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Original article

Efficacy and safety of discontinuing antibiotic treatment for uncomplicated respiratory tract infections when deemed unnecessary. A multicentre, randomized clinical trial in primary care

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ABSTRACT

Objectives: To determine the benefits and harms of discontinuing unnecessary antibiotic therapy for uncomplicated respiratory tract infections (RTI) when antibiotics are considered no longer necessary.
Methods: Multicentre, open-label, randomized controlled clinical trial in primary care centres from 2017 to 2020 (ClinicalTrials.gov, NCT02900820). Adults with RTIs—acute rhinosinusitis, sore throat, influenza or acute bronchitis—who had previously taken any dose of antibiotic for less than 3 days, which physicians no longer deemed necessary were recruited. The patients were randomly assigned in a 1:1 ratio to discontinuing antibiotic therapy or the usual strategy of continuing antibiotic treatment. The primary outcome was the duration of severe symptoms (number of days scoring 5 or 6 on a six-item Likert scale). Secondary outcomes included days with symptoms, moderate symptoms (scores of 3 or 4), antibiotics taken, adverse events, patient satisfaction and complications within the first 3 months.
Results: A total of 467 patients were randomized, out of which 409 were considered valid for the analysis. The mean (SD) duration of severe symptoms was 3.0 (1.5) days for the patients assigned to discontinuation and 2.8 (1.3) days for those allocated to the control group (mean difference 0.2 days; 95% CI −0.1 to 0.4 days). Patients randomized to the discontinuation group used fewer antibiotics after the baseline visit (52/207 (25.1%) versus 182/202 (90.1%); p 0.001). Patients assigned to antibiotic continuation presented a relative risk of adverse events of 1.47 (95% CI 0.80–2.71), but the need for further health-care contact in the following 3 months was slightly lower (RR 0.61; 95% CI 0.28–1.37).
Conclusions: Discontinuing antibiotic treatment for uncomplicated RTIs when clinicians consider it unnecessary is safe and notably reduces antibiotic consumption. **Carl Llor, Clin Microbiol Infect 2022;28:241**

Introduction

Most acute uncomplicated respiratory tract infections (RTIs) are caused by viruses, and in otherwise healthy adults these infections are typically self-limiting [1]. However, many patients may seek attention in primary care, which often leads to inappropriate antibiotic prescription [2]. More than 60% of adults presenting with acute rhinosinusitis, acute bronchitis or sore throat are prescribed an antibiotic [2–4]. It is well known that inappropriate antibiotic use has negative implications, including a risk of subsequent

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infection with resistant organisms, *Clostridioides difficile* infections and adverse events [5].

Completion of an antibiotic treatment once initiated has classically been postulated. Discontinuing an unnecessary antibiotic course is seldom carried out in routine clinical practice because most physicians are concerned about hypothetical negative consequences of discontinuation, in other cases because they do not wish to offend other colleagues who have prescribed the antibiotic course (prescriber etiquette) or because they think that continuing an antibiotic regimen prevents the patient from acquiring resistant organisms [6,7]. However, 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 [8,9]. This dogma of completing an antibiotic regimen once started in order to prevent the development of antimicrobial resistance might not thereby be true, and when this treatment is deemed to be unnecessary it should be discontinued. However, studies evaluating the efficacy and safety of discontinuing an antibiotic course that has been inadequately used for uncomplicated RTIs are lacking [10]. In this context, we have conducted a non-commercial, investigator initiated, randomized clinical trial aimed to investigate the efficacy and safety of discontinuing antibiotic therapy when it is considered not indicated by the investigator.

Materials and methods

Study design

This was a multicentre, open-label, randomized, parallel-group trial conducted between January 2017 and February 2020. The trial design has been published previously [11], and the trial protocol and statistical analysis plan are available in the Supplementary material. Written informed consent was obtained from all patients before screening. The study was approved by the Research Ethics Committee Jordi Gol, Barcelona, Spain (reference number, 16/093).

