: NCT02900820.

Strengths and limitations of this study

- The open design will allow us to study the perceptions of patients in a situation similar to usual practice. Apart from its pragmatic design our study will be the first trial to assess if discontinuation of antibiotic therapy when a GP no longer considers it necessary makes any difference in terms of the number of days with severe symptoms.
- Some patients might not complete the symptom diaries. However, strategies to improve diary return rates will be implemented and non-respondents will be telephoned.
- The open nature of the study may cause a placebo effect favouring antibiotics. However, this effect will be minimised by the similar structured information all patients will receive about the self-limiting nature of respiratory tract infections and advice about the use of non-antibiotic medications.
- This trial might be underpowered for the detection of differences between the two groups in terms of adverse events and complications within the first three months, since these outcomes are considered secondary endpoints in this study.
- Another possible limitation of this study is the fact that microbiological studies will not be taken into account. In primary care the response to treatment in respiratory tract infections is mainly judged by clinical rather than microbiological criteria.

BACKGROUND

Acute respiratory tract infections (RTIs) are among the most common reasons for a healthcare encounter in Western countries, accounting for about 15% of all visits [1]. Most episodes are caused by viruses, and in otherwise healthy adults these infections are typically self-limiting and do not require a visit to a physician or a prescription medication. Nevertheless, many patients with uncomplicated, self-limited RTIs seek care in primary care offices. A recent study found that 72% of primary care visits due to an acute respiratory tract infection did not seem to require an office visit [2], which subsequently increases healthcare costs and often leads to inappropriate antibiotic prescription [3,4]. Very importantly, inappropriate overuse of antibiotic medications can be very detrimental and may lead to antibiotic resistance [5,6], which has a tremendous impact on the economy [7], and patients often experience adverse effects such as diarrhoea, thrush, nausea, urticaria, and rash, which give rise to further office visits and time off work. Despite being uncommon, patients might also experience serious complications such as anaphylaxis and *Clostridium difficile* infection [8]. In addition, medicalisation of a self-limited condition makes it more likely for patients to visit a healthcare provider the next time they have a similar episode [9].

General practitioners (GP) have generally been told to continue an antibiotic regimen once the patient has initiated it in order to prevent the patient from acquiring resistant organisms. However, this dogma of completing an antibiotic regimen once initiated might not be associated with less antimicrobial resistance. Some studies have shown that short-course regimens can be as effective as longer courses of therapy, resulting in less emergence of antibiotic resistance, which is consistent with what we know about natural selection, the driver of antibiotic resistance [10-12]. The use of shorter therapies, defined as the taking of an antibiotic for 5 days or less, is commonly used by women with acute uncomplicated urinary tract infections. However, in other infections, such as community-acquired pneumonia, acute exacerbations of chronic obstructive pulmonary disease, acute bacterial sinusitis, cellulitis, and pyelonephritis, shorter regimens of 3 to 6 days, which have also been shown to be as effective as longer therapies, are seldom used by GPs [13].

This often-heard statement of completing an antibiotic course once initiated and the perceived need to treat beyond resolution of symptoms is usually driven by a desire to prevent worse outcomes and relapses. Giving the right antibiotic at an adequate dose, along with good compliance with the daily regimen by the patient (i.e. taking the correct dose at the

appropriate intervals), has been said to be the most important strategy for treatment success in bacterial infections [14]. However, GPs very often see patients with suspected viral infections of the upper and lower airways, for which antibiotic treatment makes little or no difference in terms of clinical outcomes and, conversely, can cause some side effects and might also prompt the acquisition of resistant organisms [15]. Despite this, GPs are reluctant and feel that it is unsafe to discontinue an antibiotic once the patient has already started it, mainly due to the ambiguity about the appropriateness of discontinuing medication felt by GPs, and in part because the clinical guidelines do not encourage discontinuation of medication, as they offer GPs a weak rationale for discontinuation [16]. Moreover, when it comes to acute infections, nobody wants to be seen as having withheld or discontinued antibiotic treatment from a patient who subsequently deteriorates, especially if the patient winds up in hospital [17].

Since 2011 the Spanish Society of Family Medicine has recommended GPs to ask their patients to stop taking antibiotics given by other clinicians when they suspect a viral infection [18]. Despite this recommendation, this strategy is seldom used in routine clinical practice. There is limited evidence about the efficacy and safety of continuing an antibiotic regimen if not needed, but concomitantly, evidence as to whether discontinuing antibiotic therapy for these conditions is safe is lacking, and studies demonstrating the safety of this practice should be carried out.

Discontinuing an antibiotic regimen could be undertaken in one of the following two situations:

1. *Patients diagnosed with infectious diseases for which antibiotics – prescribed by other physicians – are not necessary, i.e. an antibiotic course for suspected viral infections.*

According to the World Health Organization, 80% of the RTIs in the community have a viral origin. Most of these infections are self-limiting, and recent systematic reviews have suggested that antibiotics only slightly modify the course of most of these infections. A recent systematic review suggested that antibiotics do not improve the duration of symptoms in patients with common cold compared to those receving placebo [19]. Antibiotics are associated with modest benefits in sore throat; they reduce soreness and fever, the duration of symptoms, and the incidence of suppurative and non-suppurative complications compared to placebo mainly in patients with infection caused by group A β-haemolytic streptococcus [20].

This modest effect of antibiotics has also been observed in acute rhinosinusitis in which antibiotics can shorten the time to cure, but only five participants per 100 cure faster at any time point between one and two weeks if they receive antibiotics instead of placebo [21]. In acute bronchitis, no difference has been shown between antibiotic and placebo groups in terms of the percentage of patients described as achieving clinical improvement at follow-up [22]. However, the participants in all these clinical trials had a significantly greater risk of adverse effects with antibiotics than with placebo [23].

