National Institute for Health and Care Excellence

APG: sore throat (acute)

Sore throat (acute): antimicrobial prescribing guideline

Evidence review

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Final

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1 Context

1.1 Background

Acute sore throat (including 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 [2012]). 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 scoring 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).

Public Health England publishes guidance on the characteristics, diagnosis and management of group A streptococci (GAS) infections, including invasive GAS (iGAS). See Group A streptococcal infections: guidance and data.

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 (2008) has recommendations for managing self-limiting respiratory tract infections relating to the use of 3 antibiotic prescribing strategies (either no prescribing, back-up antibiotic prescribing or immediate prescribing).

The NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) 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 (2017) 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 (2008) recommends that when a no antibiotic prescribing strategy is adopted, people should be offered reassurance that antibiotics are not needed immediately and offered a clinical review if the condition worsens or becomes prolonged.

When a back-up antibiotic prescribing strategy is adopted, people should be offered reassurance that antibiotics are not needed immediately. They should also be offered advice about using the back-up antibiotic 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. Furthermore, they should be given advice about re-consulting if there is a significant worsening of symptoms despite using the back-up antibiotic prescription. Back-up antibiotic prescriptions can be given to the person at the time of consultation 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 (2015) provides recommendations for prescribers for prescribing antimicrobials. The recommendations guide prescribers in decisions about antimicrobial prescribing and include recommending that prescribers follow local and national guidelines, use the shortest effective course length and record their decisions, particularly when these decisions are not in line with guidelines. The recommendations also advise that prescribers take into account the benefits and harms for a person when prescribing an antimicrobial, such as possible interactions, co-morbidities, drug allergies and the risks of healthcare associated infections.

The NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population (2017) 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 and 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 (2017) 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, such as 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 and when to 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 is 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)
- 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 scarlet fever, rheumatic fever and glomerulonephritis, although the incidence of these in the UK is very low.

2 Evidence selection

A range of evidence sources are used to develop antimicrobial prescribing guidelines. These fall into 2 broad categories:

- Evidence identified from the literature search (see section 2.1 below)
- Evidence identified from other information sources. Examples of other information sources used are shown in the interim process guide (2017).

See appendix A: evidence sources for full details of evidence sources used for acute sinusitis.

2.1 Literature search

A literature search was developed to identify evidence for the effectiveness and safety of interventions for managing acute sore throat (see appendix C: literature search strategy for full details). The literature search identified 7,159 references. These references were screened using their titles and abstracts and 327 full text references were obtained and assessed for relevance. Eighty full text references of systematic reviews and randomised controlled trials (RCTs) were assessed as relevant to the guideline review question (see appendix B: review protocol). Ten percent of studies were screened to establish inter-rater reliability, and this was within the required threshold of 90%. One additional reference was published after the search was completed.

The methods for identifying, selecting and prioritising the best available evidence from the literature search are described in the interim process guide (2017). Twenty of the 80 references, plus 1 additional reference identified by the committee and published after the literature search, were prioritised by the committee as the best available evidence and were included in this evidence review (see appendix F: included studies).

The 60 references that were not prioritised for inclusion are listed with reasons in appendix I: not prioritised studies. Studies that assessed Chinese herbal medicines were not prioritised by the Committee as all the RCTs identified were non-UK studies with preparations unlikely to be available in the UK. Also see appendix E: evidence prioritisation for more information on study selection.

The remaining 246 references were excluded. These are listed in appendix J: excluded studies with reasons for their exclusion.

See also appendix D: 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 F: included studies. An overview of the quality assessment of each included study is shown in appendix G: 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.

[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
Back-up 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	Back-up 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	Back-up 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 antigen testing (based on score)	Back-up antibiotic prescribing strategy	Symptom severity on days 2 to 4
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-	Antibiotic (including cephalosporins, macrolides and sulphonamides)	Another antibiotic (penicillin or ampicillin)	Cure or improvement in signs and symptoms,

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
		haemolytic streptococci (GABHS), confirmed by a throat culture and/or rapid test			
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					
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 H: 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, non-medicated mouthwashes or any other non-pharmacological interventions 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 clinically meaningful (low to moderate 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, moderate 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, 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, 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 with diclofenac potassium 12.5 mg and 25 mg compared with placebo, although diclofenac 6.25 mg and paracetamol 1,000 mg were not significantly better than placebo (low to moderate 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 (low to moderate quality evidence).

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 (moderate 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, therefore improvements seen for benzocaine may be clinically meaningful.

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 −1.95, p=0.004, low quality evidence). The clinical relevance of a 1-point improvement of this scale is unclear.

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, moderate quality evidence).

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 higher in the flurbiprofen

8.75 mg group (17.9 points) compared with placebo (15.6 points, p=0.037) but this was not statistically significant (NICE analysis; moderate quality evidence).

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 (moderate 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).

3.2.3 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 phenoxymethylpenicillin (also known as 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; high 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; high 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 (moderate quality evidence).

3.2.4 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 3 to 6). 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 3 to 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; low 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; low 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 (low to 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 (moderate 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, no statistically significant difference; moderate 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%, risk ratio [RR] 1.31, 95% confidence interval [CI] 1.02 to 1.68, NNT 12, 95% CI 6 to 137, p=0.03, moderate quality evidence). There was no significant difference between groups for time to onset of pain relief or time to complete resolution of symptoms (moderate quality evidence).

3.3 Antimicrobials

The evidence review for antimicrobials is based on 6 systematic reviews and 2 RCTs. The included studies cover back-up 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 Back-up antibiotics

One RCT in adults (de la Poza Abad et al. 2016) found that a back-up 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 (moderate 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 back-up collection prescription group (26.0%, p<0.001) and patient-led back-up 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 back-up collection prescription group (23%, p<0.001) and patient-led back-up 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 back-up antibiotic prescribing (Spurling et al. 2013) reported conflicting results for studies involving people with acute sore throat. Immediate antibiotics were significantly more effective than back-up antibiotics for fever, pain and malaise in some studies, while in others there was no significant difference between groups (low to moderate quality evidence). Back-up antibiotics resulted in a significant reduction in antibiotic use compared to immediate antibiotics (32% versus 93% of prescriptions dispensed respectively). There was no statistically significant difference in patient satisfaction for back-up antibiotic prescription (93.2%) compared an immediate prescription (95.7%) or no antibiotic prescription (90.2%, moderate quality evidence).

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 (RR 0.68, 95% CI 0.59 to 0.79, p<0.00001, NNT 6, 95% CI 5 to 7, 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, NNT 21, 95% CI 14 to 49, 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, NNT 5, 95% CI 4 to 7, 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 compared with placebo appeared to be greater in those people with positive GABHS throat swabs. Just under half the people with a positive throat swab treated with antibiotics were still experiencing pain on day 3, compared to 71% given placebo (RR 0.58, 95% CI 0.48 to 0.71, p<0.00001, NNT 4 [95% CI 4 to 5], moderate quality evidence). Of those with negative swabs, 57% of people treated with antibiotics were still experiencing pain on day 3, compared to just under three-quarters of people who were given placebo (RR 0.78, 95% CI 0.63 to 0.97, p=0.028, NNT 7 [95% CI 5 to 12], low quality evidence). Similar results were seen at 1 week.

3.3.3 Identifying people more likely to benefit from an antibiotic

An open-label RCT conducted in a UK primary care setting (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. Back-up 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 back-up 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 back-up 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 on days 2 to 4 (adjusted for baseline symptom severity and fever) was lower in the FeverPAIN group (2.88 points) and the FeverPAIN plus rapid antigen testing group (2.83 points) compared with the back-up antibiotics group (3.11 points, mean difference 0.33 to 0.30, 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'. However, the mean difference is consistent with there being no meaningful difference between either FeverPAIN groups compared with back-up antibiotics. When the results were adjusted for clustering by practice there was no statistically significant difference between FeverPAIN or FeverPAIN plus rapid antigen test compared with back-up antibiotics (p=0.08 and p=0.16 respectively).

Compared with back-up antibiotics, the median duration of symptoms was significantly shorter in the FeverPAIN group (4 days) compared with the back-up 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 (4 days) compared with back-up antibiotics (5 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 back-up antibiotics group (46%, p=0.02 and p=0.03 respectively; low quality evidence).

The authors conclude that additional use of rapid antigen tests for people with a high FeverPAIN score had no clear advantage over FeverPAIN alone (moderate quality evidence). However, it should be noted that different treatment and test thresholds were used across the study groups. In the FeverPAIN only group, people with a score of 4 or more received immediate antibiotics and people with a score of 2 or 3 received a back-up antibiotic. In the FeverPAIN plus rapid antigen test group a lower threshold was used, people with a score of 3 or more received a rapid antigen test, and people with a score of 2 received a back-up antibiotic.

3.3.4 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, low 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, moderate 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, 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).

3.3.5 Frequency of antibiotic dosing

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 (low quality evidence). The comparison of twice daily dosing with three or four times daily dosing found no statistically significant difference between the 2 dosing schedules (low quality evidence). 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 BNF-C 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). However, this result was not statistically significant when the RR was calculated (NICE analysis). There were also no significant differences between 5 to 7 days treatment compared with 10 days treatment in the rate of relapse of recurrence (very low quality evidence).

4 Safety and tolerability

Details of safety and tolerability outcomes from studies included in the evidence review are shown in in appendix H: 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 found that adverse events were reported by a similar proportion of people taking aspirin (17/139, 12.2%) compared with placebo (17/133, 12.8%, no significant difference, Eccles et al. 2003, low quality evidence). Adverse events included headache, abdominal pain and nausea.

An RCT by Voelker et al. (2016) found that significantly fewer adverse events were reported by people taking paracetamol (10/70, 14.3%) compared with placebo (12/36, 33%, RR 0.43, 95% CI 0.21 to 0.90 [NICE analysis], low quality evidence). The same study found no significant difference in adverse events for aspirin (13/71, 18.3%) compared with paracetamol (10/70, 14.3%, very low quality evidence) or placebo (12/36, 33.3%, low quality evidence).

