Symptom response to antibiotic prescribing strategies in acute sore throat in adults: results from the DESCARTE prospective cohort study

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*DESCARTE stands for Decision rule for the Symptoms and Complications of Acute Red Throat in Everyday practice

Abstract

Background

A delayed or just in case prescription has been identified as having potential to reduce antibiotic use in sore throat.

Aim

To determine the symptomatic outcome of acute sore throat in adults according to antibiotic prescription strategy in routine care.

Design and Setting A prospective cohort study comprising adults age over 16 presenting with acute sore throat (<=2 weeks duration) managed with treatment as usual in primary care.

Methods. A random sample of 2876 from the full cohort were requested to complete a symptom diary. A brief clinical proforma was used to collect symptom severity and examination findings at presentation. Outcomes details collected by notes review and a detailed symptom diary. The primary outcome was poorer 'global' symptom control (defined as longer than the median duration *or* higher than median symptom severity). Analyses controlled for confounding by indication (propensity to prescribe antibiotics).

Results. 1629/2876 (57%) of those requested returned a symptom diary of whom 1512 had information on prescribing strategy. The proportion with poorer global symptom control was greater in those not prescribed antibiotics 393/578 (68%) compared to those prescribed immediate antibiotics 423/723 (60%) or delayed antibiotic prescription 112/193 (58%); adjusted risk ratio (95% confidence interval), immediate 0.87 (0.70-0.96) p=0.006, delayed 0.88 (0.78-1.00). p=0.042.

Conclusions. In the routine care of adults with sore throats a delayed antibiotic strategy confers similar symptomatic benefits to immediate antibiotics compared to no antibiotics. If a decision is made to prescribe an antibiotic, a delayed antibiotic strategy is likely to yield similar symptomatic benefit to immediate antibiotics.

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Introduction.

Acute sore throat is common in everyday primary care practice and antibiotics still frequently prescribed[1]. The Cochrane review of acute sore throat management included 27 trials and over 12000 cases of sore throat[2] and found that antibiotics reduced the duration of pain symptoms by an average of one day. Current UK guidelines recommend a delayed or no prescription strategy for acute sore throat. [3] Despite the guidelines and systematic review evidence described, most patients presenting with acute sore throat are prescribed immediate antibiotics.[1,4]. An alternative strategy - using a delayed antibiotic prescription - has been shown to reduce antibiotic uptake without any effect on recovery or patient satisfaction[5] and to confer a similar protective effect against complications compared to an immediate prescription[6]. However the rationale of a delayed prescription has been called into question since it results in higher antibiotic uptake than a no prescription strategy with a suggestion that a delayed strategy was inferior to immediate antibiotics for some sore throat symptoms.[7] Observational studies provide useful evidence to complement experimental studies, given the concerns that randomised trial participants and their behavior during trials (e.g. for adherence) may be atypical, and hence that estimates of effectiveness may not be applicable to routinely consulting patients. In order to describe current practice and outcome related to prescribing strategy in adults we interrogated a large observational cohort which had been recruited to investigate potential prediction of septic complications of acute sore throat. In a subset of participants completing a symptom diary, we investigated the symptomatic outcomes and illness duration in relation to prescribing strategy.

Methods.

Overall study design.

As reported elsewhere[6,8], the study used a simple one page paper/web based clinical proforma documenting clinical features to facilitate the generation of a large prospective cohort of patients presenting to general practitioners in the UK with acute sore throat and treated as usual. Smaller studies were nested in the cohort to develop and trial a clinical scoring method for bacterial infection. The nested studies were two consecutive diagnostic cohorts (n=1107) where a clinical score to predict bacterial infection was developed, and a randomised trial (n=1781) which compared the use of the clinical score and the targeted use of a rapid antigen detection test with delayed antibiotic prescribing. [9] Participants in the trial were not included in this analysis because antibiotics were targeted according to trial criteria. Initial recruitment was among six local Networks (based in Southampton, Bristol, Birmingham Oxford, Cardiff, Exeter) but was extended nationally during the last 18 months of recruitment.

Patient inclusion criteria. Previously well subjects aged 16 years and over with acute illness (14 days or less), presenting in primary care with sore throat as the main symptom, and with an abnormal examination of the pharynx (identical criteria to our previous studies[5]). Exclusion criteria were severe mental health problems (e.g. cognitive impairment associated with being unable to consent or assess history) and known immune suppression. Practitioners recorded detailed history and examination findings as detailed below and then treated as usual. Antibiotic treatment was therefore determined by individual practitioners in accordance with their usual practice.