Despite the low percentage of bacterial infections, antibiotic prescription is very high in these infectious diseases, with over 60% of adults presenting with acute rhinosinusitis, acute bronchitis and acute sore throat receiving an antibiotic in Spain [24]. Antibiotic prescription in our country has increased over the last years and Spain now constitutes one of the leading countries in the world when it comes to the percentage of antibiotics prescribed [25,26]. This unnecessary antibiotic prescription in RTIs has also been seen in other affluent countries; in addition, these antibiotics are increasingly broad-spectrum antimicrobial agents [27,28]. Even in Holland, the country with the lowest antibiotic consumption in Europe, 46% of the antibiotics prescribed for RTIs are not needed while in only 4% of the situations in which antibiotics are not prescribed they should have been recommended according to the Dutch guidelines [29]. This unnecessary antibiotic prescription might mainly be explained by uncertainty in the diagnosis and by GPs' perceptions regarding patient expectations for a prescription [30,31]. Data from the GRACE (Genomics to combat resistance against antibiotics in community-acquired lower respiratory tract infections in Europe) study clearly show that antibiotics are expected by 45% of the patients with lower RTIs [32].

2. *Patients who have taken several doses of an antibiotic not prescribed by a health professional for an infectious disease for which antibiotics are not necessary, i.e. from leftovers found in the household or an antibiotic bought without prescription at the pharmacy.*

The sale of antibiotics and other antimicrobial medicines without a prescription remains widespread, with many countries lacking standard treatment guidelines, thereby increasing the potential for overuse of antimicrobial medicines by the public and medical professionals [33]. This practice is common outside Northern Europe and North America. The percentage of non-prescription access to antimicrobials is often underestimated and also depends on the

methodology used for making estimations. In 2016, the European Commission published a questionnaire-based study (Eurobarometer) which was carried out in 28 European countries, including 1,053 respondents in Spain. This study described that 6% of users reported having obtained antibiotics in the previous year without a prescription or stated that they had used the leftovers from a previous course [34]. However, when more reliable methods are used to know how many individuals obtain antibiotics from sources other than their GPs, these percentages clearly increase [35]. Self-medication with antimicrobials is also widespread, occurring among the population in the same countries in which over-the-counter sales are available [36].

STUDY AIMS

The main objective of the present trial is to know if the discontinuation of antibiotic therapy when a GP no longer considers it necessary makes any difference in terms of the number of days with severe symptoms.

Secondary objectives:

1. Assessment of the incidence of adverse effects of medication.
2. Assessment of antibiotic consumption.
3. Assessment of the satisfaction with healthcare and belief in the effectiveness of antibiotics by the patients included.
4. Assessment of the number of complications observed within the first 3 months.

METHODS AND ANALYSIS

Study design

This will be a multicentre, open-label, randomised controlled clinical trial comparing two therapeutic strategies for uncomplicated acute RTIs. Patients will be randomly assigned to either the usual strategy of continuing antibiotic treatment or discontinuing antibiotic therapy. The randomisation will be stratified by condition of interest – acute sore throat, rhinosinusitis (including common cold), acute bronchitis, and influenza -. GPs will randomise patients using a centralised electronic online platform. An open-label study has been designed given

the type of the two strategies used and considering that an effect on their beliefs is expected. Neither patients nor health professionals will be blinded.

Eligibility criteria

Any patient from 18 to 75 years of age attending the GP consultation with an uncomplicated RTI who has previously taken any dose of antibiotic for less than three days due to either of the 2 following clinical scenarios and accepts to participate in the clinical trial will be included:

- Patients diagnosed with clinical conditions for which antibiotics prescribed by other health professionals are not necessary.
- Patients who have taken several doses of an antibiotic (from leftovers found in the household or obtained at the pharmacy without a medical prescription) for a clinical condition for which an antibiotic is not necessary.

Exclusion criteria

- Subjects under 18 or over 75 years of age.
- Confirmed bacterial infection.
- Patients requiring hospital admission.
- Severe impairment of clinical signs of infection (impairment of consciousness, respiratory rate > 30 respirations per minute, heart rate > 125 beats per minute, systolic blood pressure < 90 mm Hg, diastolic blood pressure < 60 mm Hg, temperature > 40°C, oxygen saturation < 92%).
- Problems to comply with treatment at home, such as sociopathy or psychiatric problems, or drug or alcohol addiction.
- Lack of tolerance to oral treatment, such as the presence of nausea and vomiting, gastrectomy, post-surgery and/or diarrhoea.
- Significant comorbidity including severe renal failure, hepatic cirrhosis, severe heart failure, immunosuppression – chronic HIV infection, transplantation, neutropenia, or patients receiving immunosuppressive drugs or corticosteroids.
- Terminal disease, defined as a life expectancy less than 12 months.

- Patients admitted to a long-term residence.
- Patients who state that they are unable to see their doctor at the practice office.
- Refusal to participate in the study.

Outcome measures

The primary outcome measure will be the duration of severe symptoms. Each symptom will be scored using a six-point Likert scale and symptoms scoring 5 or 6 will be considered as severe. We will include common symptoms such as fever, discomfort or general pain, cough, difficulty in sleeping, and changes in everyday life in all patients, and specific symptoms according to the condition (Table 1) [37].

Secondary endpoints

- Adverse events of the medication given for this infection reported by the patients.
- Antibiotic consumption. Patients will be asked about antibiotic use in the two study arms.
- Patient satisfaction with healthcare by means of a questionnaire with a Likert scale.
- Patient belief in the effectiveness of antibiotics by means of a questionnaire with a Likert scale.
- Complications related to the RTIs will be registered during the first 3 months after randomisation. As in the recent study of Gulliford et al, we will consider the cases of pneumonia, empyema, peritonsillar abscess, mastoiditis, otitis media, bacterial meningitis, and intracranial abscess [38]. These complications will be prospectively recorded by the GPs by means of a standardised questionnaire and will be reported within a maximum of 48 hours to the study clinical coordinator, who will report to the Safety and Data Monitoring Committee which will assess the safety of the two strategies.

Sample size calculation

Excellence guidelines for treatment of RTIs include estimates of average duration of the illness (before and after seeing a doctor) of one week for acute sore throat, one and a half weeks for rhinosinusitis, including common cold, and three weeks for acute cough or bronchitis [39]. In a recent study on the effectiveness of delayed prescribing strategies carried

out in Spain, the mean duration of severe symptoms in uncomplicated acute RTIs including acute sore throat, rhinosinusitis, and acute bronchitis, among patients not treated with antibiotics was 4.7 days (standard deviation of 3.6) [37]. Considering a reduction of one day in the duration of severe symptoms as a clinically relevant outcome, with a bilateral approximation, a sample of 240 patients per group will be able to detect this difference with an alpha error of 5% and a power of 80% (beta =0.2), considering 15% of losses (based on the percentage of patients who did not return symptom diaries in a previous study) [37]. In terms of the number of investigators to be included in this clinical trial, we anticipate that over a two-year period each GP will include 32 patients. Thus, we are planning to invite 15 GPs from 10 different healthcare centres.