An RCT by Gehanno et al. (2003) found no significant difference in adverse events between people taking paracetamol (n=67) compared with placebo (n=71, very low quality evidence). The RCT by Gehanno et al. (2003) also reported no significant difference in adverse events for diclofenac potassium 6.25 mg, 12.5mg and 25 mg compared with placebo or paracetamol (very low quality evidence).

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, 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 to 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 (moderate 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; low quality evidence).

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).

Common side effects with penicillins (such as phenoxymethylpenicillin) include anaphylaxis, angioedema, diarrhoea, fever, hypersensitivity reactions, joint pains and rashes (BNF November 2017). 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.

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 (BNF Novemberr 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 with sore throat treated with antibiotics there were 2 fewer cases of acute otitis media (as a complication of the sore throat, NNT 50). However, over time the background rate of acute otitis media complications with sore throat has dropped, 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 1 case of acute otitis media to nearly 200.

4.3.1 Back-up antibiotics

Across the 1 RCT and 1 systematic review there was generally no difference in adverse events between back-up 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 moderate quality evidence).

4.3.2 Antibiotics versus placebo

Spinks et al. (2013) reported on the incidence of complications associated with sore throat. The incidence of acute otitis media within 14 days of the sore throat 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 of the sore throat 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, low quality evidence).

Acute glomerulonephritis as a complication of sore throat 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, very 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 penicillins (very low to low quality evidence). There was also no significant difference in adverse events between clindamycin and ampicillin (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 effects compared with a longer course of penicillin V (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 Antimicrobial 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.

Concerns have been raised that common infections are becoming increasing difficult to treat in general practice (Butler et al. 2006). Furthermore, there is an association at an individual patient level between the prescribing of antibiotics and antimicrobial resistance in bacteria, including for amoxicillin which is often used as a first line antibiotic for upper respiratory tract infections (Costelloe et al. 2010). The effect is greatest in the month immediately after treatment but may persist for up to 12 months.

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 (2012).

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 back-up 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 back-up collection prescription group (26.0%, $p<0.001$) and patient-led back-up prescription group (34.7%, $p<0.001$) compared with the immediate prescription group (89.1%; 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 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.

FeverPAIN score

The FeverPAIN score gives an indication of the likelihood of a sore throat being due to bacterial infection. The criteria are:

1. Fever (during previous 24 hours).
2. Purulence (pus on tonsils).
3. Attend rapidly (within 3 days after onset of symptoms).
4. Severely Inflamed tonsils.
5. No cough or coryza (inflammation of mucus membranes in the nose).

Each of the FeverPAIN criteria score 1 point (maximum score of 5).

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: Evidence sources

Key area	Key question(s)	Evidence sources
Background	• What is the natural history of the infection? • What is the expected duration and severity of symptoms with or without antimicrobial treatment? • What are the most likely causative organisms? • What are the usual symptoms and signs of the infection? • What are the known complication rates of the infection, with and without antimicrobial treatment? • Are there any diagnostic or prognostic factors to identify people who may or may not benefit from an antimicrobial?	• NICE guideline CG69: Respiratory tract infections (self-limiting): prescribing antibiotics (2008) • NICE guideline CG160: Fever in under 5s: assessment and initial management (2017) • European Society for Clinical Microbiology and Infectious Diseases Sore Throat Guideline (2012) • English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) report (2016) • Spinks et al. 2013 • Kronman et al. 2014 • Gulliford et al. 2009 • Gulliford et al. 2014 • Committee experience
Safety netting	• What safety netting advice is needed for managing the infection?	• NICE guideline NG63: Antimicrobial stewardship: changing risk-related behaviours in the general population (2017) • NICE clinical knowledge summary on sore throat • Committee experience
Red flags	• What symptoms and signs suggest a more serious illness or condition (red flags)?	• NICE guideline NG51: Sepsis: recognition, diagnosis and early management (2016) • NICE clinical knowledge summary on sore throat • Dunn et al. 2007 • Committee experience

Key area	Key question(s)	Evidence sources
Non-pharmacological interventions	• What is the clinical effectiveness and safety of non-pharmacological interventions for managing the infection or symptoms?	• No evidence identified
Non-antimicrobial pharmacological interventions	• What is the clinical effectiveness and safety of non-antimicrobial pharmacological interventions for managing the infection or symptoms?	• Evidence review – see appendix F for included studies • NICE guideline CG160: Fever in under 5s: assessment and initial management (2017) • British National Formulary (BNF) (November 2017) • Drug Safety Update (December 2007) • Drug Safety Update (October 2012)
Antimicrobial prescribing strategies	• What is the clinical effectiveness and safety of antimicrobial prescribing strategies (including back-up prescribing) for managing the infection or symptoms?	• Evidence review – see appendix F for included studies
Antimicrobials	• What is the clinical effectiveness and safety of antimicrobials for managing the infection or symptoms?	• Evidence review – see appendix F for included studies • NICE guideline CG160: Fever in under 5s: assessment and initial management (2017) • BNF (May 2017) • NICE clinical knowledge summary (CKS): diarrhoea – antibiotic associated
	• Which people are most likely to benefit from an antimicrobial?	• Evidence review – see appendix F for included studies
	• Which antimicrobial should be prescribed if one is indicated (first, second and third line treatment, including people with drug allergy)?	• Evidence review – see appendix F for included studies
	• What is the optimal dose, duration and route of administration of antimicrobials?	• Evidence review – see appendix F for included studies • BNF (November 2017) • BNF for children (BNF-C) (November 2017) • Summary of product characteristics

Key area	Key question(s)	Evidence sources
Antimicrobial resistance	• What resistance patterns, trends and levels of resistance exist both locally and nationally for the causative organisms of the infection • What is the need for broad or narrow spectrum antimicrobials? • What is the impact of specific antimicrobials on the development of future resistance to that and other antimicrobials?	• NICE guideline NG15: Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) • Chief medical officer (CMO) report (2011) • ESPAUR report (2016) • European Society for Clinical Microbiology and Infectious Diseases Sore Throat Guideline (2012) • Public Health England (PHE) report on group A streptococcal infections (2016 to 2017)
Resource impact	• What is the resource impact of interventions (such as escalation or de-escalation of treatment)?	• Evidence review – see appendix F for included studies • Drug Tariff (November 2017) • Gulliford et al. 2014
Medicines adherence	• What are the problems with medicines adherence (such as when longer courses of treatment are used)?	• Evidence review – see appendix F for included studies • NICE guideline NG76: Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence (2009)
Regulatory status	• What is the regulatory status of interventions for managing the infection or symptoms?	• Summary of product characteristics

Appendix B: 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 reference (gold) standard	Any other plausible strategy or comparator, including: • Placebo or no treatment. • Non-pharmacological interventions • Non-antimicrobial pharmacological interventions. • Antimicrobial pharmacological interventions	
VII	Outcomes and prioritisation	a) Clinical outcomes such as: • mortality	The committee has agreed that the following outcomes are critical:

1 Non-pharmacological interventions include: no intervention, watchful waiting, delayed (back-up) 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

		• 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 was 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).	• 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 has 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	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.

		• 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	
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 –	Medline; Medline in Progress; Embase; PubMed; Cochrane database of systematic reviews (CDSR); Database of abstracts of effectiveness (DARE) (legacy); Cochrane	

	databases and dates	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 at this time.	
XV	Author contacts	Web: https://www.nice.org.uk/guidance/indevelopment/gid-apg10000 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 C.	
XVIII	Data collection process – forms/ duplicate	GRADE profiles will be used, for details see appendix H.	
XIX	Data items – define all variables to be collected	GRADE profiles will be used, for details see appendix H.	
XX	Methods for assessing bias at	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	

	outcome/study level	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.	

