National Institute for Health and Care Excellence

APG: sore throat (acute) - draft for consultation

Sore throat (acute): antimicrobial prescribing guideline

Evidence review

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Draft for Consultation

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ISBN:

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1 Context

1.1 Background

Acute sore throat (including include pharyngitis and tonsillitis) is a self-limiting upper respiratory tract infection (Respiratory tract infections (self-limiting): prescribing antibiotics [2008] NICE guideline CG69). In people who are not treated, over 80% will be free from symptoms after 1 week (Spinks et al. 2013).

Most cases of acute sore throat are caused by a viral infection and occur as a part of a common cold. Bacterial pathogens can also cause a pharyngeal infection, the most common causative pathogen being group A beta-haemolytic streptococcus (GABHS). Groups C or G beta-haemolytic streptococci, *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* have also been suggested to be pathogens (European Society for Clinical Microbiology and Infectious Diseases Sore Throat Guideline). A meta-analysis estimated that the prevalence of *Streptococcus pyogenes* during pharyngitis was approximately 20% (Kronman et al. 2014).

Most people with acute sore throat present with non-specific symptoms, including pain on swallowing, headache and cough and flu-like symptoms. Pharyngitis and tonsillitis may be difficult to diagnose in very young children. Clinical score systems, for example FeverPAIN and Centor criteria, can help to identity people who are more likely to have a bacterial infection. Children aged under 5 who present with fever should be assessed and managed as outlined in the NICE guideline on fever in under 5s: assessment and initial management.

Respiratory tract infections, including acute sore throat, are a common reason for consultations in primary care, and therefore are a common reason for potential antibiotic prescribing. In 2005 it was estimated that a quarter of the population visited their GP because of a respiratory tract infection each year (NICE guideline on respiratory tract infections (self-limiting): prescribing antibiotics: full guideline). However, consultation rates for acute respiratory tract infections in primary care have been decreasing (Gulliford et al. 2009), as have prescriptions for antimicrobials generally in primary care (ESPAUR 2016).

UK primary care data for adults from 2011 found there was a mean rate of 217 respiratory tract infection consultations per 1000 person years, and a mean rate of 119 antibiotic prescriptions for respiratory tract infections per 1000 person years (Gulliford et al. 2014). Consultations for sore throat accounted for 27% of all respiratory tract infection consultations, and the median practice issued an antibiotic prescription for 60% of these (varying between 35% in the lowest prescribing practices to 83% in the highest prescribing practices).

1.2 Managing self-limiting infections

Acute sore throat is a self-limiting condition, and complications are likely to be rare if antibiotics are withheld. The NICE guideline on respiratory tract infections (self-limiting): prescribing antibiotics has recommendations for managing self-limiting respiratory tract infections relating to the use of 3 antibiotic prescribing strategies (either no prescribing, delayed prescribing or immediate prescribing). For acute sore throat, a no antimicrobial prescribing strategy or a delayed antimicrobial prescribing strategy is recommended. This should be accompanied with advice about the usual natural history of acute sore throat, which can last 1 week, and advice about managing symptoms, including fever. The guideline recommends that, depending on clinical assessment of severity, an immediate antibiotic strategy can also be considered (in addition to a no antibiotic or a delayed antibiotic prescribing strategy) for people with acute sore throat when 3 or more Centor criteria are present.

An immediate antimicrobial prescription or further appropriate investigation and management should only be offered to people who are systemically very unwell, have 'red flags' (signs or symptoms of a more serious illness or condition), or are at high risk of serious complications because of pre-existing comorbidity. This includes people with significant heart, lung, renal, liver or neuromuscular disease, immunosuppression, cystic fibrosis, and young children who were born prematurely.

The NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use also has recommendations to not issue immediate antimicrobial prescriptions to people who are likely to have a self-limiting condition. Instead other options such as self-care with over-the-counter preparations, back-up or delayed prescribing, or other non-pharmacological interventions should be discussed alongside the natural history of the condition and safety netting advice.

The NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population recommends that resources should be available for healthcare professionals to use with the public to provide information about self-limiting infections, to encourage people to manage their infection themselves at home with self-care if it is safe to do so.

1.2.1 Self-care

The NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population recommends that people should be given verbal advice and written information that they can take away about how to manage their infection themselves at home with self-care if it is safe to do so.

Self-care options that have been used to relieve symptoms of acute sore throat include paracetamol or ibuprofen, medicated lozenges and mouth sprays. However, the evidence for these is limited (see clinical effectiveness).

1.2.2 No antibiotic prescribing strategies

The NICE guideline on respiratory tract infections (self-limiting): prescribing antibiotics recommends that when a no antibiotic prescribing strategy is adopted, patients should be offered:

- reassurance that antibiotics are not needed immediately because they are likely to make little difference to symptoms and may have side effects, for example, diarrhoea, vomiting and rash
- a clinical review if the condition worsens or becomes prolonged.

When a delayed antibiotic prescribing strategy is adopted, patients should be offered:

- reassurance that antibiotics are not needed immediately because they are likely to make little difference to symptoms and may have side effects, for example, diarrhoea, vomiting and rash
- advice about using the delayed prescription if symptoms are not starting to settle in accordance with the expected course of the illness or if a significant worsening of symptoms occurs
- advice about re-consulting if there is a significant worsening of symptoms despite using the delayed prescription.

A delayed prescription with instructions can either be given to the patient or left at an agreed location to be collected at a later date.

1.2.3 Antibiotic prescribing strategies

The NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use recommends that when antimicrobials are prescribed, prescribers should:

- Consider supplying antimicrobials in pack sizes that correspond to local (where available) and national guidelines on course lengths.
- Follow local (where available) or national guidelines on prescribing the shortest effective course, the most appropriate dose, and route of administration.
- Undertake a clinical assessment and document the clinical diagnosis (including symptoms) in the patient's record and clinical management plan.
- Document in the patient's records (electronically wherever possible):
  - the reason for prescribing an antimicrobial
  - the plan of care as discussed with the patient, their family member or carer (as appropriate), including the planned duration of any treatment.
- Take into account the benefits and harms for an individual patient associated with the particular antimicrobial, including:
  - possible interactions with other medicines or any food and drink
  - the patient's other illnesses, for example, the need for dose adjustment in a patient with renal impairment
  - any drug allergies (these should be documented in the patient's record)
  - the risk of selection for organisms causing healthcare associated infections, for example, *C. difficile*.
- Document in the patient's records the reasons for the any decision to prescribe outside local (where available) or national guidelines.

The NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population recommends that resources and advice should be available for people who are prescribed antimicrobials to ensure they are taken as instructed at the correct dose, via the correct route, for the time specified. Verbal advice and written information that people can take away about how to use antimicrobials correctly should be given, including:

- not sharing prescription-only antimicrobials with anyone other than the person they were prescribed or supplied for
- not keeping them for use another time
- returning unused antimicrobials to the pharmacy for safe disposal and not flushing them down toilets or sinks.

1.3 Safety netting advice

The NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population recommends that people with self-limiting infections should be given explicit advice on when to seek medical help, which symptoms should be considered red flags and safety-netting advice. Safety-netting advice should include:

- how long symptoms are likely to last with and without antimicrobials
- what to do if symptoms get worse
- what to do if they experience adverse effects from the treatment
- when they should ask again for medical advice.

The NICE clinical knowledge summary on sore throat recommends that people with acute sore throat should seek urgent medical attention if they develop any difficulty breathing, stridor, drooling, a muffled voice, severe pain, dysphagia, or if they are not able to swallow adequate fluids or become systemically very unwell.

1.4 Symptoms and signs of a more serious illness or condition (red flags)

A referral to hospital may be required for people if they have symptoms and signs of acute sore throat associated with:

- a severe systemic infection (see the NICE guideline on sepsis) or is at risk of immunosuppression
- dehydration or inability to take any fluids
- severe suppurative complications (such as, peri-tonsillar abscess or cellulitis, parapharyngeal abscess or retropharyngeal abscess).

Peri-tonsillar abscess (quinsy) is a rare complication of sore throat in the UK, with an annual incidence of 96 cases per 100,000 patients (Dunn et al. 2007). Other serious complications associated with bacterial sore throat include rheumatic fever and glomerulonephritis, although the incidence of these in the UK is very low.

2 Evidence selection

2.1 Literature search

A literature search identified 7,159 references (see appendix B: literature search strategy for full details). These references were screened using their titles and abstracts and 327 full text references were obtained and assessed for relevance. Ninety-seven full text references of systematic reviews and randomised controlled trials (RCTs) were assessed as relevant to the guideline review question (see appendix A: review protocol). Ten percent of studies were screened to establish inter-rater reliability. One reference was published after the search was completed.

Twenty-three references were prioritised by the Committee as the best available evidence and were included in this evidence review (see appendix D: included studies). Studies that assessed Chinese herbal medicines were not prioritised by the Committee. The methods for identifying, selecting and prioritising the best available evidence are described in the interim process guide. The 75 references that were not prioritised for inclusion are listed in appendix G: not prioritised studies.

The remaining 230 references were excluded. These are listed in appendix H: excluded studies with reasons for their exclusion.

See also appendix C: study flow diagram.

2.2 Summary of included studies

A summary of the included studies is shown in tables 1 and 2. Details of the study citation can be found in appendix D: included studies. An overview of the quality assessment of each included study is shown in appendix E: quality assessment of included studies.

Table 1: Summary of included studies: non-pharmacological interventions

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Oral analgesia versus placebo					
Moore et al. 2002 RCT. France. Follow-up 7 days	n=2,815	Adults with cold and flu symptoms and sore throat pain	Ibuprofen 200 mg	Aspirin Paracetamol	Significant adverse events (no efficacy outcomes)
Eccles et al. 2003 RCT. Multiple countries. Follow-up 2 hours	n=272	Adults (18 to 60 years) with symptoms of upper respiratory tract infection and sore throat	Aspirin 800 mg, taken at the start of the study, then every 4 to 6 hours	Placebo	Pain on swallowing from baseline to 2 hours
Gehanno et al. 2003 RCT. Multiple centres in France. Follow-up 4 hours	n=343	Adults with acute sore throat and pyrexia (≥38ºC)	Single dose of: Diclofenac potassium (6.25 mg, 12.5 mg and 25 mg) or Paracetamol 1,000 mg	Placebo	Change in oral temperature from baseline to 4 hours
Voelker et al. 2016 RCT. Conducted in the USA. Follow-up 2 hours	n=177	Adults with acute sore throat due to an upper respiratory tract infection (presenting within 6 days of onset)	Single dose of: Paracetamol 1,000 mg or Aspirin 1,000 mg	Placebo	Time to meaningful pain relief
Benzocaine lozenges versus placebo					
Chrubasik et al. 2012 RCT. Multiple centres. Follow-up 2 hours	n=165	Adults with sore throat for at least 24 hours and mild or moderate pain	Benzocaine 8 mg lozenge	Placebo	Sum of the pain intensity differences (SPID) over 2 hours
Hexylresorcinol lozenges versus placebo					
McNally et al. 2012 RCT. Multiple centres in Northern Ireland. Follow-up 2 hours	n=126	Adults with a sore throat associated with an upper respiratory tract infection	Hexylresorcinol 0.6 mg lozenge[2]	Placebo[2]	Change in throat soreness from baseline to 2 hours (measured on an 11-point scale; with 0 being not sore and 10 being very sore)
Flurbiprofen lozenges versus placebo					

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Watson et al. 2000 RCT. Follow-up 2 hours.	n=301	Adults with sore throat associated with an upper respiratory tract infection.	Flurbiprofen 8.75 mg or 12.5 mg (single dose)	Placebo	Total pain relief summed over 15-120 minutes ($TOTPAR_{15\text{-}120\ min}$)
Benrimoj et al. 2001 RCT. Follow-up 2 hours.	n=320	Adults with sore throat associated with an upper respiratory tract infection.	Single dose of: Flurbiprofen 8.75 mg or 12.5 mg lozenge	Placebo	Total pain relief summed over 15-120 minutes ($TOTPAR_{15\text{-}120\ min}$)
Blagden et al. 2001 RCT. Follow-up 4 days	n=459	People aged 12 years and over	Flurbiprofen 8.75 mg lozenge, taken at the start of the study, followed by 1 lozenge as needed every 3 hours (maximum 5 daily)	Placebo	Total pain relief summed over 1 to 4 days ($TOTPAR_{1\text{-}4\ days}$)
Schachtel et al. 2014 RCT. Follow-up 24 hours	n=198	Adults with a sore throat and moderate to severe pain	Flurbiprofen 8.75 mg lozenge, taken at the start of the study, followed by 1 lozenge as needed every 3 to 6 hours (maximum 5 daily)	Placebo	Sum of the pain intensity differences (SPID) over 24 hours
Chlorhexidine gluconate and benzydamine mouth spray versus placebo					
Cingi et al. (2011) RCT. Follow-up 7 days.	n=147	Adults with a sore throat and moderate to severe pain	Chlorhexidine gluconate 0.12% plus benzydamine hydrochloride 0.15% spray[1]	Placebo[1]	Change in intensity of clinical signs
Corticosteroids versus placebo					
Hayward et al. 2012 Systematic review and meta-analysis. Multiple countries. Follow-up to 48 hours	n=743 (8 RCTs)	Adults and children with sore throat, including tonsillitis and pharyngitis	Corticosteroid (oral or intramuscular)[1]	Placebo[1]	Time to complete resolution of pain Mean time to onset of pain relief
Hayward et al. 2017 RCT. Multiple UK centres. Follow-up 48 hours	n=576	Adults with sore throat	Dexamethasone 10mg (single oral dose)	Placebo	Complete symptom resolution at 24 hours

Abbreviations: GABHS, group A beta-haemolytic streptococci; RCT, Randomised controlled trial

[1] Antibiotics were administered to all participants.

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
[2] A third treatment arm involving amylmetacresol/2,4-dichlorobenzyl alcohol plus lidocaine lozenges was included, although this product is not available in the UK					

Table 2: Summary of included studies: antimicrobials

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Delayed antibiotics					
de la Poza Abad et al. (2015) Open-label RCT. Spain. Follow-up to 30 days	n=405	Adults with acute uncomplicated respiratory infections, including 184 people with pharyngitis	Delayed antibiotic prescribing (patient-led or collection)	Immediate antibiotic prescribing No antibiotic prescribing	Duration of symptoms
Spurling et al. (2013) Systematic review and meta-analysis. Multiple countries. Follow-up to 3 days	n=3,157 (10 RCTs) 4 RCTs on acute pharyngitis / sore throat	People of all ages with acute respiratory tract infections	Delayed antibiotic prescribing	Immediate antibiotic prescribing No antibiotic prescribing	Duration and severity of symptoms. Antibiotic use. Patient satisfaction. Antibiotic resistance
Antibiotics versus placebo					
Spinks et al. 2013 Systematic review and meta-analysis. Multiple countries. Follow-up to 7 days	n=12,385 (27 RCTs and quasi-RCTs)	Adults and children with symptoms of sore throat	Antibiotic (including penicillins, sulfonamides, macrolides, cephalsporins and co-trimoxazole)	Placebo	Symptoms of sore throat (on day 3 and day 7)
Identifying people more likely to benefit from antibiotics					
Little et al. (2013) Open-label RCT. England. Follow-up up to 2 years	n=631	Adults and children with acute sore throat	FeverPAIN clinical scoring system FeverPAIN clinical scoring system followed by rapid	Delayed antibiotic prescribing strategy	Symptom severity on days 2 to 4

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
			antigen testing (based on score)		
Aalbers et al. (2011) Systematic review and meta-analysis. Multiple countries.	n=4,839 (21 RCTs)	People aged 15 years and over with acute sore throat	Centor score	Throat culture (the reference standard)	Diagnostic accuracy of the Centor scoring system
Cohen et al. (2016) Systematic review and meta-analysis. Multiple countries.	n=101,121 (98 studies)	Children aged 21 years and less with sore throat	Rapid antigen test	Laboratory throat culture	Diagnostic accuracy of rapid antigen testing
Antibiotics versus other antibiotics					
van Driel et al. 2016 Systematic review and meta-analysis. Multiple countries. Follow-up to 10 days	n=5,839 (19 RCTs)	Adults and children with symptoms of sore throat and with an infection caused by group A beta-haemolytic streptococci (GABHS), confirmed by a throat culture and/or rapid test	Antibiotic (including cephalosporins, macrolides and sulphonamides)	Another antibiotic (penicillin or ampicillin)	Cure or improvement in signs and symptoms,
Altamimi et al. 2012 Systematic review and meta-analysis. Multiple countries. Follow-up to 10 days	n=13,102 (20 RCTs)	Children 1 to 18 years of age, with acute streptococcal pharyngitis	Late-generation antibiotic (including macrolides, cephalosporins, amoxicillin and co-amoxiclav) for 2 to 6 days	Penicillin V for 10 days	Resolution of symptoms
Duration of antibiotic treatment					
Falagas et al. 2008 Systematic review and meta-analysis. Multiple countries. Follow-up to 10 days	n=2,329 (11 RCTs) Penicillin V assessed in 5 RCTs (n=991)	People with acute streptococcal tonsillopharyngitis	Penicillin V for 5 to 7 days	Penicillin V for 10 days	Microbiological cure
Frequency of antibiotic dosing					

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Lan and Colford (2000) Systematic review and meta-analysis. Multiple countries. Follow-up to 14 days	n=1,208 (6 RCTs)	People with acute streptococcal tonsillopharyngitis	Penicillin V once or twice daily	Penicillin V 3 or 4 times daily	Microbiological cure

3 Clinical effectiveness

Full details of clinical effectiveness are shown in appendix F: GRADE profiles. The main results are summarised below.

3.1 Non-pharmacological interventions

No systematic reviews or randomised controlled trials (RCTs) were identified that compared non-medicated lozenges or non-medicated mouthwashes with placebo or another intervention in people with acute sore throat.

3.2 Non-antimicrobial pharmacological interventions

3.2.1 Oral analgesia in adults

The evidence review for oral analgesia is based on 3 RCTs (Eccles et al. 2003, Gehanno et al. 2003 and Voelker et al. 2016) in adults with sore throat associated with an upper respiratory tract infection. Although different scales were used to measure pain, all participants appeared to have at least moderate throat pain at baseline. Participants were not required to have a confirmed group A beta-haemolytic *Streptococcus* (GABHS) infection and antibiotics were not used in any of the RCTs.

Overall, the 3 RCTs found that aspirin, paracetamol and diclofenac potassium were all more effective than placebo at improving pain and reducing fever in adults with acute sore throat, although it's not clear whether many of the improvements were clinical clinically meaningful (very low to low quality evidence).

A double-blind RCT investigated the effectiveness of **aspirin** in adults with sore throat pain associated with an upper respiratory tract infection (n=272; Eccles et al. 2003). People who in the opinion of the investigator required medical attention (for example, those with a likely streptococcal infection) were excluded from the study. Over 2 hours, aspirin 800 mg significantly reduced pain on swallowing compared with placebo, with a sum of pain intensity difference (SPID) of 3.81 points in the aspirin group and 2.41 points in the placebo group (p=0.0001, low quality evidence).

A double-blind RCT by Voelker et al. (2016) investigated the effectiveness of **aspirin** or **paracetamol** compared with placebo for the treatment of acute mild-to-moderate pain (sore throat pain and dental pain) in 177 adults (mean age 19.5 years) with an upper respiratory tract infection. The mean time to meaningful pain relief was 48.0 minutes for aspirin and 40.4 minutes for paracetamol. Meaningful pain relief was not achieved with placebo in the observation period of 2 hours. Aspirin and paracetamol were significantly better than placebo (both p<0.001); whereas, the difference between aspirin and paracetamol was not significant (p=0.772, very low quality evidence).

A further double-blind RCT (Gehanno et al. 2003) compared **diclofenac potassium** (3 doses: 6.25 mg, 12.5 mg and 25 mg) with **paracetamol** 1,000 mg or placebo for pain and fever in people with acute febrile sore throat. Participants were required to have a temperature of 38°C or higher and inflammation of the pharynx associated with spontaneous pain and pain on swallowing. Participants were excluded if they had 'streptococcal pain' (not defined). Diclofenac potassium (all doses) and paracetamol significantly reduced oral temperature compared with placebo, with improvements of between 1.94 and 2.27°C/hour for the active treatments compared with 1.46°C/hour for placebo (all p<0.05, very low quality evidence). The clinical

relevance of this reduction in temperature over placebo is unclear. Spontaneous pain and pain on swallowing (measured using TOTPAR$_{0-4}$ score) were significantly improved in the diclofenac potassium 12.5 mg, 25 mg and paracetamol 1,000 mg compared with placebo, although diclofenac 6.25 mg was not significantly better than placebo (very low quality evidence).

3.2.2 Medicated lozenges in adults

The evidence review for medicated lozenges is based on 6 RCTs (Chrubasik et al. 2012, McNally et al. 2012, Watson et al. 2000, Benrimoj et al. 2001, Blagden et al. 2001 and Schachtel et al. 2014) that assessed lozenges containing benzocaine, hexylresorcinol or flurbiprofen in adults with acute sore throat associated with an upper respiratory tract infection. Overall, results from the RCTs found statistically significant improvements in pain scores with medicated lozenges compared with placebo, although the absolute improvements were small and may not be clinically meaningful for some lozenges (very low to low quality evidence).

3.2.3 Benzocaine lozenges

A small RCT (n=165; Chrubasik et al. 2012) compared benzocaine lozenges with placebo in adults with mild or moderate throat pain (scoring 5 or more on a 10-point visual analogue scale [VAS]). People with a known or suspected bacterial infection were excluded. Change in pain intensity (measured as SPID) over 2 hours was −12 points in the benzocaine group and −5 points in the placebo group (p=0.001), from a baseline of 7 points, giving a between difference treatment difference of 7 points (low quality evidence). Farrar et al. (2000) suggested that a change in SPID score of 2 points or more per hour represents a minimal important clinical difference, meaning improvements seen for benzocaine may be clinically meaningful.