Investigators were selected among primary care physicians with at least 15 years of clinical experience. Candidates were given a questionnaire asking about clinical aspects of RTIs, recommendations of guidelines and clinical vignettes in order to assess if they were confident and comfortable identifying and stopping inadequate antibiotic treatment. Ten investigators from five centres were finally selected from a group of 31 candidates. A detailed description of the selection of investigators has been published elsewhere [12].

Eligible patients were 18–75 years of age, attending the primary care consultation for an uncomplicated RTI: acute sore throat, acute rhinosinusitis, acute bronchitis, or influenza, for which the investigator deemed that antibiotic treatment was not indicated, but for which the patient had already started an antibiotic for less than 3 days. The exclusion criteria are described in the Supplementary material (Appendix S1).

Randomization and intervention

Eligible patients were randomly assigned in a 1:1 ratio to either continue or discontinue with their initiated antibiotic treatment. Randomization was conducted using a centralized electronic online platform in real time and was stratified by diagnosis. No blocks were used. Due to the characteristics and setting of the study, blinding was considered not feasible and an open-label design was adopted.

Patients were informed about the objectives of the study before randomization in all the participating centres. Participants were given this information in a standardized way and it was explained to them that the use of antibiotics was not warranted for the condition they presented. Patients gave written informed consent for participation.

Outcomes

The primary outcome was the time to resolution of severe symptoms in the autocompleted Likert scales, evaluated as the time for all symptoms to be less than 5. In the case of more than one severe symptom, we considered the time until resolution of the last symptom.

Secondary end points were (a) difference in time to resolution of moderate symptoms, or time until all symptoms were less than 3; (b) difference in time to complete resolution of symptoms or all scores below 1; and (c) difference in time to resolution of individual severe symptoms.

Other outcomes: (a) antibiotic and symptomatic therapy consumption, collected in the symptom diaries; (b) patient satisfaction with health care and belief in the effectiveness of antibiotics by means of a questionnaire with a six-point Likert scale; (c) complications related to the RTIs within the first 3 months after randomization and (d) adverse events.

Follow-up and outcome assessment

Information about the diagnosis, type of antibiotic and number of days taken were collected during the baseline visit. Patients completed a daily symptoms diary for the duration of the illness, as established in the NICE guidelines; i.e. 14 days for acute sore throat and influenza and 28 days for acute rhinosinusitis and acute bronchitis [13]. Five symptoms were common for the four infectious diseases: feeling of fever, discomfort or general malaise, cough, difficulty sleeping and changes in everyday life; others were specific according to the condition [14] (questionnaires are available in the protocol). Each symptom was scored on a Likert scale from 0 to 6 (0 = no problem, 1 = very little problem, 2 = slight problem, 3 = moderately bad, 4 = bad, 5 = very bad, 6 = as bad as it could be), where 1 and 2 were considered mild, 3 and 4 were moderate and 5 and 6 were severe symptoms. These diaries have previously been validated and are sensitive to change and internally reliable [14–16]. The use of antibiotics and the degree of satisfaction with different aspects of the therapy were also recorded in the diary.

Follow up consisted of a telephone interview 2 or 3 days after inclusion in the study, a clinical visit at days 14 or 28 depending on the infection, at which time the symptom diaries were collected and a final visit at day 90.

Statistical analysis

The null hypothesis was that stopping antibiotic therapy resulted in no significant differences in symptomatic outcomes for patients. For the sample size calculation, we considered a mean duration of severe symptoms in uncomplicated acute RTIs not treated with antibiotics of 4.7 days (SD 3.6) and a reduction of 1 day in the duration of severe symptoms as a clinically relevant outcome [14]. Considering 15% of losses based on the percentage of patients who did not return symptom diaries in a previous study carried out in our area [14], it would be necessary to enrol a sample size of 240 patients per group.

The primary analysis was the comparison of days with severe symptoms in the intention-to-treat (ITT) population, including all randomized patients but, because of the nature of the primary endpoint, excluding patients who did not return the diaries. No

imputation of missing values was performed. If no significant differences were observed, we conducted a non-inferiority analysis considering a non-inferiority limit of 1 day [14]. The analysis was repeated for the per-protocol population including all randomized patients who complied with the treatment protocol and returned the diaries. The two-sided *t* test was used for continuous variables. Differences in duration of symptoms were described with means and 95% CI. The χ^2 test was used to compare dichotomous variables. The level of significance was 5%.