Appendix C: 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>

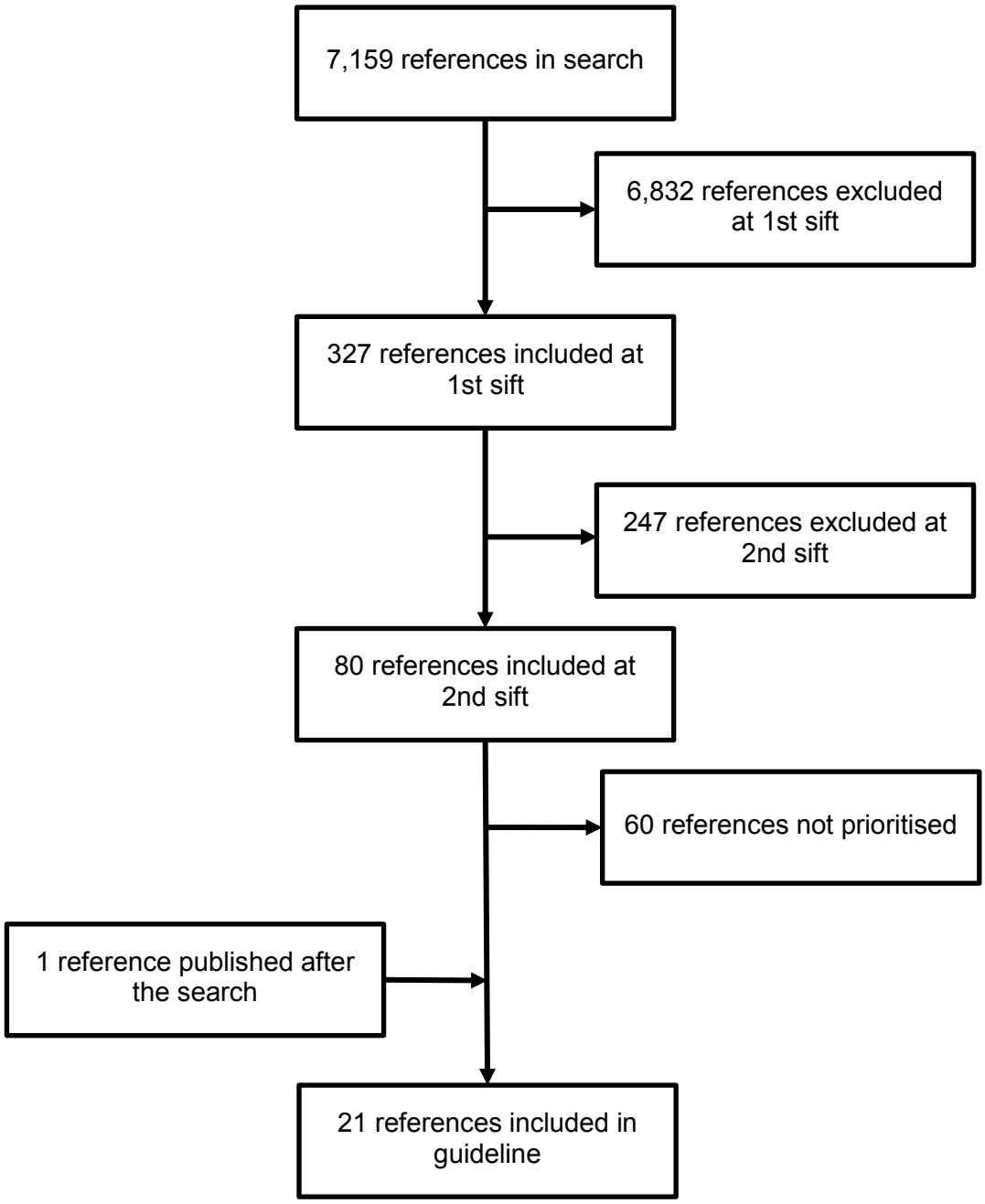
1	exp pharyngitis/ or exp tonsillitis/ or exp LARYNGITIS/ or PERITONSILLAR ABSCESS/ or epiglottitis/ or supraglottitis/	20051
2	(pharyngitis or tonsillitis).tw.	9787
3	(tonsillopharyngitis or tonsillo-pharyngitis).tw.	335
4	tonsillitides.tw.	3
5	(sore* adj3 throat*).tw.	4889
6	(laryngitis or quinsy or 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 D: Study flow diagram



Appendix E: Evidence prioritisation

Key questions	Included studies[1]		Studies not prioritised[2]	
	Systematic reviews	RCTs	Systematic reviews	RCTs
Which non-pharmacological interventions are effective?				
Non-pharmacological interventions	–	–	–	–
Which non-antimicrobial pharmacological interventions are effective?				
Oral analgesia	–	Eccles et al. 2003 Gehanno et al. 2003 Moore et al. 2002 Voelker et al. 2016	–	–
Medicated lozenges	–	Benrimoj et al. 2001 Blagden et al. 2001 Chrubasik et al. 2012 McNally et al. 2012 Schachtel et al. 2014 Watson et al. 2000	–	Aspley et al. 2016 Schachtel et al. 2016 Shephard et al. 2015
Throat sprays	–	Cingi et al. 2011	–	–
Systemic corticosteroids	Hayward et al. 2012	Hayward et al. 2017	Hayward et al. 2009 Mullarkey et al. 2011 Wing et al. 2010	Bulloch et al. 2003 Kiderman et al. 2005 Korb et al. 2010 Marvez-Valls et al. 2002 Olympia et al. 2005 Tasar et al. 2008 Wei et al. 2002
Which antibiotic prescribing strategies are effective (including back-up antibiotics)?				
Back-up antibiotics	Spurling et al. 2013	de la Poza Abad et al. 2015	Spurling et al. 2004	–

Key questions	Included studies[1]		Studies not prioritised[2]	
	Systematic reviews	RCTs	Systematic reviews	RCTs
			Spurling et al. 2007	
Is an antibiotic effective?				
Antibiotics versus placebo	Spinks et al. 2013	–	Del Mar et al. 2000 Del Mar et al. 2004 Del Mar et al. 2006	Leelarasamee et al. 2000
Which people are most likely to benefit from an antibiotic?				
Sub-group analyses of antibiotics versus placebo	–	–	–	–
Treatment based on clinical score	–	Little et al. 2013	–	Llor et al. 2011 Worrall et al. 2007
Which antibiotic is most effective?				
Antibiotics versus different antibiotics	Altamimi et al. 2012 van Driel et al. 2016	–	Casey et al. 2004a Casey et al. 2004b Kenealy 2007 Kenealy 2014 van Driel et al. 2010 van Driel et al. 2013	Berezin et al. 2003 Brook et al. 2005 Kafetzis et al. 2004 Esposito et al. 2000 Gooch et al. 2000 Haczynski et al. 2003 Ioannidis et al. 2001 Kaplan et al. 2001 Kuroki et al. 2013 Lennon et al. 2008 Mahakit et al. 2006 McCarty et al. 2000 Pichichero et al. 2007 Portier et al. 2002 Rimoin et al. 2011 Schaad et al. 2002 Scholz 2004

Key questions	Included studies[1]		Studies not prioritised[2]	
	Systematic reviews	RCTs	Systematic reviews	RCTs
				Syrogiannopoulos et al. 2004 Takker et al. 2003 Uysal et al. 2000
What is the optimal dosage, duration and route of administration of antibiotic?				
Dosage	Lan and Colford 2000	–	–	Adam et al. 2000 Aguilar et al. 2000 Block et al. 2006 Casey et al. 2005 Clegg et al. 2006
Course length	Falagas et al. 2008	–	Casey et al. 2005	Altamimi et al. 2009 Zwart et al. 2000 Zwart et al. 2003
Route of administration	–	–	–	–

Appendix F: Included studies

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

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

Falagas Matthew E, Vouloumanou Evridiki K, Matthaiou Dimitrios K, Kapaskelis Anastasios M, and Karageorgopoulos Drosos E (2008) Effectiveness and safety of short-course vs long-course antibiotic therapy for group a beta hemolytic streptococcal tonsillopharyngitis: a meta-analysis of randomized trials. Mayo Clinic proceedings 83(8), 880-9

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

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 G: Quality assessment of included studies

G.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				

G.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

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
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
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

G.3 Throat sprays

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

Study reference	Cingi et al. 2011
[a] All participants also received antibiotics. The effectiveness of sprays in people not taking antibiotics is not known.	

G.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

G.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
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	

G.6 Identifying people more likely to benefit from an antibiotic

Table 10: 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
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

Study reference	Little et al. 2013
Are the benefits worth the harms and costs?	See GRADE profiles

Appendix H: GRADE profiles

H.1 Oral analgesia in adults

Table 11: GRADE profile – aspirin versus placebo

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	not applicable	no serious indirectness	serious[3]	none	139	133	Significantly higher improvements in the aspirin group (3.81 points; ±2.8 [SD]) compared with placebo (2.41 points; ±2.3 [SD], p=0.0001) NICE analysis: MD 1.40 (95% CI 0.79 to 2.01)	⊕⊕⊕O MODERATE	CRITICAL
Pain relief (measured with: Sum of improvements in pain relief scores over 2 hours [TOTPAR$_{0\text{-}2}$])											
1[2]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	serious[4]	none	139	133	Significantly higher improvements for aspirin compared with placebo (p=0.0001)	⊕⊕⊕O MODERATE	CRITICAL
Time to meaningful pain relief (Better indicated by lower values)											
1[5]	randomised trials	serious[6]	not applicable	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)	⊕⊕OO 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]	not applicable	no serious indirectness	no serious imprecision	none	71	36	Aspirin = 15.0 points (±12.6 [SD]) Placebo = 4.2 points (±8.6 [SD]) p<0.001 NICE analysis: MD 10.8 (95% CI 6.74 to 14.86)	⊕⊕⊕O MODERATE	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]	not applicable	no serious indirectness	no serious imprecision	none	71	36	Aspirin = 48.0 points (±33.3 [SD]) Placebo = 13.4 points (±22.0 [SD]) p<0.001 NICE analysis: MD 34.6 (95% CI 24.0 to 45.17)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events (overall)											
1[2]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[7]	none	17/139 12.2%	17/133 12.79%	17 participants in each treatment group reported adverse events, including headache, abdominal pain and nausea. NICE analysis: RR 0.96 (95% CI 0.51 to 1.79)	⊕⊕OO LOW	CRITICAL
Adverse events, number of participants reporting at least 1 event											

Quality assessment							No of patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Aspirin	Placebo			
1[5]	randomised trials	serious[6]	not applicable	no serious indirectness	serious[8]	none	13/71	12/36	Fewer adverse events reported in people treated with aspirin (18.3%) compared with placebo (33.3%) NICE analysis: RR 0.55 (95% CI 0.28 to 1.08)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI, Confidence interval; MD, Mean difference; RR, Relative risk; SD, Standard deviation; TOTPAR, Total pain relief.											