3.2.4 Hexylresorcinol lozenges

An RCT by McNally et al. (2012) compared hexylresorcinol lozenges with placebo in 126 adults with acute sore throat (scoring 6 or more on an 11-point throat soreness scale). The mean change in pain score from baseline at 2 hours (measured on an 11-point scale) was 2.22 points with hexylresorcinol lozenges and 0.97 points with placebo (least squares mean difference 1.16, 95% CI 0.37 to 1.09, p=0.004, low quality evidence). The clinical relevance of a 1-point improvement of this scale is unclear.

3.2.5 Flurbiprofen lozenges

Four RCTs compared flurbiprofen lozenges with placebo for acute sore throat. An RCT by Watson et al. (2000) randomised 301 adults with sore throat and a Tonsillo-Pharyngitis Assessment (TPA) score of 5 or more. There was no significant difference in total pain relief in the 2 hours following a single dose (measured by TOTPAR$_{15\text{-}120\ min}$ score) in the flurbiprofen 8.75 mg group (12.68 points) compared with placebo (10.47 points, p=0.060).

An RCT published in 2001 by Benrimoj et al. compared flurbiprofen lozenges with placebo in adults with acute sore throat, with the same inclusion criteria as Watson et al (2000). Improvements in TOTPAR$_{15\text{-}120\ min}$ score were significantly higher in the flurbiprofen 8.75 mg group (17.9 points) compared with placebo (15.6 points, p=0.037), although it's not clear whether a difference of 2.3 points is clinically meaningful.

An RCT by Blagden et al. (2001) recruited people aged 12 years and over with acute sore throat of 7 days duration or less (n=459). People treated with flurbiprofen lozenges had significantly greater improvement in $TOTPAR_{day\ 1\text{-}4}$ compared with placebo (12.4 points and 11.1 points respectively, p<0.05), although the clinical relevance of a difference of 1.3 points over 4 days is not clear (very low quality evidence).

An RCT by Schachtel et al. (2014) also compared flurbiprofen 8.75 mg lozenges with placebo in adults with acute sore throat and moderate to severe pain (measured using the Throat Pain Scale, n=198). People in the flurbiprofen 8.75 mg group reported a 59% greater reduction in pain intensity (measured by the Sore Throat Pain Intensity Scale [STPIS]), than people taking placebo (difference –196.6 mm/hour, 95% confidence interval (CI) −321.0 to −72.2; p<0.01, low quality evidence).

3.12.6 Throat sprays

The evidence review for throat sprays is based on 1 double-blind RCT of chlorhexidine plus benzydamine throat spray in adults with GABHS positive sore throat (Cingi et al. 2011). All participants received a 10-day course of penicillin V twice daily. The combination throat spray product is not available in the UK.

Intensity of clinical signs was scored out of 18 (lower scores indicate fewer symptoms). From a mean pre-treatment score of approximately 13 points, on day 7 people treated with chlorhexidine plus benzydamine had a mean score of 3.12 points, compared with 6.07 points for people treated with placebo, the difference between groups was statistically significant (p<0.001; low quality evidence). Chlorhexidine plus benzydamine improved patient-reported health state by approximately 4.5 cm (on a 10 cm VAS) compared with an improvement of 3.5 cm in the placebo group (baseline score approximately 7.5 cm, p<0.001; low quality evidence). Quality of life was assessed using the Short Form 36 Health Questionnaire on day 7, and were was no statistically significant difference between groups (low quality evidence).

3.12.7 Corticosteroids

The evidence review for corticosteroids is based on 1 systematic review of RCTs (Hayward et al. 2012) and 1 RCT Hayward et al. 2017).

Hayward et al. (2012) investigated the use of oral or intramuscular corticosteroids in adults and children (aged over 3 years) with acute sore throat, including tonsillitis and pharyngitis. Exudative sore throat was present in 47% of participants and 44% of participants had a GABHS positive swab. Antibiotics were administered to both treatment groups in all studies, most studies were conducted in accident and emergency departments.

At 24 hours, complete resolution of pain occurred in 38.8% of people in the corticosteroid group compared with 12.2% in the placebo group (RR 3.16, 95% CI 1.97 to 5.08, high quality evidence). The number needed to treat (NNT) at 24 hours was 4 (95% CI 2.8 to 5.9). At 48 hours, 75.5% of the corticosteroid group experienced complete resolution of pain compared with 46.8% of the placebo group (RR 1.65, 95% CI 1.32 to 2.06; high quality evidence). The NNT at 48 hours was 4 (95% CI 2.4 to 5.6).

The mean time to onset of pain relief was significantly lower in the corticosteroid group (7.71 hours) compared with the 14.03 hours in the placebo group (mean difference 6.32 hours, 95% CI 3.35 to 9.29, p<0.0001; moderate quality evidence).

Subgroup analyses found that the effect on mean time to onset of pain relief was greater in people with severe, exudative and GABHS positive sore throat. Mean time to complete resolution of pain was also significantly lower with corticosteroids (31.71 hours) compared with placebo (46.12 hours). The mean difference was 14.41 hours (95% CI 3.84 to 24.99; moderate quality evidence).

There was no significant difference between corticosteroids and placebo in recurrence or relapse of symptoms or in the number of days missed from work or school (moderate quality evidence).

In adults who were assessed as not needing an immediate antibiotic prescription, an RCT Hayward et al. (2017) found that a single dose of dexamethasone 10 mg did not significantly increase the proportion of people with resolution of symptoms at 24 hours compared with placebo, although a significant difference was seen at 48 hours (low quality evidence). Complete resolution of symptoms at 24 hours occurred in 22.6% of people treated with dexamethasone and in 17.7% of people treated with placebo (RR 1.28, 95% CI 0.92 to 1.78, low quality evidence). Resolution of symptoms at 48 hours was reported as a secondary outcome, with significantly more people in the dexamethasone group (35.4%) being symptom free compared with the placebo group (27.1%, p=0.03, low quality evidence). There was no significant difference between groups for time to onset of pain relief or time to complete resolution of symptoms (low quality evidence).

3.3 Antimicrobials

The evidence review for antimicrobials is based on 7 systematic reviews and 2 RCTs. The included studies cover delayed antibiotic prescribing, antibiotics versus placebo, antibiotics versus other antibiotics, duration of antibiotic treatment, antibiotic dosing frequency and clinical scoring systems. The studies that compared different antibiotics only included people with a confirmed GABHS infection.

3.3.1 Delayed antibiotics

One RCT in adults (de la Poza Abad et al. 2016) found that a delayed antibiotic prescription (either patient-led or prescription collection) or no antibiotic prescription was as effective as an immediate antibiotic prescription for reducing duration and severity of swallowing difficulties in people with pharyngitis (low quality evidence). Across the whole study population (including people with other upper respiratory tract infections), there were significantly lower rates of antibiotic collection in the delayed collection prescription group (26%, p<0.001) and patient-led delayed prescription group (34.7%, p<0.001) compared with the immediate prescription group (89.1%; low quality evidence). Antibiotic use was also significantly lower in the delayed collection prescription group (23%, p<0.001) and patient-led delayed prescription group (32.6%, p<0.001), compared with an immediate prescription (91.1%; low quality evidence).

One systematic review of RCTs (including open label studies) of delayed antibiotic prescribing (Spurling et al. 2013) reported conflicting results for studies involving people with acute sore throat. Immediate antibiotics were significantly more effective than placebo for fever, pain and malaise in some studies, while in others there was no significant difference between groups (very low to low quality evidence). Delayed antibiotics resulted in a significant reduction in antibiotic use compared to immediate antibiotics (32% versus 93% of prescriptions dispensed respectively).

3.3.2 Antibiotics compared with placebo

A systematic review and meta-analysis of 27 RCTs and quasi-RCTs (Spinks et al. 2013; n=12,835) compared antibiotics with placebo in adults and children with acute sore throat. Participants were not required to have a confirmed GABHS infection. Most of the studies were older, with a large number conducted in the 1950s.

On day 3 of the illness, approximately 51% of people in the antibiotic group did not have symptoms of sore throat, compared with 34% in the placebo group, the difference was statistically significant (risk ratio [RR] 0.68, 95% confidence interval [CI] 0.59 to 0.79, p<0.00001, low quality evidence). After 1 week, approximately 87% of people treated with antibiotics no longer had symptoms of sore throat, compared with 82% of those treated with placebo (RR 0.49, 95% CI 0.32 to 0.76, p=0.0014, low quality evidence). Overall, antibiotics shortened the duration of symptoms by about 16 hours over 7 days.

At day 3, significantly fewer people treated with antibiotics had headache symptoms (22.1%) compared with placebo (40.9%, RR 0.44, 95% CI 0.27 to 0.71, p=0.0007, moderate quality evidence). There was no significant difference between antibiotics and placebo for fever at day 3 (low quality evidence).

The authors report on a number of subgroup analyses. The effectiveness of antibiotics increased in those people with positive GABHS throat swabs. Just over half the people with a positive throat swab were still experiencing pain on day 3 (RR 0.58, 95% CI 0.48 to 0.71, moderate quality evidence) compared with three-quarters of those with negative swabs (RR 0.78, 95% CI 0.63 to 0.97, low quality evidence). Similar results were seen at 1 week.

3.3.3 Identifying people more likely to have a bacterial infection

Centor criteria

A systematic review by Aalbers et al. (2011) found that individual signs and symptoms could not distinguish between GABHS infection and other causes of sore throat. The review assessed the diagnostic accuracy of the Centor score, concluding that the Centor score is a well calibrated tool for estimating the probability of GABHS pharyngitis, and can enhance appropriate prescribing of antibiotics. A Centor score of 3 or more had a specificity of 0.82 and a sensitivity of 0.49 (low quality evidence). The authors suggested that Centor but should be used with caution in low prevalence settings of GABHS pharyngitis such as primary care.

FeverPAIN

An open-label RCT conducted in a UK primary care setting (Little et al. 2013) found the targeted use of antibiotics using the FeverPAIN clinical scoring system improved symptoms on days 2 to 4, and reduced antibiotic use compared with a delayed antibiotic prescribing strategy. The additional use of rapid antigen tests for people with a high FeverPAIN score had no clear advantage over FeverPAIN alone (low quality evidence).

Little et al. (2013) randomised 631 people aged 3 years and over who had acute sore throat and an abnormal throat on observation (erythema and/or pus). Participants were randomised to 1 of 3 groups:

1. Delayed antibiotics (control group): a prescription for antibiotics could be collected after 3 to 5 days if symptoms did not settle or were getting worse.

2. Clinical score (FeverPAIN): the FeverPAIN score was applied. People with a low score (0 or 1 points) were not offered an antibiotic. People with a moderate score (2 or 3 points) were offered a delayed prescription, and people with a high score (4 points or more) were offered an immediate antibiotic prescription.

3. FeverPAIN plus rapid antigen testing: the FeverPAIN score was applied. People with a low score (0 or 1 points) were not offered antibiotics or a rapid antigen test. People with a score of 2 points were offered a delayed antibiotic prescription but no rapid antigen test. People with a higher score (3 points or more) had a rapid antigen test and those people with a negative result were not offered antibiotics.

Mean symptom severity score was significantly lower in the FeverPAIN group (2.88 points) and the FeverPAIN plus rapid antigen testing group (2.83 points) compared with the delayed antibiotics group (3.11 points, mean difference 0.30 to 0.33, p=0.04 and p=0.05 respectively, low quality evidence). This is equivalent to 1 in 3 people rating their sore throat and swallowing difficulty as 'slight' rather than 'moderate'.

Compared with delayed antibiotics, the median duration of symptoms was significantly shorter in the FeverPAIN group (4 days) compared with the delayed antibiotic (control) group (5 days, hazard ratio [HR] 1.30, 95% CI 1.03 to 1.63, p=0.03; low quality evidence). Duration of symptoms was not significantly different in the FeverPAIN plus rapid antigen testing group compared with delayed antibiotics (4 days; HR 1.11, 95% 0.88 to 1.40, p=0.37; low quality evidence).

Significantly fewer people in the FeverPAIN group (37%) and the FeverPAIN plus rapid antigen test group (35%) reported using antibiotics compared with the delayed antibiotics group (46%, p=0.02 and p=0.03 respectively).

Rapid antigen testing

A systematic review of RCTs (Cohen et al. 2016) found the specificity of rapid antigen testing is sufficiently high to identify GABHS infection and minimise unnecessary antibiotic use. In studies comparing rapid antigen testing and throat culture (105 test evaluations, 58,244 participants, median prevalence of group A streptococcus 29.5%), rapid antigen testing had a summary sensitivity of 85.6% (95% CI 83.3 to 87.6) and a summary specificity of 95.4% (95% CI 94.5 to 96.2, very low quality evidence). The authors concluded that in a population of 1,000 children with a GABHS prevalence of 30%, 43 children with GABHS infection will not be detected.

6.4 Antibiotics compared with other antibiotics

Overall, evidence from 2 systematic reviews and meta-analyses of RCTs in adults and children with GABHS positive sore throat (Altamimi et al. 2012 and van Driel et al. 2016) did not suggest major differences in clinical effectiveness between classes of antibiotics, including penicillins, cephalosporins, macrolides, and sulphonamides (very low to moderate quality evidence).

The systematic review by van Driel et al. (2016) included 19 double-blind RCTs (n=5,839) involving adults and children that compared different classes of antibiotics for the treatment of sore throat caused by a confirmed GABHS infection. The majority of studies compared penicillin V with a broader spectrum antibiotic.

Altamimi et al. (2012) included 20 RCTs involving 13,102 children (1 to 18 years) with acute sore throat caused by GABHS infection (tonsillitis, pharyngitis or

tonsillopharyngitis). The RCTs compared a short course of a late-generation (not defined) antibiotic (2 to 6 days) with 10 days of penicillin V. The majority of studies (17/20) were published between 1994 and 2004.

Penicillins compared with cephalosporins

There was no significant difference between cephalosporin and penicillin for the resolution of symptoms after treatment, with approximately 24% of participants remaining symptomatic in both treatment groups (odds ratio [OR] 0.79, 95% CI 0.55 to 1.12, p=0.87, intention to treat [ITT] analysis, low quality evidence). The results for adults and children were similar.

The incidence of relapse in evaluable participants was significantly lower in people treated with cephalosporins (2.8%) compared with penicillin (4.6%; OR 0.55, 95% CI 0.30 to 0.99, p=0.045, NNT 50, moderate quality evidence).

Penicillins compared with macrolides

There was also no significant difference between macrolides and penicillin for resolution of symptoms after treatment, with around 43% of participants remaining symptomatic in both treatment groups (OR 1.11, 95% CI 0.92 to 1.35, p=0.51, low quality evidence). There was no significant difference in relapse rate for macrolides (5.0%) compared with penicillin (4.4%, p=0.69, very low quality evidence).

Late generation antibiotics (broader spectrum) compared with penicillin V

In Altamimi et al. (2012), the duration of fever (the primary outcome) was significantly less with a late-generation antibiotic (2.61 days) compared with penicillin V (2.91 days; mean difference 0.3 days, 95% CI 0.14 to 0.45, p=0.0002, moderate quality evidence).

The duration of sore throat was reported in 1 RCT included in Altamimi et al. (n=188), which found that children treated with a late-generation antibiotic had a shorter duration of sore throat (2.19 days) compared with penicillin V (2.69, mean difference 0.50 days, 95% CI 0.22 to 0.78, p=0.0004, very low quality evidence).

Early treatment failure, occurring 1 to 10 days after completion of antibiotics, was significantly less likely in children receiving a late-generation antibiotic (5.10%) compared with penicillin V (6.07%; OR 0.80, 95% CI 0.67 to 0.94, p=0.0078, low quality evidence).

2.5 Frequency of antibiotic dosing

One systematic review and meta-analysis of RCTs (Lan and Colford 2000) found twice daily dosing of penicillin V was as effective as 3 or 4 times daily dosing for microbiological cure in adults and children with GABHS positive sore throat (low quality evidence). Once daily dosing was significantly less effective compared with 3 or 4 times daily dosing of penicillin V (very low quality evidence).

A meta-analysis of 6 studies (n=1,208) compared once or twice daily dosing of oral penicillin V with three or four times daily dosing for the treatment of confirmed acute GABHS tonsillopharyngitis (Lan and Colford 2000). The total daily dose was comparable between treatment arms. The primary end point was microbiological cure at follow-up, defined as a negative culture for all follow-up cultures. The investigators found that once daily dosing was 12% (95% CI 3 to 21) less effective than three or four times daily dosing. The comparison of twice daily dosing with three or four times

daily dosing found no statistically significant difference between the 2 dosing schedules. Sub-analyses also found no significant difference in children-only studies, and studies that used low or high doses of penicillin.

3.3.6 Antibiotic course length

A systematic review by Falagas et al. (2008) included 3 RCTs that compared 5 to 7 days of penicillin V with 10 days of penicillin V in people with GABHS positive sore throat. The dose of penicillin V varied across the RCTs, and was broadly in line with the doses recommended in the BNF and BNFC for most age groups. Treatment with penicillin V for 5 to 7 days was associated with significantly lower microbiological eradication rates compared with penicillin V for 10 days (OR 0.36, 95% CI 0.13 to 0.99; low quality evidence).

4 Safety and tolerability

Details of safety and tolerability outcomes from studies included in the evidence review are shown in appendix F: GRADE profiles. The main results are summarised below.

4.1 Non-pharmacological interventions

No systematic review or RCTs were identified and included that compared non-medicated lozenges or non-medicated mouthwashes with placebo or another intervention in people with acute sore throat.

4.2 Non-antimicrobial pharmacological interventions

See the summaries of product characteristics for information on contraindications, cautions and adverse effects of individual medicines.

4.2.1 Oral analgesia

Diclofenac is associated with cardiovascular risks that are higher than other non-selective NSAIDs, and similar to selective COX-2 inhibitors. Naproxen and low-dose ibuprofen are considered to have the most favourable cardiovascular safety profiles (Drug Safety Update, October 2012). Of the non-selective NSAIDs, low-dose ibuprofen has the lowest gastrointestinal risk (Drug Safety Update, December 2007).

A double-blind RCT (n=2,815) compared the tolerability of ibuprofen (up to 1.2 gram daily), aspirin (up to 3 gram daily) and paracetamol (up to 3 gram daily) for the treatment of people with mild to moderate pain due to sore throat or cold and flu symptoms (Moore et al. 2002). The study did not report efficacy outcomes. Approximately one-third of participants (990/2,815) had pain associated with sore throat. Rates of significant adverse events (defined as an event that was serious, severe or moderate, or resulted in a second doctor consultation or discontinuation of treatment) were: ibuprofen 12.0%, paracetamol 12.3% and aspirin 15.7%, with a statistically significant difference between ibuprofen and aspirin (p=0.02, very low quality evidence).

4.2.2 Medicated lozenges

Few adverse events were reported in the RCTs involving lozenges containing benzocaine or hexylresorcinol.

Adverse events were reported by between 31% and 51% of participants in the 4 RCTs that investigated flurbiprofen lozenges. The most commonly reported adverse events for flurbiprofen lozenges were taste perversion, paraesthesia, dry mouth and nausea (very low quality evidence).

4.2.3 Throat sprays

In the RCT by Cingi et al. (2011), 39% (28/72) of people who received chlorhexidine plus benzydamine throat spray reported mild taste disturbance and mild to moderate oral mucosal numbness (low quality evidence).

4.2.4 Corticosteroids

Adverse events were reported in detail in 1 out of the 8 RCTs included in the systematic review by Hayward et al. (2012). In this RCT 5/125 participants (4%, 3 from corticosteroid group and 2 from placebo group) were hospitalised for fluid rehydration, and 3/125 participants (2%; 1 from corticosteroid group and 2 from placebo group) developed a peritonsillar abscess. Three RCTs reported no adverse events attributable to dexamethasone, 1 RCT reported no complications of GABHS infections and another RCT reported that no participants had additional complaints or required additional medications.

In the RCT by Hayward et al. (2017) 5 serious adverse events were reported. Two occurred among participants in the dexamethasone group, 1 of which was considered by the authors to be related to the trial (hospital admission with parapharyngeal abscess). Three serious adverse events occurred in the placebo group (hospital admission with peritonsillar abscess, hospital admission with severe tonsillitis, and hospital admission with pneumonia, with subsequent death after hospital discharge).

4.3 Antimicrobials

Acute sore throat is a self-limiting infection usually triggered by a viral infection of the upper respiratory tract, and the possible adverse effects of antibiotics need to be considered alongside any possible benefits. Antibiotic-associated diarrhoea is estimated to occur in 2 to 25% of people taking antibiotics, depending on the antibiotic used (NICE clinical knowledge summary [CKS]: diarrhoea – antibiotic associated).

Allergic reactions to penicillins occur in 1 to 10% of treated people and anaphylactic reactions occur in less than 0.05%. People with a history of atopic allergy (for example, asthma, eczema, and hayfever) are at a higher risk of anaphylactic reactions to penicillins. People with a history of immediate hypersensitivity to penicillins may also react to cephalosporins and other beta-lactam antibiotics. The most common side effect with penicillins is diarrhoea, which can also cause antibiotic-associated colitis. Diarrhoea is most common with broad-spectrum penicillins (such as amoxicillin and co-amoxiclav) (Penicillins, BNF June 2017).

