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Efficacy and safety of rapid tests to guide antibiotic prescriptions for sore throat (Review)

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Efficacy and safety of rapid tests to guide antibiotic prescriptions for sore throat.
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TABLE OF CONTENTS

[Intervention Review]

Efficacy and safety of rapid tests to guide antibiotic prescriptions for sore throat

Jérémie F Cohen[1,2], Jean-Yves Pauchard[3], Nils Hjelm[4], Robert Cohen[5], Martin Chalumeau[1,2]

[1]Department of General Pediatrics and Pediatric Infectious Diseases, AP-HP, Hôpital Necker, Paris, France. [2]Université de Paris, CRESS, INSERM, Paris, France. [3]Département Médico-Chirurgical de Pédiatrie, Hôpital de l'Enfance de Lausanne, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland. [4]Obstetrical, Perinatal and Pediatric Epidemiology Research Team (EPOPé), Centre de Recherche Épidémiologie et Statistique Sorbonne Paris Cité (CRESS), Inserm UMR1153, Paris Descartes University, Paris, France. [5]Association Clinique et Thérapeutique Infantile du Val-de-Marne (ACTIV), Saint-Maur-des-Fossés, France

Contact: Jérémie F Cohen, jeremie.cohen@inserm.fr, jim.cohen75@gmail.com.

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ABSTRACT

Background

Sore throat is a common condition caused by viruses or bacteria, and is a leading cause of antibiotic prescription in primary care. The most common bacterial species is group A streptococcus ('strep throat'). Between 50% to 70% of pharyngitis cases are treated with antibiotics, despite the majority of cases being viral in origin. One strategy to reduce antibiotics is to use rapid tests for group A streptococcus to guide antibiotic prescriptions. Rapid tests can be used alone or in combination with a clinical scoring system.

Objectives

To assess the efficacy and safety of strategies based on rapid tests to guide antibiotic prescriptions for sore throat in primary care settings.

Search methods

We searched CENTRAL, MEDLINE, Embase, CINAHL, Web of Science, and LILACS, as well as the trial registries ClinicalTrials.gov and the WHO ICTRP on 5 June 2019.

Selection criteria

We included randomised controlled trials (RCTs) comparing rapid tests with management based on clinical grounds to guide the prescription of antibiotics for people with a sore throat in ambulatory care settings. We included trials that randomised individuals, as well as cluster-RCTs in which individual practitioners (or practices) or emergency departments were randomised.

Data collection and analysis

Two review authors independently extracted data on the primary outcomes (number of participants provided with an antibiotic prescription; number of participants with an antibiotic dispensed) and secondary outcomes (duration of sore throat symptoms; duration of other symptoms; quality of life measures; number of participants with a complication attributed to the index infection; number of participants in need of re-consultation by the end of follow-up; number of participants in need of hospital admission by the end of follow-up; number of satisfied participants; number of participants with an adverse event attributed to the rapid test). We assessed the risk of bias of all included trials and used GRADE to assess the certainty of the evidence. We performed meta-analyses and sensitivity analyses when feasible.

Main results

We included five trials (2891 children and adult participants in total; 2545 participants after adjusting for clustering). Management in the intervention group was as follows: in three trials rapid tests were used in combination with a clinical scoring system; in one trial, some physicians were asked to use rapid tests alone, while others were asked to use rapid tests in combination with a clinical scoring system; in one trial, rapid tests were used alone.

Based on data from five trials (2545 participants), a large reduction in prescribed antibiotics was found in the rapid test group (481/1197) versus management based on clinical grounds (865/1348), for a summary risk difference (RD) of −25%, 95% confidence interval (CI) −31% to −18%; I^2 = 62%; moderate-certainty evidence. Estimates of effect on antibiotic prescription rates were stable in various sensitivity analyses.

Based on data from two trials (900 people) originating from the same overarching study, the evidence suggests that rapid tests may not reduce dispensed antibiotic treatments: rapid test group (156/445) versus management based on clinical grounds (197/455); summary RD −7%, 95% CI −17% to 2%; I^2 = 53%; low-certainty evidence.

Four trials (2075 participants) reported data on the number of participants with a complication attributed to the index infection; the summary odds ratio (OR) was 0.85, 95% CI 0.03 to 26.65; P = 0.93; I^2 = 62%; very low-certainty evidence, which means that people in the rapid testing group were less likely to develop complications of the index infection, but the evidence is very uncertain.

Two trials (1161 participants) reported on the number of participants in need of re-consultation by the end of follow-up; the summary OR was 1.12, 95% CI 0.57 to 2.21; P = 0.74; I^2 = 59%; low-certainty evidence, which means that participants in the rapid testing group were more likely to be in need of re-consultation by the end of the study follow-up, but the evidence is uncertain.

Lack of data impeded assessment of other secondary outcomes (including safety outcomes) and of sources of heterogeneity.

Authors' conclusions

Rapid testing to guide antibiotic treatment for sore throat in primary care probably reduces antibiotic prescription rates by 25% (absolute risk difference), but may have little or no impact on antibiotic dispensing. More studies are needed to assess the efficacy and safety of rapid test-guided antibiotic prescribing, notably to evaluate patient-centred outcomes and variability across subgroups (e.g. adults versus children).

PLAIN LANGUAGE SUMMARY

Use of rapid point-of-care testing for strep throat to guide doctors prescribing antibiotics for sore throat in primary care settings

Review question

Can rapid point-of-care tests help reduce antibiotic use in people with acute sore throat in primary care?

Background

Sore throat is one of the most common reasons for primary care visits. It can be caused by viruses or bacteria. The bacterial species most frequently identified in cases of sore throat is group A streptococcus ('strep throat'). Antibiotics are commonly prescribed for people with a sore throat, even though the majority of sore throats are caused by viruses, in which case antibiotics are ineffective and unnecessary. The concern is that antibiotics may cause side effects and contribute to antibiotic resistance, causing difficult-to-treat infections. It is particularly challenging for physicians to distinguish between sore throats of viral and bacterial origin by observation alone (clinically distinguish), even for experienced physicians. Throat swab cultures may take up to 48 hours to grow. This has led to the development of rapid tests. Several rapid tests are currently available to identify sore throat cases caused by group A streptococcus and can be used by doctors during primary care consultations for sore throat. These rapid tests could help reduce antibiotic prescriptions by withholding antibiotics in people with a negative test result. We assessed the available evidence from randomised controlled trials (a type of study in which participants are assigned to one of two or more treatment groups using a random method) to evaluate the effectiveness and safety of using rapid tests in primary care.

Study characteristics

We searched for randomised controlled trials published in any language up to June 2019. We identified five randomised controlled trials with a total of 2545 participants with sore throat in primary care settings.

Key results

Participants in the rapid test group were less likely to be prescribed antibiotics than participants managed based on clinical grounds (481/1197 versus 865/1348). A 25% reduction (i.e., a decrease of 25 percentage points) in antibiotic prescription rates is likely to be achieved by using rapid testing in people with sore throat in primary care. However, there may be little or no reduction between groups in dispensed antibiotic treatments. Antibiotic prescriptions refer to medicines prescribed by healthcare providers. Antibiotic dispensing

refers to medicines accessed in pharmacies. In some cases, patients may not present to the pharmacy to get their prescription filled. Four trials reported data on the number of participants with a complication attributed to the initial infection (e.g., tonsil abscess): complications were rare (0 to 3 per trial), and there may be little or no difference between people managed on clinical grounds alone and those managed with rapid testing but the evidence is very uncertain.

Certainty of the evidence

We ranked the certainty of the evidence as moderate for the number of participants provided with an antibiotic prescription, low for the number of participants with an antibiotic dispensed, and very low for the number of participants with a complication attributed to the episode of sore throat (e.g., abscess of the tonsils), respectively.

Conclusion

Compared with usual decision-making based on clinical examination alone, implementing rapid tests can reduce antibiotic prescription rates, but may have little or no impact on antibiotic dispensing. More studies are needed to assess other outcomes that are important to patients, including safety.

SUMMARY OF FINDINGS

Summary of findings 1. Rapid test (with and without scoring system combined) versus clinical grounds (with and without scoring system combined) to guide antibiotic prescriptions for sore throat

Rapid test (with and without scoring system combined) versus clinical grounds (with and without scoring system combined) to guide antibiotic prescriptions for sore throat

Patient or population: patients with sore throat
Setting: primary care settings
Intervention: management based on rapid tests
Comparison: management based on clinical grounds

Outcome	Illustrative comparative risks* (95% CI)		Effect size (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Clinical grounds (with and without scoring system combined)	Rapid test (with and without scoring system combined)			
Number of participants provided with an antibiotic prescription	636 per 1000	394 per 1000 (343 to 445)	RD −25% (−31% to −18%)	2545 (5 trials)	⊕⊕⊕⊖ Moderate[a]
Number of participants with an antibiotic dispensed	419 per 1000	344 per 1000 (277 to 432)	RD -7% (−17% to +2%)	900 (2 trials)	⊕⊕⊖⊖ Low[b,c]
Number of participants with a complication attributed to the index infection	2 per 1000	2 per 1000 (0 to 52)	OR 0.85 (0.03 to 26.65)	2075 (4 trials)	⊕⊖⊖⊖ Very low[d,e,f]
Number of participants in need of re-consultation by the end of follow-up	85 per 1000	94 per 1000 (51 to 174)	OR 1.12 (0.57 to 2.21)	1161 (2 trials)	⊕⊕⊖⊖ Low[g,h]

No trial reported data on the other predefined outcomes.

*__Assumed risk in the control group__ (clinical grounds): mean control group risk across studies.
CI: confidence interval; **OR:** odds ratio; **RD:** risk difference

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

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[a]Downgraded due to high heterogeneity (I^2 = 62%).
[b]Downgraded due to high heterogeneity (I^2 = 53%).
[c]Downgraded due to study limitations: two trials embedded within the same overarching study.
[d]Downgraded due to high heterogeneity (I^2 = 62%).
[e]Downgraded due to study limitations: two trials embedded within the same overarching study.
[f]Downgraded due to imprecision.
[g]Downgraded due to high heterogeneity (I^2 = 59%).
[h]Downgraded due to study limitations: two trials embedded within the same overarching study.

BACKGROUND

Description of the condition

Sore throat accounts for an estimated 1.0% of ambulatory care visits to physicians in the USA (including visits to physician offices, walk-in clinics, family medicine centres, and hospital outpatient and emergency departments) (CDC 2012), for a total of 7 million visits by adults (Hong 2011), and about the same number of visits by children each year (Linder 2005). Group A streptococcus (GAS) is found in about 35% of cases of childhood sore throat, Shaikh 2010, and 5% to 25% of adulthood cases (Ebell 2000; Wessels 2011). Non-GAS cases are considered viral.

Antibiotic treatment may be indicated for GAS infection to prevent suppurative (e.g. retropharyngeal abscess and quinsy) and non-suppurative complications (e.g., acute rheumatic fever and rheumatic heart disease) and to reduce the duration of symptoms and the spread of the infection (Spinks 2013). In industrialised settings where poststreptococcal diseases have become uncommon, the public health goal is shifting from preventing complications to minimising the inappropriate use of antibiotic agents in order to contain antimicrobial resistance.

About 50% to 70% of visits by patients with sore throat to ambulatory care result in antibiotic agents being prescribed (Fleming-Dutra 2016; Hong 2011; Linder 2005; Pouwels 2018). The association between antibiotic use and antibiotic resistance in bacteria has been clearly demonstrated (Goossens 2005), and reducing antibiotic resistance has become a public health priority internationally (Carlet 2012; Laxminarayan 2013). Antibiotics also carry a risk of side effects for patients, including adverse digestive effects such as diarrhoea and *Clostridioides difficile* infection, and allergic reactions such as skin rash and anaphylaxis (a whole-body and life-threatening allergic reaction).

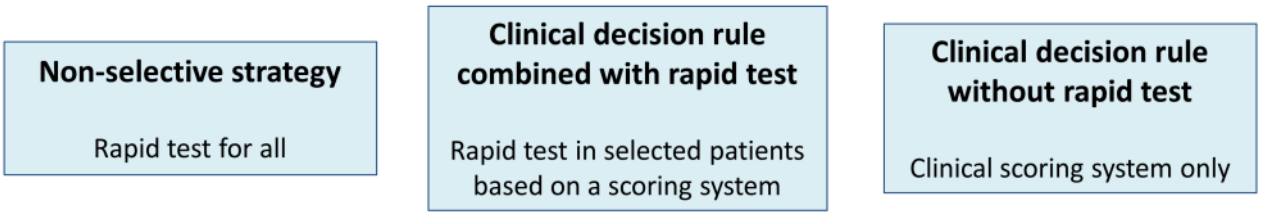
Description of the intervention

Because the signs and symptoms of GAS and viral sore throat overlap, some guidelines recommend that the diagnosis of GAS infection be confirmed by a throat culture or rapid test, both based on a throat swab, before using antibiotics (AAP 2015; Shulman 2012). Throat culture on a blood agar plate is the reference standard for the diagnosis of GAS in patients with sore throat. The major advantage of throat culture is its detection of GAS from swabs with a very low number of bacteria, thus conferring a high sensitivity. Its limitations are the need for special laboratory equipment and trained personnel and the 48-hour delay in obtaining results.

Rapid tests detect a cell wall carbohydrate, a GAS-specific antigen, by an immunologic reaction (Gerber 2004). They provide an indication for the clinician about the presence or absence of GAS in the throat sample within 5 to 10 minutes and can be performed directly on throat swabs at the point-of-care. They produce binary results (positive or negative) based on a colour change induced by a specific immunologic reaction with a sensing material (e.g. a test strip). Most rapid tests do not require any specific equipment. Their sensitivity is on average around 85% for a specificity of 95% (Cohen 2016; Lean 2014). In a recent cost-effectiveness study in primary care in the UK, a cost of GBP 3.25 (around USD 4.00) per rapid test was applied (Little 2014). Rapid tests are easy to perform, but specific training is needed (a one-hour training session is usually sufficient before implementation). A limitation of rapid tests is their inability to detect other bacteria that can cause sore throat (e.g. groups C and G beta-haemolytic streptococci). The decision to prescribe antibiotics is guided by the result of the rapid test: patients with a positive test result receive antibiotics, whereas those with a negative result are managed without antibiotics.