[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 - at a default minimal important difference (MID) of 0.5 of SD of placebo arm (1.15) data are consistent with no meaningful difference or appreciable benefit with aspirin
[4] Downgraded 1 level - not assessable
[5] Voelker et al. (2016)
[6] Downgraded 1 level - no details on methods of randomisation or blinding reported
[7] Downgraded 2 levels - at a default MID of 25% data suggest no meaningful difference, appreciable benefit or appreciable harm
[8] Downgraded 1 level - at a default MID of 25% data are consistent with no meaningful difference or appreciable benefit with aspirin

Table 12: GRADE profile – paracetamol versus placebo

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]	not applicable	no serious indirectness	serious[3]	none	70	36	Paracetamol = 40.4 minutes Placebo = not achieved within 2 hour observational period p<0.001	⊕⊕OO 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[1]	randomised trials	serious[2]	not applicable	no serious indirectness	no serious imprecision	none	70	36	Paracetamol = 16.1 points (±14.6 [SD]) Placebo = 4.2 points (±8.6 [SD]) p<0.001 NICE analysis: MD 11.90 (95% CI 7.47 to 16.33)	⊕⊕⊕O MODERATE	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[1]	randomised trials	serious[2]	not applicable	no serious indirectness	no serious imprecision	none	70	36	Paracetamol = 47.1 points (±3.4 [SD]) Placebo = 13.4 points (±22.0 [SD]) p<0.001 NICE analysis: MD 33.70 (95% CI 26.47 to 40.93)	⊕⊕⊕O MODERATE	CRITICAL
Change in temperature from baseline to 4 hours, area under curve (AUC_{0-4}) (Better indicated by higher values)											
1[4]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[5]	none	65	69	Paracetamol = 2.01ºC/hour (±1.47 [SD]) Placebo = 1.46ºC/hour (±1.57 [SD]) p≤0.05	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Paracetamol	Placebo			
									NICE analysis: MD 0.55 (95% CI 0.04 to 1.06)		
Change in pain on swallowing, total pain relief summed over 4 hours ($TOTPAR_{0-4}$) (Better indicated by higher values)											
1[4]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[5]	none	63	67	Paracetamol = 4.06 points (±2.88 [SD]) Placebo = 3.28 points (±2.84 [SD]) p<0.01	⊕⊕OO LOW	CRITICAL
									NICE analysis: MD 0.78 (95% CI −0.20 to 1.76)		
Adverse events, number of participants reporting at least 1 event											
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[6]	none	10/70	12/36	Paracetamol = 10 participants (14.3%) Placebo = 12 participants (33.3%)	⊕⊕OO LOW	CRITICAL
									NICE analysis: RR 0.43 (95% CI 0.21 to 0.90)		
Adverse events, percentage of participants reporting at least 1 event											
1[4]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[7]	none	67	71	Paracetamol = 9.0% Placebo = 5.6%	⊕OOO VERY LOW	CRITICAL
									NICE analysis: RR 1.59 (95% CI 0.47 to 5.39)		
Abbreviations: CI, Confidence interval; MD, Mean difference; RR, Relative risk; SD, Standard deviation; TOTPAR, Total pain relief											

[1] Voelker et al. (2016)
[2] Downgraded 1 level - no details on methods of randomisation or blinding reported
[3] Downgraded 1 level - not assessable
[4] Gehanno et al. (2003)
[5] Downgraded 1 level – at a default minimal important difference (MID) of 0.5 of SD of placebo arm data are consistent with no meaningful difference or appreciable benefit with paracetamol
[6] Downgraded 1 level – at a default MID of 25% data are consistent with no meaningful difference or appreciable benefit with paracetamol
[7] Downgrade 2 levels –at a default MID of 25% data are consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 13: GRADE profile – diclofenac potassium versus placebo

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]	not applicable	no serious indirectness	serious[3]	none	66	66	70	69	6.25mg = 1.94 °C/hour (±1.64 [SD]) 12.5 mg = 2.09 °C/hour (±1.83 [SD]) 25 mg = 2.27 °C/hour (±1.75 [SD]) Placebo = 1.46 °C/hour (±1.57 [SD])	⊕⊕OO LOW	CRITICAL
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[4]	none	66	-	-	69	NICE analysis 6.25 mg vs. placebo: MD 0.48 (95% CI −0.06 to 1.02)	⊕⊕OO LOW	CRITICAL
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[4]	none	-	66	-	69	NICE analysis: 12.5 mg vs. placebo: MD 0.63 (95% CI 0.05 to 1.21)	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients				Effect	Quality	Importance
							Diclofenac potassium			Placebo			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	6.25 mg	12.5 mg	25 mg				
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[4]	none	-	-	70	69	NICE analysis: 25 mg vs. placebo: MD 0.81 (95% CI 0.26 to 1.36)	⊕⊕OO 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]	not applicable	no serious indirectness	serious[3]	none	62	66	68	67	6.25mg = 3.71 points (±2.81 [SD]) 12.5 mg = 4.64 points (±3.03 [SD]) 25 mg = 5.01 points (±3.22 [SD]) Placebo = 3.28 points (±2.84 [SD])	⊕⊕OO LOW	CRITICAL
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	no serious imprecision	none	62	-	-	67	NICE analysis: 6.25 mg vs. placebo: MD 0.43 (95% CI −0.55 to 1.41)	⊕⊕⊕O MODERATE	CRITICAL
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[4]	none	-	66	-	67	NICE analysis: 12.5 mg vs. placebo: MD 1.36 (95% CI 0.36 to 2.36)	⊕⊕OO LOW	CRITICAL
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[4]	none	-	-	68	67	NICE analysis: 25 mg vs. placebo: MD 1.73 (95% CI 0.71 to 2.75)	⊕⊕OO LOW	CRITICAL
Adverse events, percentage of participants reporting at least 1 event													
1[1]	randomised trials	serious[2]	Not applicable	no serious indirectness	serious[3]	none	67	67	71	71	6.25mg = 6.0% 12.5 mg = 6.0% 25 mg = 2.8% Placebo = 5.6%	⊕⊕OO LOW	CRITICAL
1[1]	randomised trials	serious[2]	Not applicable	no serious indirectness	very serious[5]	none	4/67	-	-	4/71	NICE analysis: 6.25 mg vs. placebo: RR 1.06 (95% CI 0.28 to 4.07)	⊕OOO VERY LOW	CRITICAL
1[1]	randomised trials	serious[2]	Not applicable	no serious indirectness	very serious[5]	none	-	4/67	-	4/71	NICE analysis: 12.5 mg vs. placebo: RR 1.06 (95% CI 0.28 to 4.07)	⊕OOO VERY LOW	CRITICAL
1[1]	randomised trials	serious[2]	Not applicable	no serious indirectness	very serious[5]	none	-	-	2/71	4/71	NICE analysis: 25 mg vs. placebo: RR 0.50 (95% CI 0.09 to 2.64)	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI, Confidence interval; MD, Mean difference; RR, Relative risk; SD, Standard deviation; TOTPAR, Total pain relief.

[1] Gehanno et al. (2003)
[2] Downgraded 1 level - no details on methods of randomisation or blinding reported
[3] Downgraded 1 level – author analysis not assessable
[4] Downgraded 1 level - at a default minimal important difference (MID) of 0.5 of SD of placebo arm data are consistent with no meaningful difference or appreciable benefit with diclofenac
[5] Downgraded 2 levels – at a default MID of 25% data are consistent with no meaningful difference, appreciable benefit or appreciable harm, with very wide 95% CI

Table 14: GRADE profile – aspirin versus paracetamol

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]	not applicable	no serious indirectness	serious[3]	none	71	70	Aspirin = 48.0 minutes Paracetamol = 40.4 minutes p=0.772	⊕⊕OO 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]	not applicable	no serious indirectness	no serious imprecision	none	71	70	Aspirin = 15.0 (±12.6 [SD]) Paracetamol = 16.1 (±14.6 [SD]) p=0.632 NICE analysis: MD -1.10 (-5.60 to 3.40)	⊕⊕⊕O MODERATE	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]	not applicable	no serious indirectness	very serious[4]	none	71	70	Aspirin = 48.0 (±33.3 [SD]) Paracetamol = 47.1 (±3.4 [SD]) p=0.869 NICE analysis: MD 0.90 (95% CI -6.89 to 8.69)	⊕OOO VERY LOW	CRITICAL
Adverse events, number of participants reporting at least 1 event											
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[4]	none	71	70	Aspirin = 13 (18.3%) Paracetamol = 10 (14.3%) No p-value reported NICE analysis: RR 1.28 (95% CI 0.6 to 2.73)	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI, Confidence interval; MD, Mean difference; RR, Relative risk; SD, Standard deviation

[1] Voelker et al. (2016)
[2] Downgraded 1 level - no details on methods of randomisation or blinding reported
[3] Downgraded 1 level - not assessable
[4] Downgrade 2 levels - at a default minimal important difference (MID) of 0.5 of SD of paracetamol arm data are consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 15: GRADE profile – diclofenac potassium versus paracetamol

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]	Not applicable	no serious indirectness	serious[3]	none	66	66	70	65	6.25 mg=1.94 °C/hour (±1.64) 12.5 mg=2.09 °C/hour (±1.83)	⊕⊕OO LOW	CRITICAL