Macrolides, including clarithromycin and erythromycin, are an alternative to penicillins in people with penicillin allergy. They should be used with caution in people with a predisposition to QT interval prolongation. Nausea, vomiting, abdominal discomfort, and diarrhoea are the most common side effects of macrolides. These are less frequent with clarithromycin than with erythromycin (Macrolides, BNF June 2017).

When estimating the effectiveness of antibiotics in reducing complication rates, the authors of Spinks et al. (2013) noted that the background risk of complications must be considered. In trials conducted in the 1950s, for every 100 people treated with antibiotics there were 2 fewer cases of acute otitis media (NNT=50). However, over time the background rate of acute otitis media complications has dropped over time, falling from 3% in trials conducted before 1975 to 0.7% in studies after 1975. Applying this reduction in risk increased the NNT to prevent one case of otitis media to nearly 200.

4.3.1 Delayed antibiotics

Across the 1 RCT and 1 systematic review there was generally no difference in adverse events between delayed antibiotic prescription and no prescription

strategies, compared with an immediate antibiotic prescription (de la Poza Abad et al. 2016 and Spurling et al. 2013; very low to low quality evidence).

4.3.2 Antibiotics versus placebo

Spinks et al. (2013) did report on the incidence of complications associated with sore throat. The incidence of acute otitis media within 14 days was significantly lower in the antibiotic group (0.5%) compared with the placebo group (2.0%, RR 0.30, 95% CI 0.15 to 0.58, p=0.0003, high quality evidence). Incidence of quinsy within 2 months was lower in the antibiotic group (0.1%) compared with placebo (2.3%, RR 0.15, 95% CI 0.05 to 0.47, p=0.0011, high quality evidence), although the absolute rates of quinsy in both groups were low. There was no significant difference in incidence of sinusitis within 14 days (RR 0.48, 95% CI 0.08 to 2.76, p=0.41, moderate quality evidence).

Acute glomerulonephritis occurred in 2 people (0.1%) treated with placebo and in 0 people treated with antibiotics (RR 0.22, 95% CI 0.02 to 2.08, p=0.19, low quality evidence), although the absolute number of cases was very low and the difference between groups was not statistically significant. Sixteen studies (n=10,101) reported on rheumatic fever within 2 months, finding a significantly higher incidence in people treated with placebo (1.7%) compared with antibiotics (0.7%, RR 0.27, 95% CI 0.12 to 0.60, p=0.0014).

The systematic review by Spinks et al. (2013) was unable to present the adverse effects of antibiotic use compared with placebo because of inconsistencies in recording these symptoms.

4.3.3 Antibiotics versus another antibiotic

The systematic review by van Driel et al. (2016) found no significant difference in adverse events for cephalosporins, macrolides or sulfonamide versus penicillin (very low quality evidence). There was also no significant difference in adverse events between clindamycin and ampicillin (very low quality evidence). Adverse events include gastrointestinal problems (including diarrhoea, nausea and vomiting, constipation), vaginal candidiasis, headaches and dizziness.

The systematic review by Altamimi et al. (2012) found that a shorter course of late-generation antibiotics were associated with significantly more adverse events compared with a longer course of penicillin (low quality evidence). The authors reported that all adverse events were mild to moderate and self-limiting. Most adverse events involved the gastrointestinal system (diarrhoea, vomiting and abdominal pain) in both antibiotic groups.

5 Resistance

The consumption of antimicrobials is a major driver for the development of antibiotic resistance in bacteria, and the 3 major goals of antimicrobial stewardship are to:

- optimise therapy for individual patients
- prevent overuse, misuse and abuse, and
- minimise development of resistance at patient and community levels.

The NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use recommends that the risk of antimicrobial resistance for individual patients and the population as a whole should be taken into account when deciding whether or not to prescribe an antimicrobial.

When antimicrobials are necessary to treat an infection that is not life-threatening, a narrow-spectrum antibiotic should generally be first choice. Indiscriminate use of broad-spectrum antibiotics creates a selective advantage for bacteria resistant even to these 'last-line' broad-spectrum agents, and also kills normal commensal flora leaving people susceptible to antibiotic-resistant harmful bacteria such as *C. difficile*. For infections that are not life-threatening, broad-spectrum antibiotics (for example, co-amoxiclav, quinolones and cephalosporins) need to be reserved for second-choice treatment when narrow-spectrum antibiotics are ineffective (CMO report 2011).

The ESPAUR report 2016 reported that antimicrobial consumption declined significantly between 2014 and 2015, with community prescribing from general and dental practice decreasing by more than 6%. Antibiotic prescribing in primary care in 2015 is at the lowest level since 2011, with broad-spectrum antibiotic use (antibiotics that are effective against a wide range of bacteria) continuing to decrease in primary care. Overall, there have been year-on year reductions in the use of antibiotics for respiratory tract infections in primary care, mainly driven by reductions in amoxicillin prescribing. Macrolide prescribing as a class is relatively unchanged, and the prescribing of doxycycline has increased slightly.

In acute bacterial sore throat, the most common causative pathogen is group A beta-haemolytic streptococcus (GABHS), although groups C or G beta-haemolytic streptococci as well as *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* have also been suggested to be pathogens (European Society for Clinical Microbiology and Infectious Diseases Sore Throat Guideline).

The Public Health England report on group A streptococcal infections (2016 to 2017) states that antimicrobial susceptibility results from routine laboratory surveillance indicate erythromycin non-susceptibility in 6% of group A streptococcal sterile site isolates, which is slightly higher than at the same point in the last few seasons (5%). The susceptibility testing of invasive group A streptococcal isolates against other key antimicrobials (tetracycline, 11%; clindamycin, 5%; and penicillin, 0%) indicates no changes in resistance patterns.

6 Other considerations

6.1 Resource impact

In a 2011 survey of UK primary care (Gulliford et al. 2014), consultations for sore throat accounted for 27% of all respiratory tract infection consultations, and the median practice issued an antibiotic prescription for 60% of these. There is potential for resource savings if a no antibiotic or a delayed antibiotic prescription strategy is used. One open label RCT (de la Poza Abad et al. 2016) found there were significantly lower rates of antibiotic collection in the delayed collection prescription group (26%, $p<0.001$) and patient-led delayed prescription group (34.7%, $p<0.001$) compared with the immediate prescription group (89.1%; very low quality evidence).

Recommended antibiotics are penicillin V, clarithromycin and erythromycin. All these antibiotics are available as generic formulations, see Drug Tariff for costs.

6.2 Medicines adherence

Medicines adherence may be a problem for some people with medicines that require frequent dosing (for example, some antibiotics) (NICE guideline on medicines adherence). Longer treatment durations for an acute illness (for example, for nasal corticosteroids) may also cause problems with medicines adherence for some people.

7 Terms used in the guideline

Centor criteria

The Centor criteria give an indication of the likelihood of a sore throat being due to bacterial infection. The criteria are:

1. Tonsillar exudate
2. Tender anterior cervical adenopathy
3. Fever over 38°C (100.5°F) by history
4. Absence of cough

Sore Throat Pain Intensity Scale (STPIS)

A 100 mm visual analogue scale for reporting throat pain.

Sum of Pain Intensity Difference (SPID)

A measure of change in pain over time. Obtained as the sum of each pain intensity difference (PID), which are calculated from the baseline pain intensity score minus pain intensity score during treatment. The SPID is weighted by time interval for the period of time it is measured over. Weighting by time gives a similar result to area-under-the-curve analysis (Eccles et al. 2003).

Tonsillo- Pharyngitis Assessment (TPA)

An index of distinct clinical features of pharyngitis, scored from 0 to 21 (higher scores indicating more severe symptoms.

7 features reported on:

- Oral temperature
- Oropharyngeal color
- Size of tonsils
- Number of oropharyngeal enanthems (vesicles, petechiae, or exudates)
- Largest size of anterior cervical lymph nodes
- Number of anterior cervical lymph nodes
- Maximum tenderness of some anterior cervical lymph nodes

(Schachtel et al. 2014)

Total pain relief (TOTPAR)

The sum of changes from baseline in pain score, reported over a predefined period of time (given in subscript). A low score will mean less pain relief and a high score more pain relief (Watson et al. 2000).

Throat Pain Scale

A four-category pain intensity scale (Schachtel et al. 2014).

Appendices

Appendix A: Review protocol

I	Review question	What pharmacological (antimicrobial and non-antimicrobial) and non-pharmacological interventions are effective in managing acute sore throat (including tonsillitis and pharyngitis)?	• antimicrobial includes antibiotics • non-antimicrobial includes analgesia, antiseptic lozenge/spray etc. • search will include terms for acute sore throat (including tonsillitis and pharyngitis)
II	Types of review question	Intervention questions will primarily be addressed through the search.	These will, for example, also identify natural history in placebo groups and causative organisms in studies that use laboratory diagnosis, and relative risks of differing management options.
III	Objective of the review	To determine the effectiveness of prescribing and other management interventions in managing acute sore throat (including tonsillitis and pharyngitis) in line with the major goals of antimicrobial stewardship. This includes interventions that lead prescribers to: • optimise outcomes for individuals • reduce overuse, misuse or abuse of antimicrobials. All of the above will be considered in the context of national antimicrobial resistance patterns where available, if not available committee expertise will be used to guide decision-making.	The secondary objectives of the review of studies will include: • indications for prescribing an antimicrobial (for example 'red flags', individual patient factors including adverse events and illness severity), thresholds for treatment (using scoring systems such as FeverPAIN, Centor criteria or rapid diagnostics • indications for no or delayed antimicrobial • indications for non-antimicrobial interventions

			• antimicrobial choice, optimal dose, duration (specifically length of treatment) and route for specified antimicrobial(s) • the natural history of the infection
IV	Eligibility criteria – population/ disease/ condition/ issue/domain	Population: Adults and children (aged 72 hours and older) with acute sore throat of any severity. Studies that use for example symptoms or signs (prognosis), clinical diagnosis, imaging, microbiological methods, laboratory testing of blood, scoring systems such as FeverPAIN, Centor criteria or rapid diagnostics for diagnosing the condition.	Subgroups of interest, those: • with protected characteristics under the Equality Act 2010. • with chronic conditions (such as high blood pressure, diabetes, heart or chronic kidney disease). • with true allergy.
V	Eligibility criteria – intervention(s)/exposure(s)/ prognostic factor(s)	The review will include studies which include: • Non-pharmacological interventions[1] • Non-antimicrobial pharmacological interventions[2] • Antimicrobial pharmacological interventions[3] For the treatment of acute sore throat (including pharyngitis and tonsillitis) in primary, secondary or other care settings (for example walk-in-centres, urgent care, and minor ailment schemes) either by prescription or by any other legal means of supply of medicine (for example patient group direction).	Limited to those interventions commonly in use (as agreed by the committee)
VI	Eligibility criteria – comparator(s)/ control or	Any other plausible strategy or comparator, including: • Placebo or no treatment. • Non-pharmacological interventions	

1 Non-pharmacological interventions include: no intervention, watchful waiting, delayed prescribing, stopping smoking, surgery

2 Non-antimicrobial pharmacological interventions include: analgesics (paracetamol, ibuprofen, aspirin), antiseptic lozenge/spray etc.

3 Antimicrobial pharmacological interventions include: delayed (back-up) prescribing, standby or rescue therapy, narrow or broad spectrum, single, dual or triple therapy, escalation or de-escalation of treatment. Antibiotics included in the search include those named in current guidance (plus the class to which they belong) plus other antibiotics agreed by the committee

	reference (gold) standard	• Non-antimicrobial pharmacological interventions. • Antimicrobial pharmacological interventions	
VII	Outcomes and prioritisation	a) Clinical outcomes such as: • mortality • infection cure rates (number or proportion of people with resolution of symptoms at a given time point, incidence of escalation of treatment) • time to clinical cure (mean or median time to resolution of illness) • reduction in symptoms (duration or severity) • rate of complications with or without treatment • safety, tolerability, and adverse effects. b) Thresholds or indications for antimicrobial treatment (which people are most, or least likely to benefit from antimicrobials) c) Changes in antimicrobial resistance patterns, trends and levels as a result of treatment. d) Patient-reported outcomes, such as medicines adherence, patient experience and patient satisfaction. e) Ability to carry out activities of daily living. f) Service user experience. g) Health and social care related quality of life, including long-term harm or disability. h) Health and social care utilisation (including length of stay, planned and unplanned contacts). The Committee considered which outcomes should be prioritised when multiple outcomes are reported (critical and important outcomes). Additionally, the Committee were asked to consider what clinically important features of study design may be important for this condition (for example length of study follow-up, treatment failure/recurrence, important outcomes of interest such as sequela or progression to more severe illness).	The committee have agreed that the following outcomes are critical: • reduction in symptoms (duration or severity) for example difference in time to substantial improvement • time to clinical cure (mean or median time to resolution of illness) • rate of complications (including mortality) with or without treatment, including escalation of treatment • health and social care utilisation (including length of stay, ITU stays, planned and unplanned contacts). • thresholds or indications for antimicrobial treatment (which people are most, or least likely to benefit from antimicrobials) The committee have agreed that the following outcomes are important: • patient-reported outcomes, such as medicines adherence, patient experience • changes in antimicrobial resistance patterns, trends and levels as a result of treatment

VIII	Eligibility criteria – study design	The search will look for: • Systematic review of randomised controlled trials (RCTs) • RCTs If insufficient evidence is available progress to: • Controlled trials • Systematic reviews of non-randomised controlled trials • Non-randomised controlled trials • Observational and cohort studies • Pre and post intervention studies (before and after) • Time series studies	Committee to advise the NICE project team on the inclusion of information from other condition specific guidance and on whether to progress due to insufficient evidence.
IX	Other inclusion exclusion criteria	The scope sets out what the guidelines will and will not include (exclusions). Further exclusions specific to this guideline include: • non-English language papers, studies that are only available as abstracts • for antimicrobial resistance non-UK papers.	
X	Proposed sensitivity/ sub-group analysis, or meta-regression	The search may identify studies in population subgroups (for example adults, older adults, children (those aged under 18 years of age), and people with co-morbidities or characteristics that are protected under the Equality Act 2010 or in the NICE equality impact assessment). These will be analysed within these categories to enable the production of management recommendations.	
XI	Selection process – duplicate screening/ selection/ analysis	All references from the database searches will be downloaded, de-duplicated and screened on title and abstract against the criteria above. A randomly selected initial sample of 10% of records will be screened by two reviewers independently. The rate of agreement for this sample will be recorded, and if it is over 90% then remaining references will screened by one reviewer only. Disagreement will be resolved through discussion. Where abstracts meet all the criteria, or if it is unclear from the study abstract whether it does, the full text will be retrieved. If large numbers of papers are identified and included at full text, the Committee may consider prioritising the evidence for example, evidence of higher quality in terms of study type or evidence with critical or highly important outcomes.	

XII	Data management (software)	Data management will be undertaken using EPPI-reviewer software. Any pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome.	
XIII	Information sources – databases and dates	Medline; Medline in Progress; Embase; PubMed; Cochrane database of systematic reviews (CDSR); Database of abstracts of effectiveness (DARE) (legacy); Cochrane Central Register of Controlled Trials (CENTRAL); Health Technology Assessment (HTA) database; Clinicaltrials.gov • All the above to be searched from 2000 to present day. • Filters for systematic reviews, RCTs and comparative studies to be applied, unless numbers without filters are low • Searches to be limited to studies reported in English. • Animal studies and conference abstracts to be excluded Medicines and Healthcare products Regulatory Agency (MHRA) website; European Medicines Agency (EMA) website; U.S. Food and Drug Administration (FDA) website; Drug Tariff; MIMs • The above to be searched for advice on precautions, warnings, undesirable effects of named antimicrobials.	
XIV	Identify if an update	Not applicable.	
XV	Author contacts	Web: https://www.nice.org.uk/guidance/indevelopment/gid-ng10050/consultation/html-content Email: infections@nice.org.uk	
XVI	Highlight if amendment to previous protocol	For details please see the interim process guide (2017).	
XVII	Search strategy – for one database	For details see appendix B.	

XVIII	Data collection process – forms/ duplicate	GRADE profiles will be used, for details see appendix F.	
XIX	Data items – define all variables to be collected	GRADE profiles will be used, for details see appendix F.	
XX	Methods for assessing bias at outcome/study level	Standard study checklists will be used to critically appraise individual studies. For details please see the interim process guide (2017). The risk of bias across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/	
XXI	Criteria for quantitative synthesis (where suitable)	For details please see the interim process guide (2017).	
XXII	Methods for analysis – combining studies and exploring (in)consistency	For details please see the interim process guide (2017).	
XXIII	Meta-bias assessment – publication bias, selective reporting bias	For details please see the interim process guide (2017).	
XXIV	Assessment of confidence in cumulative evidence	For details please see the interim process guide (2017).	

XXV	Rationale/ context – Current management	For details please see the introduction to the evidence review in the guideline.	
XXVI	Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by NICE and chaired by Dr Tessa Lewis in line with the interim process guide (2017). Staff from NICE undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods chapter of the full guideline.	
XXVII	Sources of funding/support	Developed and funded by NICE.	
XXVIII	Name of sponsor	Developed and funded by NICE.	
XXIX	Roles of sponsor	NICE funds and develops guidelines for those working in the NHS, public health, and social care in England.	

1

Appendix B: Literature search strategy

Database name: Medline - Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

	Strategy	
1	exp pharyngitis/ or exp tonsillitis/ or exp LARYNGITIS/ or PERITONSILLAR ABSCESS/ or epiglottitis/ or supraglottitis/	20051
2	(pharyngitis or tonsillitis).tw.	9787
3	(tonsillopharyngitis or tonsillo-pharyngitis).tw.	335
4	tonsillitides.tw.	3
5	(sore* adj3 throat*).tw.	4889
6	(laryngitis or quinsy or epiglottitis or supraglottitis).tw.	3252
7	(throat* adj3 infect*).tw.	910
8	((strep* or pain* or inflam* or itch* or swollen) adj3 throat*).tw.	1695
9	or/1-8	29065
10	amoxicillin/ or Clarithromycin/ or Penicillin V/ or Penicillin G/	24704
11	(amoxicillin* or amix or amoram or amoxident or galenamox or rimoxallin or amoxil).tw.	13341
12	(clarithromycin* or klaricid or mycifor XL or klaricid XL).tw.	8433
13	penicillin*.tw.	54870
14	(Phenoxymethylpenicillin or Phenoxymethyl penicillin).tw.	655
15	(benzylpenicillin or benzyl penicillin).tw.	2787
16	Trimethoprim, Sulfamethoxazole Drug Combination/ or (Cotrimoxazole or "Co-trimoxazole" or Septrin).tw.	10788
17	(moxifloxacin or avelox).tw.	4032
18	exp macrolides/	109980
19	macrolide*.tw.	15033
20	exp penicillins/	82728
21	penicillin*.tw.	54870
22	or/10-21	234123

23	9 and 22	3235
24	Acetaminophen/ or Ibuprofen/	24986
25	(paracetamol or acetaminophen or panadol or perfalgan or calpol).tw.	22743
26	(ibuprofen or arthrofen or ebufac or rimafen or brufen or brufen retard or calprofen or nuromol).tw.	11996
27	(anadin or cuprofen or nurofen or fenpaed or mandofen or obifen or feverfen).tw.	28
28	("acetylsalicylic acid" or disprin or zorprin or resprin or colfarit).tw. or aspirin/	48529
29	analgesics/ or analgesics, non-narcotic/ or analgesics, short-acting/	57180
30	(analgesi* or pain relief or pain reliev*).tw.	131376
31	(spray* or lozenge* or pastille* or mouthwash*).tw.	35667
32	(strepsil* or chloraseptic* or glycerin or tyrozet* or vocalzone or olbas).tw.	2015
33	mouthwashes/ or oral spray/	5130
34	or/24-33	272479
35	9 and 34	780
36	("self care" or self-care).tw. or Self Care/	40434
37	watchful waiting/	2633
38	((self or selves or themselves or themself) adj4 (care or manag*)).tw.	37053
39	"no intervention*".tw.	7108
40	(watchful* adj2 wait*).tw.	2267
41	(wait adj2 see).tw.	1309
42	(active* adj2 surveillance*).tw.	6421
43	(expectant* adj2 manage*).tw.	2954
44	((prescription* or prescrib*) adj4 ("red flag" or strateg* or appropriat* or inappropriat* or unnecessary or defer* or delay* or no or non or behaviour* or behavior* or optimal or optimi* or reduc* or decreas* or declin* or rate* or improv*)).tw.	24522
45	((misuse or "mis-use" or overuse or "over-use" or "over-prescri*" or abuse) adj4 (bacter* or antibacter* or anti-bacter* or "anti bacter*" or antimicrobial or anti-microbial or "anti microbial" or antibiot* or anti-biot* or "anti biot*")).tw.	1763
46	((delay* or defer*) adj3 (treat* or therap* or interven*)).tw.	29441
47	or/36-46	130948