Data collection and ascertainment of visits

The patients will be randomised to one of the 2 treatment strategies. Baseline data will be collected in the clinic by the physician or with the help of the nursing staff. To standardize data collection, all of the participating healthcare professionals will be trained by the coordinating centre. Only experienced GPs (those working for more than 15 years) and those who feel comfortable with the design of the study will participate in the study. This will be achieved by the administration of a questionnaire with clinical questions, recommendations of local guidelines and vignettes to check if they are confident and comfortable with the strategy of stopping an already commenced antibiotic course. The patients will receive information on the study and, if they are interested in participating, they will be provided with an informed consent form to read and sign. A maximum length of 15-20 minutes is expected for the interview and the introduction of the data. The study scheme and the visit programme will be explained to the patient (Table 2).

On the basal visit, GPs will collect information about the type of diagnoses, prior time elapsed with symptoms, number of days taking an antibiotic, and type of antibiotic taken. Patients who made the decision to take an antibiotic by themselves (either purchased at the pharmacy or taken from leftovers stored at home) and are assigned to the usual strategy of continuing antibiotic treatment will be provided with a medical prescription of the same antibiotic until completing the recommended therapy duration according to local guidelines, even if the antibiotic is not first-line treatment.

After randomisation, information on the strategy to which they have been allocated will be given to the participants, and they will be informed as to the appropriate measures to take in case their condition worsens or there is no improvement. In addition, they will be given a diary with a validated questionnaire of symptoms for each condition, which they should complete while symptoms related to the respiratory condition are present. The degree of satisfaction or concern with different aspects of the therapy as well as the use of antibiotics will also be recorded in this diary.

Patients will be interviewed by telephone 2 or 3 days after their inclusion in the study. At this first follow-up visit, a worsening of the clinical situation of the patient will be evaluated to determine whether antibiotic treatment is necessary among patients in the group assigned to discontinuation (first-line antibiotics will be recommended in this case) or whether the antibiotic regimen should be continued or changed to the first-line drug in patients in the group allocated to continuation. We will provide the patients with the opportunity to ask questions and discuss any problems with diary completion. In addition, compliance and possible secondary effects of the treatment will be evaluated. The second follow-up visit will be scheduled at 14-28 days after inclusion and will depend on the infection involved at patient recruitment as established in the NICE guidelines [39]. On this visit, the clinical evolution of the signs and symptoms will be evaluated and the need to change or continue the antibiotic treatment, respectively, in the case of worsening of the clinical manifestations will be determined. The symptom diaries will be collected on this visit. Participants who do not return their diary will be telephoned by the trial team in order to provide a reminder and enquire whether they need any assistance in returning their diary. Possible secondary effects of the treatment will also be assessed. Patients will be asked to revisit if symptoms continue or they present recurrence of the infection. On the last follow-up visit, scheduled at day 90, recurrences, medical visits or hospital admissions due to the basal infectious disease will be reported.

Data analysis procedure

Characteristics of the study population will be described using frequencies for categorical variables and mean and standard deviation (SD) for quantitative variables. To compare the two strategies studied, we will use the t test for continuous variables. To compare the duration of symptoms across strategies, we will use the t test for continuous variables for

each symptom, and a linear regression model per symptom, with symptom duration as the dependent variable, and both antibiotic consumption and symptom duration prior to the visit as the independent variables. The same approach will be performed to compare the severity of symptoms between the two strategies, but the dependent variable for each model will be symptom severity. The Chi-square test will be used to compare antibiotic consumption, satisfaction, percentage of adverse effects, and the appearance of complications between the two groups. The level of significance will be 5% (α=0.05).

Criteria for withdrawals will be evidence of protocol violation, withdrawal of informed consent or a serious adverse event, defined as any untoward medical circumstance that results in death, is life-threatening, requires inpatient hospitalisation or prolongs existing hospitalisation, results in persistent or significant disability/incapacity, or requires intervention to prevent permanent impairment or damage. Patients will be able to choose to interrupt the medication at any time during the course of the study. However, they will be followed in the same way as the other patients. Analyses will follow the intention-to-treat principle.

ETHICS AND DISSEMINATION

Each patient should provide written consent to participate in the study after being informed in intelligible language for him/her on the nature, scope and possible consequences of the trial. After consent is submitted, the patients will be randomised. Data confidentiality will be ensured at all times, as stated in the researcher's commitment sheet, as will compliance with the current legislation regarding the protection of personal data. This is a clinical trial based on the outpatient setting, and neither patients nor researchers will receive any monetary compensation. From an ethical point of view, this is to certify that the objective of the study is relevant for primary care, the power of the study may be considered as reasonable, this is an original study, the risks which the participants may incur justify the study being carried out with a totally favourable benefit/risk quotient, and we ensure the external validity of the study to the primary care reality, with clearly described inclusion and exclusion criteria. Vulnerable populations will not participate in this study.

The trial has been registered with the National Institutes of Health (NIH) trial registry (NCT02900820). This protocol was presented in the last Conference of the Spanish Society of Family Medicine held in La Coruña in June 2016. A range of dissemination activities are

planned at national and international conferences. We will publish the final report in an open access peer-review journal. A summary of the findings will be sent to the participating practices on completion of the STOP-AB study.

DISCUSSION

Overprescribing of antibiotics for RTIs is considerable in Western countries. The results of this study will be applicable to patients diagnosed with clinical conditions for which antibiotics are not or might not be necessary. Few GPs ask patients to discontinue antibiotic therapy because of fear of possible worsening of symptoms and the appearance of complications even in cases of suspected viral infections. Guidelines usually provide dominating triggers for prescribing and weak priming for discontinuation. In other situations, GPs do not wish to contradict the decision made by other doctors because it might look unfair. If the results of this study do not find any difference between the two groups, there will be no reason to continue an antibiotic regimen when a GP no longer considers it necessary. We believe that there is no risk – and every advantage – in stopping a course of an antibiotic immediately after a bacterial infection has been excluded or is unlikely, as Gilbert recently suggested [15]. The most obvious circumstances in which it is appropriate to stop antibiotics are when the antibiotics are initiated without certainty of what infection is being treated, if any treatable bacterial infection is present at all, and for infections that are almost always self-limiting, e.g. episodes of acute bronchitis. Patient expectation often plays a role in the decision to start antibiotic treatment in these cases.