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				
											25 mg=2.27 ºC/hour (±1.75) Paracetamol=2.01 ºC/hour (±1.47)		
1[1]	randomised trials	serious[2]	Not applicable	no serious indirectness	no serious imprecision	none	66	-	-	65	NICE analysis 6.25 mg vs. paracetamol: MD -0.07 (95% CI -0.60 to 0.46)	⊕⊕⊕O MODERATE	CRITICAL
1[1]	randomised trials	serious[2]	Not applicable	no serious indirectness	no serious imprecision	none	-	66	-	65	NICE analysis: 12.5 mg vs. paracetamol: MD 0.08 (95% CI -0.49 to 0.65)	⊕⊕⊕O MODERATE	CRITICAL
1[1]	randomised trials	serious[2]	Not applicable	no serious indirectness	serious[4]	none	-	-	70	65	NICE analysis: 25 mg vs. paracetamol: MD 0.26 (95% CI -0.28 to 0.80)	⊕⊕OO 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]	Not applicable	no serious indirectness	serious[3]	none	62	66	68	63	6.25mg = 3.71 points (±2.81) 12.5 mg = 4.64 points (±3.03) 25 mg = 5.01 points (±3.22) Paracetamol=4.06 points (±2.88)	⊕⊕OO LOW	CRITICAL
1[1]	randomised trials	serious[2]	Not applicable	no serious indirectness	no serious imprecision	none	62	-	-	63	NICE analysis 6.25 mg vs. paracetamol: MD -0.35 (95% CI -1.35 to 0.65)	⊕⊕⊕O MODERATE	CRITICAL
1[1]	randomised trials	serious[2]	Not applicable	no serious indirectness	serious[4]	none	-	66	-	63	NICE analysis 12.5 mg vs. paracetamol: MD 0.58 (95% CI -0.44 to 1.60)	⊕⊕OO LOW	CRITICAL
1[1]	randomised trials	serious[2]	Not applicable	no serious indirectness	serious[4]	none	-	-	68	63	NICE analysis: 25 mg vs. paracetamol: MD 0.95 (95% CI -0.09 to 1.99, p=0.07)	⊕⊕OO LOW	CRITICAL
Adverse events, percentage of participants reporting at least 1 event													
1[1]	randomised trials	serious[2]	Not applicable	no serious indirectness	serious[3]	none	67	67	71	67	6.25mg = 6.0% 12.5 mg = 6.0% 25 mg = 2.8% Paracetamol = 9.0%	⊕⊕OO LOW	CRITICAL
1[1]	randomised trials	serious[2]	Not applicable	no serious indirectness	very serious[5]	none	4/67	-	-	6/67	NICE analysis 6.25 mg vs. paracetamol: RR 0.67	⊕⊕OO VERY LOW	CRITICAL

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				
											(95% CI 0.20 to 2.26, p=0.51)		
1[1]	randomised trials	serious[2]	Not applicable	no serious indirectness	very serious[5]	none	-	4/67	-	6/67	NICE analysis 12.5 mg vs. paracetamol: RR 0.67 (95% CI 0.20 to 2.26, p=0.51)	⊕⊕OO VERY LOW	CRITICAL
1[1]	randomised trials	serious[2]	Not applicable	no serious indirectness	very serious[5]	none	-	-	2/71	6/67	NICE analysis: 25 mg vs. paracetamol RR 0.31 (95% CI 0.07 to 1.50, p=0.15)	⊕⊕OO VERY LOW	CRITICAL
Abbreviations: CI, Confidence interval; MD, Mean difference; RR, Relative risk; SD, Standard deviation													

[1] Gehanno et al. (2003)
[2] Downgraded 1 level - no details on methods of randomisation or blinding reported
[3] Downgraded 1 level – authors analysis not assessable
[4] Downgraded 1 level - at a default minimal important difference (MID) of 0.5 of SD of paracetamol arm data are consistent with no meaningful difference or appreciable benefit with diclofenac
[5] Downgrade 2 levels - at a default MID of 25% data are consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 16: GRADE profile – tolerability of ibuprofen versus aspirin versus paracetamol

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]	Not applicable	no serious indirectness	serious[3]	none	113/940	148/942	115/933	Ibuprofen = 12.0% Aspirin = 15.7% Paracetamol = 12.3% Significantly significant difference between ibuprofen and aspirin (p=0.02)	⊕⊕OO LOW	CRITICAL
1[1]	randomised trials	serious[2]	Not applicable	no serious indirectness	no serious imprecision	none	113/940	-	115/933	NICE analysis: ibuprofen vs. paracetamol RR 0.98 (95% CI 0.76 to 1.24)	⊕⊕⊕O MODERATE	CRITICAL
1[1]	randomised trials	serious[2]	Not applicable	no serious indirectness	serious[4]	none	113/940	148/942	-	NICE analysis: ibuprofen vs. aspirin RR 0.77 (95% CI 0.61 to 0.96, p=0.02)	⊕⊕OO LOW	CRITICAL
1[1]	randomised trials	serious[2]	Not applicable	no serious indirectness	serious[4]	none	-	148/942	115/933	NICE analysis: aspirin vs. paracetamol RR 1.27 (95% CI 1.02 to 1.60, p=0.04)	⊕⊕OO LOW	CRITICAL
Adverse events leading to study discontinuation, percentage of participants within 7 days												
1[1]	randomised trials	serious[2]	Not applicable	no serious indirectness	serious[3]	none	940	942	933	Ibuprofen = 4.3% Aspirin = 6.5% Paracetamol = 5.1%	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients			Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ibuprofen	Aspirin	Paracetamol			
										Significantly significant difference between ibuprofen and aspirin (p=0.033)		
1[1]	randomised trials	serious[2]	Not applicable	no serious indirectness	very serious[5]	none	41/940	-	48/933	NICE analysis: Ibuprofen vs. paracetamol: RR 0.85 (95% CI 0.56 to 1.27, p=0.43)	⊕OOO VERY LOW	CRITICAL
1[1]	randomised trials	serious[2]	Not applicable	no serious indirectness	serious[4]	none	41/940	61/942	-	NICE analysis: Ibuprofen vs. aspirin: RR 0.67 (95% CI 0.46 to 0.99, p=0.04)	⊕⊕OO LOW	CRITICAL
1[1]	randomised trials	serious[2]	Not applicable	no serious indirectness	serious[4]	none	-	61/942	48/933	NICE analysis: aspirin vs. paracetamol RR 1.26 (95% CI 0.87 to 1.82, p=0.22)	⊕⊕OO LOW	CRITICAL

Abbreviations: CI, Confidence interval; MD, Mean difference; RR, Relative risk

[1] Moore et al. (2002)
[2] Downgraded 1 level - no details on methods of randomisation or blinding reported
[3] Downgraded 1 level – author analysis not assessable
[4] Downgraded 1 level – at a default minimal important difference (MID) of 25% data suggest no meaningful difference or appreciable harm with aspirin

[5] Downgraded 2 levels – at a default minimal important difference (MID) of 25% data suggest no meaningful difference, appreciable benefit or appreciable harm

H.2 Lozenges in adults

Table 17: GRADE profile – benzocaine lozenges versus placebo

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]	Not applicable	no serious indirectness	no serious imprecision[3]	none	83	82	At baseline the median VAS score was 7 across both groups. The median SPID over 2 hours was −12 points (IQR -21 to -5) in the benzocaine group and −5 points (IQR -15 to -1) in the placebo group (p=0.001), giving a between difference treatment difference of 7 points.	⊕⊕⊕O MODERATE	CRITICAL
Adverse events											

Quality assessment							No of patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Benzocaine lozenges	Placebo			
1[1]	randomised trials	serious[2]	Not applicable	no serious indirectness	serious[4]	none	83	82	Only 1 adverse event was reported; a case of vertigo in a person treated with placebo	⊕⊕OO LOW	CRITICAL
Abbreviations: IQR, Interquartile range											

[1] Chrubasik, Beime and Magora (2012)
[2] Downgraded 1 level - no details on methods of randomisation reported. Unclear whether allocation was concealed
[3] Based on a minimal important difference (MID) of 2 points for SPID (Farrar et al. 2000)
[4] Downgraded 1 level - only 1 event reported

Table 18: GRADE profile – hexylresorcinol lozenges versus placebo

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]	not applicable	no serious indirectness	serious[3]	none	64	62	LS MD -1.16 (lower with intervention) (95% CI -0.37 to -1.95 higher)	⊕⊕OO LOW	CRITICAL
Adverse events											
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[4]	none	1/64 (1.6%)	4/62 (6.5%)	NICE analysis: RR 0.24 (95% CI 0.03 to 2.11)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI, Confidence interval; LS, Least-squares; MD, Mean difference; RR, Relative risk; SD, Standard deviation											

[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 – at a default minimal important difference (MID) of 0.5 SD of placebo arm (0.98) data suggest no meaningful difference or appreciable benefit with hexylresorcinol lozenges
[4] Downgraded 2 levels – at a default minimal important difference (MID) of 25% data suggest no meaningful difference, appreciable benefit or appreciable harm

Table 19: GRADE profile – flurbiprofen lozenges versus placebo

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	Absolute		
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]	not applicable	no serious indirectness	no serious imprecision	none	128	128	Flurbiprofen = 12.68 points (±0.8 SE) Placebo = 10.47 points (±0.8 SE)		CRITICAL

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	Absolute		
									p=0.060 NICE analysis: MD 2.21 (95% CI 0.00 to 4.42)	⊕⊕⊕O MODERATE	
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[3]	randomised trials	serious[4]	not applicable	no serious indirectness	no serious imprecision	none	120	125	Flurbiprofen = 17.9 points (±0.9 SE) Placebo = 15.6 points (±0.9 SE) p=0.037 NICE analysis: unadjusted MD 2.30 (95% CI -0.19 to 4.79)	⊕⊕⊕O MODERATE	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[5]	randomised trials	serious[6]	not applicable	no serious indirectness	no serious imprecision	none	184	179	Flurbiprofen = 12.4 points (±0.4 SE) Placebo = 11.1 points (±0.4 SE) p<0.05 NICE analysis: MD 1.30 (95% CI 0.19 to 2.41)	⊕⊕⊕O MODERATE	CRITICAL
Mean 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[7]	randomised trials	serious[8]	not applicable	no serious indirectness	serious[9]	none	99	95	Flurbiprofen = -529.2 mm/hour Placebo = -332.6 mm/hour p<0.01	⊕⊕OO LOW	CRITICAL
Adverse events											
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[10]	none	129	129	Flurbiprofen = 51/129 (39.5%) Placebo = 30/129 (23.3%) NICE analysis: RR 1.70 (95% CI 1.16 to 2.48)	⊕⊕OO LOW	CRITICAL
Adverse events											
1[3]	randomised trials	serious[4]	not applicable	no serious indirectness	serious[10]	none	128	128	Flurbiprofen = 66/128 (51.6%) Placebo = 48/128 (37.5%) NICE analysis: RR 1.38 (95% CI 1.04 to 1.82)	⊕⊕OO LOW	CRITICAL
Adverse events reported by patients											
1[5]	randomised trials	serious[6]	not applicable	no serious indirectness	serious[10]	none	230	228	Flurbiprofen = 103/230 (44.8%) Placebo = 71/228 (31.1%) NICE analysis: RR 1.44 (95% CI 1.13 to 1.83)	⊕⊕OO LOW	CRITICAL
Adverse events in the first 24 hours											
1[7]	randomised trials	serious[8]	not applicable	no serious indirectness	very serious[11]	none	99	95	Flurbiprofen = 25.7% Placebo = 19.6% p>0.1	⊕OOO VERY LOW	CRITICAL

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	Absolute		
									NICE analysis: RR 1.19 (95% CI 0.72 to 1.96)		

Abbreviations: CI, Confidence interval; MD, Mean difference; RR, Relative risk; SE, Standard error; TOTPAR, Total pain relief.