Rapid tests can be used alone or in combination with a clinical scoring system. Various scoring systems, such as Centor's, McIsaac's, and the feverPAIN scores, have been proposed. They combine signs and symptoms to help clinicians define groups of patients according to the clinical likelihood of GAS infection (Ebell 2000; Shaikh 2012). These scoring systems can be used alone to guide the decision to prescribe antibiotics. They can also be used to select patients in whom a rapid test should be performed (Figure 1) (Cohen 2015). Clinicians often make decisions based on clinical observation: in the USA, GAS testing (rapid test or throat culture) may be performed in only one-third of adults with a sore throat (Hong 2011), and in only half of cases in children (Linder 2005).

Figure 1. Type of interventions: Rapid tests can be used alone or in combination with a clinical scoring system.



How the intervention might work

Rapid tests can be performed at the point-of-care to assist decision-making regarding the need for an antibiotic in patients with sore throat. Such a test-treatment strategy may prevent against unnecessary use of antibiotics compared to standard care.

Potential limitations of rapid tests compared to clinical management include the time and expertise needed to collect the throat sample and perform the test, and patient dissatisfaction. In terms of misclassification, patients with false-negative results may be exposed to complications of untreated GAS infection, and patients with false-positive results may receive unnecessary antibiotics.

Why it is important to do this review

It is critical to implement strategies that allow limiting antibiotic prescriptions in ambulatory care settings to curtail the emergence of antibiotic resistance. Rapid tests could be effective in achieving

this goal. There is no systematic review of the literature investigating this question.

OBJECTIVES

To assess the efficacy and safety of strategies based on rapid tests to guide antibiotic prescriptions for sore throat in primary care settings.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs) comparing rapid tests with management based on clinical grounds, to guide the prescription of antibiotic treatment in people with sore throat in primary care settings. In the intervention arm, rapid tests could have been used non-selectively in all participants or in a selected group of participants based on a scoring system (Figure 1); initiation of antibiotic treatment in the intervention arm must have been based on a positive rapid test result. We defined management based on clinical grounds as unstructured clinical examination, use of a scoring system without a rapid test, or treatment as usual. We included trials that randomised individuals as well as cluster-RCTs in which individual practitioners (or practices) or emergency departments were randomised.

Types of participants

We included ambulatory care participants of all ages with a chief complaint of acute sore throat, or a clinical diagnosis of pharyngitis or tonsillitis, regardless of sex, severity, or duration of symptoms. In this review, ambulatory care settings included physician offices, walk-in clinics, family medical centres, and hospital outpatient and emergency departments.

Types of interventions

Use of a rapid test, alone or in combination with a scoring system, with antibiotics being prescribed in case of a positive result. The comparator was management based on clinical grounds (with or without a scoring system).

Types of outcome measures

We focused on efficacy (antibiotic use) and patient-relevant outcomes, including safety. We did not extract microbiological outcomes, such as microbiological cure.

Primary outcomes

1. Number of participants provided with an antibiotic prescription.
2. Number of participants with an antibiotic dispensed.

Secondary outcomes

1. Duration of sore throat symptoms.
2. Duration of other symptoms (e.g. fever).
3. Quality of life measures.
4. Number of participants with a complication attributed to the index infection (e.g. quinsy, acute rheumatic fever).
5. Number of participants in need of re-consultation by the end of follow-up.
6. Number of participants in need of hospital admission by the end of follow-up.
7. Number of satisfied participants.
8. Number of participants with an adverse event attributed to the rapid test (i.e. discomfort, dissatisfaction, vomiting).

Search methods for identification of studies

Electronic searches

We developed the search strategy in consultation with a medical librarian and the Information Specialist for the Cochrane Acute Respiratory Infections Group. We searched the following bibliographic databases:

1. Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 5, May), which includes the Cochrane Acute Respiratory Infections Group Specialised Register, in the Cochrane Library (searched 5 June 2019);
2. MEDLINE Ovid (1946 to 5 June 2019);
3. Embase Elsevier (1947 to 5 June 2019);
4. CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature, 1982 to 5 June 2019);
5. LILACS (Latin American and Caribbean Health Science Information database, 1982 to 5 June 2019); and
6. Web of Science (1900 to 5 June 2019).

The search strategies are shown in Appendix 1, Appendix 2, Appendix 3, Appendix 4, Appendix 5, and Appendix 6. We did not use any language or publication restrictions.

Searching other resources

We searched the following trial registries for additional clinical trials:

1. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov) (searched 5 June 2019); and
2. World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch/) (searched 5 June 2019).

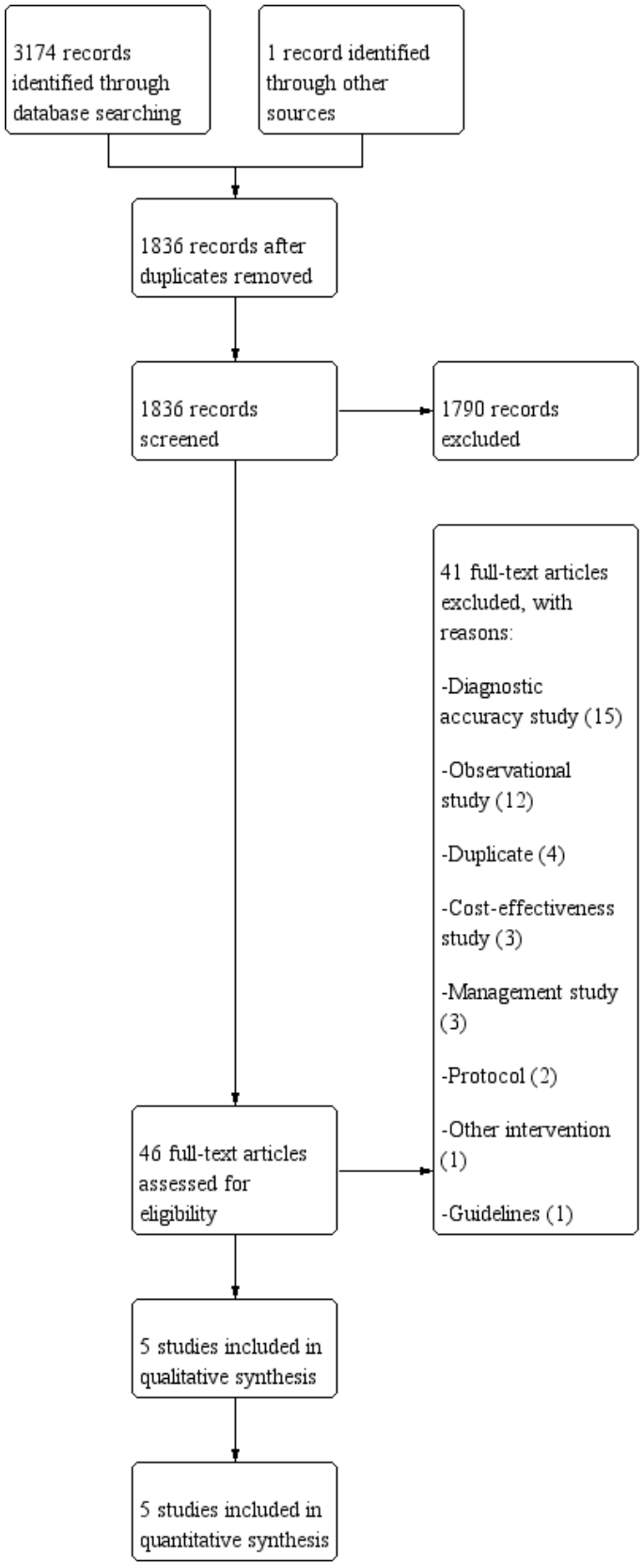
We handsearched reference lists of included articles and any relevant review articles identified by the search.

Data collection and analysis

Selection of studies

Two review authors (JYP, NH) independently assessed studies for inclusion, first by screening titles and abstracts, and then by evaluating the full texts of relevant articles. One review author (JFC) acted as arbiter in case of discrepancies. We recorded and reported reasons for excluding studies. We summarised the selection process in a PRISMA flowchart (Figure 2) (Moher 2009).

Figure 2. Study flow diagram.



Data extraction and management

Two review authors (JYP, NH) independently extracted a standard set of data from each included study using a prespecified data extraction form (Table 1); one review author (JFC) acted as arbiter in case of discrepancies. We extracted the following data:

1. intervention characteristics: type of intervention (rapid test used alone or in combination with a scoring system), type of rapid test system used (latex agglutination, enzyme immunoassay, optical immunoassay), commercial name and brand of the rapid test used;
2. outcome data: number of participants, number of participants provided with an antibiotic prescription, number of antibiotic prescriptions dispensed, duration of symptoms, quality of life measures, number of participants with a complication attributed to the index GAS infection (quinsy, acute rheumatic fever), number of participants in need of re-consultation by the end of follow-up, number of participants in need of hospital admission by the end of follow-up, number of satisfied participants, number of participants with an adverse event attributed to the rapid test;
3. population characteristics: mean age, clinical severity (McIsaac/Centor score); and
4. study characteristics: year of publication, funding.

One review author (NH) transferred data into Review Manager 5 (Review Manager 2014). We double-checked that data were entered correctly by comparing the data presented in the systematic review with the study reports.

Assessment of risk of bias in included studies

Two review authors (JYP, NH) independently assessed the risk of bias of included RCTs using the Cochrane 'Risk of bias' tool (Higgins 2011). We scored studies as high, low, or unclear risk of bias in the following domains: random sequence generation, allocation concealment, blinding of participants, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting. One review author (JFC) acted as arbiter in case of discrepancies.

Measures of treatment effect

We expected antibiotic prescriptions to be reported dichotomously. We expressed the result from each RCT in tables, where we summarised the number of participants receiving and not receiving antibiotics in each arm. We reported the primary outcome as a risk difference (RD) to summarise the reduction in antibiotic prescription rate between the intervention and control arms. If the baseline risks varied substantially across studies, we would use risk ratios (RRs) instead of RDs. Binary secondary outcomes were reported as odds ratios (OR).

Unit of analysis issues

The unit of analysis was the individual participant. If we included cluster-RCTs (e.g. where general practitioners were randomised), we adjusted the unit of analysis accordingly. We adjusted for clustering by calculating the effective sample size, based on the number of clusters and the intracluster correlation coefficient (Higgins 2011). If the number of clusters and the intracluster correlation coefficient were not published, we used external estimates obtained from similar studies.

Studies with multiple treatment groups

In case of RCTs with several intervention arms (e.g. rapid test alone and rapid test used in combination with a scoring system), we extracted data from each arm separately. Similarly, in the case of multiple control groups (e.g. unstructured clinical examination and use of a scoring system without a rapid test), we extracted data separately.

Dealing with missing data

We extracted data to permit an intention-to-treat analysis, that is participants were analysed according to the group to which they had been randomised. We reported any discrepancies between randomised and analysed participants. In a sensitivity analysis, we considered participants with missing outcome data as having received antibiotics in the meta-analysis (i.e. intervention failures).

Assessment of heterogeneity

We assessed the statistical heterogeneity across included RCTs using the I^2 statistic.

Assessment of reporting biases

We planned to use funnel plots to assess the presence of a small-study effect.

Data synthesis

Because the between-study variance was a priori expected to be substantial, we used random-effects meta-analysis models to summarise the data from the included RCTs, regardless of the estimate of the I^2 statistic results. We planned that if the data allowed, we would perform the following separate meta-analyses.

1. Comparison 1: Rapid test (with and without scoring system combined) versus clinical grounds (with and without scoring system combined).
2. Comparison 2: Rapid test alone versus clinical grounds (with scoring system).
3. Comparison 3: Rapid test alone versus clinical grounds (without scoring system).
4. Comparison 4: Rapid test used with a scoring system versus clinical grounds (with scoring system).
5. Comparison 5: Rapid test used with a scoring system versus clinical grounds (without scoring system).

We carried out each meta-analysis for the two primary outcomes (number of participants provided with an antibiotic prescription and number of antibiotic prescriptions dispensed). We performed other analyses (secondary outcomes, subgroup analyses, and sensitivity analyses) only for Comparison 1.

Subgroup analysis and investigation of heterogeneity

We planned that if the data allowed, we would perform the following subgroup analyses:

1. children (≤ 18 years) versus adults (> 18 years);
2. type of rapid test (latex agglutination, enzyme immunoassay, or optical immunoassay); and
3. setting: office-based versus hospital-based.

Sensitivity analysis

We carried out sensitivity analyses to explore the robustness of the results when restricting to:

1. RCTs with low risk of bias (i.e. risk of bias judged as low in at least three domains) according to the 'Risk of bias' tool; and
2. RCTs where individual participants were randomised (versus cluster-RCTs).

We also carried out a sensitivity analysis in which participants with missing outcome data were considered as having received antibiotics (i.e. intervention failures).

Summary of findings and assessment of the certainty of the evidence

For Comparison 1 (Rapid test (with and without scoring system combined) versus clinical grounds (with and without scoring system combined)), we created a Summary of findings 1 for the following outcomes:

1. number of participants provided with an antibiotic prescription;
2. number of participants with an antibiotic dispensed;
3. number of participants with a complication attributed to the index infection; and
4. number of participants in need of re-consultation by the end of follow-up.

We used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the certainty of a body of evidence as it relates to the studies which contribute data to the meta-analyses for the prespecified outcomes (Atkins 2004). We used methods and recommendations described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We justified all decisions to down- or upgrade the certainty of studies using footnotes, and made comments to aid the reader's understanding of the review where necessary.

RESULTS

Description of studies

See Characteristics of included studies, Characteristics of excluded studies, and Characteristics of studies awaiting classification.