Baseline clinical proforma. This consisted of a simple clinical sheet documenting age, gender, current smoking status, prior duration of illness and the presence and severity of baseline symptoms (sore throat, difficulty swallowing, fever during the illness, runny nose, cough, feeling unwell, diarrhoea, vomiting, abdominal pain, headache, muscles ache, sleep disturbance, earache). Symptoms were recorded using 4 point Likert scales (none, a slight problem, a moderately bad problem, a severe problem), and the presence of signs (pus, cervical nodes, temperature, fetor, palatal oedema, difficulty speaking due to sore throat). No laboratory tests were specified.

Documentation of primary outcome.

A request to complete a symptom diary was randomly allocated to a proportion of those recruited to the study to achieve a pre-specified target of 1800 diaries. Initial allocation was randomly allocated to 1:10 participants by including the diary in recruitment packs. The allocation ratio was altered partway through the study to 1:2 packs in most centres on account of observed low return rates. Allocation was to 1:4 recruitment packs in Southampton due to the inclusion of an alternative questionnaire. The diary was similar to that used in other studies.[5,10] Patients completed the diary each night until symptoms resolved, or for up to 14 nights. Each symptom was scored (0=no problem to 6=as bad as it could be): sore throat, difficulty swallowing, feeling unwell, fevers, sleep disturbance. Adverse symptomatic outcome was defined as being *either* above the median for symptom severity at days 2-4 *or* above the median duration of moderately bad symptoms, (ie either or both qualified for adverse symptomatic outcome).

Other outcomes.

In order to allow comparison with other studies we also assessed symptom severity on day 2-4 and the duration of moderately bad symptoms (in days).[5,10]

Sample size. Sample size calculations calculated using NQuery sample size program (Statistical Solutions) for the main study were based on the prediction of complications- a rare outcome. For the proposed analysis of diary data a sample of 1800 patients allowing for 20% loss to follow-up of diaries (900 of whom would not be expected to have antibiotics), would have power to detect variables with prevalence between 20% to 80% with an odds ratio of 2 for adverse symptomatic outcome among the no antibiotic group.

Analysis. . Duration of symptoms was analysed using Cox regression, linear regression was used for symptom severity and generalised linear model with a log-link and binomial distribution for worsening of illness and adverse symptomatic outcome. Missing data on outcome was not imputed. We have reported both the univariate statistics as well as the relationships after controlling for the severity of all baseline symptoms and clustering of patients by practice. The Centor score is used widely to target treatment at those at higher risk of streptococcal infection, the score was derived in an emergency room setting where a score of 3 or more predicted a 32% risk of positive culture[11]. The FeverPAIN score (which comprises fever in the past 24 hours, purulence, rapid (within three days) attendance, inflamed tonsils and no cough or cold symptoms), may also be used to predict the probability of streptococcal infection in community samples and has been shown to be highly predictive of time to symptom resolution and symptom severity.[12] We tested for an interaction between Centor/FeverPAIN and antibiotic prescribing strategy- to determine if those more likely to have streptococcal infection had evidence of a differential response to antibiotics. We used the scores to dichotomise the sample into those more or less likely to have a streptococcal infection, for Centor we used the cut point of 3 or more and for FeverPAIN we used the cut point of 0-2 vs. 3 and over. At the cut point of 0-2 the probability of a streptococcus swab positive result is 26% whilst for those with a score of 3 and above it is 60%.[12]

Analyses were carried out in Stata version 12.1. To control for potential confounding by indication, we calculated a propensity score based on predictors of antibiotic prescribing (none versus immediate and none versus delayed) using a chained equations multiple imputation model. Results are presented both for complete cases and for models with significant predictors of the propensity score imputed. Outcome measures were not imputed as it was not possible to distinguish between individuals who were missing data because they did not complete a diary when asked and those who were not asked to complete one.

Results.

Descriptive data

In the full cohort study 14610 adult patients were recruited between 10th November 2006 and the 1st June 2009 from 616 general medical practices. 1629/2876 (57%) returned a symptom diary of whom 1512 had information on prescribing strategy. The baseline characteristics of patients recruited and of those who maintained a symptom diary are shown in Appendix Table 1. Those given immediate antibiotics had more severe symptoms at baseline and were more likely to have a history of fever and severe inflammation or pus on tonsils[6]. Those returning the diary were slightly older, more likely to be female and a non-smoker compared to the whole sample (Appendix Table 1).
In those returning a diary no antibiotics were prescribed for 587/1512 (39%), immediate antibiotics were for 728/1512 (48%) and delayed antibiotics for 197/1512 (13%) similar proportions to the full cohort 40%, 42% and 18% respectively. In those completing a diary, 60% of those issued a delayed prescription reported using the prescription. Delayed prescribing was only reported by those recruited from approximately one half of participating practices (52.1%).