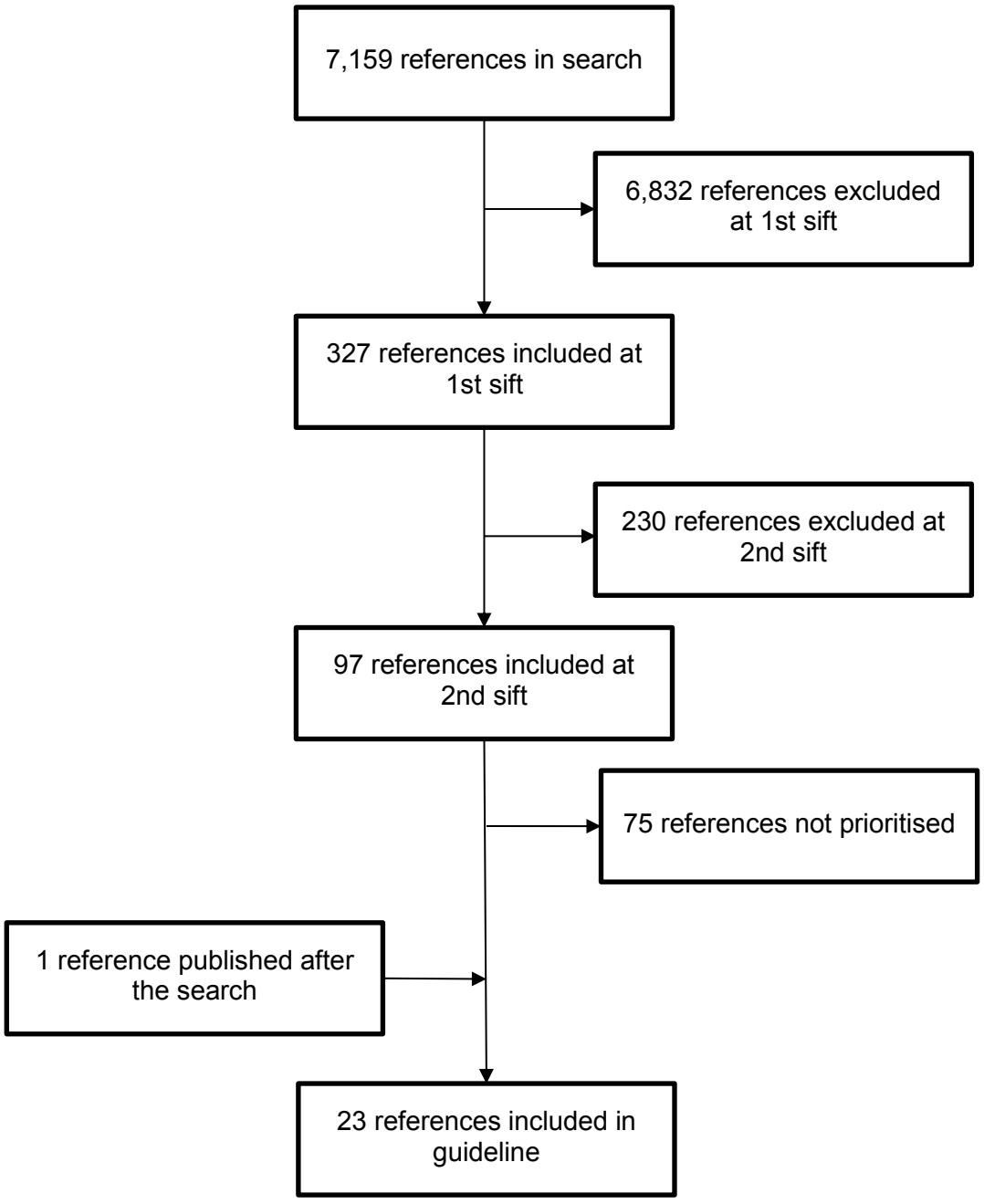
48	9 and 47	625
49	anti-infective agents/ or exp anti-bacterial agents/ or exp anti-infective agents, local/	922660
50	(antibacter* or anti-bacter* or antibiot* or anti-biot* or antimicrobial* or anti-microbial*).tw.	438229
51	(delay* or defer* or back-up* or backup* or immediate* or rapid* or short* or long* or standby or "stand by" or rescue or escalat* or "de-escalat*" or (prescribing adj strateg*) or "red flag*").tw.	4157783
52	(49 or 50) and 51	164679
53	9 and 52	1372
54	Smoking Cessation/	29158
55	"tobacco use cessation"/	1119
56	Smoking/pc	19316
57	"Tobacco Use Disorder"/pc	2044
58	((quit or quits or quitting or stop or stops or stopping or stopped or stoppage or cease or ceases or ceasing or cessation or cut or cuts or cutting or abstain* or abstinen* or rate* or reduc* or give* up or giving up) adj3 (smoking or cigar* or cigs or tobacco* or smoker* or bidi or bidis or kretek or hand roll* or handroll* or rollup* or roll up*)).ti,ab.	48283
59	antismok*.ti,ab.	914
60	(anti smok* or anti-smok*).ti,ab.	1245
61	or/54-60	67304
62	9 and 61	37
63	23 or 35 or 48 or 53 or 62	5169
64	limit 63 to (english language and yr="2000 -Current")	2095
65	Animals/ not (Animals/ and Humans/)	4824996
66	64 not 65	2075
67	limit 66 to (letter or historical article or comment or editorial or news)	104
68	66 not 67	1971
69	exp Drug Resistance, Bacterial/	79362
70	exp Drug Resistance, Multiple/	31723
71	((bacter$ or antibacter$ or anti-bacter$ or "anti bacter$") adj4 (resist$ or tolera$)).tw.	37409

72	((antibiot$ or anti-biot$ or "anti biot$") adj4 (resist$ or tolera$)).tw.	46520
73	(multi$ adj4 drug$ adj4 (resist$ or tolera$)).tw.	13509
74	(multidrug$ adj4 (resist$ or tolera$)).tw.	42614
75	(multiresist$ or multi-resist$ or "multi resist$").tw.	6458
76	((microb$ or antimicrob$ or anti-microb$ or "anti microb$") adj4 (resist$ or tolera$)).tw.	24311
77	(superbug$ or super-bug$ or "super bug$").tw.	511
78	Superinfection/	1851
79	(superinvasion$ or super-invasion$ or "super invasion$" or superinfection$ or super-infection$ or "super infection$").tw.	5831
80	R Factors/	4483
81	"r factor$".tw.	3977
82	(resist$ factor$ or "r plasmid$" or resist$ plasmid$).tw.	5706
83	or/69-82	198487
84	22 and 83	34904
85	limit 84 to (english language and yr="2000 -Current")	18030
86	Animals/ not (Animals/ and Humans/)	4824996
87	85 not 86	16190
88	Meta-Analysis.pt.	87182
89	Network Meta-Analysis/	24
90	Meta-Analysis as Topic/	17589
91	Review.pt.	2461328
92	exp Review Literature as Topic/	10398
93	(metaanaly$ or metanaly$ or (meta adj3 analy$)).tw.	123028
94	(review$ or overview$).ti.	422099
95	(systematic$ adj5 (review$ or overview$)).tw.	120821
96	((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw.	8233
97	((studies or trial$) adj2 (review$ or overview$)).tw.	40479
98	(integrat$ adj3 (research or review$ or literature)).tw.	9952
99	(pool$ adj2 (analy$ or data)).tw.	25675

100	(handsearch$ or (hand adj3 search$)).tw.	8790
101	(manual$ adj3 search$).tw.	5196
102	or/88-101	2742631
103	animals/ not humans/	4824996
104	102 not 103	2582479
105	68 and 104	396
106	Randomized Controlled Trial.pt.	509604
107	Controlled Clinical Trial.pt.	98304
108	Clinical Trial.pt.	548712
109	exp Clinical Trials as Topic/	339207
110	Placebos/	37138
111	Random Allocation/	98693
112	Double-Blind Method/	158560
113	Single-Blind Method/	26702
114	Cross-Over Studies/	45501
115	((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw.	1130237
116	(random$ adj3 allocat$).tw.	31002
117	placebo$.tw.	211691
118	((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.	167936
119	(crossover$ or (cross adj over$)).tw.	81743
120	or/106-119	1920723
121	animals/ not humans/	4824996
122	120 not 121	1799977
123	68 and 122	600
124	123 not 105	434
125	Observational Studies as Topic/	2324
126	Observational Study/	36300
127	Epidemiologic Studies/	8224
128	exp Case-Control Studies/	923993

129	exp Cohort Studies/	1814684
130	Cross-Sectional Studies/	269316
131	Controlled Before-After Studies/	259
132	Historically Controlled Study/	115
133	Interrupted Time Series Analysis/	308
134	Comparative Study.pt.	1963208
135	case control$.tw.	117818
136	case series.tw.	56000
137	(cohort adj (study or studies)).tw.	154650
138	cohort analy$.tw.	6267
139	(follow up adj (study or studies)).tw.	48071
140	(observational adj (study or studies)).tw.	78330
141	longitudinal.tw.	216352
142	prospective.tw.	505684
143	retrospective.tw.	412573
144	cross sectional.tw.	275997
145	or/125-144	4370957
146	animals/ not humans/	4824996
147	145 not 146	3864306
148	68 and 147	745
149	148 not (123 or 105)	436
150	68 not (105 or 123 or 148)	705

Appendix C: Study flow diagram



Appendix D: Included studies

Aalbers Jolien, O'Brien Kirsty K, Chan Wai-Sun, Falk Gavin A, Teljeur Conor, Dimitrov Borislav D, and Fahey Tom (2011) Predicting streptococcal pharyngitis in adults in primary care: a systematic review of the diagnostic accuracy of symptoms and signs and validation of the Centor score. BMC medicine 9, 67

Altamimi Saleh, Khalil Adli, Khalaiwi Khalid A, Milner Ruth A, Pusic Martin V, Al Othman, and Mohammed A (2012) Short-term late-generation antibiotics versus longer term penicillin for acute streptococcal pharyngitis in children. The Cochrane database of systematic reviews 8, CD004872

Benrimoj S I, Langford J H, Christian J, Charlesworth A, and Steans A (2001) Efficacy and Tolerability of the Anti-inflammatory Throat Lozenge Flurbiprofen 8.75mg in the Treatment of Sore Throat : A Randomised, Double-Blind, Placebo-Controlled Study. Clinical drug investigation 21(3), 183-93

Blagden M, Christian J, Miller K, and Charlesworth A (2002) Multidose flurbiprofen 8.75 mg lozenges in the treatment of sore throat: a randomised, double-blind, placebo-controlled study in UK general practice centres. International journal of clinical practice 56(2), 95-100

Chrubasik Sigrun, Beime Beate, and Magora Florella (2012) Efficacy of a benzocaine lozenge in the treatment of uncomplicated sore throat. European archives of oto-rhino-laryngology : official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery 269(2), 571-7

Cingi C, Songu M, Ural A, Erdogmus N, Yildirim M, Cakli H, and Bal C (2011) Effect of chlorhexidine gluconate and benzydamine hydrochloride mouth spray on clinical signs and quality of life of patients with streptococcal tonsillopharyngitis: multicentre, prospective, randomised, double-blinded, placebo-controlled study. The Journal of laryngology and otology 125(6), 620-5

Cohen Jeremie F, Bertille Nathalie, Cohen Robert, and Chalumeau Martin (2016) Rapid antigen detection test for group A streptococcus in children with pharyngitis. The Cochrane database of systematic reviews 7, CD010502

de la Poza Abad, Mariam , Mas Dalmau, Gemma , Moreno Bakedano, Mikel , Gonzalez Gonzalez, Ana Isabel, Canellas Criado, Yolanda , Hernandez Anadon, Silvia , Rotaeche del Campo, Rafael , Toran Monserrat, Pere , Negrete Palma, Antonio , Munoz Ortiz, Laura , Borrell Thio, Eulalia , Llor Carl, Little Paul, Alonso-Coello Pablo, Delayed Antibiotic Prescription, and Group (2016) Prescription Strategies in Acute Uncomplicated Respiratory Infections: A Randomized Clinical Trial. JAMA internal medicine 176(1), 21-9

Eccles Ron, Loose Irene, Jawad Martez, and Nyman Lars (2003) Effects of acetylsalicylic acid on sore throat pain and other pain symptoms associated with acute upper respiratory tract infection. Pain medicine (Malden, and Mass.) 4(2), 118-24

Gehanno P, Dreiser R L, Ionescu E, Gold Morris, and Liu Jiun-Min (2003) Lowest effective single dose of diclofenac for antipyretic and analgesic effects in acute febrile sore throat. Clinical drug investigation 23(4), 263-71

Hayward Gail, Thompson Matthew J, Perera Rafael, Glasziou Paul P, Del Mar, Chris B, and Heneghan Carl J (2012) Corticosteroids as standalone or add-on treatment for sore throat. The Cochrane database of systematic reviews 10, CD008268

Hayward Gail, Hay Alastair, Moore Michael, Jawad Sena, Williams Nicola, Voysey Merryn, Cook Johanna, Allen Julie, Thompson Matthew, Little Paul, Perera Rafael, Wolstenholme Jane, Harman Kim, Heneghan Carl (2017) Effect of Oral Dexamethasone Without Immediate Antibiotics vs Placebo on Acute Sore Throat in Adults- A Randomized Clinical Trial. JAMA 317(15), 1535-1543. doi:10.1001/jama.2017.3417

Kronman Matthew P, Zhou Chuan, and Mangione-Smith Rita (2014) Bacterial prevalence and antimicrobial prescribing trends for acute respiratory tract infections. Pediatrics 134(4), e956-65

Lan A J, Colford J M, Colford J M, and Jr (2000) The impact of dosing frequency on the efficacy of 10-day penicillin or amoxicillin therapy for streptococcal tonsillopharyngitis: A meta-analysis. Pediatrics 105(2), E19

Little P, Richard Hobbs, F D, Moore M, Mant D, Williamson I, McNulty C, Cheng Y E, Leydon G, McManus R, Kelly J, Barnett J, Glasziou P, and Mullee M (2013) Clinical score and rapid antigen detection test to guide antibiotic use for sore throats: Randomised controlled trial of PRISM (primary care streptococcal management). BMJ (Online) 347(7930), no pagination

McNally D, Shephard A, and Field E (2012) Randomised, double-blind, placebo-controlled study of a single dose of an amylmetacresol/2,4-dichlorobenzyl alcohol plus lidocaine lozenge or a hexylresorcinol lozenge for the treatment of acute sore throat due to upper respiratory tract infection. Journal of pharmacy & pharmaceutical sciences : a publication of the Canadian Society for Pharmaceutical Sciences, and Société canadienne des sciences pharmaceutiques 15(2), 281-94

Moore N, Le Parc , J M, van Ganse , E , Wall R, Schneid H, and Cairns R (2002) Tolerability of ibuprofen, aspirin and paracetamol for the treatment of cold and flu symptoms and sore throat pain. International journal of clinical practice 56(10), 732-4

Schachtel Bernard, Aspley Sue, Shephard Adrian, Shea Timothy, Smith Gary, and Schachtel Emily (2014) Utility of the sore throat pain model in a multiple-dose assessment of the acute analgesic flurbiprofen: a randomized controlled study. Trials 15, 263

Spinks Anneliese, Glasziou Paul P, Del Mar , and Chris B (2013) Antibiotics for sore throat. The Cochrane database of systematic reviews 11, CD000023

Spurling Geoffrey K. P, Del Mar , Chris B, Dooley Liz, Foxlee Ruth, and Farley Rebecca (2013) Delayed antibiotics for respiratory infections. The Cochrane database of systematic reviews 4, CD004417

van Driel , Mieke L, De Sutter , An Im, Habraken Hilde, Thorning Sarah, and Christiaens Thierry (2016) Different antibiotic treatments for group A streptococcal pharyngitis. The Cochrane database of systematic reviews 9, CD004406

Voelker M, Schachtel B P, Cooper S A, and Gatoulis S C (2016) Efficacy of disintegrating aspirin in two different models for acute mild-to-moderate pain: sore throat pain and dental pain. Inflammopharmacology 24(1), 43-51

Watson N, Nimmo W S, Christian J, Charlesworth A, Speight J, and Miller K (2000) Relief of sore throat with the anti-inflammatory throat lozenge flurbiprofen 8.75 mg: a randomised,

double-blind, placebo-controlled study of efficacy and safety. International journal of clinical practice 54(8), 490-6

Appendix E: Quality assessment of included studies

E.1 Oral analgesia

Table 3: Overall risk of bias/quality assessment – randomised controlled trials (**RCT checklist**)

Study reference	Eccles et al. 2003	Gehanno et al. 2003	Moore et al. 2002	Voelker et al. 2016
Did the trial address a clearly focused issue?	Yes	Yes	Yes	Yes
Was the assignment of patients to treatments randomised?	Yes	Yes	Yes	Unclear[a]
Were patients, health workers and study personnel blinded?	Yes	Yes	Yes	Unclear[b]
Were the groups similar at the start of the trial?	Yes	Yes	Yes	Yes
Aside from the experimental intervention, were the groups treated equally?	Yes	Yes	Yes	Yes
Were all of the patients who entered the trial properly accounted for at its conclusion?	No[c]	No[c]	Yes	Yes
How large was the treatment effect?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles
How precise was the estimate of the treatment effect?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles
Can the results be applied in your context? (or to the local population)	Yes	Yes	Yes	Yes
Were all clinically important outcomes considered?	Yes	Yes	Yes	Yes
Are the benefits worth the harms and costs?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles

Study reference	Eccles et al. 2003	Gehanno et al. 2003	Moore et al. 2002	Voelker et al. 2016

[a] Details on randomisation method not reported
[b] Blinding details not reported
[c] Not all randomised participants were included in the efficacy analyses

E.2 Lozenges

Table 4: Overall risk of bias/quality assessment – randomised controlled trials (RCT checklist)

Study reference	Benrimoj et al. 2001	Blagden et al. 2001	Chrubasik et al. 2012	McNalty et al. 2012	Schachtel et al. 2014	Watson et al. 2000
Did the trial address a clearly focused issue?	Yes	Yes	Yes	Yes	Yes	Yes
Was the assignment of patients to treatments randomised?	Unclear[a]	Unclear[b]	Yes	Yes	Yes	Unclear[b]
Were patients, health workers and study personnel blinded?	Yes	Unclear[c]	Yes	Yes	Unclear[c]	Unclear[c]
Were the groups similar at the start of the trial?	Yes	Yes	Yes	Yes	Yes	Yes
Aside from the experimental intervention, were the groups treated equally?	Yes	Yes	Yes	Yes	Yes	Yes
Were all of the patients who entered the trial properly accounted for at its conclusion?	No[d]	No[d]	Yes	Yes	Yes	Yes
How large was the treatment effect?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles
How precise was the estimate of the treatment effect?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles
Can the results be applied in your context? (or to the local population)	Yes	Yes	Yes	Yes	Yes	Yes

Study reference	Benrimoj et al. 2001	Blagden et al. 2001	Chrubasik et al. 2012	McNalty et al. 2012	Schachtel et al. 2014	Watson et al. 2000
Were all clinically important outcomes considered?	Yes	Yes	Yes	Yes	Yes	Yes
Are the benefits worth the harms and costs?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles

[a] Unclear whether allocation was concealed
[b] Details of randomisation methods not reported
[c] Details of blinding methods not reported
[d] Not all randomised participants were included in the efficacy analyses

E.3 Throat spray

Table 5: Overall risk of bias/quality assessment – randomised controlled trials (RCT checklist)

Study reference	Cingi et al. 2011
Did the trial address a clearly focused issue?	Yes
Was the assignment of patients to treatments randomised?	Yes
Were patients, health workers and study personnel blinded?	Yes
Were the groups similar at the start of the trial?	Yes
Aside from the experimental intervention, were the groups treated equally?	Yes
Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes
How large was the treatment effect?	See GRADE profiles
How precise was the estimate of the treatment effect?	See GRADE profiles
Can the results be applied in your context? (or to the local population)	Unclear[a]
Were all clinically important outcomes considered?	Yes
Are the benefits worth the harms and costs?	See GRADE profiles
[a] All participants also received antibiotics. The effectiveness of sprays in people not taking antibiotics is not known.	

E.4 Corticosteroids

Table 6: Overall risk of bias/quality assessment – systematic reviews (SR checklist)

Study reference	Hayward et al. 2012
Did the review address a clearly focused question?	Yes
Did the authors look for the right type of papers?	Yes
Do you think all the important, relevant studies were included?	Yes
Did the review's authors do enough to assess the quality of the included studies?	Yes
If the results of the review have been combined, was it reasonable to do so?	Yes
What are the overall results of the review?	See GRADE profiles
How precise are the results?	See GRADE profiles
Can the results be applied to the local population?	No
Were all important outcomes considered?	Yes
Are the benefits worth the harms and costs?	See GRADE profiles

Table 7: Overall risk of bias/quality assessment – randomised controlled trials (RCT checklist)

Study reference	Hayward et al. 2017
Did the trial address a clearly focused issue?	Yes
Was the assignment of patients to treatments randomised?	Yes
Were patients, health workers and study personnel blinded?	Yes
Were the groups similar at the start of the trial?	Yes
Aside from the experimental intervention, were the groups treated equally?	Yes
Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes
How large was the treatment effect?	See GRADE profiles
How precise was the estimate of the treatment effect?	See GRADE profiles
Can the results be applied in your context? (or to the local population)	Yes
Were all clinically important outcomes considered?	Yes
Are the benefits worth the harms and costs?	See GRADE profiles

E.5 Antimicrobials

Table 8: Overall risk of bias/quality assessment – systematic reviews (SR checklist)

Study reference	Altamimi et al. 2012	Falagas et al. 2008	Lan and Colford 2000	Spinks et al. 2013	Spurling et al. 2013	van Driel et al. 2016
Did the review address a clearly focused question?	Yes	Yes	Yes	Yes	Yes	Yes
Did the authors look for the right type of papers?	Yes	Yes	Yes	Yes	Yes	Yes
Do you think all the important, relevant studies were included?	Yes	Yes	Yes	Yes	Yes	Yes
Did the review's authors do enough to assess the quality of the included studies?	Yes	Yes	No[a]	Yes	Yes	Yes
If the results of the review have been combined, was it reasonable to do so?	Yes	No[b]	Unclear[c]	Yes	Not applicable	Yes
What are the overall results of the review?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles
How precise are the results?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles
Can the results be applied to the local population?	Yes	Yes	Yes	Unclear[d]	Yes	Yes

Study reference	Altamimi et al. 2012	Falagas et al. 2008	Lan and Colford 2000	Spinks et al. 2013	Spurling et al. 2013	van Driel et al. 2016
Were all important outcomes considered?	Yes	Yes	Yes	Yes	Yes	Yes
Are the benefits worth the harms and costs?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles

[a] Quality assessment was reported but it was unclear if the tool used was validated

[b] The same duration of antibiotic could be classified as 'short' or 'long' in different studies.