Results of the search

We performed the electronic searches on 5 June 2019. The searches identified 2217 titles (1836 non-duplicates), of which 1790 articles were excluded based on title or abstract (Figure 2). After assessing the full text of 46 articles, we excluded 41 trials. We included five trials at this stage (Little 2013a; Little 2013b; Llor 2011a; Maltezou 2008; Worrall 2007a). We searched other resources, including trial registries, and identified one additional clinical trial that is currently awaiting classification (Wächtler 2018).

Included studies

The included RCTs were conducted in Canada (Worrall 2007a), Greece (Maltezou 2008), Spain (Llor 2011a), and the UK (Little 2013a; Little 2013b), between 2005, Worrall 2007a, and 2011, Little 2013a; Little 2013b.

Two included trials, Little 2013a; Little 2013b, were part of the same overarching study, the PRImary care Streptococcal Management (PRISM) study (Little 2014).

In Maltezou 2008, children were enrolled in three groups:

1. Group A: enrolment by private-practice paediatricians with diagnosis by clinical picture only;
2. Group B: recruitment by private-practice paediatricians with diagnosis by a rapid antigen detection test (RADT) and culture; and
3. Group C: enrolment by hospital-affiliated paediatricians in the paediatric outpatient clinic with diagnosis by RADT and culture.

We contacted the trial authors for clarification, who informed us that only participants enrolled by private-practice paediatricians were truly randomised, thus only participants from Groups A and B were included in the review.

Three trials included subgroups that were not eligible for inclusion (Little 2013a; Little 2013b; Maltezou 2008). In Little 2013a and Little 2013b, the “Delayed antibiotics” group (“Group 1”) was excluded because, by definition, all participants were expected to be prescribed antibiotics. In Maltezou 2008, Group C was excluded because participants were not truly randomised. After exclusion of these participants (n = 764), the review contained a total of 2891 participants.

Three RCTs included both adults and children (Little 2013a; Little 2013b; Llor 2011a); one included only children (Maltezou 2008); and one included only adults (Worrall 2007a).

The unit of randomisation was the participant in two RCTs (Little 2013a; Little 2013b), the physician in two RCTs (Maltezou 2008; Worrall 2007a), and the healthcare centre in one RCT (Llor 2011a). The number of clusters ranged from 17, Maltezou 2008, to 37, Worrall 2007a; average cluster size ranged from 14, Worrall 2007a, to 38, Maltezou 2008. We adjusted for clustering by calculating the effective sample size, using an intracluster correlation coefficient of 0.01 (Adams 2004); the total number of participants included in the quantitative synthesis after adjusting for clustering was 2545. Effective sample sizes were used in both numerators and denominators in every table, figure, and analysis. The design effect was of 1.26 in Llor 2011a, 1.37 in Maltezou 2008, and 1.13 in Worrall 2007a.

Management in the intervention group was based on the use of an RADT combined with a clinical scoring system, with RADT use initiated above a prespecified score in three RCTs (Little 2013a; Little 2013b; Maltezou 2008). In Worrall 2007a, some physicians were asked to use RADT on all participants, whilst others were asked to use RADT only above a certain clinical score. In Llor 2011a, RADT was used on all participants in the intervention group.

Management in the control group relied on a clinical scoring system in three RCTs (Little 2013a; Llor 2011a; Maltezou 2008). In Worrall 2007a, some physicians were asked to use a clinical scoring system, whilst others were asked to rely on usual clinical practice for decision-making. Management in Little 2013b was not clearly described for either the intervention or the control group.

Clinical scoring systems used across studies were the Centor score, Llor 2011a; Maltezou 2008; Worrall 2007a, and FeverPAIN (Little 2013a; Little 2013b).

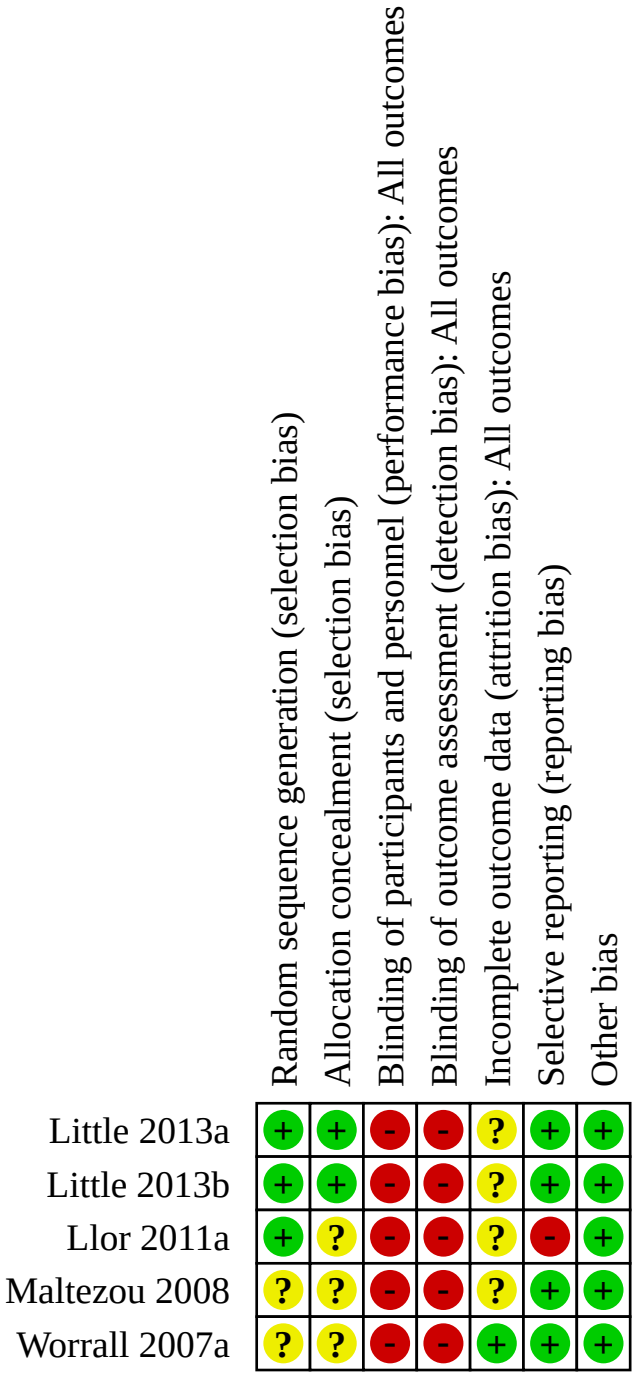
Excluded studies

Of the 46 trials assessed as full text, we excluded 41. Thirty-three trials were not RCTs (diagnostic accuracy studies, n = 15; observational studies, n = 12; cost-effectiveness studies, n = 3; management studies, n = 3). Four trials were duplicates; two references led to trial protocols; one trial evaluated another intervention; and one led to a clinical guideline.

Risk of bias in included studies

The overall risk of bias is presented graphically and summarised in Figure 3. For further information on the included studies, see Characteristics of included studies table.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Random sequence generation (selection bias)

In three trials, participants were randomised to treatment and control groups using appropriate random sequence generation methods. Two trials did not report random sequence generation; we assessed the risk of bias for these studies as unclear.

Allocation

In two trials, we judged the method used to randomise participants to the treatment and control groups as appropriate. Allocation concealment of individuals does not apply to cluster-RCTs at the physician or practice level, so we graded these three studies as at unclear risk of bias.

Blinding

Rapid test results were used in decision-making, thus clinicians and participants were considered to be non-blinded, resulting in a judgement of high risk of bias for all included RCTs.

Incomplete outcome data

The numbers of participants with missing data on prescribed antibiotics were as follows: one in Little 2013a (intervention group); one in Little 2013b (control group); 14 in Llor 2011a (10 in the control group and four in the intervention group); nine in Maltezou 2008 (control group); and none in Worrall 2007a.

The numbers of participants with missing data on dispensed antibiotics were as follows: 99 in Little 2013a; 178 in Little 2013b; 14 in Llor 2011a; nine in Maltezou 2008; and none in Worrall 2007a.

Selective reporting

We assessed the risk of selective reporting as low in four studies (Little 2013a; Little 2013b; Maltezou 2008; Worrall 2007a). We judged the risk of selective reporting as high in one study because of inconsistencies in outcome reporting (Llor 2011a).

Other potential sources of bias

None.

Effects of interventions

See: **Summary of findings 1** Rapid test (with and without scoring system combined) versus clinical grounds (with and without scoring system combined) to guide antibiotic prescriptions for sore throat

COMPARISON 1: Rapid test (with and without scoring system combined) versus clinical grounds (with and without scoring system combined)

Primary outcomes

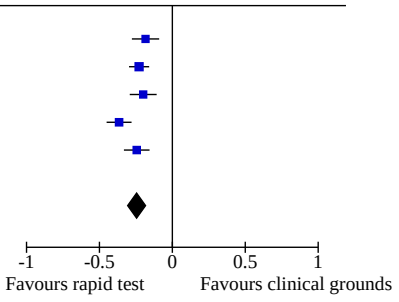
1. Number of participants provided with an antibiotic prescription

Five trials (2545 participants) reported on this outcome. The proportion of participants who received a prescription of antibiotics ranged from 32% to 46% in the intervention group and from 57% to 70% in the control group. The summary result for all included trials showed a statistically significant effect of using a rapid test on the number of participants provided with an antibiotic prescription (risk difference (RD) −0.25, 95% confidence interval (CI) −0.31 to −0.18; P < 0.001; I^2 = 62%; moderate-certainty evidence; Analysis 1.1; Figure 4). We did not use a funnel plot to assess reporting bias because of the low number of included trials. See Summary of findings 1.

Figure 4. Comparison 1: Rapid test (with and without scoring system combined) versus clinical grounds (with and without scoring system combined), outcome: 1.1 Number of participants provided with an antibiotic prescription.

Study or Subgroup	Rapid test Events	Rapid test Total	Clinical grounds Events	Clinical grounds Total	Weight	Risk Difference M-H, Random, 95% CI
Little 2013a	86	213	124	211	18.6%	-0.18 [-0.28 , -0.09]
Little 2013b	167	367	263	385	23.1%	-0.23 [-0.30 , -0.16]
Llor 2011a	98	223	133	208	18.8%	-0.20 [-0.29 , -0.11]
Maltezou 2008	67	198	190	270	20.0%	-0.37 [-0.45 , -0.28]
Worrall 2007a	63	196	155	274	19.6%	-0.24 [-0.33 , -0.16]
Total (95% CI)		**1197**		**1348**	**100.0%**	**-0.25 [-0.31 , -0.18]**
Total events:	481		865			

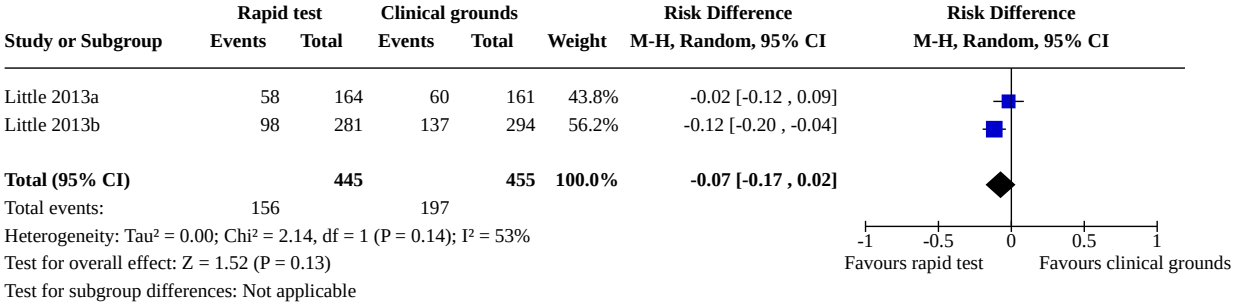
Heterogeneity: Tau² = 0.00; Chi² = 10.40, df = 4 (P = 0.03); I² = 62%
Test for overall effect: Z = 7.84 (P < 0.00001)
Test for subgroup differences: Not applicable



2. Number of participants with an antibiotic dispensed

Two trials (900 participants) reported on this outcome (Little 2013a; Little 2013b). In the intervention groups, the antibiotic dispensing rate was 35% in both trials. In the control groups, antibiotic dispensing rates ranged from 37% to 47%. The summary result for the two included trials showed a non-significant effect of using a rapid test on the number of antibiotic prescriptions dispensed (RD −0.07, 95% CI −0.17 to 0.02; P = 0.13; I^2 = 53%; low-certainty evidence; Analysis 1.2; Figure 5). See Summary of findings 1.

Figure 5. Comparison 1: Rapid test (with and without scoring system combined) versus clinical grounds (with and without scoring system combined), outcome: 1.2 Number of participants with an antibiotic dispensed.



Secondary outcomes

1. Duration of sore throat symptoms

No trials reported on this outcome.

2. Duration of other symptoms (e.g. fever)

No trials reported on this outcome.

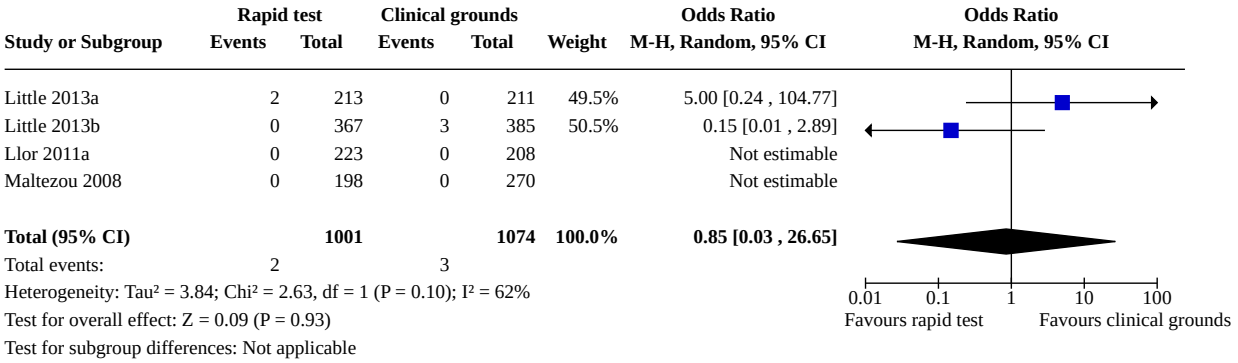
3. Quality of life measures

No trials reported on this outcome.