Impact of prescribing strategies on symptom control

When controlling for propensity to prescribe antibiotics, compared with no antibiotics, those prescribed immediate or delayed antibiotics experienced a reduction in poorer symptomatic outcomes: no antibiotics 398/587 (68%), immediate antibiotics 441/728 (61%), delayed antibiotics 116/197 (58%); Adjusted risk ratio (95% confidence interval), immediate 0.87 (0.70-0.96) p=0.006, delayed 0.88 (0.78-1.00) p=0.042 (Table 1). This finding was consistent when controlling for baseline severity. Secondary outcomes showed a reduction in symptom severity on days 2-4 (Table 2) and on average 1 day less of moderately bad symptoms in those prescribed an immediate antibiotic (No antibiotic: median 4 days Inter Quartile Range (IQR) 2 to 7 days; Immediate: median 3 days IQR 2 to 5 days; Delayed: median 3 days IQR 2 to 6 days.) Hazard ratio (HR) immediate 1.21 (1.07 to 1.38) p=0.004, hazard ratio delayed HR 1.10 (0.92 to 1.33) p=0.30 (Table 3. The duration of moderately bad symptoms is illustrated in Figure 1

Evidence for a differential effect of antibiotic prescribing among those more likely to have bacterial infection

Although throat swabs were not collected we can use diary scores to predict the probability of streptococcal infection, we created a subgroup defined by a higher Centor Score (3 or above) and FeverPAIN score (3 or above)[12]. In the subgroup where bacterial infection was more likely, the estimates of benefit are slightly greater for those given an immediate antibiotic prescription or delayed prescription than in the whole cohort. (Table 4 and Table 5). However, the difference with the main cohort were modest and we were not powered for, and did not find, statistically significant interactions with these subgroups. The fact that those in the high risk subgroups were overwhelmingly treated with immediate antibiotics further reduced the power of these analyses, particularly for the smaller numbers given delayed prescription. Individual secondary outcomes are detailed in (Appendix table 2&3). Point estimates for those at low/high risk of streptococcal infection are given in Appendix table 4 and 5.

Table 1

Table 2

Table 3

Figure 1 Proportion experiencing symptoms rated moderately bad or worse according to receipt of antibiotic prescription.

Table 4

Table 5

Discussion.

Summary

This large cohort of patients presenting to general practice with acute sore throat enabled us to study the effect of prescribing antibiotics in routine practice on symptom severity and speed of illness resolution. Compared to a no antibiotic strategy a delayed antibiotic strategy confers similar benefits to immediate antibiotics with regards to effects on global symptom outcome. Those prescribed immediate antibiotics experienced both a reduction in symptom severity on day 2-4 and a reduction in the duration of moderately bad symptoms of one day. Similar benefits were observed in those receiving a delayed prescription although this study has limited power for some outcomes in this group. Symptomatic benefits arising from delayed or 'just in case' prescribing are seen in routine care and are similar to those observed in clinical trials of this strategy[13].

Strengths and limitations.

The study was designed using a simple clinical proforma to minimise selection bias and thus to produce a large generaliseable prospective cohort. Patients were recruited at the busiest seasons for respiratory illness, and, as with other studies of acute infection,[14-16] documentation of the details of those not approached was poor due to time pressures (since time pressure to recruit also meant time pressure to document non recruitment). The large sample gathered in routine practice along with the inclusion of diary data enabled the study of different antibiotic strategies and duration of prescription on symptomatic outcomes and re-consultation, which is likely to reflect the real life experience of patients. The prescription of antibiotics however is not at random and there is clear evidence of a greater propensity to prescribe for those with more severe symptoms at baseline (Appendix Table 1). We have adjusted for propensity to prescribe and also present outcomes controlled for baseline severity of symptoms but cannot rule out residual confounding. It is possible that those given a prescription for antibiotics subsequently altered their reporting of symptom severity having had their illness 'validated' by the doctor or the converse in those not in receipt of a prescription. Any study using self reported diary data may be open to such misclassification bias but if we accept at face value the reported symptoms then the symptoms recorded in the diary will reflect the patient experience of illness. In this observational data set we do not know how delayed prescribing was operationalised, but regardless of this, a delayed prescription conferred similar symptomatic benefits to an immediate prescription with lower prescription uptake.