Results

Study participants

A total of 467 patients were randomized to the discontinuing arm ($n = 233$) or the continuation arm ($n = 234$) (Fig. 1). Despite not having completely met the expected sample size, we were forced to stop the recruitment in March 2020 by the coronavirus disease 2019 pandemic.

A total of 58 patients (12.4%) were excluded from the analysis because they failed to return the symptom diary or were lost to follow up. The comparison of characteristics between patients who completed the study and those excluded did not show significant differences (see Supplementary material, Table S1). A total of 409 patients were valid for the ITT analysis, 207 in the discontinuation arm and 202 in the continuation arm (Table 1). The description of symptoms, their frequency and intensity at baseline are presented in the Supplementary material (Table S2).

Fifty-two (25.1%) patients in the discontinuation group continued to take their antibiotic, the reasons are described in the Supplementary material (Table S3). Of the 202 who were assigned to continuing the antibiotic course, 20 (11.4%) discontinued the

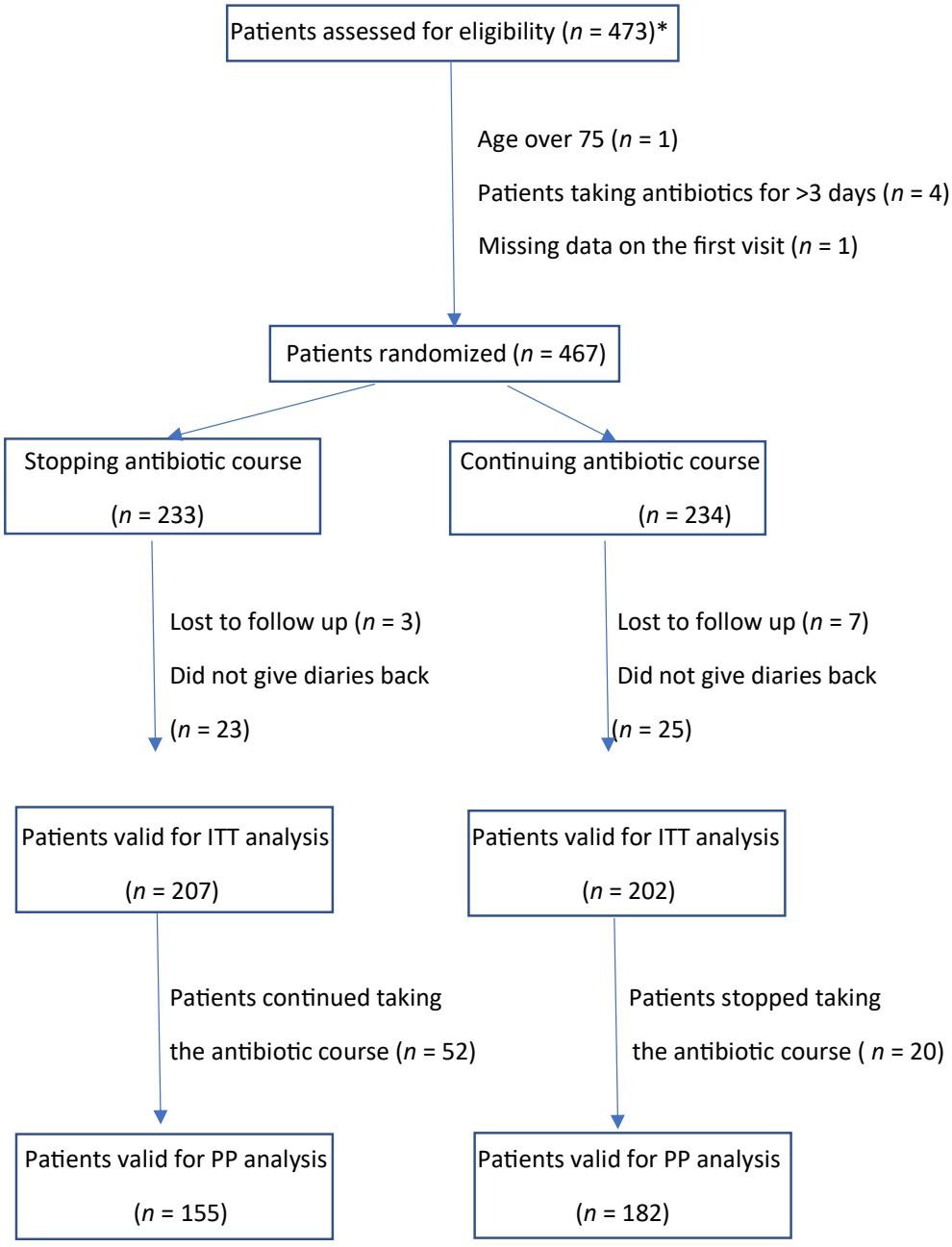

Fig. 1. Patient randomization flowchart. *Screening logs obtained from only one centre.

Table 1
Demographic and clinical characteristics of the patients at baseline (intention-to-treat population)

Characteristic	Stopping antibiotic course ($n = 207$)	Continuing antibiotic course ($n = 202$)
Women, *n* (%)	134 (64.7)	126 (62.7)
Age (years); mean ± SD	43.0 ± 16.0	44.7 ± 15.9 ±
Days taking an antibiotic prior to the visit, *n* (%)		
Less than 1 day	123 (59.4)	133 (65.8)
Between 1 and 2 days	47 (22.7)	45 (22.3)
Between 2 and 3 days	37 (17.8)	24 (11.9)
Source of the antibiotic taken by patients, *n* (%)		