4. Number of participants with a complication attributed to the index infection (e.g. quinsy, acute rheumatic fever)

Four trials (2075 participants) reported on this outcome. Two trials reported that no such complications were observed (Llor 2011a; Maltezou 2008). Two trials reported suppurative complications (Little 2013a; Little 2013b). The summary odds ratio (OR) was 0.85, 95% CI 0.03 to 26.65; P = 0.93; I^2 = 62%; very low-certainty evidence; Analysis 1.3; Figure 6, which means that participants in the rapid testing group were less likely to develop complications of the index infection, but this association was not statistically significant. See Summary of findings 1.

Figure 6. Comparison 1: Rapid test (with and without scoring system combined) versus clinical grounds (with and without scoring system combined), outcome: 1.6 Number of participants with a complication attributed to the index infection.



5. Number of participants in need of re-consultation by the end of follow-up

Two trials (1161 participants) reported on this outcome (Little 2013a; Little 2013b). The summary OR was 1.12, 95% CI 0.57 to 2.21; P = 0.74; I^2 = 59%; low-certainty evidence; Analysis 1.4, which means that participants in the rapid testing group were more likely to be in need of re-consultation by the end of study follow-up, but this association was not statistically significant. See Summary of findings 1.

6. Number of participants in need of hospital admission by the end of follow-up

No trials reported on this outcome.

7. Number of satisfied participants

No trials reported on this outcome.

8. Number of participants with an adverse event attributed to the rapid test (i.e. discomfort, dissatisfaction, vomiting).

No trials reported on this outcome.

COMPARISON 2: Rapid test alone versus clinical grounds (with scoring system)

Primary outcomes

1. Number of participants provided with an antibiotic prescription

One trial (256 participants) reported on this outcome (Worrall 2007a). This study showed a statistically significant effect of using

an RADT on the number of participants provided with an antibiotic prescription (RD −0.29, 95% CI −0.40 to −0.17; P < 0.001; Analysis 2.1).

2. Number of participants with an antibiotic dispensed

No trials reported data on this outcome.

Secondary outcomes

No trials reported on any of the secondary outcomes.

COMPARISON 3: Rapid test alone versus clinical grounds (without scoring system)

Primary outcomes

1. Number of participants provided with an antibiotic prescription

Three trials (1129 participants) reported on this outcome (Llor 2011a; Maltezou 2008; Worrall 2007a). These studies showed a statistically significant effect of using an RADT on the number of participants provided with an antibiotic prescription (RD −0.29, 95% CI −0.40 to −0.19; P < 0.001; I^2 = 71%; Analysis 3.1).

2. Number of participants with an antibiotic dispensed

No trials reported data on this outcome.

Secondary outcomes

No trials reported on any of the secondary outcomes.

COMPARISON 4: Rapid test used with a scoring system versus clinical grounds (with scoring system)

Primary outcomes

1. Number of participants provided with an antibiotic prescription

Three trials (1416 participants) reported on this outcome (Little 2013a; Little 2013b; Worrall 2007a). These studies showed a statistically significant effect of using an RADT on the number of participants provided with an antibiotic prescription (RD −0.21, 95% CI −0.26 to −0.16; P < 0.001; I^2 = 0%; Analysis 4.1).

2. Number of participants with an antibiotic dispensed

Two trials (900 participants) reported on this outcome (Little 2013a; Little 2013b). The pooled result showed a non-significant effect of using an RADT on the number of antibiotic prescriptions dispensed (RD −0.07, 95% CI −0.17 to 0.02; P = 0.13; I^2 = 53%; Analysis 4.2).

Secondary outcomes

No trials reported on any of the secondary outcomes.

COMPARISON 5: Rapid test used with a scoring system versus clinical grounds (without scoring system)

Primary outcomes

1. Number of participants provided with an antibiotic prescription

One trial (214 participants) reported on this outcome (Worrall 2007a). This study showed a statistically significant effect of using an RADT on the number of participants provided with an antibiotic prescription (RD −0.20, 95% CI −0.34 to −0.07; P = 0.003; Analysis 5.1).

2. Number of participants with an antibiotic dispensed

No trials reported data on this outcome.

Secondary outcomes

No trials reported on any of the secondary outcomes.

Subgroup analysis and investigation of heterogeneity

1. Children (≤ 18 years) versus adults (> 18 years)

Three RCTs included both adults and children (Little 2013a; Little 2013b; Llor 2011a); one RCT included only children (Maltezou 2008); and one RCT included only adults (Worrall 2007a). We judged the data as too scarce to permit subgroup analysis.

2. Type of rapid test (latex agglutination, enzyme immunoassay, or optical immunoassay)

All included studies used an enzyme immune-assay in the intervention group, therefore we could not perform this pre-planned subgroup analysis.

3. Setting: office-based versus hospital-based

Two trials were conducted in general practitioner practices (Little 2013a; Little 2013b), one in family doctors' offices (Worrall 2007a), one in paediatricians' offices (Maltezou 2008); and one in primary healthcare centres (Llor 2011a). No trial was hospital-based. We could therefore not perform this pre-planned subgroup analysis.

Sensitivity analysis

The following sensitivity analyses apply to Comparison 1: Rapid test (with and without scoring system combined) versus clinical grounds (with and without scoring system combined).

1. RCTs with low risk of bias according to the 'Risk of bias' tool

We judged three RCTs as at low overall risk of bias (Little 2013a; Little 2013b; Worrall 2007a). The summary estimate of the number of participants provided with an antibiotic prescription was comparable when restricting to RCTs judged as at low overall risk of bias (1646 participants): RD −0.22, 95% CI −0.27 to −0.17; P < 0.001; I^2 = 0%; Analysis 6.1.

2. RCTs where individual participants were randomised (versus cluster-RCTs)

The unit of randomisation was the participant in two trials (Little 2013a; Little 2013b), the physician in two trials (Maltezou 2008; Worrall 2007a), and the healthcare centre in one trial (Llor 2011a). The summary estimate of the number of participants provided with an antibiotic prescription was stable when restricting to RCTs in which individual participants were randomised (1176 participants): RD −0.21, 95% CI −0.27 to −0.16; P < 0.001; I^2 = 0%; Analysis 7.1.

3. Imputation of missing outcome data as intervention failures (i.e. receiving antibiotics)

The numbers of participants with missing data on prescribed antibiotics were as follows: one in Little 2013a (intervention group); one in Little 2013b (control group); 14 in Llor 2011a (10 in the control group and four in the intervention group); nine in Maltezou 2008 (control group); none in Worrall 2007a. The summary estimate of the number of participants provided with an antibiotic prescription was stable when imputing missing values as intervention failures

(2557 participants): RD −0.25, 95% CI −0.32 to −0.18; P < 0.001; I^2 = 61%; Analysis 8.1.

DISCUSSION

Summary of main results

We identified five RCTs evaluating the effect of using an RADT on antibiotic prescription in people with a sore throat in primary care settings, encompassing a total of 2891 participants (2545 after adjusting for clustering). We found that using RADTs reduced antibiotic prescriptions by 25% absolute risk reduction (RD) (95% CI -31% to -18%); antibiotic dispensing was not significantly affected (RD -7%, 95% CI -17% to 2%; data from only two RCTs).

Overall completeness and applicability of evidence

No data were reported concerning most of our prespecified secondary outcomes. Two included studies reported that no pharyngitis-related complications occurred during follow-up, whilst reporting observed side effects from antibiotic use, mostly skin rash and diarrhoea (Llor 2011a; Maltezou 2008). Two trials reported both suppurative complications and side effects (Little 2013a; Little 2013b), and one trial did not report information about suppurative complications and antibiotic side effects (Worrall 2007a). Hence, the risk-to-benefit balance between side effects from antibiotic use and complications resulting from withholding antimicrobial treatment remains unclear. However, intervention trials are commonly underpowered for detecting adverse events, notably rare but severe side effects (Vandenbroucke 2004).

Rapid tests can be used alone or in combination with clinical scoring systems, such as the Centor score. Similarly, the control can be clinical grounds alone, with or without a scoring system. Unsurprisingly, the most extreme contrast led to the most extreme impact: when combining data from the three trials (1129 participants) that compared RADT (without a scoring system) against clinical grounds (without a scoring system), the reduction in the number of people provided with an antibiotic prescription rose to RD −29%, 95% CI −40% to −19% (Table 2). Of note, clinical scoring systems may perform poorly in children (Cohen 2015).

Quality of the evidence

We assessed only three RCTs as at low overall risk of bias (Little 2013a; Little 2013b; Worrall 2007a), mainly due to poor reporting impeding methodological quality assessment and because blinding was impossible. The support for the impact of RADTs on antibiotics dispensing is weaker than for the impact on antibiotic prescribing, mainly due to sparse data (two RCTs). Moreover, the two RCTs reporting on antibiotic dispensing were performed by the same research team, thereby decreasing their external validity. The discrepancy between prescription rates and dispensing rates could be explained by the fact that, in order to obtain data on antibiotic dispenses, follow-up was required. One could hypothesise that people more adherent to the study protocol were both more likely to take the antibiotics from the pharmacy and to participate in the study follow-up. However, if follow-up had instead included all participants, one could have expected a greater RD in antibiotic dispensing between intervention and control groups. Moreover, in both studies, antibiotic dispensing rates in the control groups were rather low (< 50%) (Little 2013a; Little 2013b). Participant behaviour with regard to filling their prescriptions may have been influenced by the knowledge that the trial was aimed at reducing antibiotic use.

Potential biases in the review process

The search strategy was developed by a medical librarian and included grey literature (e.g. conference abstracts and poster presentations). Also, as per Cochrane standards, the literature search was performed independently by two review authors.

Our meta-analysis is based on aggregated data. An analysis of individual patient data would have been preferable and would have offered the possibility of performing multiple imputations of missing data and multivariate adjustments.

Agreements and disagreements with other studies or reviews

This review included RCTs originating from high-income countries, involving both adults and children, and using recent RADT devices. Antibiotic prescription rates in the control groups ranged between 57% and 70%, which is consistent with reported antibiotic use for sore throat in high-income countries (range 53% to 93% in Chahwakilian 2011, Fleming-Dutra 2016, Hong 2011, Linder 2005, and Pouwels 2018).

In Worrall 2007a, the sample calculation was based on the trialists' aim of detecting a 25% reduction in the rate of antibiotic prescribing, which is in line with our findings.

Our estimates are also coherent with results from non-randomised evidence (i.e. observational studies) assessing the association between RADT and antibiotic use (range −16% to −23% in Ayanruoh 2009, Cardoso 2013, Humair 2006, and McIsaac 2004). For example, in Ayanruoh's before-after study, which included more than 8000 participants, implementing rapid testing led to a decrease in antibiotic prescription rates for children with pharyngitis (41.4% for those treated before implementing rapid testing versus 22.5% for those treated after implementing rapid testing; absolute RD −18.9%) (Ayanruoh 2009).

This is the first systematic review assessing the clinical impact of rapid testing in sore throat, but several reviews have already assessed the diagnostic accuracy of such rapid tests for sore throat. These reviews have shown that rapid tests are highly accurate, with a sensitivity of about 85% and a specificity of about 95% to detect streptococcal cases, with throat culture as the reference standard (Cohen 2016; Lean 2014). In contrast, a large-scale validation study including 142,081 patients ≥ 15 years old showed that the Centor score poorly correlates with the risk of strep throat (proportion of group A streptococcus-positives: score 0, 7%; score 1, 12%; score 2, 21%; score 3, 38%; score 4, 57%) (Fine 2012). The same applies to children (Cohen 2015). Because RADTs are highly specific, they may have a greater impact on antibiotic prescribing than clinical scoring systems.

Other point-of-care interventions are available to guide antibiotic prescribing in primary care. In a recent Cochrane Review based on six trials, C-reactive protein testing had a significant impact on antibiotic prescribing in participants with acute respiratory infections in primary care settings (pooled risk ratio (RR) 0.78, 95% CI 0.66 to 0.92) (Aabenhus 2014). In comparison, our effect size was −25% in absolute RD, which is equivalent to an RR of 0.62 (95% CI

0.54 to 0.70), showing that RADTs might have a greater impact than C-reactive protein testing.

AUTHORS' CONCLUSIONS

Implications for practice

Sore throat is most often a mild and self-limiting disease, even when due to group A streptococcus (GAS). Antibiotic treatment may be indicated to prevent suppurative and non-suppurative complications (e.g. acute rheumatic fever) and reduce symptom duration and infection spread, but absolute benefits are modest (Spinks 2013), notably in high-income countries.

We found a −25% risk difference in antibiotic prescribing when using rapid testing compared to management based on clinical grounds alone in people with sore throat. With increasing antimicrobial resistance, a rapid antigen detection test (RADT) may be useful in the clinical management of people with a sore throat. The cost of a rapid test is equivalent to that of a course of a first-line antibiotic such as ampicillin. Rapid tests do not require specific equipment and can be performed at the point-of-care within 5 to 10 minutes by personnel with limited training. Hence, rapid tests seem feasible in various settings, including low-resource countries. In settings where it is recommended to treat GAS pharyngitis with antibiotics, patients, physicians, and policymakers should prioritise RADTs in their attempt to reduce antimicrobial resistance.

Implications for research

Additional randomised controlled trials (RCTs) should be conducted to explore the robustness of our estimates. Whilst we observed a significant reduction in the use of antibiotics, we were not able to assess possible sources of heterogeneity, such as differences across age groups (children versus adults) and settings (office-based versus hospital-based physicians). We also encourage future trials to investigate not only the effect of RADTs on antibiotic use, but also patient-relevant outcomes such as the duration of other symptoms of sore throat and fever, quality of life measures, and patient satisfaction. The impact of implementing rapid tests on the acquisition of antibiotic-resistant bacteria may also be of interest. Also, RADTs should be compared to other point-of-care tests available in primary care, such as C-reactive protein. A new generation of molecular point-of-care tests for detecting GAS is now on the market; first evaluations show that they may be oversensitive compared to throat culture, which might negatively impact antimicrobial stewardship efforts (Tanz 2009). We included RCTs conducted in high-income countries (Canada, Greece, Spain, and the UK), but the impact of rapid testing on antibiotic prescribing might be even more favourable in low- and middle-income settings with high antibiotic use and currently low access to point-of-care tests (Joachim 2010).