Comparison with existing literature

In routine care in England 42% of those presenting with an acute sore throat illness receive an immediate antibiotic prescription and 18% a delayed prescription and antibiotics for acute sore throat are generally well targeted to those with most severe symptoms and those most likely to benefit[17]. In this sample, 60% of those issued a delayed prescription reported using the prescription, which is greater than that reported in experimental studies[5]. Overall use of antibiotics is similar in the US (60%)[18], whereas in France and the Netherlands, reported prescribing rates are lower (20% & 23% respectively) although this is aggregated data for all respiratory consultations.[19] As would be anticipated, there is some

symptomatic benefit in those receiving an antibiotic comparable to that seen in systematic reviews and this effect is also seen in those in receipt of a delayed prescription.[2,5]

Although the study was not powered to find an interaction of the effect of antibiotic prescribing strategy with the likelihood of streptococcal infection, the point estimates for poorer symptomatic outcome with a no prescription strategy are more pronounced, which suggests that increased likelihood of streptococcal infection may make symptomatic benefit a little more likely when antibiotics are prescribed. Once again there was no clear benefit from immediate antibiotics compared with delayed antibiotics in this subgroup of individuals.

Implications for practice.

Previous systematic reviews have consistently demonstrated that antibiotics confer a modest benefit for symptom relief[2] and this study has confirmed this effect using evidence from routine practice. We have previously demonstrated that antibiotic prescriptions in routine general practice do appear to be targeted at those at greatest risk of streptococcal carriage according to baseline characteristics[6]. Judicious use of antibiotics is an international priority[20] and there is potential to reduce the uptake of antibiotics through greater use of the delayed prescription technique or through non-prescription. Although adoption of the 'non prescribing strategy' results in the lowest uptake of antibiotics[7], use of a delayed prescription may be a useful option where current prescribing rates are high or there is greater concern for complications. It is recognised that there is a trade off between lower antibiotic prescribing and patient satisfaction with both doctors and practices[21] although clinical trials have not demonstrated large differences in satisfaction between immediate and delayed prescribing[5]. There is also likely a trade off between a global reduction in prescribing and an increased risk of septic complications although the absolute increase is very small.[22] Delayed prescribing in this study was targeted at those with intermediate symptom severity however trials of delayed prescribing in sore throat were not stratified by symptom severity and symptomatic outcomes were similar for all groups[13], hence it is unlikely that more widespread use of the delayed strategy would result in worse symptomatic outcomes. Caution must be exercised in those with greater probability of streptococcal infection and although we were unable to demonstrate adverse outcomes in those with higher symptom scores using a delayed prescription this may be due to lack of power. In one study using a delayed strategy in combination with a symptoms score to target antibiotics did result in both reduced antibiotic consumption and improved outcomes compared to empirical delayed prescribing and this may be the optimal strategy[10]. In routine practice as in trials delayed prescribing offers comparable symptom control to immediate prescribing (this study), and we have previously shown it reduces re-consultation[6] and the risk of septic complications.[6] In the full cohort 18% of sore throat consultations concluded with the issue of a delayed antibiotic prescription however there is potential for higher rates to be achieved, for instance only half of participating practices in this study reported using the delayed strategy. GPs have been shown to overestimate the patient demand for antibiotics[23] and the use of a delayed strategy would be one way of countering this overestimation. If the majority of those with intermediate symptom severity were offered a delayed prescription total uptake of antibiotics would be reduced with no anticipated adverse effects for symptom control, complications or re-consultation.

Table 1 Poorer global symptomatic outcome (*either* greater than median symptom severity in days 2-4 *or* greater than median duration of symptoms) related to antibiotic strategy and antibiotic type

	Poorer global symptomatic outcome *	Univariate risk ratio (95% CI) p-value	Risk ratio controlling for baseline severity and clustering (95% CI) p-value	Risk ratio controlling for propensity score (95% CI) p-value	Risk ratio controlling for propensity score in imputed dataset (95% CI) p-value
Antibiotic prescribing strategy					
None	398/587 (67.80%)	1.00	1.00	1.00	1.00
Immediate	441/728 (60.58%)	0.88 (0.81, 0.95) p=0.002	0.81 (0.74, 0.88) p<0.001	0.87 (0.70, 0.96) p=0.006	0.89 (0.80, 0.98) p=0.024
Delayed	116/197 (58.88%)	0.85 (0.75, .097) p=0.019	0.83 (0.73, 0.95) p=0.007	0.88 (0.78, 1.00) p=0.042	0.86 (0.74, 0.97) p=0.016

* In the 1512 returning a symptom diary in which the prescribing strategy was detailed

Table 2 Symptom severity on day 2-4 according to antibiotic prescription strategy