[1] Watson et al. (2000)
[2] Downgraded 1 level - no details on methods of randomisation or blinding reported
[3] Benrimoj et al. (2001)
[4] Downgraded 1 level - unclear whether allocation was concealed
[5] Blagden et al. (2001)
[6] Downgraded 1 level - no details on methods of randomisation or blinding reported. Large number of participants withdrew from the study.
[7] Schachtel et al. (2014)
[8] Downgraded 1 level - no details on methods of blinding reported. Unclear whether allocation was concealed
[9] Downgraded 1 level - not assessable
[10] Downgraded 1 level - at a default minimal important difference (MID) of 25% data suggest no meaningful difference or appreciable harm with flurbiprofen
[11] Downgraded 2 levels – at a default minimal important difference (MID) of 25% data suggest no meaningful difference, appreciable benefit or appreciable harm

H.3 Throat sprays in adults

Table 20: GRADE profile – chlorhexidine gluconate and benzydamine combination mouth spray versus placebo

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[1]	Placebo[1]			
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[2]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	no serious imprecision	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)	⊕⊕⊕⊕ HIGH	CRITICAL

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[1]	Placebo[1]			
									NICE analysis: MD of post-treatment -2.95 (95% CI -3.37 to -2.53, p=0.00001)		
Subjective health state after 7 days treatment, measured on a 10cm visual analogue scale (VAS; Better indicated by lower values)											
1[2]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	no serious imprecision	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)	⊕⊕⊕⊕ HIGH	IMPORTANT
									NICE analysis: MD -1.18 (95% CI -1.57 to -0.79, p=0.00001)		
Quality of life, measured using Short Form 36 (SF36) Health Questionnaire											
1[2]	randomised trials	no serious risk of bias	not applicable	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 No statistically significant difference between groups (p>0.05)	⊕⊕⊕O MODERATE	IMPORTANT
									NICE analysis: MD 1.88 (95% CI -0.09 to 3.85, p=0.06)		
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[2]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	serious[4]	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	⊕⊕⊕O MODERATE	CRITICAL

Abbreviations: CI, Confidence interval; MD, Mean difference

[1] Both intervention and control groups in this study received antibiotics

[2] Cingi et al. (2011)
[3] Downgraded 1 level – at a default minimal important difference (MID) of 0.5 SD of placebo, data suggest no meaningful difference or appreciable benefit with chlorhexidine gluconate and benzydamine combination mouth spray
[4] Downgrade 1 level – not assessable

H.4 Corticosteroids

Table 21: GRADE profile – corticosteroid (oral or intramuscular) versus placebo in adults and children who were receiving antibiotics

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Corticosteroids[1]	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 (95% CI 1.97 to 5.08)	264 more per 1000 (from 119 more to 500 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Complete resolution of pain at 48 hours												
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 (95% CI 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	serious[4]	none	299	310	MD 6.32 hours lower (95% CI 9.29 to 3.35 lower)		⊕⊕OO LOW	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	serious[4]	none	239	261	MD 14.41 hours lower (95% CI 24.99 to 3.84 lower)		⊕⊕OO LOW	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	serious[3]	no serious indirectness	serious[4]	none	308	309	MD 1.3 higher (95% CI 0.61 to 2.06 higher)		⊕⊕OO LOW	CRITICAL
Recurrence or relapse of symptoms												
3[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	7/192 (3.6%)	12/161 (7.5%)	RR 0.56 (95% CI 0.24 to 1.34)	33 fewer per 1000 (from 57 fewer to 25 more)	⊕⊕OO LOW	CRITICAL
Number of days missed from work or school (Better indicated by lower values)												
1[2]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	serious[4]	none	46	46	MD 0.3 lower (95% CI 0.87 lower to 0.27 higher)		⊕⊕⊕O MODERATE	IMPORTANT
Abbreviations: CI, Confidence interval;, GABHS, group A beta-haemolytic streptococcus; MD, Mean difference; RR, Relative risk												

[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 default MID of 0.5 SD of placebo (median SD) data suggest no meaningful difference or appreciable benefit with corticosteroids
[5] Downgraded 2 levels - at a 95% confidence interval, data are consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 22: GRADE profile – dexamethasone 10 mg versus placebo in adults who were not receiving 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	Not applicable	no serious indirectness	serious[2]	none	65/288 (22.6%)	49/277 (17.7%)	RR 1.28 (95% CI 0.92 to 1.78)	50 more per 1000 (from 14 fewer to 138 more)	⊕⊕⊕O MODERATE	CRITICAL
Resolution of symptoms at 48 hours												
1[1]	randomised trials	no serious risk of bias	Not applicable	no serious indirectness	serious[2]	none	102/288 (35.4%)	75/277 (27.1%)	RR 1.31 (95% CI 1.02 to 1.68)	84 more per 1000 (from 5 more to 184 more)	⊕⊕⊕O MODERATE	CRITICAL
Median time to onset of pain relief , hours												
1[1]	randomised trials	no serious risk of bias	Not applicable	no serious indirectness	serious[2]	none	129	102	Dexamethasone = 27.5 hours (95% CI 21.0 to 44.5) Placebo = 27.0 hours (95% CI 21.4 to 45.8) Hazard ratio = 1.106 (95% CI 0.850 to 1.440)		⊕⊕⊕O MODERATE	CRITICAL
Median time to complete resolution of symptoms, hours												
1[1]	randomised trials	no serious risk of bias	Not applicable	no serious indirectness	serious[2]	none	101	94	Dexamethasone= 65.8 hours (95% CI 41.0 to 105.9) Placebo= 60.0 hours (95% CI 39.8 to 92.3) Hazard ratio= 1.043 (95% CI 0.781 to 1.393)		⊕⊕⊕O MODERATE	CRITICAL
Serious adverse events												
1[1]	randomised trials	no serious risk of bias	Not applicable	no serious indirectness	very serious[3]	none	101	94	2 serious adverse events reported in the dexamethasone group 3 serious adverse events reported in the placebo group. NICE analysis: RR 0.62 (95% CI 0.11 to 3.63, p=0.60)		⊕⊕OO LOW	CRITICAL

Abbreviations: CI, Confidence interval; RR, Relative risk

[1] Hayward et al. 2017

[2] Downgraded 1 level - at a 95% confidence interval, data are consistent with no meaningful difference or appreciable benefit with dexamethasone

[3] Downgraded 2 levels - at a 95% confidence interval, data are consistent with no meaningful difference, appreciable benefit or appreciable harm

H.5 Back-up antibiotic prescribing

Table 23: GRADE profile – back-up antibiotic prescription versus immediate antibiotic or no antibiotic in adults

Quality assessment							Effect					Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate antibiotic prescription	Patient-led back-up 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]	Not applicable	no serious indirectness	serious[5]	none	5.1 (3.8)	5.6 (3.1)	6.1 (4.3)	6.8 (4.9)	0.71	⊕⊕⊕O MODERATE	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]	Not applicable	no serious indirectness	serious[5]	none	3 (2 to 4)	2 (1 to 4)	2 (1 to 4)	3 (1 to 4)	0.41	⊕⊕⊕O MODERATE	CRITICAL
Uncomplicated upper respiratory tract infections													
Antibiotic collected, number of participants (%)													
1[3]	randomised trials	no serious risk of bias[4]	Not applicable	serious[6]	serious[5]	none	90 (89.1)	34 (34.7)	26 (26.0)	NA	<0.001	⊕⊕OO LOW	CRITICAL
Antibiotic used, number of participants (%)													
1[3]	randomised trials	no serious risk of bias[4]	Not applicable	serious[6]	serious[5]	none	92 (91.1)	32 (32.6)	23 (23.0)	12 (12.1)	<0.001	⊕⊕OO LOW	CRITICAL
Need for unscheduled health care, number of participants (%)													
1[3]	randomised trials	no serious risk of bias[4]	Not applicable	serious[6]	serious[5]	none	4 (4.0)	6 (6.1)	4 (4.0)	6 (6.1)	0.84	⊕⊕OO LOW	CRITICAL
Adverse events, number of participants (%)													
1[3]	randomised trials	no serious risk of bias[4]	Not applicable	serious[6]	serious[5]	none	1 (1.0)	1 (1.0)	0 (0)	3 (3.0)	0.27	⊕⊕OO LOW	CRITICAL

Abbreviations: SD, Standard deviation

[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 – author's analysis not assessable (see table below for NICE pairwise analysis)
[6] Downgraded 1 level - population is people with uncomplicated upper respiratory tract infections, including sore throat

Table 24: GRADE profile – back-up antibiotic prescription versus immediate antibiotic or no antibiotic in adults (NICE analysis)