Another doctor prescription	162 (78.3)	157 (77.7)
Household remains	38 (18.4)	40 (19.8)
Pharmacy	7 (3.4)	5 (2.5)
Antibiotic taken at the baseline visit, *n* (%)		
Amoxicillin	90 (43.7)	89 (44.3)
Amoxicillin-clavulanate	90 (43.7)	94 (46.8)
Azithromycin	6 (2.9)	1 (0.5)
Levofloxacin	15 (7.3)	13 (6.5)
Others	5 (2.5)	4 (2.0)
Symptomatic treatment taken at the baseline visit, *n* (%)		
Paracetamol	48 (23.2)	44 (21.8)
NSAID	36 (17.4)	41 (20.3)
Mucolytics and expectorants	24 (11.6)	20 (9.9)
Antitussives	18 (8.7)	17 (8.4)
Antihistamines	16 (7.7)	17 (8.4)
Others	13 (6.3)	11 (5.4)
Acute respiratory tract infection, *n* (%)		
Pharyngitis	75 (36.2)	74 (36.6)
Rhinosinusitis	37 (17.9)	36 (17.8)
Acute bronchitis	63 (30.4)	57 (28.2)
Influenza	32 (15.5)	35 (17.3)
Reason for the medical visit at recruitment[a], *n* (%)		
Reassuring that the treatment was appropriate	65 (47.8)	71 (52.6)
Obtaining a sick-leave certificate	44 (32.4)	42 (31.1)
Obtaining the prescription of the antibiotic	26 (19.1)	20 (14.8)
Other reasons	15 (11.0)	14 (10.4)
Severity of the common symptoms, *n* (%)		
Fever	23 (11.2)	33 (16.5)
Discomfort or general pain	49 (23.9)	56 (28.0)
Cough	52 (25.4)	46 (23.0)
Difficulty sleeping	43 (20.9)	35 (17.5)
Difficulty in carrying out daily life activities	46 (22.5)	45 (22.5)

Abbreviation: NSAID, non-steroidal anti-inflammatory drug.
[a] Information available from 273 patients. Patients could state more than one reason.

treatment. Therefore, the per-protocol population consisted of 337 individuals, 155 in the discontinuation and 182 in the continuation arms. The use of symptomatic therapy was similar in the two groups. The main reasons for the medical visit were reassuring that the treatment initiated was appropriate and obtaining a sick-leave certificate (Table 1).