	Mean symptom severity (s.d.)	Difference 95% CI) p-value	Difference controlling for clustering and, antibiotic type and baseline severity score (95% CI) p-value	Difference controlling for propensity score (95% CI) p-value	Difference controlling for propensity score in the imputed dataset (95% CI) p-value
Antibiotic prescribing strategy					
None (reference) N=585	2.13 (1.24)				
Immediate N=723	2.03 (1.20)	-0.10 (-0.23, 0.03) p=0.140	-0.30 (-0.49, -0.21) p=0.001	-0.22 (0.44, -0.01) p=0.040	-0.22 (-0.43, -0.01) p=0.043
Delayed N=196	1.95 (1.19)	-0.17 (-0.37, 0.02) p=0.834	-0.22 (-0.42, -0.02) p=0.034	-0.26 (-0.45, -0.7) p=0.009	-0.26 (-0.45, -0.07) p=0.008

Table 3 Duration of moderately bad symptoms according to antibiotic prescription strategy

	Duration of moderately bad symptoms: median days (IQR)	Univariate hazard ratio	Hazard ratio controlling for clustering and baseline severity score (95% CI) p-value	Hazard ratio controlling for propensity score (95% CI) p-value	Hazard ratio controlling for propensity score in imputed dataset (95% CI) p-value
Antibiotic prescribing strategy					
No Antibiotic (reference) N=587	4 (2,7)	1.00	1.00	1.00	1.00
Immediate N=728	3 (2,5)	1.33 (1.18, 1.50) p<0.001	1.37 (1.23, 1.53) p<0.001	1.21 (1.07, 1.38) p=0.004	1.20 (1.07, 1.3); p=0.002
Delayed N=197	3 (2,6)	1.15 (0.96, 1.37) p=0.120	1.16 (0.98, 1.37) p=0.084	1.10 (0.92, 1.33) p=0.300	1.10 (0.91, 1.33) p=0.316

Table 4. Effect of probable streptococcal infection – results for participants with a Feverpain score of 3 or more* according to antibiotic strategy

	Poorer global symptomatic outcome	Interaction term (95% CI) p-value	Univariate risk ratio (95% CI) p-value	Risk ratio controlling for baseline severity and clustering (95% CI) p-value*	Risk ratio controlling for propensity score (95% CI) p-value	Risk ratio controlling for propensity score in imputed dataset (95% CI) p-value
None (reference)	14/20 (70%)		1.00	1.00	1.00	1.00
Immediate	152/281 (54.09%)	0.94 (0.84, 1.05) p=0.253	0.78 (0.57, 1.05) p=0.099	0.66 (0.52, 0.84) p=0.001	0.67 (0.52, 0.87) p=0.002	0.78 (0.58, 1.04) p=0.087
Delayed	18/32 (56.25%)	0.97 (0.84, 1.13) p=0.711	0.80 (0.53, 1.22) p=0.306	0.79 (0.56, 1.13) p=0.198	0.68 (0.45, 1.04) p=0.493	0.73 (0.49, 1.07); p=0.108

* FeverPAIN score 1 point for each of fever in the past 24 hours, purulence, rapid (within three days) attendance, inflamed tonsils and no cough or cold symptoms

Table 5. Effect of probable streptococcal infection – results for participants with a Centor score* of 3 or more according to antibiotic strategy

	Poorer global symptomatic outcome	Interaction term (95% CI) p-value	Univariate risk ratio (95% CI) p-value	Risk ratio controlling for baseline severity and clustering (95% CI) p-value*	Risk ratio controlling for propensity score (95% CI) p-value	Risk ratio controlling for propensity score in imputed dataset (95% CI) p-value
None (reference)	23/33 (69.7%)		1.00	1.00	1.00	1.00
Immediate	207/374 (55.4%)	0.88 (0.68, 1.14) p=0.345	0.79 (0.62, 1.01) p=0.063	0.79 (0.62, 1.00) p=0.051	0.79 (0.63, 1.00) p=0.046	0.82 (0.65, 1.03) p=0.097
Delayed	21/43 (48.8%)	0.83 (0.55, 1.23) p=0.349	0.70 (0.48, 1.02) p=0.066	0.72 (0.49, 1.06) p=0.096	0.64 (0.45, 0.92) p=0.015	0.65 (0.45, 0.94) p=0.021

*Centor Score one point for each of tonsillar exudates, swollen tender anterior cervical nodes, lack of a cough, and history of fever

How this fits in:

- Antimicrobial resistance is a major threat to public health
- In the UK 75% of antibiotics are prescribed in primary care, mainly for respiratory tract infections
- Experimental studies suggests modest symptom benefit when antibiotics are prescribed for sore throat
- In routine practice, antibiotics do confer modest symptomatic improvement on average and similar effects are seen with delayed and immediate prescribing but delayed prescribing results in reduced antibiotic uptake compared to immediate prescribing