The impact of our trial is likely to be important since the evidence available in this field is still limited, and adequately designed and conducted clinical trials are warranted to clarify the efficacy and safety of discontinuing antibiotic therapy in these cases. Similarly, the inclusion of most of the uncomplicated RTIs and the fact that only patients with less than three days of antibiotic therapy will be invited to participate will increase the validity of the results. These characteristics make this study innovative and relevant to this field.

CONTRIBUTORS

CL, AM, JMC and CB were involved in the conception and design of the study. JFF, JMM, JR, IG, JA, JO, CS, JB and PR have made substantial contributions to conception and design.

AM, JFF, JMM, JR, IG, JA, JO, CS, JB and PR will be involved in carrying out the trial and recruitment. CL drafted the manuscript and all authors read and approved the final manuscript.

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ETHICAL APPROVAL

The study was approved by the Primary Care Research and Ethics Committee of the *Jordi Gol i Gurina* Foundation, Barcelona, Spain (reference number, 16/093).

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Table 1. Symptom diary

For each symptom choose the degree of affectation in the last 24 hours, according to the following Table of Codes:

Code	Explanation
0	Normal / does not hurt
1	Affectation is insignificant / mild pain
2	Mild or slightly significant affectation / moderate pain
3	Moderately significant affectation / considerable pain
4	Significant affectation / intense pain
5	Highly significant affectation / very intense pain
6	Maximum affectation / unbearable pain

Acute sore throat: 9 symptoms will be recorded daily: feeling of fever, headache, general discomfort or pain, cough, sore throat, difficulty swallowing (solids or liquids), runny nose, difficulty sleeping and difficulty in carrying out daily life activities. Each symptom will be scored following a 0-6 scale.

Rhinosinusitis: 11 symptoms will be recorded daily: feeling of fever, general discomfort or pain, headache, sudden pain in the face, pain in the face on touching, runny nose, nasal mucus colour, cough, sore throat, difficulty sleeping, and difficulty in carrying out daily life activities. Each symptom (save for nasal mucus colour) will be scored from 0 to 6. In the case of the presence of nasal mucus colour, the colour will be assessed: transparent (T), light yellow clear (Y), green (V) or other (O).

Acute bronchitis: 9 symptoms will be recorded daily: feeling of fever, general discomfort or pain, cough, expectoration or phlegm (mucus when coughing), shortness of breath (suffocation, fatigue), pain when breathing (chest pain), chest breathing sounds, difficulty sleeping and difficulty in carrying out daily life activities. Each symptom (save for expectoration or phlegm) will be scored from 0 to 6. In the case of expectoration or phlegm, the colour will be assessed: transparent (T), light yellow clear (Y), green (V) or other (O).

Influenza: 15 symptoms will be recorded daily: feeling of fever, runny nose, sore throat, headache, cough, shortness of breath (suffocation, fatigue), muscle pain, sweat or chills, diarrhoea, nausea or vomiting, abdominal pain, dizziness, general discomfort or pain, difficulty sleeping, and difficulty in carrying out daily life activities. Each symptom will be scored from 0 to 6.

Table 2. Visit schedule during the clinical trial

	Visit 1 Day 0	Visit 2* Day 2-3	Visit 3 Day 14-28**	Visit 4* Day 90
Medical history and physical examination	x		x	
Informed consent form	x			
Randomisation	x			
Giving out of symptom diaries	x			
Evaluation of clinical evolution		x	x	
Assessment of adverse events		x	x	
Collection of symptom diaries			x	
Reporting of recurrences, medical visits or hospital admissions due to the basal infection		x	x	x

*Phone call

**Depending on the infection (14 days for influenza and sore throat; 28 days for acute bronchitis, and acute rhinosinusitis). A further visit should be scheduled if symptoms persist on visit 3.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	___1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	___3,13_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____
Protocol version	3	Date and version identifier	____cover letter__
Funding	4	Sources and types of financial, material, and other support	____15_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	____1,14,15_____
	5b	Name and contact information for the trial sponsor	___15_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	____15_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	____N/A_____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-8
	6b	Explanation for choice of comparators	5-8
Objectives	7	Specific objectives or hypotheses	8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8,9
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9,10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	12
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11,12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11,12,table 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10,11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8,9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11,12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11,12

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11,12
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11,12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	3,13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Not applicable
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13,14
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

The STOP-AB Trial protocol: Efficacy and safety of discontinuing patient antibiotic treatment when physicians no longer consider it necessary.

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Title

The STOP-AB trial protocol: Efficacy and safety of discontinuing patient antibiotic treatment when physicians no longer consider it necessary.

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ABSTRACT

Introduction: Since 2011 the Spanish Society of Family Medicine has recommended general practitioners (GPs) to ask their patients to stop taking antibiotics when they suspect a viral infection. However, this practice is seldom used because uncertainty about diagnosis, and fear of consequences of discontinuing antibiotic therapy, as well as perceived pressure to continue prescribing antibiotics and potential conflict with patients are more of a concern for GPs than antibiotic resistance. The main objective of this study is to determine whether discontinuation of antibiotic therapy when a GP no longer considers it necessary has any impact on the number of days with severe symptoms.

Methods and analysis: This is a multicentre, open-label, randomised controlled clinical trial. The study will be conducted in ten primary care centres in Spain. We will include patients from 18 to 75 years of age with uncomplicated acute respiratory tract infections – acute rhinosinusitis, acute sore throat, influenza, or acute bronchitis – who have previously taken any dose of antibiotic for less than 3 days, which physicians no longer consider necessary. The patients will be randomly assigned to the usual strategy of continuing antibiotic treatment or to discontinuing antibiotic therapy. A sample size of 240 patients per group was calculated on the basis of a reduction of one day in the duration of severe symptoms being a clinically relevant outcome. The primary outcome will be the duration of severe symptoms, i.e. symptoms scored 5 or 6 by means of validated symptom diaries. Secondary outcomes will include: antibiotics taken, adverse events, patient satisfaction, and complications within the first 3 months.