Primary outcome

In the ITT population, the majority of patients, 194 (98%) in the continuation and 191 in the discontinuation arm (96.1%), experienced one or more severe symptoms. The mean duration of severe symptoms was 2.99 (SD 1.5) days for the patients assigned to discontinuation and 2.85 (SD 1.3) days for those assigned to continuation (p 0.317), with a mean difference of 0.14 days (95% CI −0.13 to 0.41 days) (Table 2, Fig. 2). Fig. S1 (see Supplementary material) shows the distribution of days with severe symptoms in both treatment arms. The results were similar in the per-protocol population (Fig. 2, Table 2).

We conducted a sensitivity analysis assuming that the 26 patients who were excluded from the ITT analysis due to lack of outcome data in the discontinuation arm had the same mean duration of severe symptoms as the remaining patients in their arm, whereas we assumed different durations of symptoms for the 32 patients excluded from the continuation arm. In order to find significant differences between groups, the missing patients in the continuation arm should have had a mean duration of symptoms of 2.10 days, which would have resulted in a mean difference of 0.24 days (95% CI 0.001–0.48 days). Even if the 32 missing patients had hypothetically a duration of symptoms of 0 days the 95% CI of the difference between the two treatment arms would not have crossed the threshold of 1 day (0.53 days, 95% CI 0.26–0.80 days), indicating the robustness of our findings.

Secondary outcomes

No significant differences in the duration of symptoms were observed either in the ITT or the per-protocol populations (Table 2, Fig. 2). Analysing the severe symptoms individually, the discontinuation arm presented a significantly longer duration of facial pain on touch, changes in everyday life, headache, spontaneous facial pain and discomfort or general pain (see Supplementary material, Fig. S2 and Table S4).

Other outcomes

The consumption of antibiotics was significantly higher in the continuation group (182 patients (90.1%) versus 52 patients (25.1%); p 0.001). Patients assigned to antibiotic continuation had slightly higher levels of satisfaction, had a relative risk of adverse

Table 2
Description of primary and secondary outcomes

	Stopping antibiotics	Continuing antibiotics	Between-group absolute difference
Primary end point			
Duration of severe symptoms (days), mean ± SD			
Intention-to-treat ($n = 409$)	2.99 ± 1.5	2.85 ± 1.3	0.14 (−0.13 to 0.41)
Per protocol ($n = 337$)	3.08 ± 1.5	2.86 ± 1.3	0.22 (−0.08 to 0.52)
Secondary end points			
Duration of moderate symptoms (days), mean (SD)			
Intention-to-treat ($n = 409$)	5.76 ± 3.9	5.26 ± 3.5	0.50 (−0.22 to 1.24)
Per protocol ($n = 337$)	5.70 ± 3.6	5.21 ± 3.5	0.49 (−0.27 to 1.26)
Duration of any symptom (days), mean (SD)			
Intention-to-treat ($n = 409$)	11.79 ± 6.4	11.82 ± 7.1	−0.03 (−1.34 to 1.29)
Per protocol ($n = 337$)	11.71 ± 6.1	11.63 ± 7.2	0.08 (−1.37 to 1.52)