Contributorship

DESCARTE Investigators:

Michael Moore (GP and Professor in Primary Care, University of Southampton), developed the protocol for funding, contributed to the management of the study, and led the drafting of the paper
Beth Stuart (study Statistician, University of Southampton) developed the protocol, and led the quantitative analysis with MM and PL, and with `MM and PL drafted the initial versions of the paper.
Chris Butler (Professor of Primary Care, Cardiff and Oxford Universities) developed the protocol for funding, supervised the running of the study in the Cardiff Network and contributed to the drafting of the paper
Paula Barratt and Sue Broomfield (senior study managers) developed the protocol, provided day to day overall management of the study, coordinated recruitment in the lead study centre and coordination of other centres, commented on drafts of the paper.
John Campbell (GP and Professor of Primary Care, University of Exeter) developed the protocol for funding, lead the running of the study in the Exeter Network and contributed to the drafting of the paper
Brendan Delaney (Department of Surgery and Cancer, Imperial College, St Mary's Hospital, London W2 1NY) developed the protocol for funding, coordinated the development and management of the web resource, and contributed to drafting of the paper..
Hazel Everitt (GP and Associate Professor, University of Southampton) developed the protocol, with SB led the reliability study, supervised data collection for the reliability study, contributed to analysis and contributed to drafting the paper
Alastair Hay (GP and Professor of Primary Care, University of Bristol) developed the protocol for funding, led the Bristol study centre and contributed to the analysis and the drafting of the paper
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David Mant Emeritus Professor of General Practice, University of Oxford) developed the protocol for funding, supervised the running of clinical studies in the Oxford centre and contributed to the analysis and the drafting of the paper
Mark Mullee (study Statistician, Director Research Design Service, University of Southampton) developed the protocol for funding, contributed to study management, supervised data management, shared the quantitative analysis with BS and PL and contributed to the drafting of the paper
Ian Williamson (GP and Associate Professor in Primary Care, University of Southampton), developed the protocol for funding, contributed to the management of the study and drafting of the paper
Kerenza Hood (Director of South East Wales Trials Unit, Cardiff University). Contributed to protocol development, supervised the running of the study in the Cardiff Network and contributed to the drafting of the paper.
Paul Little (GP and Professor of Primary Care Research, University of Southampton) had the original idea for the protocol, led protocol development and the funding application, supervised the running of the lead study centre and coordination of centres, contributed to the analysis, contributed to drafting of the paper

Other *Contributors*:

The excellent running of the project in each centre was due to several individuals: in Oxford Sue Smith managed day to day data collection; in Cardiff Dr Eleri Owen-Jones managed the centre, Amanda Iles provided administrative support; in Exeter Ms Joy Choules was the Research Administrator and Ms Emily Fletcher helped with notes review; In Bristol the Research Administrator was Catherine Derrick.

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Ethical approval was given by the South West Multicentre Research Ethics Committee (number 06/MRE06/17).

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any other organisations (other than the MRC and NIHR Service Support as detailed above) for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.
MM is the guarantor of the paper and affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained

Data sharing: no additional data available.

Patient involvement
No patients were involved in the design of this study

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Appendix

Appendix Table 1 Baseline characteristics of the sample including those who returned the symptom diary