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Little 2013a

Study characteristics	
Methods	**Clinical setting:** general practices **Single- or multicentre study:** multicentre **Country of study:** United Kingdom **Unit of allocation:** individual participants **Inclusion criteria:** people aged ≥ 3 years presenting with acute sore throat (2 weeks or less of sore throat) and an abnormal looking throat (erythema and/or pus) **Exclusion criteria:** non-infective causes of sore throat and inability of participant or parent/guardian to consent **Follow-up:** 1. participants completed a symptom diary each night until symptoms resolved or 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. Participants took their temperature with a disposable thermometer; 2. if a diary was not received by 3 weeks, a brief questionnaire was sent to document key outcomes, and then a telephone call if the brief questionnaire was not received; 3. notes were reviewed to document subsequent episodes of infection, time to return for these episodes, complications, and economic data; 4. the available follow-up time varied from 1 month to 2 years.
Participants	**Number of clusters (n):** not applicable **Number of participants (n):** 424 (as in Table 1 of the article) **Participant characteristics:** 1. age (distribution): mean age in years (SD) 31 (17) in Group 2 and 29 (17) in Group 3; 2. female participants (%): 62.8%; 3. clinical severity distribution of Centor/McIsaac score: not reported.
Interventions	**Management in intervention group(s):** RADT in combination with clinical examination/scoring system ("Group 3": clinical score 0 to 1, no antibiotics or rapid antigen test; score of 2, delayed antibiotic prescription without rapid testing; scores ≥ 3, rapid antigen test with antibiotics not offered if negative result). **Type of RADT system used:** enzyme immunoassay **Commercial name and brand of the RADT:** IMI TestPack Plus Strep A (Inverness Medical) **Management in control group(s)**: clinical grounds with a scoring system ("Group 2": clinical score 0 to 1, no antibiotics; score 2 to 3, delayed antibiotics; score ≥ 4, immediate antibiotics).

Little 2013a *(Continued)*

Outcomes	**Primary outcome(s):** symptom severity (mean score of soreness and difficulty swallowing in days 2 to 4) **Secondary outcome(s):** 1. duration of moderately bad symptoms; 2. use of antibiotics; 3. belief in need to see doctor in future; 4. return to the surgery; 5. suppurative complications.
Notes	**Type of report:** journal article **Source(s) of funding:** funded by the National Institute for Health Research Heath Technology Assessment (HTA) Programme (project number 05/10/01) **RCT registration number:** ISRCTN32027234 The PRISM RCT had 2 parts, each relying on a different clinical scoring system. The results of the first part of the trial, obtained with Score 1, are presented in the online appendices (and here referred to as Little 2013b). The results of the second part of the trial, obtained with Score 2 (acronym FeverPAIN), are presented in the text as the main findings (and here referred to as Little 2013a). We assumed that the methods were similar for the 2 parts of the trial. The "Delayed antibiotics" group ("Group 1") was excluded because by definition all participants were prescribed antibiotics.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were individually randomised with a web based computer randomisation service to one of three groups. [...] Randomisation used permuted block sizes of 3, 6, 9, and 12, which were also randomly chosen."
Allocation concealment (selection bias)	Low risk	Web-based computer randomisation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding is impossible in this context, and this lack of blinding is likely to influence the outcome.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding is impossible in this context, and this lack of blinding is likely to influence the outcome.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There are discrepancies between participants included in the initial assessments and in the follow-up (20% to 25% reduction in participants assessed for the outcome "antibiotic use" compared to initial number of participants), without any explanation.
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the Methods section are presented in the Results section. There is concordance between protocol and article.
Other bias	Low risk	None

Little 2013b

Study characteristics	
Methods	**Clinical setting:** see Little 2013a **Single- or multicentre study:** see Little 2013a **Country of study:** see Little 2013a **Unit of allocation:** see Little 2013a **Inclusion criteria:** see Little 2013a **Exclusion criteria:** see Little 2013a **Follow-up:** see Little 2013a
Participants	**Number of clusters (n):** not applicable **Number of participants (n):** 752 (as in Table B of the article) **Participant characteristics:** 1. age (distribution): not reported; 2. female participants (%): not reported; 3. clinical severity distribution of Centor/McIsaac score: not reported.
Interventions	**Management in intervention group(s):** RADT in combination with clinical examination/scoring system **Type of RADT system used:** see Little 2013a **Commercial name and brand of the RADT:** see Little 2013a **Management in control group(s):** clinical grounds with a scoring system ("Score 1")
Outcomes	**Primary outcome(s):** see Little 2013a **Secondary outcome(s):** see Little 2013a
Notes	See Little 2013a

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Patients were individually randomised with a web based computer randomisation service to one of three groups (see below). Randomisation used permuted block sizes of 3, 6, 9, and 12, which were also randomly chosen."
Allocation concealment (selection bias)	Low risk	Web-based computer randomisation
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding is impossible in this context, and this lack of blinding is likely to influence the outcome.
Blinding of outcome assessment (detection bias)	High risk	Blinding is impossible in this context, and this lack of blinding is likely to influence the outcome.

Little 2013b *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There are discrepancies between participants included in the initial assessments and in the follow-up (20% to 25% reduction in participants assessed for the outcome "antibiotic use" compared to initial number of participants), without any explanation.
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the Methods section are presented in the Results section. There is concordance between protocol and article.
Other bias	Low risk	None

Llor 2011a

Study characteristics	
Methods	**Clinical setting:** primary healthcare centres **Single- or multicentre study:** multicentre **Country of study:** Spain **Unit of allocation:** clusters **Inclusion criteria:** patients aged 14 to 60 years diagnosed with acute pharyngitis with 1 or more Centor criteria (fever, sore throat, tonsillar exudate, tender cervical nodes, and/or absence of cough). **Exclusion criteria:** patients with more than 5 episodes of pharyngitis over the last year; those with immunosuppressed condition, such as active neoplasm, AIDS, or reception of chemotherapy, radiotherapy, steroids, and/or immunosuppressive therapy; those with heart valve disease; rheumatic fever; an episode of pharyngitis treated with antibiotics in the previous 15 days; and those who had tonsillectomy. **Follow-up:** "evolution within the first month" (no more information reported).
Participants	**Number of clusters (n):** 20 centres **Number of participants (n):** 557 enrolled, 543 included in the analysis **Participant characteristics:** 1. age (distribution): mean age in years (SD) 31.7 (11.4); 2. female participants (%): 62.8%; 3. clinical severity distribution of Centor/McIsaac: Centor 1, 24.1%; Centor 2, 31.5%; Centor 3, 27.6%; Centor 4, 16.8%.
Interventions	**Management in intervention group(s):** RADT alone ("Physicians allocated to the intervention group were provided with RADT") **Type of RADT system used:** enzyme immunoassay **Commercial name and brand of the RADT:** OSOM Strep A test (Genzyme) **Management in control group(s):** clinical grounds without a scoring system ("Those assigned to the control group managed streptococcal pharyngitis with only clinical criteria")
Outcomes	**Primary outcome(s):** 1. percentage of antibiotic prescription;

Llor 2011a *(Continued)*

2. proportion of inappropriate antibiotic prescription (including both participants without GABHS infection treated with antibiotics and those with GABHS infection in which antibiotic therapy was not given).

Secondary outcome(s):

1. type of antibiotics prescribed;
2. validity of the RADT (sensitivity, specificity, predictive values);
3. full clinical recovery at the third week (including participants without side effects, visits that required a change of treatment, or the presence of complications).

Notes

Type of report: journal article

Source(s) of funding: funded by the Fondo de Investigaciones Sanitarias, the University and Innovation Department of Spain, and by the Catalan Society of Family Medicine. The Rapid Test Device OSOM StrepA of Genzyme was provided by Leti. All the trial authors declare they have received no honoraria from the Leti Laboratory for undertaking this study. Carl Llor declares having received tests free of charge from Leti for investigational studies. In the last 3 years Leti has covered the travel and accommodation costs for seeking the inclusion of physicians in a control group in the Happy Audit study in Murcia. Leti also covered the accommodation costs during an international congress on respiratory disease in primary care within the last year.

RCT registration number: ISRCTN23587778

We contacted the authors to confirm that physicians in the control group were not invited to prescribe antibiotics based on clinical criteria (although some of them might be aware of the Centor criteria).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Participating primary healthcare centres were randomised to the intervention or to the control arm of the study, with an allocation ratio of 1:1, by a random sequence generated by a computer program."
Allocation concealment (selection bias)	Unclear risk	No description exists of any concealment of allocation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding is impossible in this context, and this lack of blinding is likely to influence the outcome.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding is impossible in this context, and this lack of blinding is likely to influence the outcome.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data were incomplete for 14 out of 557 participants without any explanation. Elsewhere, there is existence of incomplete outcome data, such as with regards to evolution of pharyngitis, and without explanation.
Selective reporting (reporting bias)	High risk	Missing data in outcome in the intervention group and in the control group (complete data for 274 out of 281 and 237 out of 262 participants, respectively).
Other bias	Low risk	None

Maltezou 2008

Study characteristics	
Methods	**Clinical setting:** offices of private-practice paediatricians **Single- or multicentre study:** multicentre **Country of study:** Greece **Unit of allocation:** clusters **Inclusion criteria:** children aged 2 to 14 years with clinical evidence of pharyngitis including at least 1 of the following 4 criteria: fever (> 38.0 °C), tonsillar exudate, tender enlarged anterior cervical lymph nodes, and absence of cough. **Exclusion criteria:** having received antibiotics within the previous week or being immunocompromised. **Follow-up:** 3 weeks after enrolment, paediatricians called their participants for follow-up information (clinical course and complications, if any).
Participants	**Number of clusters (n):** 17 **Number of participants (n):** 639 **Participant characteristics:** 1. age (distribution): mean age in years (SD) 7.71 (3.17) in Group A and 6.86 (3.27) in Group B; 2. female participants (%): 51.8%; 3. clinical severity distribution of Centor/McIsaac score: not reported.
Interventions	**Management in intervention group(s):** RADT alone ("Application of the RADT in children with at least one clinical criterion and prescription of antibiotics only if positive; throat culture was also taken and if positive, but RADT-negative, prescription of antibiotics was done 48 h later" (Group B)). **Type of RADT system used:** enzyme immunoassay **Commercial name and brand of the RADT:** Link 2 Strep A Rapid Test (Becton-Dickinson) **Management in control group(s):** clinical grounds without a scoring system ("Decision to prescribe antibiotics by clinical criteria only" ("Group A")).
Outcomes	1. Prevalence of laboratory-diagnosed streptococcal pharyngitis 2. Sensitivity, specificity, and positive and negative predictive values of the RADT using culture as the reference method 3. Performance of the RADT in association with the number of clinical criteria 4. Impact of the RADT on antibiotic prescription
Notes	**Type of report:** journal article **Source(s) of funding:** funded by The Hellenic Center for Disease Control and Prevention (Athens, Greece) **RCT registration number:** not reported "Group C" was excluded because paediatricians in this group managed children using the RADT/culture strategy without being randomised. We contacted the trial authors to confirm that this was a cluster-RCT and that paediatricians in Group A were not invited to prescribe antibiotics based on clinical criteria (although they had to collect Centor criteria for the study).

Maltezou 2008 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	From correspondence with the trial authors, the following information was provided: "it was a cluster randomized trial, with private-practice pediatricians being randomized to strategy A or B (whereas hospital-affiliated pediatricians were all assigned to strategy C)". Thus, not all were randomised.
Allocation concealment (selection bias)	Unclear risk	No description exists of any concealment of allocation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding is impossible in this context, and this lack of blinding is likely to influence the outcome.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding is impossible in this context, and this lack of blinding is likely to influence the outcome.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There are unexplained inconsistencies, e.g. between the percentages mentioned in Table 3 and the actual percentage when dividing the number of prescriptions with the participants in each group. There is no mentioning of handling, or existence, of incomplete outcome data.
Selective reporting (reporting bias)	Low risk	All outcomes mentioned in the Methods section are presented in the Results section. There is no protocol to be used for comparison regarding outcomes mentioned.
Other bias	Low risk	None

Worrall 2007a

Study characteristics

Methods	**Clinical setting:** family doctors' offices **Single- or multicentre study:** multicentre **Country of study:** Canada **Unit of allocation:** clusters **Inclusion criteria:** patients aged 19 years or older who presented with acute sore throat as their primary symptom **Exclusion criteria:** not reported **Follow-up:** not reported
Participants	**Number of clusters (n):** 37 **Number of participants (n):** 533 **Participant characteristics:** 1. age (distribution): not reported;

Worrall 2007a *(Continued)*

2. female participants (%): not reported;
3. clinical severity distribution of Centor/McIsaac score: not reported.

Interventions	**Management in intervention group(s):** 1. RADT alone ("RADT arm"); 2. RADT in combination with clinical examination/scoring system ("STDR and RADT arm": score of ≤ 1, no need for antibiotics; 3 or 4, antibiotics are required; doctors were asked to use the rapid test only when the score was 2). **Type of RADT system used:** enzyme immunoassay **Commercial name and brand of the RADT:** Clearview Exact Strep A dipstick (Wampole Laboratories) **Management in control group(s):** 1. clinical grounds without a scoring system ("Control arm"); 2. clinical grounds with a scoring system ("STDR arm": score of ≤ 1, no need for antibiotics; 3 or 4, antibiotics are required; 2, antibiotics might or might not be beneficial).
Outcomes	**Primary outcome(s):** rate of antibiotic prescribing **Secondary outcome(s):** types of antibiotics prescribed
Notes	**Type of report:** journal article **Source(s) of funding:** not reported **RCT registration number:** not reported The trial had 4 arms: 1. Usual practice ("Control arm"), 2. Decision rule only ("STDR arm"), 3. Rapid antigen test only ("RADT arm"), 4. Decision rule and antigen test combined ("STDR and RADT arm"). The clinical scoring system used was a slightly modified Centor score. There is no report of participant characteristics. The authors explain that they "did not ask doctors to record clinical or demographic characteristics of the patients" because they "wanted the doctors to do as little extra work as possible".