Table 3
Description of other outcomes

	Stopping antibiotics ($n = 207$)	Continuing antibiotics ($n = 202$)	p value
Patients taking antibiotics after the baseline visit, *n* (%)	52 (25.1)	182 (90.1)	<0.001
Patients taking symptomatic treatment after the baseline visit[a], *n* (%)			
Paracetamol	66 (31.9)	58 (28.7)	0.485
NSAIDs	49 (23.7)	49 (24.3)	0-890
Mucolytics and expectorants	58 (28.0)	55 (27.2)	0.858
Antitussives	21 (10.1)	19 (9.4)	0.801
Antihistamines	15 (7.2)	13 (6.4)	0.745
Others	31 (15.0)	31 (15.3)	0.917
Patients feeling very or extremely worried about their disease, *n* (%)	32 (19.0)	29 (16.3)	0.249
Patients considering that doctors dealt very or extremely well with their concerns, *n* (%)	132 (77.7)	142 (69.7)	0.543
Patients very or extremely satisfied with health care, *n* (%)	130 (77.9)	137 (77.9)	0.799
Patients who consider that antibiotics were very or extremely effective for their disease, *n* (%)	61 (37.6)	71 (41.5)	0.626
Total number of adverse events, *n* (%)	16 (7.7)	23 (11.4)	0.240
Nausea or vomiting	6 (2.9)	8 (3.9)	
Diarrhoea	3 (1.4)	4 (1.9)	
Rash	6 (2.9)	7 (3.4)	
Candidiasis	1 (<1)	3 (1.5)	
Others	0	1 (<1)	
Need for unscheduled health care, *n* (%)	15 (7.2)	9 (4.5)	0.294
Further visit to the doctor	8 (3.8)	2 (1)	
Visit to emergency departments	6 (2.9)	7 (3.4)	
Hospital admission	1 (<1)	0	

Abbreviation: NSAID, non-steroidal anti-inflammatory drug.
[a] Includes prescribed and self-medicated medication.

events of 1.47 (95% CI 0.80–2.71), and a relative risk of unscheduled medical visits of 0.61 (95% CI 0.28–1.37) (Table 3).

Discussion

Our results have shown that discontinuing an already initiated antibiotic treatment for uncomplicated RTI when the clinician considered that it was not indicated had no influence on the clinical outcomes of the patients. The duration of severe, moderate or any symptoms was similar in patients who continued or discontinued the antibiotic treatment, and both groups had a similar incidence of adverse effects.

Although most clinicians would agree that discontinuation of an antibiotic in this context would be the right course of action, the previous lack of evidence about the efficacy and safety of this strategy might prevent them from taking the responsibility to discontinue a treatment that often was prescribed by another colleague.

The results obtained in this novel RCT are in agreement with those showing no differences in clinical outcomes between antibiotics and placebo for uncomplicated RTIs, and also resemble those obtained with the delayed antibiotic prescribing strategy [17]. In a large RCT in patients with acute lower RTIs in whom pneumonia was not suspected, the patients were treated with either a high-dose amoxicillin or placebo, patients on placebo showed no difference in either the duration of symptoms rated as moderately severe or worse or in mean symptom severity compared with the antibiotic group [15]. A recent Cochrane review including a total of 11 RCTs and 3555 patients reported no difference in the duration of symptoms in the delayed antibiotic strategy compared with the immediate prescription approach [18].

The majority of placebo-controlled studies and studies on delayed antibiotic prescribing have considered a difference of 1½ to 2 days of symptoms as clinically relevant [14,15,19]. Since our main outcome was severe symptoms, we adopted the conservative assumption that a difference of only 1 day in the duration of severe symptoms was clinically relevant. However, the main difference observed was far below this threshold, not only in severe symptoms, but also in moderate and in all symptoms. When considering the different symptoms individually, symptom duration was significantly shorter with antibiotic continuation in only five out of 17 patients, with a mean difference of more than 1 day in only one symptom (facial pain on touch). As there were only 44 patients with this symptom, our study is clearly underpowered, and we