[c] Different doses of penicillin V used in the included studies.

[d] Many of the included studies were older, with a large number conducted in the 1950s.

Table 9: Overall risk of bias/quality assessment – randomised controlled trials (RCT checklist)

Study reference	de la Poza Abad et al. 2016
Did the trial address a clearly focused issue?	Yes
Was the assignment of patients to treatments randomised?	Yes
Were patients, health workers and study personnel blinded?	No[a]
Were the groups similar at the start of the trial?	Yes
Aside from the experimental intervention, were the groups treated equally?	Yes
Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes
How large was the treatment effect?	See GRADE profiles
How precise was the estimate of the treatment effect?	See GRADE profiles
Can the results be applied in your context? (or to the local population)	Unclear[b]
Were all clinically important outcomes considered?	Yes
Are the benefits worth the harms and costs?	See GRADE profiles
[a] Open label study [b] Unclear if this study can be generalised to a UK setting	

E.6 Clinical scoring systems and rapid antigen testing

Table 10: Overall risk of bias/quality assessment – systematic reviews (SR checklist)

Study reference	Aalbers et al. 2011	Cohen et al. 2016
Did the review address a clearly focused question?	Yes	Yes
Did the authors look for the right type of papers?	Yes	Yes
Do you think all the important, relevant studies were included?	Yes	Yes
Did the review's authors do enough to assess the quality of the included studies?	Yes	Yes
If the results of the review have been combined, was it reasonable to do so?	Yes	Yes
What are the overall results of the review?	See GRADE profiles	See GRADE profiles
How precise are the results?	See GRADE profiles	See GRADE profiles
Can the results be applied to the local population?	Yes	Yes
Were all important outcomes considered?	Yes	Yes
Are the benefits worth the harms and costs?	See GRADE profiles	See GRADE profiles

Table 11: Overall risk of bias/quality assessment – randomised controlled trials (RCT checklist)

Study reference	Little et al. 2013
Did the trial address a clearly focused issue?	Yes
Was the assignment of patients to treatments randomised?	Yes
Were patients, health workers and study personnel blinded?	Yes
Were the groups similar at the start of the trial?	Yes
Aside from the experimental intervention, were the groups treated equally?	Yes
Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes
How large was the treatment effect?	See GRADE profiles

Study reference	Little et al. 2013
How precise was the estimate of the treatment effect?	See GRADE profiles
Can the results be applied in your context? (or to the local population)	Yes
Were all clinically important outcomes considered?	Yes
Are the benefits worth the harms and costs?	See GRADE profiles

Appendix F:GRADE profiles

F.1 Oral analgesia

Table 12: GRADE profile – aspirin versus placebo in adults

Quality assessment							No of patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aspirin	Placebo			
Pain on swallowing over 2 hours (measured with: Sum of pain intensity difference (SPID) over 2 hours[1]; Better indicated by higher values)											
1[2]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	serious[4]	none	139	133	Significantly higher improvements in the aspirin group (3.81 points) compared with placebo (2.41 points, p=0.0001)	⊕⊕OO LOW	CRITICAL
Pain relief (measured with: Sum of improvements in pain relief scores over 2 hours [$TOTPAR_{0-2}$])											
1[2]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	serious[4]	none	139	133	Significantly higher improvements for aspirin compared with placebo (p=0.0001)	⊕⊕OO LOW	CRITICAL
Time to meaningful pain relief (Better indicated by lower values)											
1[5]	randomised trials	serious[6]	serious[3]	no serious indirectness	serious[4]	none	71	36	Time to meaningful pain relief was 48.0 minutes in the aspirin group. Meaningful pain relief was not achieved within 2 hours in the placebo group, statistically significant difference (p<0.001)	⊕OOO VERY LOW	CRITICAL
Pain intensity from baseline to 1 hour (measured with: Sum of pain intensity difference (SPID) over 1 hour; Better indicated by higher values)											
1[5]	randomised trials	serious[6]	serious[3]	no serious indirectness	serious[4]	none	71	36	Aspirin = 15.0 points Placebo = 4.2 points p<0.001	⊕OOO VERY LOW	CRITICAL
Pain intensity) from baseline to 2 hours (measured with: Sum of pain intensity difference (SPID) over 2 hours; Better indicated by higher values)											
1[5]	randomised trials	serious[6]	serious[3]	no serious indirectness	serious[4]	none	71	36	Aspirin = 48.0 points Placebo = 13.4 points p<0.001	⊕OOO VERY LOW	CRITICAL
Adverse events											
1[2]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	serious[4]	none	139	133	17 participants in each treatment group reported adverse events, including headache, abdominal pain and nausea.	⊕⊕OO LOW	CRITICAL
Adverse events											

1[5]	randomised trials	serious[6]	serious[3]	no serious indirectness	serious[4]	none	71	36	Fewer adverse events reported in people treated with aspirin (18.3%) compared with placebo (33.3%)	⊕OOO VERY LOW	CRITICAL

[1] Recorded on an 11-point scale on which the person records how much their throat hurts, scored from 0 (not at all) to 10 (very much)
[2] Eccles et al. 2003
[3] Downgraded 1 level - not assessable, single RCT
[4] Downgraded 1 level - not assessable
[5] Voelker et al. (2016)
[6] Downgraded 1 level - no details on methods of randomisation or blinding reported

Table 13: GRADE profile – paracetamol versus placebo in adults

Quality assessment							No of patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Paracetamol	Placebo			
Time to meaningful pain relief (Better indicated by lower values)											
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[4]	none	70	36	Paracetamol = 40.4 minutes Placebo = not achieved within 2 hour observational period p<0.001	⊕OOO VERY LOW	CRITICAL
Change in pain intensity from baseline to 1 hour (Better indicated by higher values)											
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[4]	none	70	36	Paracetamol = 16.1 points Placebo = 4.2 points p<0.001	⊕OOO VERY LOW	CRITICAL
Change in pain intensity from baseline to 2 hours (Better indicated by higher values)											
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[4]	none	70	36	Paracetamol = 47.1 points Placebo = 13.4 points p<0.001	⊕OOO VERY LOW	CRITICAL
Change in temperature from baseline to 4 hours, area under curve (AUC_{0-4}) (Better indicated by higher values)											
1[5]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[4]	none	65	69	Paracetamol = 2.01ºC/hour Placebo = 1.46ºC/hour p≤0.05	⊕OOO VERY LOW	CRITICAL
Change in pain on swallowing, total pain relief summed over 4 hours ($TOTPAR_{0-4}$) (Better indicated by higher values)											
1[5]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[4]	none	63	67	Paracetamol = 4.06 points Placebo = 3.28 points p<0.01	⊕OOO VERY LOW	CRITICAL
Adverse events, number of participants reporting at least 1 event											
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[4]	none	70	36	Paracetamol = 10 participants (14.3%)	⊕OOO VERY LOW	CRITICAL

									Placebo = 12 participants (33.3%)		
Adverse events, percentage of participants reporting at least 1 event											
1[5]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[4]	none	67	71	Paracetamol = 9.0% Placebo = 5.6%	⊕OOO VERY LOW	CRITICAL

[1] Voelker et al. (2016)
[2] Downgraded 1 level - no details on methods of randomisation or blinding reported
[3] Downgraded 1 level - not assessable, single RCT
[4] Downgraded 1 level - not assessable
[5] Gehanno et al. (2003)

Table 14: GRADE profile – diclofenac potassium versus placebo in adults

Quality assessment							No of patients				Effect	Quality	Importance
							Diclofenac potassium						
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	6.25 mg	12.5 mg	25 mg	Placebo			
Change in temperature from baseline to 4 hours, area under curve (AUC_{0-4}) (Better indicated by higher values)													
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[4]	none	66	66	70	69	6.25mg = 1.94 °C/hour 12.5 mg = 2.09 °C/hour 25 mg = 2.27 °C/hour Placebo = 1.46 °C/hour	⊕OOO VERY LOW	CRITICAL
Change in pain on swallowing, total pain relief summed over 4 hours ($TOTPAR_{0-4}$) (Better indicated by higher values)													
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[4]	none	62	66	68	67	6.25mg = 3.71 points 12.5 mg = 4.64 points 25 mg = 5.01 points Placebo = 3.28 points	⊕OOO VERY LOW	CRITICAL
Adverse events, percentage of participants reporting at least 1 event													
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[4]	none	67	67	71	71	6.25mg = 6.0% 12.5 mg = 6.0% 25 mg = 2.8% Placebo = 5.6%	⊕OOO VERY LOW	CRITICAL

[1] Gehanno et al. (2003)
[2] Downgraded 1 level - no details on methods of randomisation or blinding reported
[3] Downgraded 1 level - not assessable, single RCT
[4] Downgraded 1 level - not assessable

Table 15: GRADE profile – aspirin versus paracetamol in adults

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aspirin	Paracetamol			
Median time to meaningful pain relief, minutes (Better indicated by lower values)											
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[4]	none	71	70	Aspirin = 48.0 minutes Paracetamol = 40.4 minutes p=0.772	⊕OOO VERY LOW	CRITICAL
Change in pain intensity from baseline to 1 hour (Sum of pain intensity difference (SPID) over 1 hour, Better indicated by higher values)											
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[4]	none	71	70	Aspirin = 15.0 Paracetamol = 16.1 p=0.632	⊕OOO VERY LOW	CRITICAL
Change in pain intensity from baseline to 2 hours (Sum of pain intensity difference (SPID) over 2 hours, Better indicated by higher values)											
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[4]	none	71	70	Aspirin = 48.0 Paracetamol = 47.1 p=0.869	⊕OOO VERY LOW	CRITICAL
Adverse events, number of participants reporting at least 1 event											
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[4]	none	71	70	Aspirin = 13 (18.3%) Paracetamol = 10 (14.3%)	⊕OOO VERY LOW	CRITICAL

[1] Voelker et al. (2016)
[2] Downgraded 1 level - no details on methods of randomisation or blinding reported
[3] Downgraded 1 level - not assessable, single RCT
[4] Downgraded 1 level - not assessable

Table 16: GRADE profile – diclofenac versus paracetamol in adults

Quality assessment							No of patients				Effect	Quality	Importance
							Diclofenac potassium			Paracetamol			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	6.25mg	12.5mg	25mg				
Change in temperature from baseline to 4 hours, area under curve (AUC_{0-4}) (Better indicated by higher values)													
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[4]	none	66	66	70	65	6.25mg = 1.94 °C/hour 12.5 mg = 2.09 °C/hour 25 mg = 2.27 °C/hour Paracetamol = 2.01 °C/hour	⊕OOO VERY LOW	CRITICAL
Change in pain on swallowing, total pain relief summed over 4 hours ($TOTPAR_{0-4}$) (Better indicated by higher values)													
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[4]	none	62	66	68	63	6.25mg = 3.71 points 12.5 mg = 4.64 points 25 mg = 5.01 points Placebo = 4.06 points	⊕OOO VERY LOW	CRITICAL
Adverse events, percentage of participants reporting at least 1 event													

1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[4]	none	67	67	71	67	6.25mg = 6.0% 12.5 mg = 6.0% 25 mg = 2.8% Placebo = 9.0%	⊕OOO VERY LOW	CRITICAL

[1] Gehanno et al. (2003)
[2] Downgraded 1 level - no details on methods of randomisation or blinding reported
[3] Downgraded 1 level - not assessable, single RCT
[4] Downgraded 1 level - not assessable

Table 17: GRADE profile – tolerability of ibuprofen versus aspirin versus paracetamol in adults

Quality assessment							No of patients			Effect	Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Ibuprofen**	**Aspirin**	**Paracetamol**			
Significant adverse events, percentage of participants reporting at least 1 event within 7 days												
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[4]	none	940	942	933	Ibuprofen = 12.0% Aspirin = 15.7% Paracetamol = 12.3% Significantly significant difference between ibuprofen and aspirin (p=0.02)	⊕OOO VERY LOW	CRITICAL
Adverse events leading to study discontinuation, percentage of participants within 7 days												
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[4]	none	940	942	933	Ibuprofen = 4.3% Aspirin = 6.5% Paracetamol = 5.1% Significantly significant difference between ibuprofen and aspirin (p=0.033)	⊕OOO VERY LOW	CRITICAL

[1] Moore et al. (2002)
[2] Downgraded 1 level - no details on methods of randomisation or blinding reported
[3] Downgraded 1 level - not assessable, single RCT
[4] Downgraded 1 level - not assessable

F.2 Lozenges

Table 18: GRADE profile – benzocaine lozenges versus placebo in adults with acute sore throat

Quality assessment							No of patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Benzocaine lozenges	Placebo			
Change in pain over 2 hours (measured with: 10-point visual analogue scale [VAS], reported as sum of the pain intensity differences over 2 hours [SPID]; Better indicated by lower values)											
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	no serious imprecision	none	83	82	At baseline the median VAS score was 7 across both groups. The SPID over 2 hours was −12 points in the benzocaine group and −5 points in the placebo group (p=0.001), giving a between difference treatment difference of 7 points.	⊕⊕OO LOW	CRITICAL
Adverse events											
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[4]	none	83	82	Only 1 adverse event was reported; a case of vertigo in a person treated with placebo	⊕OOO VERY LOW	CRITICAL

[1] Chrubasik, Beime and Magora (2012)
[2] Downgraded 1 level - no details on methods of randomisation reported. Unclear whether allocation was concealed
[3] Not assessable - single RCT
[4] Downgraded 1 level - only 1 event reported

Table 19: GRADE profile – hexylresorcinol lozenges versus placebo in adults with acute sore throat

Quality assessment							No of patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hexylresorcinol lozenges	Placebo	Absolute		
Change in throat soreness from baseline to 2 hours (measured with: 11-point scale (with 0 being not sore and 10 being very sore); Better indicated by lower values)											
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	no serious imprecision	none	64	62	LS mean difference 1.16 higher (0.37 to 1.09 higher)	⊕⊕OO LOW	CRITICAL
Adverse events											

1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	no serious imprecision	none	1/64 (1.6%)	4/62 (6.5%)	65 fewer per 1000 (from 65 fewer to 65 fewer)	⊕⊕OO LOW	CRITICAL

[1] McNally, Shephard and Field (2012)
[2] Downgraded 1 level - no details on methods of randomisation reported. Unclear whether allocation was concealed
[3] Downgraded 1 level - not assessable, single RCT

Table 20: GRADE profile – flurbiprofen 8.75 mg lozenges versus placebo in adults with acute sore throat

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Flurbiprofen 8.75 mg lozenges**	**Placebo**	**Flurbiprofen 8.75 mg lozenges**	**Placebo**		
Change in pain over 2 hours (measured with: total pain relief summed over 15-120 minutes ($TOTPAR_{15\text{-}120\ min}$); Better indicated by higher values)												
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[4]	none	128	128	12.68 points	10.47 points p=0.060	⊕OOO VERY LOW	CRITICAL
Change in pain over 2 hours (measured with: total pain relief summed over 15-120 minutes ($TOTPAR_{15\text{-}120\ min}$); Better indicated by higher values)												
1[5]	randomised trials	serious[6]	serious[3]	no serious indirectness	serious[4]	none	120	125	17.9 points	15.6 points p=0.037	⊕⊕OO LOW	CRITICAL
Change in pain on days 1 to 4 (measured with: Total pain relief summed over 15-120 minutes ($TOTPAR_{15\text{-}120\ min}$); Better indicated by lower values)												
1[7]	randomised trials	serious[8]	serious[3]	no serious indirectness	serious[4]	none	184	179	12.4 points	11.1 points p<0.05	⊕OOO VERY LOW	CRITICAL
Change in pain over 24 hours after first dose (Sum of the pain intensity differences [SPID]) (measured with: Sore Throat Pain Intensity Scale (STPIS), which records pain on a 100 mm scale. mm/hour; Better indicated by lower values)												
1[9]	randomised trials	serious[10]	serious[3]	no serious indirectness	serious[4]	none	99	95	-529.2 mm/hour	-321.0 mm/hour p<0.01	⊕⊕OO LOW	CRITICAL
Adverse events												
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[4]	none	129	129	51/129 (39.5%)	30/129 (23.3%)	⊕OOO VERY LOW	CRITICAL
Adverse events												
1[5]	randomised trials	serious[6]	serious[3]	no serious indirectness	serious[4]	none	128	128	66/128 (51.6%)	48/128 (37.5%)	⊕OOO VERY LOW	CRITICAL
Adverse events reported by patients												

1[7]	randomised trials	serious[8]	serious[3]	no serious indirectness	serious[4]	none	230	228	103/230 (44.8%)	71/228 (31.1%)	⊕OOO VERY LOW	CRITICAL
Adverse events in the first 24 hours												
1[9]	randomised trials	serious[10]	serious[3]	no serious indirectness	serious[4]	none	99	95	25.7%	19.6% p>0.1	⊕OOO VERY LOW	CRITICAL

[1] Watson et al. (2000)
[2] Downgraded 1 level - no details on methods of randomisation or blinding reported
[3] Downgraded 1 level - not assessable, single RCT
[4] Downgraded 1 level - not assessable
[5] Benrimoj et al. (2001)
[6] Downgraded 1 level - unclear whether allocation was concealed
[7] Blagden et al. (2001)
[8] Downgraded 1 level - no details on methods of randomisation or blinding reported. Large number of participants withdrew from the study.
[9] Schachtel et al. (2014)
[10] Downgraded 1 level - no details on methods of blinding reported. Unclear whether allocation was concealed

F.3 Throat spray

Table 21: GRADE profile – chlorhexidine gluconate and benzydamine mouth spray versus placebo in adults (16 to 64 years)

Quality assessment							No of patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chlorhexidine gluconate and benzydamine mouth spray	Placebo			
Intensity of clinical signs (sore throat, erythema and oedema of the posterior pharynx, exudate, cervical lymphadenopathy, and headache) (measured with: Investigator assessed, maximum score = 18; Better indicated by lower values)											
1[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	72	75	**Chlorhexidine gluconate and benzydamine mouth spray:** Pre-treatment = 12.86 points Post-treatment = 3.12 points p<0.001 **Placebo:** Pre-treatment = 13.08 points Post-treatment = 6.07 points p<0.001 Significantly greater improvements in the treatment group (p<0.001)	⊕⊕OO LOW	CRITICAL
Subjective health state after 7 days treatment, measured on a xx-point visual analogue scale (VAS)											
1[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	72	75	**Chlorhexidine gluconate and benzydamine mouth spray:** Pre-treatment = 7.47 points Post-treatment = 2.78 points **Placebo:** Pre-treatment = 7.45 points Post-treatment = 3.96 points Significantly significant difference between groups (p<0.001)	⊕⊕OO LOW	IMPORTANT
Quality of life, measured using Short Form 36 (SF36) Health Questionnaire											
1[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	72	75	**Chlorhexidine gluconate and benzydamine mouth spray:** Pre-treatment = 106.99 points Post-treatment = 110.60 points p<0.001 **Placebo:** Pre-treatment = 104.84 points Post-treatment = 108.72 points p<0.001	⊕⊕OO LOW	IMPORTANT

									No statistically significant difference between groups (p>0.05)		
Adverse events, side effect score used a 4-point Likert scale that assessed local and systemic side effects, higher scores indicate more severe side effects											
1[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	72	75	Significantly higher side effect score in the treatment group at day 3 (p=0.004), but no significant difference by day 7 (p=0.937). Mild taste disturbance and mild to moderate oral mucosal numbness were the most frequent side effects, reported by 28 people (39%) in the treatment group	⊕⊕OO LOW	CRITICAL

[1] Cingi et al. (2011)
[2] Downgraded 1 level - not assessable, single RCT
[3] Downgraded 1 level - not assessable

F.4 Corticosteroids

Table 22: GRADE profile – corticosteroid (oral or intramuscular) versus placebo in adults and children (aged 3 years and over) with GABHS positive sore throat who are also receiving antibiotics

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids	Placebo	Relative (95% CI)	Absolute		
Complete resolution of pain at 24 hours												
4[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	54/139 (38.8%)	18/147 (12.2%)	RR 3.16 (1.97 to 5.08)	264 more per 1000 (from 119 more to 500 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Complete resolution of pain at 48 hours (follow-up What to put here?)												
3[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	74/98 (75.5%)	52/111 (46.8%)	RR 1.65 (1.32 to 2.06)	305 more per 1000 (from 150 more to 497 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Mean time to onset of pain relief (Better indicated by lower values)												
6[2]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	no serious imprecision	none	299	310	-	MD 6.32 lower (9.29 to 3.35 lower)	⊕⊕⊕O MODERATE	CRITICAL
Mean time to complete resolution of sore throat pain (Better indicated by lower values)												
5[2]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	no serious imprecision	none	239	261	-	MD 14.41 lower (24.99 to 3.84 lower)	⊕⊕⊕O MODERATE	CRITICAL
Mean absolute reduction in sore throat pain at 24 hours (measured with: Visual analogue scale or McGrath scale; range of scores: 0-10; Better indicated by lower values)												
6[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	308	309	-	MD 1.3 higher (0.61 to 2.06 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Recurrence or relapse of symptoms												
3[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	7/192 (3.6%)	12/161 (7.5%)	RR 0.56 (0.24 to 1.34)	33 fewer per 1000 (from 57 fewer to 25 more)	⊕⊕⊕O MODERATE	CRITICAL
Number of days missed from work or school (Better indicated by lower values)												
1[2]	randomised trials	no serious risk of bias	serious[5]	no serious indirectness	no serious imprecision	none	46	46	-	MD 0.3 lower (0.87 lower to 0.27 higher)	⊕⊕⊕O MODERATE	IMPORTANT

[1] Betamethasone 8 mg (1 study), dexamethasone up to 10 mg (6 studies), prednisolone 60 mg (1 study). Administered intramuscularly in 3 studies, orally in 4 studies and both in 1 study.
[2] Hayward et al. (2012)
[3] Downgraded 1 level - heterogeneity >50%
[4] Downgraded 1 level - at a 95% confidence interval, data are consistent with no meaningful difference or appreciable benefit with corticosteroids
[5] Downgraded 1 level - not assessable, single RCT

Table 23: GRADE profile –dexamethasone 10 mg versus placebo in adults with acute sore throat who did not receive an immediate antibiotic

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dexamethasone 10mg	Placebo				
Resolution of symptoms at 24 hours												
1[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	65/288 (22.6%)	49/277 (17.7%)	RR 1.28 (0.92 to 1.78)	50 more per 1000 (from 14 fewer to 138 more)	⊕⊕OO LOW	CRITICAL
Resolution of symptoms at 48 hours												
1[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	102/288 (35.4%)	75/277 (27.1%)	RR 1.31 (1.02 to 1.68)	84 more per 1000 (from 5 more to 184 more)	⊕⊕OO LOW	CRITICAL
Median time to onset of pain relief , hours (95% confidence interval)												
1[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	129	102	Dexamethasone= 27.5 hours (21.0 to 44.5) Placebo= 27.0 hours (21.4 to 45.8) Hazard ratio= 1.106 (0.850 to 1.440)		⊕⊕OO LOW	CRITICAL
Median time to complete resolution of symptoms, hours (95% confidence interval												
1[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	101	94	Dexamethasone= 65.8 hours (41.0 to 105.9) Placebo= 60.0 hours (39.8 to 92.3) Hazard ratio= 1.043 (0.781 to 1.393)		⊕⊕OO LOW	CRITICAL
Serious adverse events												
1[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	101	94	2 serious adverse events reported in the dexamethasone group 3 serious adverse events reported in the placebo group.			