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The 40 physicians who agreed to take part in the study were randomly allocated to 1 of 4 trial arms [...]." No description exists on the generation of the allocation sequence.
Allocation concealment (selection bias)	Unclear risk	No description exists of any concealment of allocation.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding is impossible in this context, and this lack of blinding is likely to influence the outcome.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Blinding is impossible in this context, and this lack of blinding is likely to influence the outcome.
Incomplete outcome data (attrition bias)	Low risk	All participants entered into the study appear to have been assessed for antibiotic prescription. There is no mentioning of handling, or existence, of incom-

Worrall 2007a *(Continued)*

All outcomes		plete outcome data (exclusion, attrition, etc.), but the risk of bias is considered low.
Selective reporting (reporting bias)	Low risk	Unclear description of what outcomes are included in study; despite this, relevant outcomes are reported in the Results. There is no protocol to be used for comparison regarding outcomes mentioned.
Other bias	Low risk	None

GABHS: group A beta-haemolytic streptococcus
RADT: rapid antigen detection test
RCT: randomised controlled trial
SD: standard deviation
STDR: sore throat decision rule

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Al-Najjar 2008	Diagnostic accuracy study
Alper 2013	Diagnostic accuracy study
Bird 2018	Observational study
Bottaro 2007	Observational study
Buchbinder 2007	Diagnostic accuracy study
Cardoso 2013	Diagnostic accuracy study
Cohen 2017	Guidelines
Contessotto 2000	Diagnostic accuracy study
Dodd 2018	Observational study
Frost 2019	Management study
Harris 1995	Diagnostic accuracy study
Hedges 1991	Management study
Humair 2006	Diagnostic accuracy study
Lieu 1986	Diagnostic accuracy study
Little 2014a	Duplicate
Little 2014b	Duplicate
Llor 2011b	Observational study
Llor 2014a	Observational study

Study	Reason for exclusion
Llor 2014b	Observational study
Llor 2018	Observational study
Llor 2019	Observational study
Luo 2019	Management study
Madurell 2010	Study protocol
Maizia 2012	Cost-effectiveness study
Majeed 1993	Cost-effectiveness study
Makela 1989	Diagnostic accuracy study
McGinn 2013	Different intervention
McIsaac 2004	Diagnostic accuracy study
NCT03744832	Study protocol
Orda 2016	Diagnostic accuracy study
Papastergiou 2018	Observational study
Ralph 2019	Diagnostic accuracy study
Rao 2019	Diagnostic accuracy study
Regueras 2012	Diagnostic accuracy study
Reichardt 2009	Observational study
Tanz 2018	Observational study
Thornton 2017	Observational study
True 1986	Diagnostic accuracy study
Worrall 2007b	Duplicate
Worrall 2007c	Duplicate

Characteristics of studies awaiting classification *[ordered by study ID]*

Wächtler 2018

Methods	Cluster-randomised trial
Participants	520 participants with sore throat
Interventions	The study had 3 arms:

Wächtler 2018 *(Continued)*

	1. DEGAM-guideline (GL); 2. modified guideline with a RADT for scores ≥ 3 (GL-RADT); 3. usual care (UC).
Outcomes	Antibiotic prescription rate
Notes	Preliminary results presented at a conference in 2018. We have contacted the trial authors for more information.

DEGAM: German College of General Practitioners and Family Physicians
RADT: rapid antigen detection test

DATA AND ANALYSES

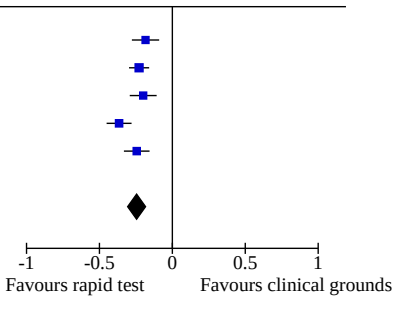
Comparison 1. Comparison 1: Rapid test (with and without scoring system combined) versus clinical grounds (with and without scoring system combined)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Number of participants provided with an antibiotic prescription	5	2545	Risk Difference (M-H, Random, 95% CI)	-0.25 [-0.31, -0.18]
1.2 Number of participants with an antibiotic dispensed	2	900	Risk Difference (M-H, Random, 95% CI)	-0.07 [-0.17, 0.02]
1.3 Number of participants with a complication attributed to the index infection	4	2075	Odds Ratio (M-H, Random, 95% CI)	0.85 [0.03, 26.65]
1.4 Number of participants in need of re-consultation by the end of follow-up	2	1161	Odds Ratio (M-H, Random, 95% CI)	1.12 [0.57, 2.21]

Analysis 1.1. Comparison 1: Comparison 1: Rapid test (with and without scoring system combined) versus clinical grounds (with and without scoring system combined), Outcome 1: Number of participants provided with an antibiotic prescription

Study or Subgroup	Rapid test Events	Rapid test Total	Clinical grounds Events	Clinical grounds Total	Weight	Risk Difference M-H, Random, 95% CI
Little 2013a	86	213	124	211	18.6%	-0.18 [-0.28 , -0.09]
Little 2013b	167	367	263	385	23.1%	-0.23 [-0.30 , -0.16]
Llor 2011a	98	223	133	208	18.8%	-0.20 [-0.29 , -0.11]
Maltezou 2008	67	198	190	270	20.0%	-0.37 [-0.45 , -0.28]
Worrall 2007a	63	196	155	274	19.6%	-0.24 [-0.33 , -0.16]
Total (95% CI)		**1197**		**1348**	**100.0%**	**-0.25 [-0.31 , -0.18]**
Total events:	481		865			

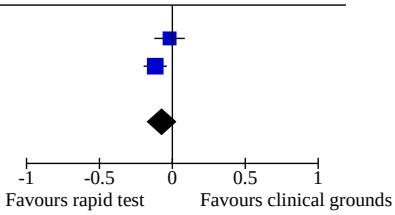
Heterogeneity: Tau² = 0.00; Chi² = 10.40, df = 4 (P = 0.03); I² = 62%
Test for overall effect: Z = 7.84 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Comparison 1: Rapid test (with and without scoring system combined) versus clinical grounds (with and without scoring system combined), Outcome 2: Number of participants with an antibiotic dispensed

Study or Subgroup	Rapid test Events	Rapid test Total	Clinical grounds Events	Clinical grounds Total	Weight	Risk Difference M-H, Random, 95% CI
Little 2013a	58	164	60	161	43.8%	-0.02 [-0.12 , 0.09]
Little 2013b	98	281	137	294	56.2%	-0.12 [-0.20 , -0.04]
Total (95% CI)		**445**		**455**	**100.0%**	**-0.07 [-0.17 , 0.02]**
Total events:	156		197			

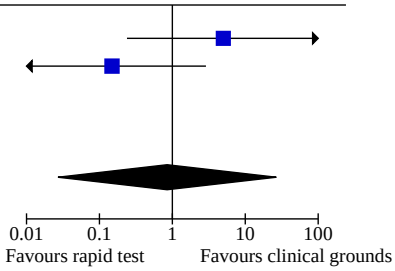
Heterogeneity: Tau² = 0.00; Chi² = 2.14, df = 1 (P = 0.14); I² = 53%
Test for overall effect: Z = 1.52 (P = 0.13)
Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1: Comparison 1: Rapid test (with and without scoring system combined) versus clinical grounds (with and without scoring system combined), Outcome 3: Number of participants with a complication attributed to the index infection

Study or Subgroup	Rapid test Events	Rapid test Total	Clinical grounds Events	Clinical grounds Total	Weight	Odds Ratio M-H, Random, 95% CI
Little 2013a	2	213	0	211	49.5%	5.00 [0.24 , 104.77]
Little 2013b	0	367	3	385	50.5%	0.15 [0.01 , 2.89]
Llor 2011a	0	223	0	208		Not estimable
Maltezou 2008	0	198	0	270		Not estimable
Total (95% CI)		**1001**		**1074**	**100.0%**	**0.85 [0.03 , 26.65]**
Total events:	2		3			

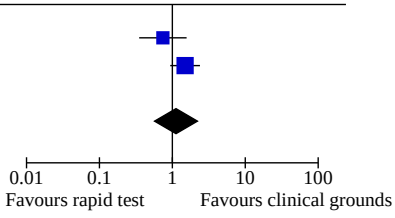
Heterogeneity: Tau² = 3.84; Chi² = 2.63, df = 1 (P = 0.10); I² = 62%
Test for overall effect: Z = 0.09 (P = 0.93)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Comparison 1: Rapid test (with and without scoring system combined) versus clinical grounds (with and without scoring system combined), Outcome 4: Number of participants in need of re-consultation by the end of follow-up

Study or Subgroup	Rapid test Events	Rapid test Total	Clinical grounds Events	Clinical grounds Total	Weight	Odds Ratio M-H, Random, 95% CI
Little 2013a	13	212	17	210	41.0%	0.74 [0.35 , 1.57]
Little 2013b	46	359	34	380	59.0%	1.50 [0.94 , 2.39]
Total (95% CI)		**571**		**590**	**100.0%**	**1.12 [0.57 , 2.21]**
Total events:	59		51			

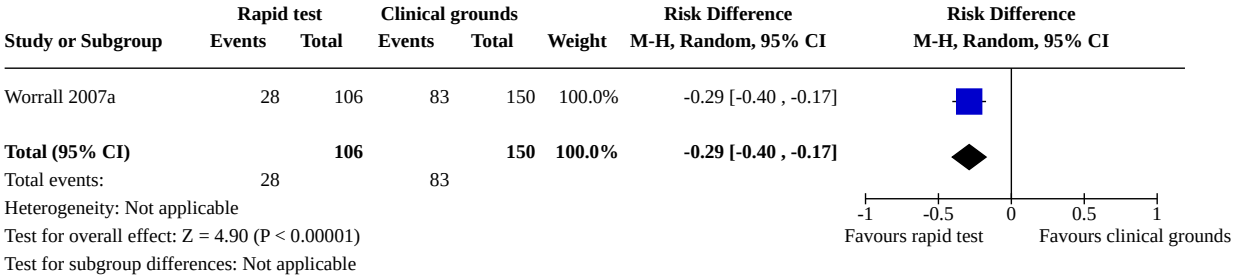
Heterogeneity: Tau² = 0.14; Chi² = 2.42, df = 1 (P = 0.12); I² = 59%
Test for overall effect: Z = 0.33 (P = 0.74)
Test for subgroup differences: Not applicable



Comparison 2. Comparison 2: Rapid test alone versus clinical grounds (with scoring system)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Number of participants provided with an antibiotic prescription	1	256	Risk Difference (M-H, Random, 95% CI)	-0.29 [-0.40, -0.17]

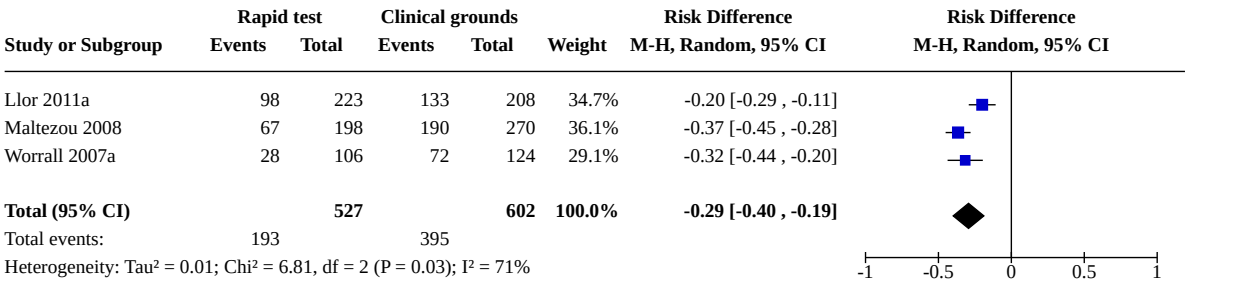
Analysis 2.1. Comparison 2: Comparison 2: Rapid test alone versus clinical grounds (with scoring system), Outcome 1: Number of participants provided with an antibiotic prescription



Comparison 3. Comparison 3: Rapid test alone versus clinical grounds (without scoring system)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Number of participants provided with an antibiotic prescription	3	1129	Risk Difference (M-H, Random, 95% CI)	-0.29 [-0.40, -0.19]

Analysis 3.1. Comparison 3: Comparison 3: Rapid test alone versus clinical grounds (without scoring system), Outcome 1: Number of participants provided with an antibiotic prescription



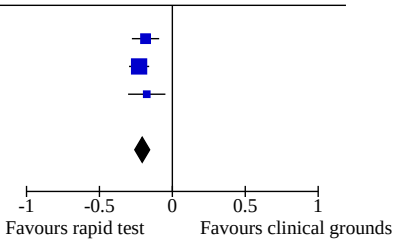
Comparison 4. Comparison 4: Rapid test used with a scoring system versus clinical grounds (with scoring system)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Number of participants provided with an antibiotic prescription	3	1416	Risk Difference (M-H, Random, 95% CI)	-0.21 [-0.26, -0.16]
4.2 Number of participants with an antibiotic dispensed	2	900	Risk Difference (M-H, Random, 95% CI)	-0.07 [-0.17, 0.02]

Analysis 4.1. Comparison 4: Comparison 4: Rapid test used with a scoring system versus clinical grounds (with scoring system), Outcome 1: Number of participants provided with an antibiotic prescription

Study or Subgroup	Rapid test Events	Rapid test Total	Clinical grounds Events	Clinical grounds Total	Weight	Risk Difference M-H, Random, 95% CI
Little 2013a	86	213	124	211	29.6%	-0.18 [-0.28 , -0.09]
Little 2013b	167	367	263	385	54.5%	-0.23 [-0.30 , -0.16]
Worrall 2007a	34	90	83	150	15.8%	-0.18 [-0.30 , -0.05]
Total (95% CI)		**670**		**746**	**100.0%**	**-0.21 [-0.26 , -0.16]**
Total events:	287		470			