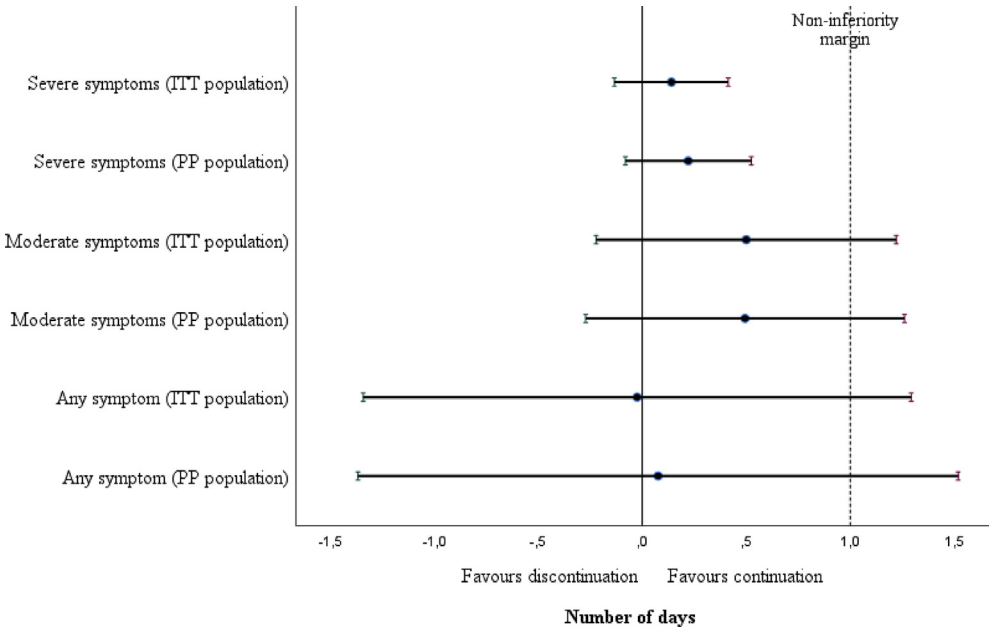

Fig. 2. Mean difference of number of days with symptoms in the two groups in the intention-to-treat and the per-protocol populations.

cannot rule out a spurious result due to multiple comparisons. However, a previous study in patients with acute sinusitis showed a difference of 2 days in severe facial pain on touch between patients assigned to immediate antibiotic treatment and those without antibiotics [14]. Therefore, studies on the impact of antibiotic treatment in patients with rhinosinusitis and severe facial pain on touch are required.

This study has several limitations. First, the sample size was not fully achieved because of the onset of the coronavirus disease 2019 pandemic. Nevertheless, the final ITT population was 96% of the expected sample size, therefore, we do not believe that our study can be considered underpowered Second, lack of blinding, with patients aware of their strategy, may constitute a source of bias, but the direction of this bias is always unpredictable. Third, 25% of patients assigned to discontinuation continued to take their antibiotic, which may have reduced the differences in time to resolution of symptoms between the study groups, if they really existed. The comparison of characteristics between these patients and those who discontinued the antibiotic showed no differences in clinical severity, and an additional analysis excluding these patients (per-protocol analysis) did not observe any difference in the results. Fifty-eight patients (21.7%) did not return the symptom diaries or were lost for follow up. The ITT population was constituted by randomized patients who returned the diaries, as outcomes could only be evaluated through the analysis of diaries, and no imputation of missing data was performed. Although intensity of symptoms may be considered a subjective variable, our symptom questionnaires have been validated and used in similar clinical trials in primary care [14,19]. Finally, investigators were selected among those who felt confident with the strategy of discontinuing antibiotics in the indications of the trial. It is possible that this strategy may not be easily implemented in areas in which general practitioners are not familiar with these strategies or are not confident of the safety of discontinuing antibiotics.

In conclusion, discontinuation of an antibiotic treatment for uncomplicated RTIs in otherwise healthy individuals when an experienced physician considers that antibiotics are not indicated is a safe strategy to reduce unnecessary antibiotic use in the community and does not result in increased duration of symptoms.

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Author contributions

All authors contributed to the study design. CL, AM and JMC conceived the study. AM and JMC obtained funding. AM, CB, SH, OC and MR collected the data. CL and MM performed the statistical analyses, wrote the first draft of the report, and designed the tables and figures. CL, AM and MM were involved in the interpretation of the data. All authors critically revised the report and approved the final version to be submitted for publication. The corresponding author confirms that she had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Transparency declaration

CL reports receiving research grants from Abbott Diagnostics. MM has received speaker fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, Menarini, Rovi, Bial, Sandoz, Zambon, CSL Behring, Grifols and Novartis, consulting fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Bial, Gebro Pharma, CSL Behring, Laboratorios Esteve, Ferrer, Mereo Biopharma, Verona Pharma, Spin Therapeutics, pH Pharma, Novartis, Sanofi and Grifols and research grants from GlaxoSmithKline and Grifols. The other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2021.07.035.

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