Ethics and dissemination: The study was approved by the Ethical Board of *Fundació Jordi Gol i Gurina* (reference number: 16/093). The findings of this trial will be disseminated through research conferences and peer-reviewed journals.

Trial registration number: NCT02900820.

Strengths and limitations of this study

- The open design of this study will allow us to study the perceptions of patients in a situation similar to that of usual practice. Apart from its pragmatic design our study will be the first trial to assess if discontinuation of antibiotic therapy when a GP no longer considers it necessary has any impact on the number of days with severe symptoms.
- Some patients might not complete the symptom diaries. However, strategies to improve diary return rates will be implemented and reminder telephone calls will be made to non-respondents.
- The open nature of the study may cause a placebo effect favouring antibiotics. However, this effect will be minimised by the similar structured information all patients will receive about the self-limiting nature of respiratory tract infections and advice about the use of non-antibiotic medications.
- This trial might be underpowered for the detection of differences between the two groups in terms of adverse events and complications within the first three months, since these outcomes are considered secondary endpoints in this study.
- Another possible limitation of this study is the fact that microbiological studies will not be taken into account. In primary care the response to treatment in respiratory tract infections is mainly judged by clinical rather than microbiological criteria.

BACKGROUND

Acute respiratory tract infections (RTIs) are among the most common reasons for a healthcare encounter in Western countries, accounting for about 15% of all visits [1]. Most episodes are caused by viruses, and in otherwise healthy adults these infections are typically self-limiting and do not require a visit to a physician or a prescription medication. Nevertheless, many patients with uncomplicated, self-limited RTIs seek care in primary care offices. A recent study found that 72% of primary care visits due to an acute respiratory tract infection did not seem to require an office visit [2], which subsequently increases healthcare costs and often leads to inappropriate antibiotic prescription [3,4]. Very importantly, inappropriate overuse of antibiotic medications can be very detrimental and may lead to antibiotic resistance [5,6], which has a tremendous impact on the economy [7], and patients often experience adverse effects such as diarrhoea, thrush, nausea, urticaria, and rash, which give rise to further office visits and time off work. Despite being uncommon, patients might also experience serious complications such as anaphylaxis and *Clostridium difficile* infection [8]. In addition, medicalisation of a self-limited condition makes it more likely for patients to visit a healthcare provider the next time they have a similar episode [9].

General practitioners (GP) have generally been told to continue an antibiotic regimen once the patient has initiated it in order to prevent the patient from acquiring resistant organisms. However, this dogma of completing an antibiotic regimen once initiated might not be associated with less antimicrobial resistance. Some studies have shown that short-course regimens can be as effective as longer courses of therapy, resulting in less emergence of antibiotic resistance, which is consistent with what we know about natural selection, the driver of antibiotic resistance [10-12]. The use of shorter therapies, defined as the taking of an antibiotic for 5 days or less, is commonly used for uncomplicated urinary tract infections. Short course regimens – from 3 to 5 days – have also shown to be as effective as longer therapies in community-acquired pneumonia, acute bacterial sinusitis and acute exacerbations of chronic obstructive pulmonary disease but are seldom used by GPs [13]. When it comes to pneumonia, despite the efforts of infectious committees and guidelines developed by different societies, the duration of antibiotic use is still a major issue for which there is a lack of adherence both in primary and secondary care worldwide [14].

This often-heard statement of completing an antibiotic course once initiated and the perceived need to treat beyond resolution of symptoms is usually driven by a desire to prevent worse

outcomes and relapses. Giving the right antibiotic at an adequate dose, along with good compliance with the daily regimen by the patient (i.e. taking the correct dose at the appropriate intervals), has been said to be the most important strategy for treatment success in bacterial infections [15]. However, GPs very often see patients with suspected viral infections of the upper and lower airways, for which antibiotic treatment makes little or no difference in terms of clinical outcomes and, conversely, can cause some side effects and might also prompt the acquisition of resistant organisms [16].

Since 2011 the Spanish Society of Family Medicine has recommended GPs to ask their patients to stop taking antibiotics given by other clinicians when they suspect a viral infection [17]. Despite this recommendation, this strategy is seldom used in routine clinical practice. GPs are reluctant and feel that it is unsafe to discontinue an antibiotic once the patient has already started it, mainly due to the ambiguity about the appropriateness of discontinuing medication felt by GPs, and in part because the clinical guidelines do not encourage discontinuation of medication, as they offer GPs a weak rationale for discontinuation [18]. In addition, some studies have also shown that other issues such as uncertainty about diagnosis, ease of follow-up and fear of consequences of non-prescribing, as well as perceived pressure to prescribe and potential conflict with patients which might lead to consequences for the future doctor–patient relationship are more of a concern for GPs continuing to prescribe antibiotics than antibiotic resistance [19]. When it comes to acute infections, GPs might feel uncomfortable to discontinue antibiotic therapy from a patient who subsequently deteriorates, especially if the patient needs to be admitted to hospital [20]. There is limited evidence about the efficacy and safety of continuing an antibiotic regimen if not needed, but concomitantly, evidence as to whether discontinuing antibiotic therapy for these conditions is safe is lacking, and studies demonstrating the safety of this practice should be carried out.

Discontinuing an antibiotic regimen could be undertaken in one of the following two situations:

1. *Patients diagnosed with infectious diseases for which antibiotics – prescribed by other physicians – are not necessary, i.e. an antibiotic course for suspected viral infections.*

According to the World Health Organization, 80% of the RTIs in the community have a viral origin. Most of these infections are self-limiting, and recent systematic reviews have suggested that antibiotics only slightly modify the course of most of these infections. A

recent systematic review suggested that antibiotics do not improve the duration of symptoms in patients with common cold compared to those receving placebo [21]. Antibiotics are associated with modest benefits in sore throat; they reduce soreness and fever, the duration of symptoms, and the incidence of suppurative and non-suppurative complications compared to placebo mainly in patients with infection caused by group A β-haemolytic streptococcus [22]. This modest effect of antibiotics has also been observed in acute rhinosinusitis in which antibiotics can shorten the time to cure, but only five participants per 100 cure faster at any time point between one and two weeks if they receive antibiotics instead of placebo [23]. In acute bronchitis, no difference has been shown between antibiotic and placebo groups in terms of the percentage of patients described as achieving clinical improvement at follow-up [24]. However, the participants in all these clinical trials had a significantly greater risk of adverse effects with antibiotics than with placebo [25].