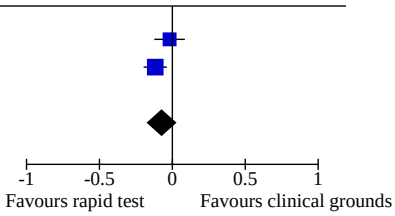
Heterogeneity: Tau² = 0.00; Chi² = 0.82, df = 2 (P = 0.66); I² = 0%
Test for overall effect: Z = 7.95 (P < 0.00001)
Test for subgroup differences: Not applicable



Analysis 4.2. Comparison 4: Comparison 4: Rapid test used with a scoring system versus clinical grounds (with scoring system), Outcome 2: Number of participants with an antibiotic dispensed

Study or Subgroup	Rapid test Events	Rapid test Total	Clinical grounds Events	Clinical grounds Total	Weight	Risk Difference M-H, Random, 95% CI
Little 2013a	58	164	60	161	43.8%	-0.02 [-0.12 , 0.09]
Little 2013b	98	281	137	294	56.2%	-0.12 [-0.20 , -0.04]
Total (95% CI)		**445**		**455**	**100.0%**	**-0.07 [-0.17 , 0.02]**
Total events:	156		197			

Heterogeneity: Tau² = 0.00; Chi² = 2.14, df = 1 (P = 0.14); I² = 53%
Test for overall effect: Z = 1.52 (P = 0.13)
Test for subgroup differences: Not applicable



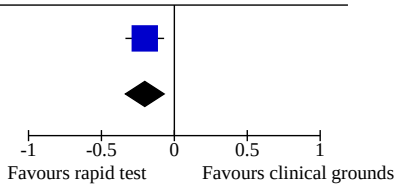
Comparison 5. Comparison 5: Rapid test used with a scoring system versus clinical grounds (without scoring system)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Number of participants provided with an antibiotic prescription	1	214	Risk Difference (M-H, Random, 95% CI)	-0.20 [-0.34, -0.07]

Analysis 5.1. Comparison 5: Comparison 5: Rapid test used with a scoring system versus clinical grounds (without scoring system), Outcome 1: Number of participants provided with an antibiotic prescription

Study or Subgroup	Rapid test Events	Rapid test Total	Clinical grounds Events	Clinical grounds Total	Weight	Risk Difference M-H, Random, 95% CI
Worrall 2007a	34	90	72	124	100.0%	-0.20 [-0.34 , -0.07]
Total (95% CI)		**90**		**124**	**100.0%**	**-0.20 [-0.34 , -0.07]**
Total events:	34		72			

Heterogeneity: Not applicable
Test for overall effect: Z = 3.00 (P = 0.003)
Test for subgroup differences: Not applicable



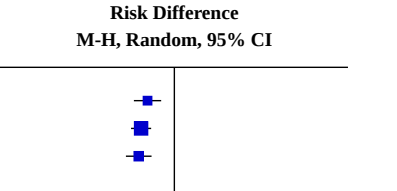
Comparison 6. Sensitivity analysis: studies at low risk of bias

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 Sensitivity analysis: studies at low risk of bias	3	1646	Risk Difference (M-H, Random, 95% CI)	-0.22 [-0.27, -0.17]

Analysis 6.1. Comparison 6: Sensitivity analysis: studies at low risk of bias, Outcome 1: Sensitivity analysis: studies at low risk of bias

Study or Subgroup	Rapid test Events	Rapid test Total	Clinical grounds Events	Clinical grounds Total	Weight	Risk Difference M-H, Random, 95% CI
Little 2013a	86	213	124	211	25.2%	-0.18 [-0.28 , -0.09]
Little 2013b	167	367	263	385	46.3%	-0.23 [-0.30 , -0.16]
Worrall 2007a	63	196	155	274	28.5%	-0.24 [-0.33 , -0.16]
Total (95% CI)		**776**		**870**	**100.0%**	**-0.22 [-0.27 , -0.17]**
Total events:	316		542			

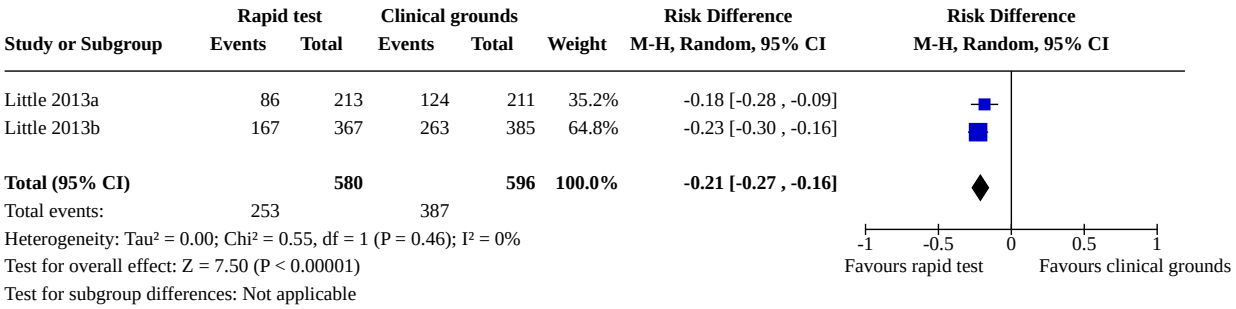
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.91$, df = 2 (P = 0.63); $I^2 = 0\%$
Test for overall effect: Z = 9.25 (P < 0.00001)
Test for subgroup differences: Not applicable



Comparison 7. Sensitivity analysis: Studies with individual randomisation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 Sensitivity analysis: Studies with individual randomisation	2	1176	Risk Difference (M-H, Random, 95% CI)	-0.21 [-0.27, -0.16]

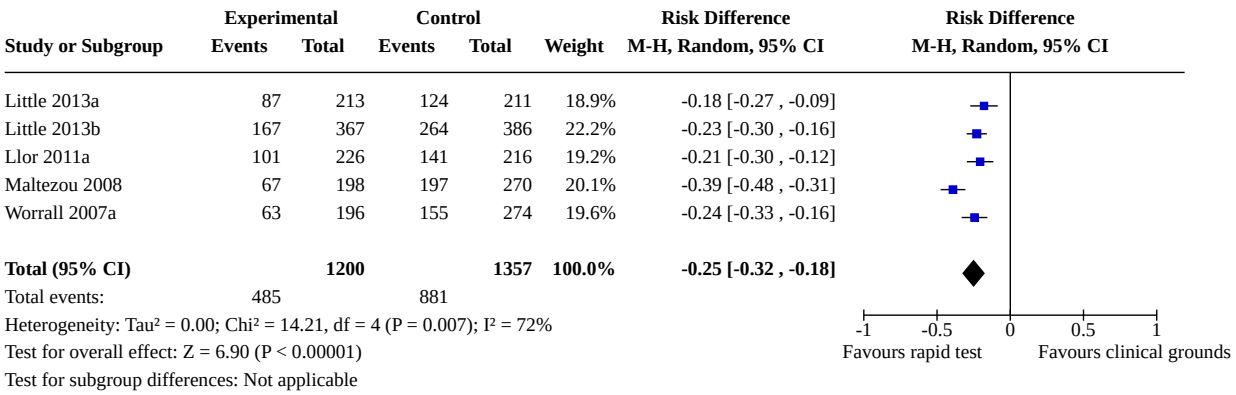
Analysis 7.1. Comparison 7: Sensitivity analysis: Studies with individual randomisation, Outcome 1: Sensitivity analysis: Studies with individual randomisation



Comparison 8. Sensitivity analysis: Missing data as failures

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 Number of participants provided with an antibiotic	5	2557	Risk Difference (M-H, Random, 95% CI)	-0.25 [-0.32, -0.18]

Analysis 8.1. Comparison 8: Sensitivity analysis: Missing data as failures, Outcome 1: Number of participants provided with an antibiotic



ADDITIONAL TABLES

Table 1. Data extracted from each study

Study ID	First author and year of publication
	RCT registration number
Type of study	Journal article or conference abstract
Methods	Clinical setting (office-based, walk-in clinics, hospital outpatient clinics, emergency department, family medicine centres, mixed, other)

Table 1. Data extracted from each study *(Continued)*

	Single- or multicentre study
	Country of study
	Unit of allocation (clusters, individual participants)
	Inclusion criteria
	Exclusion criteria
	Follow-up (follow-up method, duration, outcome(s) assessed)
Intervention(s)	Management in intervention group(s) (rapid test alone or in combination with clinical examination/scoring system)
	Type of rapid test system used (EIA, OIA, or latex agglutination)
	Commercial name and brand of the rapid test
Control(s)	Management in control group(s) (management based on clinical grounds, with or without a scoring system)
Participants	Number of clusters (n)
	Number of participants (n)
	Participant characteristics: 1. Age (distribution) 2. Sex (% of females) 3. Clinical severity distribution of Centor/McIsaac score
Outcomes	Primary outcome(s): 1. Total number of participants prescribed antibiotic treatment 2. Total number of antibiotic prescriptions dispensed
	Secondary outcome(s): 1. Duration of sore throat symptoms 2. Duration of other symptoms (e.g. fever) 3. Quality of life measures 4. Number of participants with a complication attributed to the index infection (e.g. quinsy, acute rheumatic fever) 5. Number of participants in need of re-consultation by the end of follow-up 6. Number of participants in need of hospital admission by the end of follow-up 7. Number of satisfied participants 8. Number of participants with an adverse event attributed to the rapid test 9. Other outcomes
Funding	Source(s) of funding (whether any of the authors are affiliated with the manufacturer of the rapid test, the study was directly funded by the manufacturer, authors reported conflicts of interests related to the manufacturer or other funding sources)
Notes	Anything else of relevance

EIA: enzyme immunoassay
OIA: optical immunoassay
RCT: randomised controlled trial

Table 2. Summary of the various comparisons assessed in the review

Comparison	Intervention: management based on the results of rapid testing	Control: management based on clinical grounds	Number of trials	Number of participants	Number of participants provided with an antibiotic prescription, risk difference (95% confidence interval)
1	Rapid test with and without using a scoring system (arms combined)	Clinical grounds with and without using a scoring system (arms combined)	5	2545	−25% (−31% to −18%)
2	Rapid test for all	With a scoring system	1	256	−29% (−40% to −17%)
3	Rapid test for all	Without a scoring system	3	1129	−29% (−40% to −19%)
4	Rapid testing only if above a certain clinical score	With a scoring system	3	1416	−21% (−26% to −16%)
5	Rapid testing only if above a certain clinical score	Without a scoring system	1	214	−20% (−34% to −7%)

APPENDICES

Appendix 1. MEDLINE (Ovid) search strategy

#	Searches
1	exp Pharyngitis/
2	pharyngitis.tw.
3	Tonsillitis/
4	tonsillitis.tw.
5	(tonsillopharyngitis or pharyngotonsillitis).tw.
6	(sore* adj2 throat*).tw.
7	((throat* or pharyn* or tonsil*) adj3 (infect* or inflam* or strep*)).tw.
8	Pharynx/mi [Microbiology]
9	Streptococcal Infections/

(Continued)

10	(strep* adj5 (throat* or pharyn* or tonsil*)).tw.
11	("group a" adj5 streptococc*).tw.
12	gabhs.tw.
13	(beta-hemoly* or beta-haemoly*).tw.
14	lancefield group a.tw.
15	Streptococcus pyogenes/
16	(streptococcus pyogenes or "s. pyogenes" or "s.pyogenes").tw.
17	or/1-16
18	Immunoassay/
19	exp Immunoenzyme Techniques/
20	(enzyme adj2 (immunoassay* or immuno-assay* or immunosorbent)).tw.
21	Immunochromatography/
22	immunochromatograph*.tw.
23	Immunosorbent Techniques/
24	exp Enzyme-Linked Immunosorbent Assay/
25	(elisa or elisas or eia or eias).tw.
26	(sandwich* adj2 assay*).tw.
27	(lateral flow adj2 assay).tw.
28	(optical adj2 (immunoassay* or immuno-assay*)).tw.
29	(oia or oias).tw.
30	Antigens, Bacterial/
31	Reagent Kits, Diagnostic/
32	Point-of-Care Systems/
33	((rapid or "point of care" or "near patient" or poc or poct or bedside) adj5 (test or tests or testing or detect* or diagnos* or screen* or kit or kits or assay*)).tw.
34	(radt or radts or rdt or rdts).tw.
35	(antigen* adj3 detect*).tw.
36	or/18-35
37	17 and 36

(Continued)

38	((randomized controlled trial or controlled clinical trial).pt. or drug therapy.fs. or (randomized or randomised or placebo or randomly or trial or groups).ab.) not (animals/ not (humans/ and animals/)) [Cochrane highly sensitive filter 2008]
39	37 and 38

Appendix 2. Embase (Elsevier) search strategy

#	Searches
1	'pharyngitis'/exp
2	pharyngitis:ti,ab
3	tonsillitis:ti,ab
4	tonsillopharyngitis:ti,ab OR pharyngotonsillitis:ti,ab
5	(sore* NEAR/2 throat*):ti,ab
6	((throat* OR pharyn* OR tonsil*) NEAR/3 (infect* OR inflam* OR strep*)):ti,ab
7	'pharynx'/de
8	'streptococcus infection'/de OR 'group a streptococcal infection'/de OR 'streptococcal pharyngitis'/de
9	(strep* NEAR/5 (throat* OR pharyn* OR tonsil*)):ti,ab
10	('group a' NEAR/5 streptococc*):ti,ab
11	gabhs:ti,ab
12	'beta hemoly*':ti,ab OR 'beta haemoly*':ti,ab
13	'lancefield group a':ti,ab
14	'streptococcus pyogenes'/de
15	'streptococcus pyogenes':ti,ab OR 's pyogenes':ti,ab OR s pyogenes:ti,ab
16	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15
17	'immunoassay'/exp
18	(enzyme NEAR/2 (immunoassay* OR 'immuno assay*' OR immunosorbent)):ti,ab
19	'immunoaffinity chromatography'/de
20	immunochromatograph*:ti,ab
21	'immunoadsorption'/de