	Total cohort n=14610			**Patients who completed diaries and where prescribing strategy known n=1512**		
	Not given antibiotics	Given antibiotics	Delayed antibiotics	Not given antibiotics	Given antibiotics	Delayed antibiotics
Clinical assessment						
Number in cohort	6057	6089	2464	587	728	197
Mean severity of sore throat/difficulty swallowing on a 4 point Likert scale (SD)	2.93 (0.72)	3.32 (0.63)	3.06 (0.70)	2.93 (0.68)	3.35 (0.63)	3.01 (0.68)
Mean severity of all baseline symptoms* on a 4 point Likert scale (SD)	1.89 (0.39)	2.19 (0.39)	1.99 (0.40)	1.88 (0.40)	2.21 (0.38)	1.95 (0.36)
Mean FeverPain score	0.33 (0.58)	1.21 (1.09)	0.72 (0.84)	0.26 (0.52)	1.19 (1.11)	0.73 (0.84)
Prior duration in days (SD)	4.96 (6.48)	4.61 (4.10)	4.29 (3.34)	4.75 (4.14)	4.57 (3.39)	4.17 (3.15)
Age in years (SD)	34.72 (15.44)	32.65 (14.18)	34.07 (14.57)	37.61 (15.47)	36.04 (13.85)	35.68 (14.15)
Female gender	3,610/5,243 (68.85%)	4,147/6,269 (66.15%)	1,770/2,501 (70.77%)	443/587 (75.47%)	521/728 (71.57%)	147/197 (74.62%)
Smoker	1,016/5,212 (19.49%)	1,445/6,240 (23.16%)	481/2,484 (19.36%)	89/594 (15.24%)	127/726 (17.49%)	22/194 (11.34%)
Fever in last 24 hours	2,279/4,852 (46.97%)	4,109/5,704 (72.04%)	1,268/2,317 (54.73%)	261/585 (44.62%)	515/724 (71.13%)	113/197 (57.36%)
Temperature ^{o}C (SD)	36.66 (0.61)	37.00 (0.75)	36.77 (0.62)	36.64 (0.61)	36.99 (0.74)	36.74 (0.50)
Pus on tonsils	376/5,213 (7.21%)	3,751/6,232 (60.19%)	654/2,495 (26.21%)	30/581 (5.16%)	418/721 (57.98%)	50/197 (25.38%)
Severely inflamed tonsils	86/4,923 (1.75%)	1,418/5,855 (24.22%)	178/2,344 (7.59%)	6/572 (1.05%)	181/720 (25.14%)	12/191 (6.28%)
Number of prior medical problems	0.22 (0.49)	0.24 (0.51)	0.17 (0.43)	0.28 (0.55)	0.24 (0.51)	0.17 (0.39)
Return within 4 weeks with new or worsening symptoms	803/4,974 (16.14%)	864/5,932 (14.57%)	222/2,382 (9.49%)	107/564 (18.97%)	101/694 (14.55%)	24/186 (12.90%)
Return within 4 weeks with complications	75/4,974 (1.51%)	78/5,932 (1.31%)	21/2,382 (0.88%)	12/564 (2.13%)	8/694 (1.15%)	3/186 (1.15%)
Individual complications:						
Quinsy	11/4,974 (0.22%)	30/5,932 (0.52%)	6/2,382 (0.26%)	4/564 (0.71%)	3/694 (0.43%)	1/186 (0.54%)
Sinusitis	23/4,974 (0.46%)	12/5,932 (0.21%)	3/2,382 (0.13%)	2/564 (0.35%)	0/694	0/186
Otitis media	31/4,974 (0.62%)	27/5,932 (0.47%)	11/2,382 (0.47%)	5/564 (0.89%)	5/694 (0.72%)	2/186 (1.08%)

Cellulilitis/impetigo	10/4,974 (0.20%)	9/5,932 (0.16%)	1/2,382 (0.04%)	1/564 (0.18%)	0/694	0/186

*Baseline severity comprised of: sore throat, difficulty swallowing, feeling generally unwell, headache, disturbed sleep, muscle ache, fever during illness, fever in the last 24 hours, abdominal pain, diarrhoea, cough during illness, vomiting, runny nose, earache, inflamed pharynx, inflamed tonsils, cervical glands

Appendix Table 2

Effect of probability of streptococcal infection (FeverPAIN 3 or above) on duration of symptoms, symptom severity according to antibiotic prescribing strategy

		Interaction term	Univariate risk ratio (95% CI; p-value)	Risk ratio controlling for baseline severity and clustering (95% CI, p-value)*	Risk ratio controlling for propensity score	Risk ratio controlling for propensity score in imputed dataset
	Duration of symptoms (median, IQR)					
None	4 (2,7)					
Immediate	3 (2,4)	1.02 (0.87, 1.19; p=0.819)	1.26 (0.80, 1.99; p=0.323)	1.28 (0.97, 1.69; p=0.078)	1.18 (0.88, 1.57; p=0.278)	1.16 (0.86, 1.56; p=0.321)
Delayed	3 (2,6)	0.92 (0.76, 1.13; p=0.446)	0.92 (0.52, 1.63; p=0.771)	0.91 (0.60, 1.37; p=0.643)	1.04 (0.67, 1.62; p=0.859)	1.02 (0.66, 1.56; p=0.927)
	Mean symptom severity score		Difference	Difference controlling for clustering and, Antibiotic type and baseline severity score (CI)	Difference controlling for propensity score	Difference controlling for propensity score in the imputed dataset
None	2.42 (1.32)					
Immediate	1.95 (1.22)	-0.14 (-0.33, 0.05; p=0.142)	-0.47 (-1.04, 0.09; p=0.102)	-0.68 (-1.19, -0.17; p=0.010)	-0.81 (-1.48, -0.13; p=0.020)	-0.78 (-1.30, 0.25; p=0.004)
Delayed	2.16 (1.35)	-0.02 (-0.26, 0.22; p=0.884)	-0.26 (-0.96, 0.44; p=0.461)	-0.26 (-0.94, 0.41; p=0.443)	-0.41 (-1.07, 0.26; p=0.222)	-0.40 (-1.04, 0.24; p=0.240)