Despite the low percentage of bacterial infections, antibiotic prescription is very high in these infectious diseases, with over 60% of adults presenting with acute rhinosinusitis, acute bronchitis and acute sore throat receiving an antibiotic in Spain [26]. Antibiotic prescription in our country has increased over the last years and Spain now constitutes one of the leading countries in the world when it comes to the percentage of antibiotics prescribed [27,28]. This unnecessary antibiotic prescription in RTIs has also been seen in other affluent countries; in addition, these antibiotics are increasingly broad-spectrum antimicrobial agents [29,30]. Even in Holland, the country with the lowest antibiotic consumption in Europe, 46% of the antibiotics prescribed for RTIs are not needed while in only 4% of the situations in which antibiotics are not prescribed they should have been recommended according to the Dutch guidelines [31]. This unnecessary antibiotic prescription might mainly be explained by uncertainty in the diagnosis and by GPs' perceptions regarding patient expectations for a prescription [32,33]. Data from the GRACE (Genomics to combat resistance against antibiotics in community-acquired lower respiratory tract infections in Europe) study clearly show that antibiotics are expected by 45% of the patients with lower RTIs [34].

2. *Patients who have taken several doses of an antibiotic not prescribed by a health professional for an infectious disease for which antibiotics are not necessary, i.e. from leftovers found in the household or an antibiotic bought without prescription at the pharmacy.*

The sale of antibiotics and other antimicrobial medicines without a prescription remains widespread, with many countries lacking standard treatment guidelines, thereby increasing the potential for overuse of antimicrobial medicines by the public and medical professionals [35]. This practice is common outside Northern Europe and North America. The percentage of non-prescription access to antimicrobials is often underestimated and also depends on the methodology used for making estimations. In 2016, the European Commission published a questionnaire-based study (Eurobarometer) which was carried out in 28 European countries, including 1,053 respondents in Spain. This study described that 6% of users reported having obtained antibiotics in the previous year without a prescription or stated that they had used the leftovers from a previous course [36]. However, when more reliable methods are used to know how many individuals obtain antibiotics from sources other than their GPs, these percentages clearly increase [37]. Self-medication with antimicrobials is also widespread, occurring among the population in the same countries in which over-the-counter sales are available [38].

STUDY AIMS

The main objective of the present trial is to know if the discontinuation of antibiotic therapy when a GP no longer considers it necessary has any impact on the number of days with severe symptoms.

Secondary objectives:

1. Assessment of the incidence of adverse effects.
2. Assessment of antibiotic consumption.
3. Assessment of the satisfaction with healthcare and belief in the effectiveness of antibiotics by the patients included.
4. Assessment of the number of complications observed within the first 3 months.

METHODS AND ANALYSIS

Study design

This will be a multicentre, open-label, randomised controlled clinical trial comparing two therapeutic strategies for uncomplicated acute RTIs. Patients will be randomly assigned to

either the usual strategy of continuing antibiotic treatment or discontinuing antibiotic therapy. The randomisation will be stratified by condition of interest – acute sore throat, rhinosinusitis (including common cold), acute bronchitis, and influenza -. GPs will randomise patients using a centralised electronic online platform. An open-label study has been designed taking into account the type of the two strategies used and considering that an effect on GPs' and patients' beliefs is expected. Neither patients nor health professionals will be blinded.

Eligibility criteria

Any patient from 18 to 75 years of age attending the GP consultation with an uncomplicated RTI who has previously taken any dose of antibiotic for less than three days due to either of the 2 following clinical scenarios and accepts to participate in the clinical trial will be included:

- Patients diagnosed with clinical conditions for which antibiotics prescribed by other health professionals are not necessary.
- Patients who have taken several doses of an antibiotic (from leftovers found in the household or obtained at the pharmacy without a medical prescription) for a clinical condition for which an antibiotic is not necessary.

Exclusion criteria

- Subjects under 18 or over 75 years of age.
- Confirmed bacterial infection.
- Patients requiring hospital admission.
- Severe impairment of clinical signs of infection (impairment of consciousness, respiratory rate > 30 respirations per minute, heart rate > 125 beats per minute, systolic blood pressure < 90 mm Hg, diastolic blood pressure < 60 mm Hg, temperature > 40°C, oxygen saturation < 92%).
- Problems to comply with treatment at home, such as sociopathy or psychiatric problems, or drug or alcohol addiction.
- Lack of tolerance to oral treatment, such as the presence of nausea and vomiting, gastrectomy, post-surgery and/or diarrhoea.

- Significant comorbidity including severe renal failure, hepatic cirrhosis, severe heart failure, immunosuppression – chronic HIV infection, transplantation, neutropenia, or patients receiving immunosuppressive drugs or corticosteroids.
- Terminal disease, defined as a life expectancy less than 12 months.
- Patients admitted to a long-term residence.
- Patients who state that they are unable to see their doctor at the practice office.
- Refusal to participate in the study.

Outcome measures

The primary outcome measure will be the duration of severe symptoms. Each symptom will be scored using a six-point Likert scale and symptoms scoring 5 or 6 will be considered as severe. We will include common symptoms such as feeling of fever, discomfort or general malaise, cough, difficulty in sleeping, and changes in everyday life in all patients, and specific symptoms according to the condition (Table 1) [39].

Secondary endpoints

- Adverse events in the two study groups.
- Antibiotic consumption. This information will be collected in the symptom diaries and also by the pharmacy units of the different healthcare systems.
- Patient satisfaction with healthcare by means of a questionnaire with a Likert scale.
- Patient belief in the effectiveness of antibiotics by means of a questionnaire with a Likert scale.
- Complications related to the RTIs will be registered during the first 3 months after randomisation. As in the recent study of Gulliford et al, we will consider the cases of pneumonia, empyema, peritonsillar abscess, mastoiditis, otitis media, bacterial meningitis, and intracranial abscess [40]. These complications will be prospectively recorded by the GPs by means of a standardised questionnaire and will be reported within a maximum of 48 hours to the study clinical coordinator, who will report to the Safety and Data Monitoring Committee which will assess the safety of the two strategies.