(Continued)

22	elisa:ti,ab OR elisas:ti,ab OR eia:ti,ab OR eias:ti,ab
23	(sandwich* NEAR/2 assay*):ti,ab
24	('lateral flow' NEAR/2 assay):ti,ab
25	(optical NEAR/2 (immunoassay* OR 'immuno assay*')):ti,ab
26	oia:ti,ab OR oias:ti,ab
27	'bacterial antigen'/exp
28	'diagnostic kit'/exp
29	'hospital information system'/de OR 'point of care system'/de OR 'point of care testing'/de
30	((rapid OR 'point of care' OR 'near patient' OR poc OR poct OR bedside) NEAR/5 (test OR tests OR testing OR detect* OR diagnos* OR screen* OR kit OR kits OR assay*)):ti,ab
31	radt:ti,ab OR radts:ti,ab OR rdt:ti,ab OR rdts:ti,ab
32	(antigen* NEAR/3 detect*):ti,ab
33	#17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32
34	#16 AND #33
35	random* OR factorial OR crossover OR placebo OR blind OR blinded OR assign OR assigned OR allocate OR allocated OR 'crossover procedure'/exp OR 'double-blind procedure'/exp OR 'randomized controlled trial'/exp OR 'single-blind procedure'/exp NOT ('animal'/exp NOT 'animal'/exp AND 'human'/exp))
36	#34 AND #35

Appendix 3. Web of Science (Clarivate Analytics) search strategy

Databases: Web of Science (Science Citation Index Expanded (SCI-EXPANDED) 1900-present and Conference Proceedings Citation Index-Science (CPCI-S)) 1990-present

Topic=(pharyngitis or tonsillitis or tonsillopharyngitis or pharyngotonsillitis or (sore* NEAR/2 throat*) or ((throat* or pharyn* or tonsil*) NEAR/3 (infect* or inflam* or strep*)) or (strep* NEAR/5 (throat* or pharyn* or tonsil*)) or ("group a" NEAR/5 streptococc*) or gabhs or beta-hemoly* or beta-haemoly* or "lancefield group a" or "streptococcus pyogenes" or "s. pyogenes" or "s.pyogenes") AND ((enzyme NEAR/2 (immunoassay* or immuno-assay* or immunosorbent)) or immunochromatograph* or elisa or elisas or eia or eias or (sandwich* NEAR/2 assay*) or (lateral flow NEAR/2 assay) or (optical NEAR/2 (immunoassay* or immuno-assay*)) or oia or oias or ((rapid or "point of care" or "near patient" or poc or poct or bedside) NEAR/5 (test or tests or testing or detect* or diagnos* or screen* or kit or kits or assay*)) or radt or radts or rdt or rdts or (antigen* NEAR/3 detect*))

AND

Topic=(random* or placebo* or allocat* or crossover* or "cross over" or ((singl* or doubl*) NEAR/1 blind*)) OR Title=(trial)

Appendix 4. LILACS (BIREME) search strategy

(mh:C07.550.781$ OR pharyngitis OR faringit* OR tonsillitis OR tonsilit* OR (tonsillopharyngitis OR pharyngotonsillitis) OR "sore throat" OR "dolor de garganta" OR "dor de garganta" OR "sore throats" OR "dolores de garganta" OR "dores de garganta" OR ((throat* OR garganta OR pharyn* OR faringe OR tonsil* OR amígdalas) AND (infect* OR infección* OR infecção OR infecções OR inflam* OR enconado OR inflama* OR strep* OR estreptoc*)) OR mh:pharynx OR mh:"Streptococcal Infections" OR ("group a" AND streptococc*) OR gabhs

OR (beta-hemoly* OR beta-haemoly*) OR "lancefield group a" OR mh:"Streptococcus pyogenes" OR ("streptococcus pyogenes" OR "s. pyogenes" OR "s.pyogenes")) AND (mh:immunoassay OR mh:E05.478.566.350$ OR ((enzyme OR enzima) AND (immunoassay* OR inmunoensayo OR imunoensaio OR immuno-assay* OR immunosorbent)) OR mh:immunochromatography OR immunochromatograph* OR inmunocromatografía OR imunocromatografia OR mh:"Immunosorbent Techniques" OR "técnicas de inmunoadsorción" OR "técnicas de Imunoadsorção" OR mh:"Enzyme-Linked Immunosorbent Assay" OR "ensayo de inmunoadsorción enzimática" OR "ensaio de imunoadsorção enzimática" OR (elisa OR elisas OR eia OR eias) OR (sandwich* AND assay*) OR ("lateral flow" AND assay) OR (optical AND (immunoassay* OR immuno-assay*)) OR (oia OR oias) OR mh:"Antigens, Bacterial" OR mh:"Reagent Kits, Diagnostic" OR mh:point-of-care systems OR "sistemas de atención de punto" OR "sistemas automatizados de assistência junto ao leito" OR ((rapid OR "point of care" OR "near patient" OR poc OR poct OR bedside) AND (test OR tests OR testing OR detect* OR diagnos* OR screen* OR kit OR kits OR assay*)) OR (radt OR radts OR rdt OR rdts) OR (antigen* AND detect*)) AND (instance:"regional") AND (db:("LILACS"))

Appendix 5. CENTRAL (Cochrane Library) search strategy

#	Searches
1	[mh Pharyngitis]
2	pharyngitis:ti,ab
3	tonsillitis:ti,ab
4	(tonsillopharyngitis or pharyngotonsillitis):ti,ab
5	(sore* near/2 throat*):ti,ab
6	((throat* or pharyn* or tonsil*) near/3 (infect* or inflam* or strep*)):ti,ab
7	[mh ^Pharynx]
8	[mh ^"Streptococcal Infections"]
9	(strep* near/5 (throat* or pharyn* or tonsil*)):ti,ab
10	("group a" near/5 streptococ*):ti,ab
11	gabhs:ti,ab
12	(beta-hemoly* or beta-haemoly*):ti,ab
13	"lancefield group a":ti,ab
14	[mh ^"Streptococcus pyogenes"]
15	("streptococcus pyogenes" or "s. pyogenes" or s.pyogenes):ti,ab
16	{or #1-#15}
17	[mh ^Immunoassay]
18	[mh "Immunoenzyme Techniques"]
19	(enzyme near/2 (immunoassay* or immuno-assay* or immunosorbent)):ti,ab
20	[mh ^Immunochromatography]

(Continued)

21	immunochromatograph*:ti,ab
22	[mh ^"Immunosorbent Techniques"]
23	[mh "Enzyme-Linked Immunosorbent Assay"]
24	(elisa or elisas or eia or eias):ti,ab
25	(sandwich* near/2 assay*):ti,ab
26	("lateral flow" near/2 assay):ti,ab
27	(optical near/2 (immunoassay* or immuno-assay*)):ti,ab
28	(oia or oias):ti,ab
29	[mh "Antigens, Bacterial"]
30	[mh "Reagent Kits, Diagnostic"]
31	[mh "Point-of-Care Systems"]
32	((rapid or "point of care" or "near patient" or poc or poct or bedside) near/5 (test or tests or testing or detect* or diagnos* or screen* or kit or kits or assay*)):ti,ab
33	(radt or radts or rdt or rdts):ti,ab
34	(antigen* near/3 detect*):ti,ab
35	{or #17-#34}
36	#16 and #35

Appendix 6. CINAHL (EBSCO) search strategy

#	Searches
1	MH "Pharyngitis"
2	TI pharyngitis OR AB pharyngitis
3	MH "Tonsillitis"
4	TI tonsillitis OR AB tonsillitis
5	TI pharyngotonsillitis OR AB pharyngotonsillitis OR TI tonsillopharyngitis OR AB tonsillopharyngitis
6	TI (sore* N2 throat*) OR AB (sore* N2 throat*)
7	TI ((throat* or pharyn* or tonsil*) N3 (infect* or inflam* or strep*)) OR AB ((throat* or pharyn* or tonsil*) N3 (infect* or inflam* or strep*))

(Continued)

8	MH "Pharynx/MI"
9	MH "Streptococcal Infections"
10	TI (strep* N5 (throat* or pharyn* or tonsil*)) OR AB (strep* N5 (throat* or pharyn* or tonsil*))
11	TI ("group a" N5 streptococc*) OR AB ("group a" N5 streptococc*)
12	TI gabhs OR AB gabhs
13	TI (beta-hemoly* or beta-haemoly*) OR AB (beta-hemoly* or beta-haemoly*)
14	TI "lancefield group a" OR AB "lancefield group a"
15	MH "Streptococcus"
16	TI ("streptococcus pyogenes" or "s. pyogenes" or "s.pyogenes") OR AB ("streptococcus pyogenes" or "s. pyogenes" or "s.pyogenes")
17	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16
18	MH "Immunoassay"
19	MH "Immunoenzyme Techniques"
20	TI (enzyme N2 (immunoassay* or immuno-assay* or immunosorbent)) OR AB (enzyme N2 (immunoassay* or immuno-assay* or immunosorbent))
21	TI immunochromatograph* OR AB immunochromatograph*
22	MH "Immunosorbent Techniques"
23	MH "Enzyme-Linked Immunosorbent Assay"
24	TI (elisa or elisas or eia or eias) OR AB (elisa or elisas or eia or eias)
25	TI (sandwich* N2 assay*) OR AB (sandwich* N2 assay*)
26	TI ("lateral flow" N2 assay) OR TI ("lateral flow" N2 assay)
27	TI (optical N2 (immunoassay* or immuno-assay*)) OR AB (optical N2 (immunoassay* or immuno-assay*))
28	TI (oia or oias) OR AB (oia or oias)
29	MH "Antigens, Bacterial+"
30	MH "Reagent Kits, Diagnostic+"
31	MH "Clinical Information Systems+" OR MH "Point-of-Care Testing"
32	TI ((rapid or "point of care" or "near patient" or poc or poct or bedside) N5 (test or tests or testing or detect* or diagnos* or screen* or kit or kits or assay*)) OR AB ((rapid or "point of care" or "near patient" or poc or poct or bedside) N5 (test or tests or testing or detect* or diagnos* or screen* or kit or kits or assay*))

(Continued)

33	TI (radt or radts or rdt or rdts) OR AB (radt or radts or rdt or rdts)
34	TI (antigen* N3 detect*) OR AB (antigen* N3 detect*)
35	S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34
36	S17 AND S35

HISTORY

Protocol first published: Issue 11, 2016
Review first published: Issue 6, 2020

CONTRIBUTIONS OF AUTHORS

1. Original idea for the review: JFC and MC.
2. First draft of the protocol: JFC and MC.
3. Input and editing on the protocol: RC, NH, JYP.
4. Study selection and data extraction: JFC, NH, JYP.
5. Data analysis: JFC and NH.
6. First draft of the manuscript: JFC and NH.
7. Critical revisions to the manuscript: All authors.
8. Study supervision: MC.

DECLARATIONS OF INTEREST

1. Jérémie F Cohen: None known.
2. Jean-Yves Pauchard: None known.
3. Nils Hjelm: I have received three scholarships (one scholarship for conducting research abroad as part of my medical studies at the Lund University; one scholarship for conducting research in France; and one scholarship from the Erasmus Funding Programme for conducting research in another European Union country). None of the received scholarships are regarded as potential conflicts of interest.
4. Robert Cohen: RC's institution, ACTIV, has received research grant support from Pfizer, GlaxoSmithKline, Merck, and Sanofi Pasteur MSD. RC reports personal fees from Pfizer, GlaxoSmithKline, Merck, Sanofi, and AstraZeneca, outside the submitted work. These potential interests are only in the field of vaccines.
5. Martin Chalumeau: No financial competing interest in relation to the present systematic review.
6. JFC, RC, and MC have conducted diagnostic accuracy studies about rapid tests for strep throat in which rapid tests kits were provided by the manufacturer (Dectrapharm/Biosynex). These studies were not in the scope of the present review and thus were not included in the review.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We could not report on several outcomes due to lack of data.

We did not contact trial authors to obtain intraclass correlation coefficients.

We did not use GRADEpro GDT software to produce the Summary of findings 1.

We rephrased the Objectives of the review from 'To assess the efficacy and safety of using rapid tests at the point-of-care to guide antibiotic prescriptions as compared to management based on clinical grounds' (protocol) to 'To assess the efficacy and safety of strategies based on rapid tests to guide antibiotic prescriptions for sore throat in primary care settings' (review). The rationale for the change was that some studies do not only evaluate rapid tests, but strategies based on rapid tests (e.g. combinations of clinical scores and rapid tests).

We modified the wording of our second primary outcome from ‘Number of antibiotic prescriptions dispensed’ (protocol) to ‘Number of participants with an antibiotic dispensed’ (review), for the sake of consistency in wording across outcomes.

For Comparison 1, we had planned to create a 'Summary of findings' table with the following outcomes: number of participants provided with an antibiotic prescription; number of antibiotic prescriptions dispensed; duration of sore throat symptoms; duration of other symptoms (e.g. fever); number of participants with a complication attributed to the index infection (e.g. quinsy, acute rheumatic fever); number of participants in need of re-consultation by the end of follow-up; and number of participants in need of hospital admission by the end of follow-up (protocol). In the review, our final 'Summary of findings' table only included outcomes for which we could extract data in the included studies (i.e. number of participants provided with an antibiotic prescription; number of participants with an antibiotic dispensed; number of participants with a complication attributed to the index infection; and number of participants in need of re-consultation by the end of follow-up).

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [*therapeutic use]; Bacteriological Techniques; Drug Prescriptions [statistics & numerical data]; Pharyngitis [*drug therapy] [*microbiology] [virology]; Randomized Controlled Trials as Topic; Streptococcal Infections [*diagnosis] [microbiology]; Streptococcus pyogenes [*isolation & purification]

MeSH check words

Adult; Child; Female; Humans; Male