[1] Hayward et al. 2017
[2] Not assessable, single RCT
[3] Downgraded 1 level - at a 95% confidence interval, data are consistent with no meaningful difference or appreciable benefit with corticosteroids

F.5 Delayed antibiotic prescribing

Table 24: GRADE profile – delayed antibiotic prescription versus immediate antibiotic or no prescription in adults

Quality assessment							Effect					Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate antibiotic prescription	Patient-led delayed prescription[1]	Delayed collection prescription[2]	No prescription	Overall p value		

Pharyngitis													
Duration of symptoms after 1st visit - swallowing difficulties (days, mean [SD])													
1[3]	randomised trials	no serious risk of bias[4]	serious[5]	no serious indirectness	serious[7]	none	5.1 (3.8)	5.6 (3.1)	6.1 (4.3)	6.8 (4.9)	0.71	⊕⊕OO LOW	CRITICAL
Severity of symptoms after 1st visit - swallowing difficulties (score, median [interquartile range]) (measured with: Score based on a Likert scale from 0 (no problem) to 6 (as bad as it could be); Better indicated by lower values)													
1[3]	randomised trials	no serious risk of bias[4]	serious[5]	no serious indirectness	serious[7]	none	3 (2 to 4)	2 (1 to 4)	2 (1 to 4)	3 (1 to 4)	0.41	⊕⊕OO LOW	CRITICAL
Uncomplicated upper respiratory tract infections													
Antibiotic collected, number of participants (%)													
1[3]	randomised trials	no serious risk of bias[4]	serious[5]	serious[6]	serious[7]	none	90 (89.1)	34 (34.7)	26 (26.0)	NA	<0.001	⊕OOO VERY LOW	CRITICAL
Antibiotic used, number of participants (%)													
1[3]	randomised trials	no serious risk of bias[4]	serious[5]	serious[6]	serious[7]	none	92 (91.1)	32 (32.6)	23 (23.0)	12 (12.1)	<0.001	⊕OOO VERY LOW	CRITICAL
Need for unscheduled health care, number of participants (%)													
1[3]	randomised trials	no serious risk of bias[4]	serious[5]	serious[6]	serious[7]	none	4 (4.0)	6 (6.1)	4 (4.0)	6 (6.1)	0.84	⊕OOO VERY LOW	CRITICAL
Adverse events, number of participants (%)													
1[3]	randomised trials	no serious risk of bias[4]	serious[5]	serious[6]	serious[7]	none	1 (1.0)	1 (1.0)	0 (0)	3 (3.0)	0.27	⊕OOO VERY LOW	CRITICAL

[1] Patients were given an antibiotic prescription at first consultation
[2] Patients were able to collect an antibiotic prescription 3 days after the first consultation
[3] de la Poza Abad et al. (2015)
[4] Study was open label but could not be blinded due to the nature of the interventions
[5] Downgraded 1 level - not assessable (single RCT)
[6] Downgraded 1 level - population is people with uncomplicated upper respiratory tract infections, including sore throat
[7] Downgraded 1 level - not assessable

Table 25: GRADE profile – delayed antibiotic prescription versus immediate antibiotic

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Delayed antibiotics**	**Immediate antibiotics**	**Relative (95% CI)**	**Absolute**		
Pain on day 3												
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	no serious imprecision	none	106/118 (89.8%)	42/111 (37.8%)	OR 14.51 (7.14 to 29.5)	520 more per 1000 (from 435 more to 569 more)	⊕⊕OO LOW	CRITICAL

Pain severity on day 3 (Better indicated by lower values)												
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[4]	none	55	59	-	MD 0.30 higher (0.15 lower to 0.75 higher)	⊕OOO VERY LOW	CRITICAL
Malaise on day 3												
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	no serious imprecision	none	45/118 (38.1%)	4/111 (3.6%)	OR 16.49 (5.68 to 47.83)	345 more per 1000 (from 139 more to 605 more)	⊕OOO VERY LOW	CRITICAL
Malaise severity on day 3 (Better indicated by lower values)												
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[4]	none	55	59	-	MD 0.20 higher (0.11 lower to 0.51 higher)	⊕OOO VERY LOW	CRITICAL
Fever severity on day 3 (Better indicated by lower values)												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	173	70	-	SMD 0.53 higher (0.31 to 0.74 higher)	⊕⊕OO LOW	CRITICAL
Fever severity on day 1 (Better indicated by lower values)												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[4]	none	173	170	-	SMD 0.07 lower (0.29 lower to 0.14 higher)	⊕⊕OO LOW	CRITICAL
Antibiotic use: delayed (return for prescription) versus immediate antibiotics												
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	no serious imprecision	none	55/176 (31.3%)	210/211 (99.5%)	OR 0 (0 to 0.02)	995 fewer per 1000 (from 188 fewer to 995 fewer)	⊕⊕OO LOW	CRITICAL
Patient satisfaction: delayed (return for prescription) versus immediate antibiotics												
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	very serious[5]	none	165/177 (93.2%)	202/211 (95.7%)	OR 0.61 (0.25 to 1.49)	25 fewer per 1000 (from 109 fewer to 14 more)	⊕OOO VERY LOW	CRITICAL
Adverse events, delayed versus immediate antibiotics: Vomiting												
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	no serious imprecision	none	57/118 (48.3%)	4/111 (3.6%)	OR 25 (8.65 to 72.25)	447 more per 1000 (from 208 more to 694 more)	⊕⊕OO LOW	CRITICAL
Adverse events, delayed versus immediate antibiotics: Diarrhoea												
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	very serious[5]	none	23/179 (12.8%)	23/215 (10.7%)	OR 1.23 (0.67 to 2.28)	21 more per 1000 (from 33 fewer to 108 more)	⊕OOO VERY LOW	CRITICAL
Adverse events, delayed versus immediate antibiotics: Rash												
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	very serious[5]	none	11/180 (6.1%)	14/215 (6.5%)	OR 0.93 (0.41 to 2.11)	4 fewer per 1000 (from 37 fewer to 63 more)	⊕OOO VERY LOW	CRITICAL
Adverse events, delayed versus immediate antibiotics: Stomach ache												
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	very serious[5]	none	48/180 (26.7%)	66/215 (30.7%)	OR 0.82 (0.53 to 1.27)	41 fewer per 1000 (from 117 fewer to 53 more)	⊕OOO VERY LOW	CRITICAL

[1] Spurling et al. (2013)
[2] Downgraded 1 level - assessed by Cochrane authors as being at high risk of bias

[3] Downgraded 1 level - not assessable, single RCT
[4] Downgraded 1 level - not assessable
[5] Downgraded 2 levels - at a 95% confidence interval, data are consistent with no meaningful difference, appreciable benefit with delayed antibiotics or appreciable benefit with immediate antibiotics

Table 26: GRADE profile – delayed antibiotic prescription versus no antibiotic

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Delayed prescription	No antibiotics	Relative (95% CI)	Absolute		
Antibiotic use: delayed (return for prescription) versus no antibiotics												
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	no serious imprecision	none	55/176 (31.3%)	23/184 (12.5%)	OR 3.18 (1.85 to 5.46)	187 more per 1000 (from 84 more to 313 more)	⊕⊕OO LOW	
Patient satisfaction: delayed (return for prescription) versus no antibiotics												
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	very serious[4]	none	165/177 (93.2%)	166/184 (90.2%)	OR 1.49 (0.70 to 3.19)	30 more per 1000 (from 36 fewer to 65 more)	⊕OOO VERY LOW	CRITICAL
Adverse events, delayed versus no antibiotics: Vomiting.												
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	very serious[4]	none	15/179 (8.4%)	22/186 (11.8%)	OR 0.68 (0.34 to 1.36)	35 fewer per 1000 (from 75 fewer to 36 more)	⊕OOO VERY LOW	
Adverse events, delayed versus no antibiotics: Diarrhoea												
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[5]	none	23/179 (12.8%)	16/186 (8.6%)	OR 1.57 (0.8 to 3.07)	43 more per 1000 (from 16 fewer to 138 more)	⊕OOO VERY LOW	CRITICAL
Adverse events, delayed versus no antibiotics: Rash												
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[6]	none	11/179 (6.1%)	21/186 (11.3%)	OR 0.51 (0.24 to 1.10)	52 fewer per 1000 (from 83 fewer to 10 more)	⊕OOO VERY LOW	CRITICAL
Adverse events, delayed versus no antibiotics: Stomach ache												
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	very serious[4]	none	48/179 (26.8%)	52/186 (28%)	OR 0.94 (0.60 to 1.50)	12 fewer per 1000 (from 91 fewer to 88 more)	⊕OOO VERY LOW	CRITICAL

[1] Spurling et al. (2013)
[2] Downgraded 1 level - assessed by Cochrane authors as being at high risk of bias
[3] Downgraded 1 level - not assessable, single RCT
[4] Downgraded 2 levels - at a 95% confidence interval, data are consistent with no meaningful difference, appreciable benefit with delayed antibiotics or appreciable benefit with no antibiotics
[5] Downgraded 1 level - at a 95% confidence interval, data are consistent with no meaningful difference or appreciable benefit with no antibiotics
[6] Downgraded 1 level - at a 95% confidence interval, data are consistent with no meaningful difference or appreciable benefit with delayed antibiotics

F.6 Antibiotics

Table 27: GRADE profile – antibiotic versus placebo in adults and children with sore throat

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotics[1]	Placebo	Relative (95% CI)	Absolute		
Symptom of sore throat on day 3												
15[2]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	serious[4]	none	1009/2066 (48.8%)	1031/1555 (66.3%)	RR 0.68 (0.59 to 0.79)	212 fewer per 1000 (from 139 fewer to 272 fewer)	⊕⊕OO LOW	CRITICAL
Symptom of sore throat on day 3 in people with GABHS-positive throat swab												
11[2]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	no serious imprecision	none	471/1073 (43.9%)	544/766 (71%)	RR 0.58 (0.48 to 0.71)	298 fewer per 1000 (from 206 fewer to 369 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Symptom of sore throat on day 3 in people with GABHS-negative throat swab												
6[2]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	serious[4]	none	262/458 (57.2%)	202/278 (72.7%)	RR 0.78 (0.63 to 0.97)	160 fewer per 1000 (from 22 fewer to 269 fewer)	⊕⊕OO LOW	CRITICAL
Symptom of sore throat at 1 week (6 to 8 days)												
13[2]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	serious[4]	none	246/1839 (13.4%)	206/1135 (18.1%)	RR 0.49 (0.32 to 0.76)	93 fewer per 1000 (from 44 fewer to 123 fewer)	⊕⊕OO LOW	CRITICAL
Symptom of sore throat at 1 week (6 to 8 days) in people with GABHS-positive throat swab												
7[2]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	no serious imprecision	none	22/650 (3.4%)	57/467 (12.2%)	RR 0.29 (0.12 to 0.7)	87 fewer per 1000 (from 37 fewer to 107 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Symptom of sore throat at 1 week (6 to 8 days) in people with GABHS-negative throat swab												
5[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	42/315 (13.3%)	43/226 (19%)	RR 0.73 (0.5 to 1.07)	51 fewer per 1000 (from 95 fewer to 13 more)	⊕⊕⊕O MODERATE	CRITICAL
Symptom of fever on day 3												
7[2]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	serious[4]	none	87/712 (12.2%)	114/622 (18.3%)	RR 0.71 (0.45 to 1.1)	53 fewer per 1000 (from 101 fewer to 18 more)	⊕⊕OO LOW	CRITICAL
Symptom of headache on day 3												
3[2]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	no serious imprecision	none	122/552 (22.1%)	147/359 (40.9%)	RR 0.44 (0.27 to 0.71)	229 fewer per 1000 (from 119 fewer to 299 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Incidence of acute rheumatic fever within 2 months (assessed with: clinical diagnosis)												

16[2]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	no serious imprecision	none	37/5656 (0.65%)	74/4445 (1.7%)	RR 0.27 (0.12 to 0.6)	12 fewer per 1000 (from 7 fewer to 15 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Incidence of acute rheumatic fever within 2 months, early (pre-1975 studies (assessed with: clinical diagnosis)												
10[2]	randomised trials	serious[5]	serious[3]	no serious indirectness	no serious imprecision	none	37/4208 (0.88%)	74/3409 (2.2%)	RR 0.27 (0.12 to 0.6)	16 fewer per 1000 (from 9 fewer to 19 fewer)	⊕⊕OO LOW	CRITICAL
Incidence of acute rheumatic fever within 2 months, late (post-1975) studies (assessed with: Clinical diagnosis												
6[2]	randomised trials	no serious risk of bias	serious[6]	no serious indirectness	serious[6]	none	0/1448 (0%)	0/1036 (0%)	-	-	⊕⊕OO LOW	CRITICAL
Incidence of otitis media within 14 days (assessed with: clinical diagnosis)												
11[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	11/2325 (0.47%)	28/1435 (2%)	RR 0.3 (0.15 to 0.58)	14 fewer per 1000 (from 8 fewer to 17 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Incidence of otitis media within 14 days, early (pre-1975) studies (assessed with: clinical diagnosis)												
5[2]	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	10/1115 (0.9%)	23/722 (3.2%)	RR 0.30 (0.15 to 0.62)	22 fewer per 1000 (from 12 fewer to 27 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Incidence of otitis media within 14 days, late (post-1975) studies (follow-up 14 days)												
6[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	1/1210 (0.08%)	5/713 (0.7%)	RR 0.28 (0.03 to 2.74)	5 fewer per 1000 (from 7 fewer to 12 more)	⊕⊕⊕O MODERATE	CRITICAL
Incidence of sinusitis within 14 days (follow-up 14; assessed with: Clinical diagnosis)												
8[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	4/1545 (0.26%)	4/842 (0.48%)	RR 0.48 (0.08 to 2.76)	2 fewer per 1000 (from 4 fewer to 8 more)	⊕⊕⊕O MODERATE	CRITICAL
Incidence of quinsy within 2 months (assessed with: clinical diagnosis)												
8[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	2/1438 (0.14%)[8]	23/995 (2.3%)[8]	RR 0.15 (0.05 to 0.47)	20 fewer per 1000 (from 12 fewer to 22 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Incidence of acute glomerulonephritis within 1 month (follow-up 1 months; assessed with: Clinical diagnosis)												
10[2]	randomised trials	serious[9]	no serious inconsistency	no serious indirectness	serious[4]	none	0/2927 (0%)	2/2220 (0.09%)	RR 0.22 (0.02 to 2.08)	1 fewer per 1000 (from 1 fewer to 1 more)	⊕⊕OO LOW	CRITICAL

[1] Antibiotics included: penicillins, sulfonamides, macrolides, cephalsporins and co-trimoxazole
[2] Spinks et al. (2013)
[3] Downgraded 1 level - heterogeneity >50%
[4] Downgraded 1 level - at a 95% confidence interval, data are consistent with no meaningful difference or appreciable benefit with antibiotics
[5] Downgraded 1 level - 8 out of 10 studies considered at high risk of bias by the Cochrane authors
[6] Downgraded 1 level - not assessable
[7] Downgraded 1 level - 3 out of 5 studies considered at high risk of bias by the Cochrane authors
[8] 16/25 (64%) of the total cases of quinsy reported from a single RCT published in 1951
[9] Downgraded 1 level - 6 out of 10 studies considered at high risk of bias by the Cochrane authors

Table 28: GRADE profile – short-term late-generation antibiotics versus longer term penicillin in children with GABHS positive sore throat

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short-term late-generation antibiotics[1]	Longer term penicillin[2]	Relative (95% CI)	Absolute		
Duration of fever (Better indicated by lower values)												
2[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	166	182	-	MD 0.30 lower (0.45 to 0.14 lower)	⊕⊕⊕O MODERATE	CRITICAL
Duration of sore throat (Better indicated by lower values)												
1[3]	randomised trials	serious[4]	serious[5]	no serious indirectness	serious[6]	none	88	100	-	MD 0.5 lower (0.78 to 0.22 lower)	⊕OOO VERY LOW	CRITICAL
Early clinical treatment failure												
19[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[6]	none	316/6197 (5.1%)	335/5516 (6.1%)	OR 0.8 (0.67 to 0.94)	12 fewer per 1000 (from 3 fewer to 19 fewer)	⊕⊕OO LOW	CRITICAL
Late clinical recurrence												
13[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	729/4841 (15.1%)	437/3227 (13.5%)	OR 0.95 (0.83 to 1.08)	6 fewer per 1000 (from 20 fewer to 9 more)	⊕⊕⊕O MODERATE	CRITICAL
Side effects												
17[3]	randomised trials	serious[4]	serious[7]	no serious indirectness	no serious imprecision[8]	none	348/3480 (10%)	210/4517 (4.6%)	RR 1.85 (1.55 to 2.21)	40 more per 1000 (from 26 more to 56 more)	⊕⊕OO LOW	CRITICAL
Non-compliance												
6[3]	randomised trials	serious[4]	serious[7]	no serious indirectness	no serious imprecision	none	61/960 (6.4%)	225/949 (23.7%)	OR 0.21 (0.16 to 0.29)	176 fewer per 1000 (from 154 fewer to 190 fewer)	⊕⊕OO LOW	IMPORTANT
Complications												
3[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[9]	none	6/5119 (0.12%)	8/3016 (0.27%)	OR 0.53 (0.17 to 1.64)	1 fewer per 1000 (from 2 fewer to 2 more)	⊕OOO VERY LOW	CRITICAL

[1] Included amoxicillin, azithromycin, cefuroxime, erythromycin, clarithromycin, cefixime, cefprozil, cefpodoxime, co-amoxiclav, josamycin, cefdinir, ceftibuten and loracarbef
[2] Penicillin V for 10 days (various doses used)
[3] Altamimi et al. (2012)
[4] Downgraded 1 level - all studies considered at high risk of bias by Cochrane authors
[5] Downgraded 1 level - not assessable, single RCT
[6] Downgraded 1 level - at 95% confidence interval, data are consistent with no meaningful difference or appreciable benefit with short-term late-generation antibiotics
[7] Downgraded 1 level - heterogeneity >50%
[8] Downgraded 1 level - at 95% confidence interval, data are consistent with no meaningful difference or appreciable harm with short-term late-generation antibiotics
[9] Downgraded 2 levels - at a 95% confidence interval, data are consistent with no meaningful difference, appreciable benefit with short-term late-generation antibiotics and appreciable benefit with longer term penicillin.