Sample size calculation

Excellence guidelines for the treatment of RTIs include estimates of average duration of the illness (before and after seeing a doctor) of one week for acute sore throat, one and a half weeks for rhinosinusitis, including common cold, and three weeks for acute cough or bronchitis [39]. In a recent study on the effectiveness of delayed prescribing strategies carried out in Spain, the mean duration of severe symptoms in uncomplicated acute RTIs including acute sore throat, rhinosinusitis, and acute bronchitis, among patients not treated with antibiotics was 4.7 days (standard deviation of 3.6) [39]. Considering a reduction of one day in the duration of severe symptoms as a clinically relevant outcome, with a bilateral approximation, a sample of 240 patients per group will be able to detect this difference with an alpha error of 5% and a power of 80% (beta =0.2), considering 15% of losses (based on the percentage of patients who did not return symptom diaries in a previous study) [39]. In terms of the number of investigators to be included in this clinical trial, we anticipate that over a two-year period each GP will include 32 patients. Thus, we are planning to invite 15 GPs from 10 different healthcare centres.

Data collection and ascertainment of visits

The patients will be randomised to one of the 2 treatment strategies. Baseline data will be collected in the clinic by the physician or with the help of the nursing staff. To standardize data collection, all of the participating healthcare professionals will be trained by the coordinating centre. Only experienced GPs (those who have worked for 15 to 25 years) and those who feel comfortable with the design of the study will participate in the study. This will be achieved by the administration of a questionnaire with clinical questions, recommendations of local guidelines and vignettes to check if they are confident and comfortable with the strategy of stopping an already commenced antibiotic course. The patients will receive information on the study and, if they are interested in participating, they will be provided with an informed consent form to read and sign. A maximum length of 15-20 minutes is expected for the interview and the introduction of the data. The study scheme and the visit programme will be explained to the patient (Table 2). GPs will fill out a screening log with all the patients who meet all the inclusion criteria and none of the exclusion criteria regardless of whether the patients consent to participate or not. This will

allow us to evaluate the percentage of patients who accept to participate in the trial and determine the reasons why they do not wish to participate if they refuse.

On the baseline visit, GPs will collect information about the type of diagnoses, prior time elapsed with symptoms, number of days taking an antibiotic, and type of antibiotic taken. Patients who made the decision to take an antibiotic by themselves (either purchased at the pharmacy or taken from leftovers stored at home) and are assigned to the usual strategy of continuing antibiotic treatment will be provided with a medical prescription of the same antibiotic until completing the recommended therapy duration according to local guidelines, even if the antibiotic is not first-line treatment.

After randomisation, information on the strategy to which they have been allocated will be given to the participants, and they will be informed as to the appropriate measures to take in case their condition worsens or there is no improvement. In addition, they will be given a diary with a validated questionnaire of symptoms for each condition, which they should complete while symptoms related to the respiratory condition are present. The degree of satisfaction or concern with different aspects of the therapy as well as the use of antibiotics will also be recorded in this diary.

Patients will be interviewed by telephone 2 or 3 days after their inclusion in the study. At this first follow-up visit, a worsening of the clinical situation of the patient will be evaluated to determine whether antibiotic treatment is necessary among patients in the group assigned to discontinuation (first-line antibiotics will be recommended in this case) or whether the antibiotic regimen should be continued or changed to the first-line drug in patients in the group allocated to continuation. We will provide the patients with the opportunity to ask questions and discuss any problems with diary completion. In addition, compliance and possible secondary effects of the treatment will be evaluated. The second follow-up visit will be scheduled at 14-28 days after inclusion and will depend on the infection involved at patient recruitment as established in the NICE guidelines [41]. On this visit, the clinical evolution of the signs and symptoms will be evaluated and the need to change or continue the antibiotic treatment, respectively, will be determined in the case of worsening of the clinical manifestations. The symptom diaries will be collected on this visit. Participants who do not return their diary will be telephoned by the trial team as a reminder and to enquire whether they need any assistance in returning their diary. Possible secondary effects of the treatment will also be assessed. Patients will be asked to revisit if symptoms continue or they present

recurrence of the infection. On the last follow-up visit, scheduled at day 90, recurrences, medical visits or hospital admissions due to the baseline infectious disease will be reported.

Data analysis procedure

The characteristics of the study population will be described using frequencies for categorical variables and mean and standard deviation (SD) for quantitative variables. A bivariate analysis of the baseline data will be performed between patients returning and not returning symptoms diaries for assessing if the latter population differ from the patients including in the study analysis. To compare the two strategies studied, we will use the t test for continuous variables. To compare the duration of symptoms across strategies, we will use the t test for continuous variables for each symptom, and a linear regression model per symptom, with symptom duration as the dependent variable, and both antibiotic consumption and symptom duration prior to the visit as the independent variables. The same approach will be made to compare the severity of symptoms between the two strategies, but the dependent variable for each model will be symptom severity. The Chi-square test will be used to compare antibiotic consumption, satisfaction, percentage of adverse effects, and the appearance of complications between the two groups. The level of significance will be 5% (α=0.05).

Criteria for withdrawals will be evidence of protocol violation, withdrawal of informed consent or a serious adverse event, defined as any untoward medical circumstance that results in death, is life-threatening, requires inpatient hospitalisation or prolongs existing hospitalisation, results in persistent or significant disability/incapacity, or requires intervention to prevent permanent impairment or damage. Patients may choose to interrupt the medication at any time during the course of the study. However, they will be followed in the same way as the other patients. Analyses will follow the intention-to-treat principle.

ETHICS AND DISSEMINATION

Each patient should provide written consent to participate in the study after being informed in intelligible language for him/her on the nature, scope and possible consequences of the trial. After consent is submitted, the patients will be randomised. Data confidentiality will be ensured at all times, as stated in the researcher's commitment sheet, as will compliance with the current legislation regarding the protection of personal data. This is a clinical trial based

on the outpatient setting, and neither patients nor researchers will receive any monetary compensation. From an ethical point of view, this is to certify that the objective of the study is relevant for primary care, the power of the study may be considered as reasonable, this is an original study, the risks which the participants may incur justify the study being carried out with a totally favourable benefit/risk quotient, and we ensure the external validity of the study to the primary care reality, with clearly described inclusion and exclusion criteria. Vulnerable populations will not participate in this study.