Quality assessment							No of patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator			
Pharyngitis											
Duration of symptoms after 1st visit- swallowing difficulties (days, mean [SD]) (NICE pairwise analysis of immediate prescription versus delayed collection[1])											
1[3]	randomised trials	no serious risk of bias[4]	Not applicable	no serious indirectness	serious[5]	none	5.1 (3.8) n=47	6.1 (4.3) n=46	MD -1.00 (95% CI -2.65 to 0.65, p=0.24)	⊕⊕⊕O MODERATE	CRITICAL
Duration of symptoms after 1st visit- swallowing difficulties (days, mean [SD]) (NICE pairwise analysis of immediate prescription versus patient-led back-up prescription[2])											
1[3]	randomised trials	no serious risk of bias[4]	Not applicable	no serious indirectness	serious[5]	none	5.1 (3.8) n=47	5.6 (3.1) n=45	MD -0.50 (95% CI -1.91 to 0.91, p=0.49)	⊕⊕⊕O MODERATE	CRITICAL
Duration of symptoms after 1st visit- swallowing difficulties (days, mean [SD]) (NICE pairwise analysis of immediate prescription versus no prescription)											
1[3]	randomised trials	no serious risk of bias[4]	Not applicable	no serious indirectness	serious[5]	none	5.1 (3.8) n=47	6.8 (4.9) n=46	MD -1.70 (95% CI -3.48 to 0.08, p=0.06)	⊕⊕⊕O MODERATE	CRITICAL
Duration of symptoms after 1st visit- swallowing difficulties (days, mean [SD]) (NICE pairwise analysis of delayed collection[1] versus patient-led back-up prescription[2])											
1[3]	randomised trials	no serious risk of bias[4]	Not applicable	no serious indirectness	serious[6]	none	6.1 (4.3) n=46	5.6 (3.1) n=45	MD 0.50 (95% CI -1.04 to 2.04, p=0.52)	⊕⊕⊕O MODERATE	CRITICAL
Duration of symptoms after 1st visit- swallowing difficulties (days, mean [SD]) (NICE pairwise analysis of delayed collection[1] versus no prescription)											
1[3]	randomised trials	no serious risk of bias[4]	Not applicable	no serious indirectness	serious[5]	none	6.1 (4.3) n=46	6.8 (4.9) n=46	MD -0.70 (95% CI -2.58 to 1.18, p=0.47)	⊕⊕⊕OO MODERATE	CRITICAL
Duration of symptoms after 1st visit- swallowing difficulties (days, mean [SD]) (NICE pairwise analysis of patient led delayed collection versus no prescription)											
1[3]	randomised trials	no serious risk of bias[4]	Not applicable	no serious indirectness	serious[5]	none	5.6 (3.1) n=45	6.8 (4.9) n=46	MD -1.20 (95% CI -2.88 to 0.48, p=0.16)	⊕⊕⊕OO MODERATE	CRITICAL

Abbreviations: CI, Confidence interval; MD, Mean difference; SD, Standard deviation

[1] Patients were able to collect an antibiotic prescription 3 days after the first consultation
[2] Patients were given an antibiotic prescription at 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 – at a default MID of 0.5 SD of comparator data are consistent with no meaningful difference or appreciable harm with comparator
[6] Downgraded by 1 level – at a default MID of 0.5 SD of comparator data are consistent with no meaningful difference or appreciable harm with intervention

Table 25: GRADE profile – back-up antibiotic prescription versus immediate antibiotic in adults and children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Back-up prescription	Immediate antibiotics	Relative (95% CI)	Absolute		
Pain on day 3												
1[1]	randomised trials	serious[2]	Not applicable	no serious indirectness	no serious imprecision	none	106/118 (89.8%)	42/111 (37.8%)	OR 14.51 (7.14 to 29.5)			CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Back-up prescription	Immediate antibiotics	Relative (95% CI)	Absolute		
									NICE analysis: RR 2.37 (95% CI 1.86 to 3.04)	520 more per 1000 (from 435 more to 569 more)	⊕⊕OO LOW	
Pain severity on day 3 (Better indicated by lower values)												
1[1]	randomised trials	serious[2]	Not applicable	no serious indirectness	serious[3]	none	55	59	MD 0.30 higher (95% CI 0.15 lower to 0.75 higher)		⊕⊕OO LOW	CRITICAL
Malaise on day 3												
1[1]	randomised trials	serious[2]	Not applicable	no serious indirectness	no serious imprecision	none	45/118 (38.1%)	4/111 (3.6%)	OR 16.49 (95% CI 5.68 to 47.83) NICE analysis: RR 10.58 (95% CI 3.94 to 28.4)	345 more per 1000 (from 139 more to 605 more)	⊕⊕⊕O MODERATE	CRITICAL
Malaise severity on day 3 (Better indicated by lower values)												
1[1]	randomised trials	serious[2]	Not applicable	no serious indirectness	serious[3]	none	55	59	MD 0.20 higher (95% CI 0.11 lower to 0.51 higher)		⊕⊕OO 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[3]	none	173	70	SMD 0.53 higher (95% CI 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[3]	none	173	170	SMD 0.07 lower (95% CI 0.29 lower to 0.14 higher)		⊕⊕OO LOW	CRITICAL
Antibiotic use: back-up antibiotics (return for prescription) versus immediate antibiotics												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	no serious imprecision	none	55/176 (31.3%)	210/211 (99.5%)	OR 0 (95% CI 0 to 0.02) NICE analysis: RR 0.31 (95% CI 0.25 to 0.39)	995 fewer per 1000 (from 188 fewer to 995 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Patient satisfaction: back-up antibiotics (return for prescription) versus immediate antibiotics												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	no serious imprecision	none	165/177 (93.2%)	202/211 (95.7%)	OR 0.61 (95% CI 0.25 to 1.49) NICE analysis: RR 0.97 (95% CI 0.93 to 1.02)	25 fewer per 1000 (from 109 fewer to 14 more)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events, back-up antibiotics versus immediate antibiotics: Vomiting												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	no serious imprecision	none	57/118 (48.3%)	4/111 (3.6%)	OR 25 (95% CI 8.65 to 72.25) NICE analysis: RR 13.4 (95% CI 5.03 to 35.7)	447 more per 1000 (from 208 more to 694 more)	⊕⊕⊕O MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Back-up prescription	Immediate antibiotics	Relative (95% CI)	Absolute		
Adverse events, back-up antibiotics versus immediate antibiotics: Diarrhoea												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[4]	none	23/179 (12.8%)	23/215 (10.7%)	OR 1.23 (95% CI 0.67 to 2.28) NICE analysis: RR 1.20 (95% CI 0.70 to 2.07)	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]	not applicable	no serious indirectness	very serious[4]	none	11/180 (6.1%)	14/215 (6.5%)	OR 0.93 (95% CI 0.41 to 2.11) NICE analysis: RR 0.94 (95% CI 0.44 to 2.02)	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]	not applicable	no serious indirectness	serious[5]	none	48/180 (26.7%)	66/215 (30.7%)	OR 0.82 (95% CI 0.53 to 1.27) NICE analysis: RR 0.87 (95% CI 0.63 to 1.19)	41 fewer per 1000 (from 117 fewer to 53 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI, Confidence interval; MD, Mean difference; SMD, Standard Mean Difference; N/A; OR, Odds ratio; RR, Relative risk												

[1] Spurling et al. (2013)
[2] Downgraded 1 level - assessed by Cochrane authors as being at high risk of bias
[3] Downgraded 1 level – at a default MID of 0.5 SD of control (immediate antibiotics) data suggest there is no meaningful difference with intervention or appreciable harm with immediate antibiotics
[4] Downgraded 2 levels - at a 95% confidence interval, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[5] Downgraded 1 level – at a default minimal important difference (MID) of 25% data are consistent with no meaningful difference or appreciable harm with immediate antibiotics

Table 26: GRADE profile – back-up antibiotic prescription versus no antibiotic in adults and children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Back-up prescription	No antibiotics	Relative (95% CI)	Absolute		
Antibiotic use: delayed (return for prescription) versus no antibiotics												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	no serious imprecision	none	55/176 (31.3%)	23/184 (12.5%)	OR 3.18 (95% CI 1.85 to 5.46) NICE analysis: RR 2.50 (95% CI 1.61 to 3.88)	187 more per 1000 (from 84 more to 313 more)	⊕⊕⊕O MODERATE	CRITICAL
Patient satisfaction: delayed (return for prescription) versus no antibiotics												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Back-up prescription	No antibiotics	Relative (95% CI)	Absolute		
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	no serious imprecision	none	165/177 (93.2%)	166/184 (90.2%)	OR 1.49 (95% CI 0.70 to 3.19) NICE analysis: RR 1.03 (95% CI 0.97 to 1.10)	30 more per 1000 (from 36 fewer to 65 more)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events, delayed versus no antibiotics: Vomiting												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	15/179 (8.4%)	22/186 (11.8%)	OR 0.68 (95% CI 0.34 to 1.36) NICE analysis: RR 0.71 (95% CI 0.38 to 1.32)	35 fewer per 1000 (from 75 fewer to 36 more)	⊕OOO VERY LOW	CRITICAL
Adverse events, delayed versus no antibiotics: Diarrhoea												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[4]	none	23/179 (12.8%)	16/186 (8.6%)	OR 1.57 (95% CI 0.8 to 3.07) NICE analysis: RR 1.49 (95% CI 0.82 to 2.73)	43 more per 1000 (from 16 fewer to 138 more)	⊕⊕OO LOW	CRITICAL
Adverse events, delayed versus no antibiotics: Rash												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[5]	none	11/179 (6.1%)	21/186 (11.3%)	OR 0.51 (95% CI 0.24 to 1.10) NICE analysis: RR 0.54 (95% CI 0.27 to 1.10)	52 fewer per 1000 (from 83 fewer to 10 more)	⊕⊕OO LOW	CRITICAL
Adverse events, delayed versus no antibiotics: Stomach ache												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	48/179 (26.8%)	52/186 (28%)	OR 0.94 (95% CI 0.60 to 1.50) NICE analysis: RR 0.96 (95% CI 0.69 to 1.34)	12 fewer per 1000 (from 91 fewer to 88 more)	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI, Confidence interval; OR, Odds ratio; RR, Relative risk