Table 29: GRADE profile – cephalosporin versus penicillin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cephalosporins	Penicillin	Relative (95% CI)	Absolute		
Resolution of symptoms post-treatment (ITT analysis)												
5[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	282/1165 (24.2%)	209/853 (24.5%)	OR 0.79 (0.55 to 1.12)	41 fewer per 1000 (from 94 fewer to 22 more)	⊕⊕OO LOW	CRITICAL
Resolution of symptoms post-treatment (evaluable participants only)												
5[1]	randomised trials	serious[2,4]	serious[5]	no serious indirectness	no serious imprecision	none	52/935 (5.6%)	81/725 (11.2%)	OR 0.51 (0.27 to 0.97)	51 fewer per 1000 (from 3 fewer to 79 fewer)	⊕⊕OO LOW	CRITICAL
Incidence of relapse (evaluable participants)												
4[1]	randomised trials	serious[2,4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	22/797 (2.8%)	27/589 (4.6%)	OR 0.55 (0.3 to 0.99)	20 fewer per 1000 (from 0 fewer to 32 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Complications (ITT analysis)												
1[1]	randomised trials	serious[2]	serious[6]	no serious indirectness	serious[7]	none	0/119 (0%)	0/125 (0%)	No complications reported. The authors state that data on complications are too scarce to draw conclusions.		⊕OOO VERY LOW	CRITICAL
Adverse events (ITT analysis)												
3[1]	randomised trials	serious[2]	serious[5]	no serious indirectness	very serious[8]	none	210/788 (26.6%)	95/491 (19.3%)	OR 0.94 (0.27 to 3.25)	9 fewer per 1000 (from 133 fewer to 245 more)	⊕OOO VERY LOW	CRITICAL

[1] van Driel et al. (2016)
[2] Downgraded 1 level - most studies assessed as high risk of bias by Cochrane authors
[3] Downgraded 1 level - at a 95% confidence interval, data are consistent with no meaningful difference or appreciable benefit with cephalosporin
[4] Outcome assessed using only evaluable participants, people who did not continue treatment excluded from analysis
[5] Downgraded 1 level - heterogeneity >50%
[6] Downgraded 1 level - not assessable, single RCT
[7] Downgraded 1 level - not assessable
[8] Downgraded 2 levels - at a 95% confidence interval, data are consistent with no meaningful difference, appreciable benefit with cephalosporin or appreciable benefit with penicillin

Table 30: GRADE profile – macrolide versus penicillin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Macrolide	Penicillin	Relative (95% CI)	Absolute		
Resolution of symptoms post-treatment (ITT analysis)												
6[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	420/952 (44.1%)	328/776 (42.3%)	OR 1.11 (0.92 to 1.35)	26 more per 1000 (from 20 fewer to 74 more)	⊕⊕OO LOW	CRITICAL

Resolution of symptoms post-treatment (evaluable participants only)											
6[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	87/619 (14.1%)	93/540 (17.2%)	OR 0.79 (0.57 to 1.09)	31 fewer per 1000 (from 66 fewer to 13 more)	⊕⊕OO LOW	CRITICAL
Incidence of relapse (evaluable participants)											
6[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	22/441 (5%)	16/361 (4.4%)	OR 1.21 (0.48 to 3.03)	9 more per 1000 (from 23 fewer to 79 more)	⊕OOO VERY LOW	CRITICAL
Adverse events (ITT analysis)											
6[1]	randomised trials	serious[2]	serious[5]	no serious indirectness	serious[6]	none	282/952 (29.6%)	251/775 (32.4%)	OR 1.19 (0.82 to 1.73)	39 more per 1000 (from 42 fewer to 129 more)	⊕OOO VERY LOW	CRITICAL

[1] van Driel et al. (2016)
[2] Downgraded 1 level - unclear randomisation (assessed by Cochrane authors)
[3] Downgraded 1 level - at a 95% confidence interval, data are consistent with no meaningful difference or appreciable benefit with penicillin
[4] Downgraded 2 levels - at a 95% confidence interval, data are consistent with no meaningful difference, appreciable benefit with penicillin and appreciable benefit with macrolide.
[5] Downgraded 1 level - heterogeneity >50%
[6] Downgraded 1 level - at a 95% confidence interval, data are consistent with no meaningful difference or appreciable harm with penicillin

Table 31: GRADE profile – azithromycin versus amoxicillin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Azithromycin**	**Amoxicillin**	**Relative (95% CI)**	**Absolute**		
Clinical cure at 24-28 days (ITT)												
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	very serious[4]	none	98/337 (29.1%)	118/336 (35.1%)	OR 0.76 (0.55 to 1.95)	60 fewer per 1000 (from 122 fewer to 162 more)	⊕OOO VERY LOW	CRITICAL
Clinical cure at 24-28 days (bacteriological per protocol population)												
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	no serious imprecision	none	6/245 (2.4%)	19/237 (8%)	OR 0.29 (0.11 to 0.73)	56 fewer per 1000 (from 20 fewer to 71 fewer)	⊕⊕OO LOW	CRITICAL
Relapse on day 38-45 (ITT)												
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[5]	none	130/337 (38.6%)	153/336 (45.5%)	OR 0.75 (0.55 to 1.02)	70 fewer per 1000 (from 140 fewer to 5 more)	⊕OOO VERY LOW	CRITICAL
Relapse on day 38-45 (bacteriological per protocol)												
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	very serious[4]	none	16/223 (7.2%)	16/199 (8%)	OR 0.88 (0.43 to 1.82)	9 fewer per 1000 (from 44 fewer to 57 more)	⊕OOO VERY LOW	CRITICAL
Adverse events (all participants)												
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	very serious[6]	none	93/337 (27.6%)	42/336 (12.5%)	OR 2.67 (1.78 to 3.99)	151 more per 1000 (from 78 more to 238 more)	⊕OOO VERY LOW	CRITICAL

[1] van Driel et al. (2016)
[2] Downgraded 1 - high risk of bias (assessed by Cochrane authors)
[3] Downgraded 1 level - not assessable, single RCT
[4] Downgraded 2 levels - at a 95% confidence interval, data are consistent with no meaningful difference, appreciable benefit with azithromycin or appreciable benefit with amoxicillin
[5] Downgraded 1 level - at a 95% confidence interval, data are consistent with no meaningful difference or appreciable benefit with azithromycin
[6] Downgraded 2 levels - at a 95% confidence interval, data are consistent with no meaningful difference, appreciable harm with azithromycin or appreciable harm with amoxicillin

Table 32: GRADE profile – clindamycin versus ampicillin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clindamycin	Ampicillin	Relative (95% CI)	Absolute		
Adverse events (ITT analysis)												
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[4]	none	6/156 (3.8%)	14/158 (8.9%)	OR 0.41 (0.15 to 1.1)	50 fewer per 1000 (from 74 fewer to 8 more)	⊕OOO VERY LOW	CRITICAL

[1] van Driel et al. (2016)
[2] Downgraded 1 level - high risk of bias (assessed by Cochrane authors)
[3] Downgraded 1 level - not assessable, single RCT
[4] Downgraded 1 level - at a 95% confidence interval, data are consistent with no meaningful difference or appreciable harm with ampicillin

Table 33: GRADE profile – sulphonamide versus penicillin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sulfonamide	Penicillin	Relative (95% CI)	Absolute		
Adverse events (ITT analysis)												
1[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	very serious[3]	none	8/44 (18.2%)	6/43 (14%)	OR 1.37 (0.43 to 4.34)	42 more per 1000 (from 74 fewer to 274 more)	⊕OOO VERY LOW	CRITICAL

[1] van Driel et al. (2016)
[2] Downgraded 1 level - not assessable, single RCT
[3] Downgraded 2 levels - at a 95% confidence interval, data are consistent with no meaningful difference, appreciable harm with sulphonamide or appreciable harm with penicillin

Table 34: GRADE profile – penicillin V once daily versus penicillin V 3 or 4 times daily

Quality assessment							No of patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Penicillin V once daily	Penicillin V 3 or 4 times daily			
Bacteriological cure at follow-up (follow-up 1 to 14 days)											

6[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[4]	none	Total of **1,206 participants** in the included studies, although not all participants are included in the analysis	12% lower cure rate in the once daily group (95%CI 3 to 21).	⊕OOO VERY LOW	CRITICAL

[1] Lan and Colford (2008)
[2] Downgraded 1 level - not assessable, authors did not report on bias for included studies
[3] Downgraded 1 level - the authors reported significant heterogeneity
[4] Downgraded 1 level - not assessable

Table 35: GRADE profile – penicillin V twice daily versus penicillin V 3 or 4 times daily

Quality assessment							No of patients		Effect	Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Penicillin V twice daily**	**Penicillin V 3 or 4 times daily**			
Bacteriological cure at follow-up (follow-up 1 to 14 days)											
6[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	Total of **1,206 participants** in the included studies, although not all participants are included in the analysis		No statistically significant difference between groups	⊕⊕OO LOW	CRITICAL

[1] Lan and Colford (2008)
[2] Downgraded 1 level - not assessable, authors did not report on bias for included studies
[3] Downgraded 1 level - not assessable

Table 36: GRADE profile – penicillin V for 5 to 7 days versus penicillin V for 10 days

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Penicillin V 5 to 7 days**	**Penicillin V 10 days**	**Relative (95% CI)**	**Absolute**		
Eradication of group A streptococcus at the end of treatment												
3[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	205/236 (86.9%)	250/264 (94.7%)	OR 0.36 (0.13 to 0.99)	82 fewer per 1000 (from 1 fewer to 248 fewer)	⊕⊕OO LOW	CRITICAL

[1] Falagas et al. (2008)
[2] Downgraded 1 level - the authors assessed the studies using Jadad criteria, scoring two studies as a '2' (low quality) and one study as a '5' (high quality)
[3] Downgraded 1 level - at a 95% confidence interval, data are consistent with no meaningful difference or appreciable benefit with 10 days treatment

F.7 Identifying people more likely to have a bacterial infection

Table 37: GRADE profile – FeverPAIN score versus FeverPAIN score plus rapid antigen testing versus delayed prescription for people with sore throat

Quality assessment							Effect			Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FeverPAIN (n=211)	FeverPAIN plus Rapid antigen testing (n=213)	Delayed prescription (control) (n=207)		
Mean score of sore throat and difficulty swallowing for the 2 to 4 days after the consultation, 7 point score: 0= np problem, 6= as bad as could be (standard deviation)											
1[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	2.88 (1.52)	2.83 (1.62)	3.11 (1.49)	⊕⊕OO LOW	CRITICAL
Median duration of symptoms rated moderately bad or worse, days (interquartile range)											
1[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[4]	none	4 (2 to 6) Hazard ratio: 1.30 (95% CI 1.03 to 1.63; p=0.03)	4 (2 to 7) Hazard ratio: 1.11 (95% CI 0.88 to 1.40; p=0.37)	5 (3 to 7) Hazard ratio: 1	⊕⊕OO LOW	CRITICAL
Antibiotic use											
1[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[4]	none	60/161 (37%) Risk ratio: 0.71 (95% CI 0.50 to 0.95; p=0.02)	58/164 (35%) Risk ratio: 0.73 (95% CI 0.52 to 0.98; p=0.03)	75/164 (46%) Risk ratio: 1	⊕⊕OO LOW	CRITICAL
Belief in need to see doctor in future (slightly likely or less)											
1[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	54/155 (35%)	64/161 (40%)	62/163 (38%)	⊕⊕OO LOW	IMPORTANT
Return within 1 month with sore throat											
1[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	17/210 (8%)	13/212 (6%)	17/207 (8%)	⊕⊕OO LOW	CRITICAL
Suppurative complications											
1[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	2/210 (1.0%)	1/211 (0.5%)	0/207 (0%)	⊕⊕OO LOW	CRITICAL

[1] Little et al. 2013
[2] Downgraded 1 level - not assessable, single RCT
[3] Downgraded 1 level - not assessable
[4] Downgraded 1 level - at a 95% confidence interval, data are consistent with no meaningful difference or appreciable benefit with FeverPAIN or FeverPAIN plus rapid antigen testing

Table 38: GRADE profile – Diagnostic accuracy of rapid antigen detection tests for detecting group A streptococcus

Quality assessment	Summary specificity (95% CI)	Summary sensitivity (95% CI)	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations				
Diagnostic accuracy of rapid antigen detection tests for detecting group A streptococcus										
105[1]	observational studies	serious[2]	serious[3]	no serious indirectness	no serious imprecision	none	95.4% (94.5 to 96.2)	85.6% (83.3 to 87.6)	⊕OOO VERY LOW	IMPORTANT

[1] Cohen et al.2016
[2] Cochrane authors report that methodological quality was generally poor, and that quality appraisal was impeded by suboptimal reporting
[3] There was substantial heterogeneity in the results of the individual studies, especially for sensitivity, which could not be explained by the investigations

Table 39: GRADE profile – Diagnostic accuracy of Centor score (3 or more) in predicting streptococcal pharyngitis in adults

Quality assessment							Specificity (95% CI)	Sensitivity (95% CI)	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations				
Diagnostic accuracy of Centor score (3 or more) in predicting streptococcal pharyngitis in adults										
21[1]	observational studies	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	0.82 (0.72 to 0.88)	0.49 (0.38 to 0.60)	⊕⊕OO LOW	IMPORTANT

[1] Aalbers et al.2011

Appendix G: Studies not-prioritised

Selected studies are further reviewed to prioritise and select the best available evidence. The following principles are used:

- studies are of direct relevance to UK practice
- more recently published studies from those that are included to obtain the most up-to-date information (for example, a systematic review published in 2016 would be prioritised over another published in 2008 if the same studies and outcomes were addressed)
- studies reporting patient-oriented outcomes (as given in the review protocol); studies reporting resistance patterns alone will not be prioritised
- higher quality evidence based on the hierarchy of evidence will be used (for example, a randomised control trial may not be selected if a systematic review which already includes this trial has been prioritised).

See Interim process and methods guide for more information.

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Wing A, Villa-Roel C, Yeh B, Eskin B, Buckingham J, and Rowe B H (2010) Effectiveness of corticosteroid treatment in acute pharyngitis: A systematic review of the literature. Academic Emergency Medicine 17(5), 476-483

Worrall G, Hutchinson J, Sherman G, and Griffiths J (2007) Diagnosing streptococcal sore throat in adults: randomized controlled trial of in-office aids. Canadian family physician Médecin de famille canadien 53(4), 666-71

Zwart S, Sachs A P. E, Ruijs G J. H. M, Gubbcls J W, Hoes A W, de Melker , and R A (2000) Penicillin for acute sore throat: Randomised double blind trial of seven days versus three days treatment or placebo in adults. British Medical Journal 320(7228), 150-154

Zwart S, Rovers M M, De Melker , R A, and Hoes A W (2003) Penicillin for acute sore throat in children: Randomised, double blind trial. British Medical Journal 327(7427), 1324-1326

Appendix H: Excluded studies

Study reference	Reason for exclusion
(2004) Cephalosporins better for streptococcus infections in children. The Journal of family practice 53(7), 526-8	Publication / study type
(2016) Efficacy and tolerability of an ectoine mouth and throat spray compared with those of saline lozenges in the treatment of acute pharyngitis and/or laryngitis: a prospective, controlled, observational clinical trial. European Archives of Oto-Rhino-Laryngology. 273 (9) (pp 2591-2597), and 2016. Date of Publication: 01 Sep 2016.	Publication / study type
Adam D (2000) Short-course antibiotic therapy for infections with a single causative pathogen. The Journal of international medical research 28 Suppl 1, 13A-24A	Publication / study type
Adam D, Scholz H, and Helmerking M (2000) Comparison of short-course (5 day) cefuroxime axetil with a standard 10 day oral penicillin V regimen in the treatment of tonsillopharyngitis. The Journal of antimicrobial chemotherapy 45 Suppl, 23-30	Publication / study type
Adam D, Scholz H, and Helmerking M (2001) [Treatment of group A streptococcal tonsillopharyngitis. 5 days cephalosporin is as effective as 10 days penicillin]. MMW Fortschritte der Medizin 143(18), 40	Publication / study type
Adam Vd, Scholz H, and Helmerking M (2001) [Treatment of A-streptococcal tonsillopharyngitis. Five days of treatment with cephalosporin is as effective as ten with penicillin]. MMW Fortschritte der Medizin 143(18), 40	Publication / study type
Addey D, and Shephard A (2012) Incidence, causes, severity and treatment of throat discomfort: A four-region online questionnaire survey. BMC Ear, and Nose and Throat Disorders 12(1), no pagination	Publication / study type
Alho O P, Koivunen P, Penna T, Teppo H, Koskela M, and Luotonen J (2007) Tonsillectomy versus watchful waiting in recurrent streptococcal pharyngitis in adults: Randomised controlled trial. British Medical Journal 334(7600), 939-941	Population
Altamimi S, Khalil A, Khalaiwi K A, Milner R, Pusic M V, Al Othman, and M A (2010) Short versus standard duration antibiotic therapy for acute streptococcal pharyngitis in children. Sao Paulo Medical Journal 128(1), 48	Publication / study type
Altamimi Saleh, Khalil Adli, Khalaiwi Khalid A, Milner Ruth, Pusic Martin V, Al Othman, and Mohammed A (2009) Short versus standard duration antibiotic therapy for acute streptococcal pharyngitis in children. The Cochrane database of systematic reviews (1), CD004872	Not the best available evidence
Angoulvant F, Rouault A, Prot-Labarthe S, Boizeau P, Skurnik D, Morin L, Mercier J C, Alberti C, and Bourdon O (2013) Randomized Controlled Trial of Parent Therapeutic Education on Antibiotics to Improve Parent Satisfaction and Attitudes in a Pediatric Emergency Department. PLoS ONE 8(9), no pagination	Publication / study type
Anjos Lais Martins Moreira, Marcondes Mariana Barros, Lima Mariana Ferreira, Mondelli Alessandro Lia, and Okoshi Marina Politi (2014) Streptococcal acute pharyngitis. Revista da Sociedade Brasileira de Medicina Tropical 47(4), 409-13	Publication / study type
Anonymous (2000) WHO model prescribing information: Streptococcal pharyngitis and prevention of rheumatic fever. WHO Drug Information 14(2), 99-104	Publication / study type

Study reference	Reason for exclusion
Anonymous (2004) Antibiotics for acute group A streptococcal pharyngitis. Prescrire international 13(74), 227-32	Publication / study type
Anonymous (2010) Steroids are effective for relieving pain in acute pharyngitis. Australian Journal of Pharmacy 91(1084), 97	Publication / study type
Arroll B (2005) Antibiotics for upper respiratory tract infections: an overview of Cochrane reviews. Respiratory medicine 99(3), 255-61	Publication / study type
Arroll B, and Kenealy T (2002) Antibiotics for the common cold. The Cochrane database of systematic reviews (3), CD000247	Not the best available evidence
Aspley S, Schachtel B, Berry P, Shephard A, Sanner K, Shea T, and Smith G (2012) The Chief Complaint: Evidence of its use as an endpoint in a clinical trial. Journal of pain 13(4 suppl. 1), S4	Publication / study type
Aspley S, Schachtel B, Berry P, Shephard A, Shea T, Smith G, and Schachtel E (2013) Flurbiprofen lozenges in patients with a "bad sore throat". Journal of pain 14(4 suppl. 1), S59	Publication / study type
Aspley S, Schachtel B, Berry P, Shephard A, Sanner Km, Savino L, Rezuke J, Shea T, and Smith G (2012) Treatment of odynophagia and dysphagia by flurbiprofen 8.75 mg lozenges. Pain research & management 17(3), 203	Publication / study type
Ayranci U, Akgun Y, Unluoglu I, and Kiremitci A (2005) Antibiotic prescribing patterns for sore throat infections in a university-based primary care clinic. Annals of Saudi medicine 25(1), 22-8	Publication / study type
Baker I, and Barton E (2013) URTIs: Recommended diagnosis and treatment in general practice. Prescriber 24(19), 16-28	Publication / study type
Balan B J, Rozewski F, Skopinska-Rozewska E, Wojdas A, Zdanowski R, and Stankiewicz W (2012) Immunotropic activity of Echinacea. Part II. Experimental and clinical data. Central-European Journal of Immunology 37(1), 51-56	Population
Baltimore Robert S (2010) Re-evaluation of antibiotic treatment of streptococcal pharyngitis. Current opinion in pediatrics 22(1), 77-82	Publication / study type
Bansal Monika, Singh Sachin K, and Gulati Monica (2014) Lozenges as delivery system for upper respiratory catarrh medication. Recent patents on drug delivery & formulation 8(2), 92-100	Population
Barash J (2009) Group A streptococcal throat infection - To treat or not to treat? Acta Paediatrica, and International Journal of Paediatrics 98(3), 434-436	Publication / study type
Batieha A, Yahia G, Mahafzeh T, Omari M, Momani A, and Dabbas M (2002) No advantage of treating acute respiratory tract infections with azithromycin in a placebo-controlled study. Scandinavian journal of infectious diseases 34(4), 243-7	Population
Bergeson K, Rogers N, Prasad S, and Ewigman B (2013) Corticosteroids for a sore throat? Journal of Family Practice 62(7), 372-374	Publication / study type
Bird J H, Biggs T C, and King E V (2014) Controversies in the management of acute tonsillitis: an evidence-based review. Clinical otolaryngology : official journal of ENT-UK, and official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery 39(6), 368-74	Publication / study type
Bisno A L (2001) Primary care: Acute pharyngitis. New England Journal of Medicine 344(3), 205-211	Publication / study type