The trial has been registered with the National Institutes of Health (NIH) trial registry (NCT02900820). This protocol was presented in the last Conference of the Spanish Society of Family Medicine held in La Coruña in June 2016. A range of dissemination activities are planned at national and international conferences. We will publish the final report in an open access peer-review journal. A summary of the findings will be sent to the participating practices on completion of the STOP-AB study.

DISCUSSION

Overprescribing of antibiotics for RTIs is considerable in Western countries. The results of this study will be applicable to patients diagnosed with clinical conditions for which antibiotics are not or might not be necessary. Few GPs ask patients to discontinue antibiotic therapy because of fear of possible worsening of symptoms and the appearance of complications even in cases of suspected viral infections. Guidelines usually provide dominating triggers for prescribing and weak priming for discontinuation. In other situations, GPs do not wish to contradict the decision made by other doctors because it might look unfair. If the results of this study do not find any difference between the two groups, there will be no reason to continue an antibiotic regimen when a GP no longer considers it necessary. We believe that there is no risk – and every advantage – in stopping a course of an antibiotic immediately after a bacterial infection has been excluded or is unlikely, as Gilbert recently suggested [16]. The most obvious circumstances in which it is appropriate to stop antibiotics are when the antibiotics are initiated without certainty of what infection is being treated, if any treatable bacterial infection is present at all, and for infections that are almost always self-limiting, e.g. episodes of acute bronchitis. Patient expectation often plays a role in the decision to start antibiotic treatment in these cases.

The impact of our trial is likely to be important since the evidence available in this field is still limited, and adequately designed and conducted clinical trials are warranted to clarify the efficacy and safety of discontinuing antibiotic therapy in these cases. Similarly, the inclusion of most of the uncomplicated RTIs and the fact that only patients with less than three days of antibiotic therapy will be invited to participate will increase the validity of the results. These characteristics make this study innovative and relevant to this field.

CONTRIBUTORS

CL, AM, JMC and CB were involved in the conception and design of the study. JFF, JMM, JR, IG, JA, JO, CS, JB and PR have made substantial contributions to conception and design. AM, JFF, JMM, JR, IG, JA, JO, CS, JB and PR will be involved in carrying out the trial and recruitment. CL drafted the manuscript and all authors read and approved the final manuscript.

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COMPETING INTERESTS

CL reports receiving research grants from the European Commission (Sixth and Seventh Programme Frameworks), Catalan Society of Family Medicine, and Instituto de Salud Carlos III (Spanish Ministry of Health). The other authors declare no competing interests.

ETHICAL APPROVAL

The study was approved by the Primary Care Research and Ethics Committee of the *Jordi Gol i Gurina* Foundation, Barcelona, Spain (reference number, 16/093).

DATA SHARE STATEMENT

All data created during this research will be openly available from the Spanish Society of Family Medicine.

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Table 1. Symptom diary

For each symptom choose the degree of affectation in the last 24 hours, according to the following Table of Codes:

Code	Explanation
0	Normal / does not hurt
1	Affectation is insignificant / mild pain
2	Mild or slightly significant affectation / moderate pain
3	Moderately significant affectation / considerable pain
4	Significant affectation / intense pain
5	Highly significant affectation / very intense pain
6	Maximum affectation / unbearable pain

Acute sore throat. The following symptoms will be recorded daily: feeling of fever, headache, general discomfort or malaise, cough, sore throat, difficulty swallowing (solids or liquids), runny nose, ear pain, diarrhoea, nausea, vomiting, difficulty sleeping and difficulty in carrying out daily life activities. Each symptom will be scored following a 0-6 scale.

Rhinosinusitis. The following symptoms will be recorded daily: feeling of fever, general discomfort or malaise, headache, sudden pain in the face, pain in the face on touching, runny nose, nasal mucus colour, cough, sore throat, expectoration or phlegm (mucus when coughing), diarrhoea, nausea, vomiting, difficulty sleeping, and difficulty in carrying out daily life activities. Each symptom (save for nasal mucus colour) will be scored from 0 to 6. In the case of the presence of nasal mucus colour, the colour will be assessed: transparent (T), light yellow clear (Y), green (V) or other (O).

Acute bronchitis. The following symptoms will be recorded daily: feeling of fever, general discomfort or malaise, cough, expectoration or phlegm (mucus when coughing), shortness of breath (suffocation, fatigue), pain when breathing (chest pain), chest breathing sounds, diarrhoea, nausea, vomiting, difficulty sleeping and difficulty in carrying out daily life activities. Each symptom (save for expectoration or phlegm) will be scored from 0 to 6. In the

case of expectoration or phlegm, the colour will be assessed: transparent (T), light yellow clear (Y), green (V) or other (O).

Influenza. The following symptoms will be recorded daily: feeling of fever, runny nose, headache, general discomfort or malaise, cough, muscle pain, sore throat, sweat or chills, shortness of breath, weakness or fatigue, dizziness, diarrhoea, nausea or vomiting, difficulty sleeping, and difficulty in carrying out daily life activities. Each symptom will be scored from 0 to 6.

Table 2. Visit schedule during the clinical trial

	Visit 1 Day 0	Visit 2* Day 2-3	Visit 3 Day 14-28**	Visit 4* Day 90
Medical history and physical examination	x		x	
Informed consent form	x			
Randomisation	x			
Giving out of symptom diaries	x			
Evaluation of clinical evolution		x	x	
Assessment of adverse events		x	x	
Collection of symptom diaries			x	
Reporting of recurrences, medical visits or hospital admissions due to the baseline infection		x	x	x

*Phone call

**Depending on the infection (14 days for influenza and sore throat; 28 days for acute bronchitis, and acute rhinosinusitis). A further visit should be scheduled if symptoms persist on visit 3.

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	___1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	___3,13_____
	2b	All items from the World Health Organization Trial Registration Data Set	_____
Protocol version	3	Date and version identifier	____cover letter__
Funding	4	Sources and types of financial, material, and other support	____15_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	____1,14,15_____
	5b	Name and contact information for the trial sponsor	___15_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	____15_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	____N/A_____

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5-8
	6b	Explanation for choice of comparators	5-8
Objectives	7	Specific objectives or hypotheses	8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8,9
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	9,10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-12
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	12
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	11,12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11,12,table 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10,11
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	8,9
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11,12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11,12

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	12
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	12
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	11,12
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11,12
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	12
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	3,13
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	9
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	9
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Not applicable
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	15
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	13,14
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.