Appendix Table 3
Effect of probability of streptococcal infection (Centor 3 or above) on duration of symptoms, symptom severity according to antibiotic prescribing strategy

		Interaction term	Univariate risk ratio (95% CI; p-value)	Risk ratio controlling for baseline severity and clustering (95% CI, p-value)*	Risk ratio controlling for propensity score	Risk ratio controlling for propensity score in imputed dataset
	Duration of symptoms (median, IQR)					
None	4 (2,6)		1.00	1.00	1.00	1.00
Immediate	3 (2,4)	1.11 (0.84, 1.45; p=0.465)	1.33 (0.90, 1.95; p=0.153)	1.32 (1.04, 1.67; p=0.022)	1.26 (0.94, 1.68; p=0.117)	1.24 (0.94, 1.64; p=0.134)
Delayed	3 (2,6)	0.92 (0.59, 1.44; p=0.733)	1.10 (0.68, 1.80; p=0.695)	1.12 (0.76, 1.65; p=0.566)	1.01 (0.64, 1.61; p=0.953)	1.05 (0.68, 1.61; p=0.833)
	Mean symptom severity score		Difference	Difference controlling for clustering and, Antibiotic type and baseline severity score (CI)	Difference controlling for propensity score	Difference controlling for propensity score in the imputed dataset
None	2.48 (1.29)					
Immediate	2.00 (1.25)	-0.42 (-0.93, 0.08; p=0.100)	-0.48 (-0.93, -0.03; p=0.035)	-0.57 (-1.02, -0.11; p=0.015)	-0.50 (-0.98, -0.02; p=0.041)	-0.49 (-0.98, -0.01; p=0.044)
Delayed	2.03 (1.30)	-0.25 (-0.95, 0.45; p=0.476)	-0.45 (-1.02, 0.12; p=0.122)	-0.37 (-1.00, 0.26; p=0.249)	-0.45 (-1.02, -0.13; p=0.125)	-0.45 (-1.01, 0.11; p=0.113)

Appendix Table 4 Point estimates for those more and less likely to have streptococcal infection (FeverPAIN)

	Poorer symptomatic outcome: Risk ratio controlling for baseline severity and clustering (95% CI)		**Duration of symptoms** Hazard ratio controlling for baseline severity and clustering (95% CI)		**Mean symptom severity score** Difference controlling for clustering and, Antibiotic type and baseline severity score (CI)	
	Feverpain <3	Feverpain >=3	Feverpain<3	Feverpain>= 3	Feverpain<3	Feverpain>= 3
None (reference)	1.00	1.00	1.00	1.00		
Immediate	0.87 (0.79, 0.96; p=0.006)	0.71 (0.56, 0.89; p=0.004)	1.27 (1.13, 1.44; p<0.001)	1.28 (0.97, 1.69; p=0.078)	-0.22 (-0.42, -0.01; p=0.042)	-0.68 (-1.19, -0.17; p=0.010)
Delayed	0.84 (0.73, 0.97; p=0.014)	0.81 (0.57, 1.16; p=0.261)	1.18 (0.99, 1.42; p=0.072)	0.91 (0.60, 1.37; p=0.643)	-0.25 (-0.45, -0.05; p=0.014)	-0.26 (-0.94, 0.41; p=0.443)

Appendix Table 5 Point estimates for those more and less likely to have streptococcal infection (CENTOR)

	Poorer symptomatic outcome: Risk ratio controlling for baseline severity and clustering (95% CI)		**Duration of symptoms** Hazard ratio controlling for baseline severity and clustering (95% CI)		**Mean symptom severity score** Difference controlling for clustering and, Antibiotic type and baseline severity score (CI)	
	Centor<3	Centor>=3	Centor <3	Centor >=3	Centor <3	Centor >=3
None (reference)	1.00	1.00	1.00	1.00		
Immediate	0.87 (0.78, 0.97; p=0.010)	0.79 (0.62, 1.00; p=0.051)	1.26 (1.12, 1.44; p<0.001)	1.32 (1.04, 1.67; p=0.022)	-0.23 (-0.45, -0.02; p=0.036)	-0.57 (-1.02, -0.11; p=0.015)
Delayed	0.88 (0.77, 1.00; p=0.046)	0.72 (0.49, 1.06; p=0.096)	1.18 (0.98, 1.43; p=0.080)	1.12 (0.76, 1.65; p=0.566)	-0.24 (-0.44, -0.04; p=0.017)	-0.37 (-1.00, 0.26; p=0.249)