Study reference	Reason for exclusion
Block Stan L (2003) Short-course antimicrobial therapy of streptococcal pharyngitis. Clinical pediatrics 42(8), 663-71	Publication / study type
Bottaro G, Biasci P, Giudice Mlo, Mele G, Montanari G, Napoleone E, Santucci A, Tucci Pl, Fano M, and Biraghi Mg (2012) 5 Days Cefaclor vs. 10 days amoxicillin/clavulanate in the treatment of childhood streptococcal pharyngitis. Data from a randomized clinical trial. [Italian]. Minerva pediatrica 64(3), 341-6	Publication / study type
Brook I (2000) Infections of the upper respiratory tract, head, and neck. The role of anaerobic bacteria. Postgraduate medicine 108(7 Suppl Contemporaty), 37-48	Publication / study type
Brook I (2001) Failure of penicillin to eradicate group A beta-hemolytic streptococci tonsillitis: causes and management. The Journal of otolaryngology 30(6), 324-9	Publication / study type
Brook I (2001) The role of beta-lactamase producing bacteria and bacterial interference in streptococcal tonsillitis. International journal of antimicrobial agents 17(6), 439-42	Publication / study type
Brook I (2005) The role of anaerobic bacteria in tonsillitis. International Journal of Pediatric Otorhinolaryngology 69(1), 9-19	Publication / study type
Brook I (2005) The role of bacterial interference in otitis, sinusitis and tonsillitis. Otolaryngology - Head and Neck Surgery 133(1), 139-146	Publication / study type
Brook I (2007) Microbiology and Principles of Antimicrobial Therapy for Head and Neck Infections. Infectious Disease Clinics of North America 21(2), 355-391	Publication / study type
Brook I (2007) Penicillin failure in the treatment of acute and relapsing tonsillopharyngitis is associated with copathogens and alteration of microbial balance: A role for cephalosporins. Clinical Pediatrics 46(4 SUPPL.), 17S-24S	Publication / study type
Brook I (2007) The role of anaerobic bacteria in upper respiratory tract and other head and neck infections. Current Infectious Disease Reports 9(3), 207-217	Publication / study type
Brook I (2009) Anaerobic bacteria in upper respiratory tract and head and neck infections in children: Microbiology and management. Journal of Pediatric Infectious Diseases 4(1), 17-26	Publication / study type
Brook I (2013) Penicillin failure in the treatment of group A streptococcal pharyngo-tonsillitis: Causes and solutions. Journal of Pediatric Infectious Diseases 8(2), 59-69	Publication / study type
Brook Itzhak (2002) Anaerobic bacteria in upper respiratory tract and other head and neck infections. The Annals of otology, rhinology, and laryngology 111(5 Pt 1), 430-40	Publication / study type
Brook Itzhak (2002) Antibacterial therapy for acute group a streptococcal pharyngotonsillitis: short-course versus traditional 10-day oral regimens. Paediatric drugs 4(11), 747-54	Publication / study type
Brook Itzhak (2002) Antibiotic resistance of oral anaerobic bacteria and their effect on the management of upper respiratory tract and head and neck infections. Seminars in respiratory infections 17(3), 195-203	Publication / study type
Brook Itzhak (2005) A pooled comparison of cefdinir and penicillin in the treatment of group a beta-hemolytic streptococcal pharyngotonsillitis. Clinical therapeutics 27(8), 1266-73	Population
Brook Itzhak (2007) Cephalosporins in overcoming beta-lactamase-producing bacteria and preservation of the interfering bacteria in the	Publication / study type

Study reference	Reason for exclusion
treatment of otitis, sinusitis and tonsillitis. Expert review of anti-infective therapy 5(6), 939-50	
Brook Itzhak (2007) Overcoming penicillin failures in the treatment of Group A streptococcal pharyngo-tonsillitis. International journal of pediatric otorhinolaryngology 71(10), 1501-8	Publication / study type
Brook Itzhak, and Dohar Joseph E (2006) Management of group A beta-hemolytic streptococcal pharyngotonsillitis in children. The Journal of family practice 55(12), S1-S12	Publication / study type
Brunton Stephen, and Pichichero Michael (2006) Considerations in the use of antibiotics for streptococcal pharyngitis. The Journal of family practice Suppl, S9-16	Publication / study type
Casey J R (2007) Selecting the optimal antibiotic in the treatment of group A beta-hemolytic streptococci pharyngitis. Clinical Pediatrics 46(4 SUPPL.), 25S-35S	Publication / study type
Casey Janet R, and Pichichero Michael E (2007) Symptomatic relapse of group A beta-hemolytic streptococcal tonsillopharyngitis in children. Clinical pediatrics 46(4), 307-10	Publication / study type
Casey Janet R, and Pichichero Michael E (2007) The evidence base for cephalosporin superiority over penicillin in streptococcal pharyngitis. Diagnostic microbiology and infectious disease 57(3 Suppl), 39S-45S	Publication / study type
Centor R M, Allison JJ, and Cohen SJ (2007) Pharyngitis management: Defining the controversy. Journal of General Internal Medicine 22(1), 127-130	Publication / study type
Chan J Y. C, Yau F, Cheng F, Chan D, Chan B, and Kwan M (2015) Practice recommendation for the management of acute pharyngitis. Hong Kong Journal of Paediatrics 20(3), 156-162	Publication / study type
Chiappini Elena, Principi Nicola, Mansi Nicola, Serra Agostino, De Masi, Salvatore, Camaioni Angelo, Esposito Susanna, Felisati Giovanni, Galli Luisa, Landi Massimo, Speciale Anna Maria, Bonsignori Francesca, Marchisio Paola, de Martino, Maurizio, Italian Panel on the Management of Pharyngitis in, and Children (2012) Management of acute pharyngitis in children: summary of the Italian National Institute of Health guidelines. Clinical therapeutics 34(6), 1442-1458.e2	Publication / study type
Choby B A (2009) Diagnosis and treatment of streptococcal pharyngitis. American Family Physician 79(5), 383-390	Publication / study type
Clegg Herbert William, Giftos Peter Michael, Anderson William Edward, Kaplan Edward Lawrence, and Johnson Dwight Richard (2015) Clinical Perineal Streptococcal Infection in Children: Epidemiologic Features, Low Symptomatic Recurrence Rate after Treatment, and Risk Factors for Recurrence. The Journal of pediatrics 167(3), 687-2	Population
Cohen R (2000) 3-day azithromycin (AZM) (20 mg/kg or 10 mg/kg) versus 10-day penicillin V (PN) for pediatric acute Group A streptococcal tonsillopharyngitis (GAS-TP). Interscience Conference on Antimicrobial Agents and Chemotherapy . 17-20 September, and 2000 40, 453	Publication / study type
Cohen R (2004) Defining the optimum treatment regimen for azithromycin in acute tonsillopharyngitis. Pediatric infectious disease journal 23(2 Suppl), S129-34	Publication / study type
Cohen Robert (2002) Clinical efficacy of cefpodoxime in respiratory tract infection. The Journal of antimicrobial chemotherapy 50 Suppl, 23-7	Publication / study type

Study reference	Reason for exclusion
Cohen Robert (2004) Defining the optimum treatment regimen for azithromycin in acute tonsillopharyngitis. The Pediatric infectious disease journal 23(2 Suppl), S129-34	Publication / study type
Cook J, Hayward G, Thompson M, Hay Ad, Moore M, Little P, Harman K, Wolstenholme J, Perera R, Voysey M, Allen J, Breen M, and Heneghan C (2014) Oral corticosteroid use for clinical and cost-effective symptom relief of sore throat: study protocol for a randomized controlled trial. Trials 15, 365	Publication / study type
Cunha B A (2004) Therapeutic implications of antibacterial resistance in community-acquired respiratory tract infections in children. Infection 32(2), 98-108	Publication / study type
Curtin-Wirt C, Casey J R, Murray P C, Cleary C T, Hoeger W J, Marsocci S M, Murphy M L, Francis A B, and Pichichero M E (2003) Efficacy of penicillin vs. amoxicillin in children with group A beta hemolytic streptococcal tonsillopharyngitis. Clinical Pediatrics 42(3), 219-225	Publication / study type
Curtin-Wirt Correne, Casey Janet R, Murray Patrick C, Cleary Carolyn T, Hoeger William J, Marsocci Steven M, Murphy Marie Lynd, Francis Anne B, and Pichichero Michael E (2003) Efficacy of penicillin vs. amoxicillin in children with group A beta hemolytic streptococcal tonsillopharyngitis. Clinical pediatrics 42(3), 219-25	Publication / study type
Cuzzolin L, and Fanos V (2002) Use of macrolides in children: A review of the literature. Infections in Medicine 19(6), 279-285	Publication / study type
Danchin M H, Curtis N, Nolan T M, and Carapetis J R (2002) Treatment of sore throat in light of the Cochrane verdict: Is the jury still out?. Medical Journal of Australia 177(9), 512-515	Publication / study type
Darkes Malcolm J. M, and Perry Caroline M (2003) Clarithromycin extended-release tablet: a review of its use in the management of respiratory tract infections. American journal of respiratory medicine: drugs, devices, and other interventions 2(2), 175-201	Publication / study type
Darrow D H, and Buescher S E (2002) Group A streptococcal pharyngitis. Current Opinion in Otolaryngology and Head and Neck Surgery 10(6), 449-454	Publication / study type
Davis S (2013) Managing pain and fever associated with colds and flu. SA Pharmaceutical Journal 80(3), 8-14	Publication / study type
Del Mar, C B, Glasziou P P, and Spinks A B (2000) Antibiotics for sore throat. The Cochrane database of systematic reviews (4), CD000023	Not the best available evidence
Del Mar, C B, Glasziou P P, and Spinks A B (2004) Antibiotics for sore throat. The Cochrane database of systematic reviews (2), CD000023	Not the best available evidence
Del Mar, C B, Glasziou P P, and Spinks A B (2006) Antibiotics for sore throat. The Cochrane database of systematic reviews (4), CD000023	Not the best available evidence
Di Pierro, Francesco, Zanvit Alberto, and Colombo Maria (2016) Role of a proprietary propolis-based product on the wait-and-see approach in acute otitis media and in preventing evolution to tracheitis, bronchitis, or rhinosinusitis from nonstreptococcal pharyngitis. International journal of general medicine 9, 409-414	Publication / study type
Diaz M C. G, Symons N, Ramundo M L, and Christopher N C (2004) Effect of a standardized pharyngitis treatment protocol on use of antibiotics in a pediatric emergency department. Archives of Pediatrics and Adolescent Medicine 158(10), 977-981	Publication / study type

Study reference	Reason for exclusion
El Hennawi, D E D. M, and Ahmed M R (2016) Quality of life after tonsillectomy versus azithromycin. Interventional Medicine and Applied Science 8(4), 141-146	Population
Esposito S, Bianchini S, Baggi E, Castellazzi L, Fumagalli M, and Principi N (2013) Use of topical or systemic steroids in children with upper respiratory tract infection. European Journal of Inflammation 11(2), 337-344	Publication / study type
Esposito S, Bosis S, Begliatti E, Droghetti R, Tremolati E, Tagliabue C, Bellasio M, Blasi F, and Principi N (2006) Acute tonsillopharyngitis associated with atypical bacterial infection in children: Natural history and impact of macrolide therapy. Clinical Infectious Diseases 43(2), 206-209	Publication / study type
Esposito S, Noviello S, Ianniello F, and D'Errico G (2000) Treatment of streptococcal tonsillo-pharyngitis in paediatric patients: Short-course therapy with cefaclor. [Italian]. Infezioni in medicina 8(4), 227-33	Publication / study type
Esposito Susanna, Marchisio Paola, Bosis Samantha, Droghetti Roberta, Mattina Roberto, Principi Nicola, Short Therapy Study, and Group (2002) Comparative efficacy and safety of 5-day cefaclor and 10-day amoxycillin treatment of group A streptococcal pharyngitis in children. International journal of antimicrobial agents 20(1), 28-33	Publication / study type
Euctr Gb (2010) A single centre double blind randomised controlled trial investigating the use of dexamethasone in the treatment of acute tonsillitis - The use of dexamethasone in the treatment of acute tonsillitis. EUCTR [www.clinicaltrialsregister.eu]	Publication / study type
Euctr Pl (2008) Multiple site, randomized, prospective, open comparison of new locally used benzydamine product efficacy with reference product in adult patients with acute pharyngitis or tonsillitis which do not require antibiotic therapy - AAR1/1. EUCTR [www.clinicaltrialsregister.eu]	Publication / study type
Falagas Matthew E, Giannopoulou Konstantina P, Kokolakis George N, and Rafailidis Petros I (2008) Fosfomycin: use beyond urinary tract and gastrointestinal infections. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 46(7), 1069-77	Population
Farrer F (2011) Sprays and lozenges for sore throats. SA Pharmaceutical Journal 78(4), 26-31	Publication / study type
Farrer F (2012) Sprays and lozenges for sore throats. South African Family Practice 54(2), 120-122	Publication / study type
Farrer F (2013) Sprays and lozenges for sore throats. SA Pharmaceutical Journal 80(5), 8-11	Publication / study type
Fiocchi A, Calcinai E, Beghi G, and Terracciano L (2010) Paediatric upper respiratory infections: the role of antibiotics. International journal of immunopathology and pharmacology 23(1 Suppl), 56-60	Publication / study type
Flottorp S, Oxman A D, Havelsrud K, Treweek S, and Herrin J (2002) Cluster randomised controlled trial of tailored interventions to improve the management of urinary tract infections in women and sore throat. British Medical Journal 325(7360), 367-370	Outcomes
Fulton B, and Perry C M (2001) Cefpodoxime proxetil: a review of its use in the management of bacterial infections in paediatric patients. Paediatric drugs 3(2), 137-58	Publication / study type

Study reference	Reason for exclusion
Garrett C Gaelyn, and Cohen Seth M (2008) Otolaryngological perspective on patients with throat symptoms and laryngeal irritation. Current gastroenterology reports 10(3), 195-9	Publication / study type
Geffen L (2006) Common upper respiratory tract problems in the elderly - A guide to clinical diagnosis and prudent prescription. South African Family Practice 48(5), 20-23	Publication / study type
Gehanno P, Dreiser RI, Ionescu E, Gold M, and Liu Jm (2004) Lowest effective single dose of diclofenac for antipyretic and analgesic effects in acute febrile sore throat. Clinical drug investigation 23(4), 263-71	Not the best available evidence
Gerber M A (2005) Diagnosis and treatment of pharyngitis in children. Pediatric Clinics of North America 52(3), 729-747	Publication / study type
Gerber M A, and Tanz R R (2001) New approaches to the treatment of group A streptococcal pharyngitis. Current opinion in pediatrics 13(1), 51-5	Publication / study type
Giraldez-Garcia C, Rubio B, Gallegos-Braun J F, Imaz I, Gonzalez-Enriquez J, and Sarria-Santamera A (2011) Diagnosis and management of acute pharyngitis in a paediatric population: A cost-effectiveness analysis. European Journal of Pediatrics 170(8), 1059-1067	Publication / study type
Gonzalez De Dios, J, Ochoa Sangrador, C, Alvarez Calatayud, and G (2006) Rational management of antibiotherapy in ORL infections in children: Critical review of the best scientific evidences. Acta Otorrinolaringologica Espanola 57(2), 66-81	Publication / study type
Granizo J J, Gimenez M J, Barberan J, Coronel P, Gimeno M, and Aguilar L (2008) Efficacy of cefditoren in the treatment of upper respiratory tract infections: a pooled analysis of six clinical trials. Revista espanola de quimioterapia : publicacion oficial de la Sociedad Espanola de Quimioterapia 21(1), 14-21	Publication / study type
Gray G C, Witucki P J, Gould M T, Bell S J, Hiliopoulos K M, McKeehan J A, Fuller J M, Barrozo C P, Hudspeth M K, Smith T C, Ledbetter E K, and Wallace M R (2001) Randomized, placebo-controlled clinical trial of oral azithromycin prophylaxis against respiratory infections in a high-risk, young adult population. Clinical Infectious Diseases 33(7), 983-989	Population
Grief Samuel N (2013) Upper respiratory infections. Primary care 40(3), 757-70	Publication / study type
Guay D R (2000) Short-Course antimicrobial therapy for upper respiratory tract infections. Clinical therapeutics 22(6), 673-84	Publication / study type
Gurdogan K, and Senol E (2001) Comparison of 3-day course of azithromycin with penicillin V and amoxicillin+clavulonate in the treatment of upper respiratory tract infections. [Turkish]. Mikrobiyoloji bulteni 35(2), 239-43	Publication / study type
Gutierrez-Castrellon P, Mayorga-Buitron J L, Bosch-Canto V, Solomon-Santibanez G, De Colsa-Ranero , and A (2012) Efficacy and safety of clarithromycin in pediatric patients with upper respiratory infections: A systematic review with meta-analysis. Revista de Investigacion Clinica 64(2), 126-135	Publication / study type
Hahn R G, Knox L M, and Forman T A (2005) Evaluation of poststreptococcal illness. American Family Physician 71(10), 1949-1954	Publication / study type
Hanson D G, Conley D, Jiang J, and Kahrilas P (2000) Role of esophageal pH recording in management of chronic laryngitis: an	Publication / study type

Study reference	Reason for exclusion
overview. The Annals of otology, and rhinology & laryngology. Supplement 184, 4-9	
Havas T E (2003) Diagnosing and treating the acute sore throat. Medicine Today 4(4), 30-36	Publication / study type
Hayes C S, Williamson H, and Jr (2001) Management of Group A beta-hemolytic streptococcal pharyngitis. American family physician 63(8), 1557-64	Publication / study type
Hirschmann J V (2002) Antibiotics for common respiratory tract infections in adults. Archives of Internal Medicine 162(3), 256-264	Publication / study type
Hultcrantz E, and Ericsson E (2013) Factors influencing the indication for tonsillectomy: A historical overview and current concepts. ORL 75(3), 184-191	Population
Ivers N, Arroll B, and Allan G M (2011) Delayed antibiotic prescriptions for URTIs. Canadian Family Physician 57(11), 1287	Publication / study type
Jain N, Lodha R, and Kabra S K (2001) Upper respiratory tract infections. Indian journal of pediatrics 68(12), 1135-8	Publication / study type
Jerath Nameet, and Shetty Ganesh (2007) Redefining the management of pediatric tonsillopharyngitis with cefprozil. Indian journal of pediatrics 74(12), 1105-8	Publication / study type
Johnson B C, and Alvi A (2003) Cost-effective workup for tonsillitis: Testing, treatment, and potential complications. Postgraduate Medicine 113(3), 115-121	Publication / study type
Kanagalingam J, Feliciano R, Hah J H, Labib H, Le T A, and Lin J C (2015) Practical use of povidone-iodine antiseptic in the maintenance of oral health and in the prevention and treatment of common oropharyngeal infections. International journal of clinical practice 69(11), 1247-56	Publication / study type
Kannan I, Edwin B, Prasanna V, Hemlata Katiyar, V M, and Dhanapal E (2015) Aetiology and the use of antibiotics in the case of acute pharyngitis: A review. International Journal of Pharmaceutical and Clinical Research 7(4), 226-230	Publication / study type
Kaplan E L, and Johnson D R (2001) Unexplained reduced microbiological efficacy of intramuscular benzathine penicillin G and of oral penicillin V in eradication of group a streptococci from children with acute pharyngitis. Pediatrics 108(5), 1180-6	Outcomes
Kenealy Tim (2007) Sore throat. BMJ clinical evidence 2007,	Not the best available evidence
Kenealy Tim (2011) Sore throat. BMJ clinical evidence 2011,	Publication / study type
Khan A M, Hashmi S R, Elahi F, Tariq M, and Ingrams D R (2006) Laryngopharyngeal reflux: A literature review. Surgeon 4(4), 221-225	Publication / study type
Khayr W, and Taepke J (2005) Management of peritonsillar abscess: Needle aspiration versus incision and drainage versus tonsillectomy. American Journal of Therapeutics 12(4), 344-350	Population
Kljakovic Marjan, and Crampton Peter (2005) Sore throat management in New Zealand general practice. The New Zealand medical journal 118(1220), U1609	Publication / study type
Klug T E, Rusan M, Fuursted K, Ovesen T, and Jorgensen A W (2016) A systematic review of Fusobacterium necrophorum-positive acute tonsillitis: prevalence, methods of detection, patient characteristics, and	Population

Study reference	Reason for exclusion
the usefulness of the Centor score. European Journal of Clinical Microbiology and Infectious Diseases 35(12), 1903-1912	
Koo Chieh Yang, and Eisenhut Michael (2011) Towards evidence-based emergency medicine: best BETs from the Manchester Royal Infirmary. Can inflammatory markers distinguish streptococcal from viral tonsillitis?. Emergency medicine journal : EMJ 28(8), 715-7	Publication / study type
Kung Kenny, Wong Carmen Ka Man, Wong Samuel Yeung Shan, Lam Augustine, Chan Christy Ka Yan, Griffiths Sian, and Butler Chris (2014) Patient presentation and physician management of upper respiratory tract infections: a retrospective review of over 5 million primary clinic consultations in Hong Kong. BMC family practice 15, 95	Publication / study type
Lakos Adela Kolumbic, Pangercic Ana, Gasparic Maja, Kukuruzovic Mirjana Matrapazovski, Kovacic Drazen, and Barsic Bruno (2012) Safety and effectiveness of azithromycin in the treatment of respiratory infections in children. Current medical research and opinion 28(1), 155-62	Publication / study type
Law Constance, and Amsden Guy W (2004) Single-dose azithromycin for respiratory tract infections. The Annals of pharmacotherapy 38(3), 433-9	Publication / study type
Lennon P, O'Neill J P, and Fenton J E (2014) Effect of metronidazole versus standard care on length of stay of patients admitted with severe infectious mononucleosis: A randomized controlled trial. Clinical Microbiology and Infection 20(7), O450-O452	Population
Leone C A, Caruso A A, Allocca V, Barra E, and Leone R (2015) Pilot study on the effects of high molecular weight sodium hyaluronate in the treatment of chronic pharyngitis. International Journal of Immunopathology and Pharmacology 28(4), 532-538	Population
Leung Alexander K. C, and Kellner James D (2004) Group A beta-hemolytic streptococcal pharyngitis in children. Advances in therapy 21(5), 277-87	Publication / study type
Leung Alexander K. C, Newman Rachel, Kumar Ashir, and Davies H Dele (2006) Rapid antigen detection testing in diagnosing group A beta-hemolytic streptococcal pharyngitis. Expert review of molecular diagnostics 6(5), 761-6	Publication / study type
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