[1] Spurling et al. (2013)
[2] Downgraded 1 level - assessed by Cochrane authors as being at high risk of bias
[3] Downgraded 2 levels - at a 95% confidence interval, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[4] Downgraded 1 level - at a 95% confidence interval, data are consistent with no meaningful difference or appreciable harm with delayed prescription
[5] Downgraded 1 level - at a 95% confidence interval, data are consistent with no meaningful difference or appreciable harm with no antibiotics

H.6 Antibiotics

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

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 (95% CI 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 (95% CI 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 (95% CI 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 (95% CI 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 (95% CI 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 (95% CI 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 (95% CI 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 (95% CI 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)												

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		
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 (95% CI 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 (95% CI 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 (95% CI 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 (95% CI 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	very serious[8]	none	1/1210 (0.08%)	5/713 (0.7%)	RR 0.28 (95% CI 0.03 to 2.74)	5 fewer per 1000 (from 7 fewer to 12 more)	⊕⊕OO LOW	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	very serious[8]	none	4/1545 (0.26%)	4/842 (0.48%)	RR 0.48 (95% CI 0.08 to 2.76)	2 fewer per 1000 (from 4 fewer to 8 more)	⊕⊕OO LOW	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%)[9]	23/995 (2.3%)[9]	RR 0.15 (95% CI 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[10]	no serious inconsistency	no serious indirectness	very serious[8]	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)	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI, Confidence interval; RR, Relative risk

[1] Antibiotics included: penicillins, sulfonamides, macrolides, cephalosporins 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 harm with placebo
[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] Downgraded 2 levels – at a default minimal important difference (MID) of 25% data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[9] 16/25 (64%) of the total cases of quinsy reported from a single RCT published in 1951
[10] 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 (95% CI 0.45 to 0.14 lower)		⊕⊕⊕O MODERATE	CRITICAL
Duration of sore throat (Better indicated by lower values)												
1[3]	randomised trials	serious[4]	not applicable	no serious indirectness	serious[5]	none	88	100	MD 0.5 lower (95% CI 0.78 to 0.22 lower)		⊕⊕OO LOW	CRITICAL
Early clinical treatment failure												
23[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	316/6197 (5.1%)	335/5516 (6.1%)	OR 0.8 (95% CI 0.67 to 0.94) NICE analysis: RR 0.81 (95% CI 0.69 to 0.95)	12 fewer per 1000 (from 3 fewer to 19 fewer)	⊕⊕OO LOW	CRITICAL
Late clinical recurrence												
17[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 (95% CI 0.83 to 1.08) NICE analysis: RR 0.96 (95% CI 0.86 to 1.06)	6 fewer per 1000 (from 20 fewer to 9 more)	⊕⊕⊕O MODERATE	CRITICAL
Side effects												
21[3]	randomised trials	serious[4]	serious[6]	no serious indirectness	no serious imprecision	none	348/3480 (10%)	210/4517 (4.6%)	OR 1.85 (95% CI 1.55 to 2.21) NICE analysis: RR 1.74 (95% CI 1.31 to 2.32)	40 more per 1000 (from 26 more to 56 more)	⊕⊕OO LOW	CRITICAL
Non-compliance												
6[3]	randomised trials	serious[4]	serious[6]	no serious indirectness	no serious imprecision	none	61/960 (6.4%)	225/949 (23.7%)	OR 0.21 (95% CI 0.16 to 0.29) NICE analysis: RR 0.28 (95% CI 0.17 to 0.46)	176 fewer per 1000 (from 154 fewer to 190 fewer)	⊕⊕OO LOW	IMPORTANT

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		
Complications												
3[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[7]	none	6/5119 (0.12%)	8/3016 (0.27%)	OR 0.53 (95% CI 0.17 to 1.64) NICE analysis: RR 0.54 (95% CI 0.17 to 1.67)	1 fewer per 1000 (from 2 fewer to 2 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI, Confidence interval; MD, Mean difference; OR, Odds ratio; RR, Relative risk												

[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 - at 95% confidence interval, data are consistent with no meaningful difference or appreciable harm with longer term penicillin
[6] Downgraded 1 level - heterogeneity >50%
[7] Downgraded 2 levels - at a 95% confidence interval, data are consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 29: GRADE profile – cephalosporin versus penicillin in adults and 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	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 (95% CI 0.55 to 1.12) NICE analysis: RR 0.86 (95% CI 0.74 to 1.00)	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	serious[3]	none	52/935 (5.6%)	81/725 (11.2%)	OR 0.51 (95% CI 0.27 to 0.97) NICE analysis: RR 0.54 (95% CI 0.33 to 0.99)	51 fewer per 1000 (from 3 fewer to 79 fewer)	⊕OOO VERY LOW	CRITICAL
Incidence of relapse (evaluable participants)												
4[1]	randomised trials	serious[2,4]	no serious inconsistency	no serious indirectness	serious[6]	none	22/797 (2.8%)	27/589 (4.6%)	OR 0.55 (95% CI 0.3 to 0.99) NICE analysis: RR 0.57 (95% CI 0.33 to 0.99)	20 fewer per 1000 (from 0 fewer to 32 fewer)	⊕⊕OO LOW	CRITICAL

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		
Complications (ITT analysis)												
1[1]	randomised trials	serious[2]	not applicable	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.		⊕⊕OO 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 (95% CI 0.27 to 3.25) NICE analysis: RR 0.94 (95% CI 0.36 to 2.49)	9 fewer per 1000 (from 133 fewer to 245 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI, Confidence interval; OR, Odds ratio; RR, Relative risk; ITT, Intention to treat												

[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 penicillin
[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 – at a 95% confidence interval, data are consistent with no meaningful difference or appreciable harm with penicillin
[7] Downgraded 1 level - not assessable
[8] Downgraded 2 levels - at a 95% confidence interval, data are consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 30: GRADE profile – macrolide versus penicillin in adults and 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	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	no serious imprecision	none	420/952 (44.1%)	328/776 (42.3%)	OR 1.11 (95% CI 0.92 to 1.35) NICE analysis: RR 1.06 (95% CI 0.95 to 1.19)	26 more per 1000 (from 20 fewer to 74 more)	⊕⊕⊕O MODERATE	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 (95% CI 0.57 to 1.09) NICE analysis: RR 0.82 (95% CI 0.63 to 1.07)	31 fewer per 1000 (from 66 fewer to 13 more)	⊕⊕OO LOW	CRITICAL
Incidence of relapse (evaluable participants)												

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		
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 (95% CI 0.48 to 3.03) NICE analysis: RR 1.21 (95% CI 0.64 to 2.29)	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 (95% CI 0.82 to 1.73) NICE analysis: RR 1.11 (95% CI 0.88 to 1.39)	39 more per 1000 (from 42 fewer to 129 more)	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI, Confidence interval; OR, Odds ratio; RR, Relative risk; ITT, Intention to treat

[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 or appreciable harm
[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 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	Azithromycin	Amoxicillin	Relative (95% CI)	Absolute		
Clinical cure at 24-28 days (ITT)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	98/337 (29.1%)	118/336 (35.1%)	OR 0.76 (95% CI 0.55 to 1.05) NICE analysis: RR 0.83 (95% CI 0.66 to 1.03)	60 fewer per 1000 (from 122 fewer to 162 more)	⊕⊕OO LOW	CRITICAL
Clinical cure at 24-28 days (bacteriological per protocol population)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	6/245 (2.4%)	19/237 (8%)	OR 0.29 (95% CI 0.11 to 0.73) NICE analysis: RR 0.31 (95% CI 0.12 to 0.75)	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]	not applicable	no serious indirectness	serious[4]	none	130/337 (38.6%)	153/336 (45.5%)	OR 0.75 (95% CI 0.55 to 1.02)			CRITICAL

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		
									NICE analysis: RR 0.85 (95% CI 0.71 to 1.01)	70 fewer per 1000 (from 140 fewer to 5 more)	⊕⊕OO LOW	
Relapse on day 38-45 (bacteriological per protocol)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[5]	none	16/223 (7.2%)	16/199 (8%)	OR 0.88 (95% CI 0.43 to 1.82) NICE analysis: RR 0.89 (95% CI 0.46 to 1.74)	9 fewer per 1000 (from 44 fewer to 57 more)	⊕OOO VERY LOW	CRITICAL
Adverse events (all participants)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	no serious imprecision	none	93/337 (27.6%)	42/336 (12.5%)	OR 2.67 (95% CI 1.78 to 3.99) NICE analysis: RR 2.21 (95% CI 1.58 to 3.99)	151 more per 1000 (from 78 more to 238 more)	⊕⊕⊕O MODERATE	CRITICAL
Abbreviations: CI, Confidence interval; OR, Odds ratio; RR, Relative risk; ITT, Intention to treat												

[1] van Driel et al. (2016)
[2] Downgraded 1 - high risk of bias (assessed by Cochrane authors)
[3] Downgraded 1 level – at a default minimal important difference (MID) of 25% data are consistent with no meaningful difference or appreciable benefit with amoxicillin
[4] Downgraded 1 level - at a 95% confidence interval, data are consistent with no meaningful difference or appreciable harm with amoxicillin
[5] Downgraded 2 levels - at a 95% confidence interval, data are consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 32: GRADE profile – clindamycin versus ampicillin 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	Clindamycin	Ampicillin	Relative (95% CI)	Absolute		
Adverse events (ITT analysis)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	6/156 (3.8%)	14/158 (8.9%)	OR 0.41 (95% CI 0.15 to 1.1) NICE analysis: RR 0.43 (95% CI 0.17 to 1.10)	50 fewer per 1000 (from 74 fewer to 8 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI, Confidence interval; OR, Odds ratio; RR, Relative risk; ITT, Intention to treat												

[1] van Driel et al. (2016)
[2] Downgraded 1 level - high risk of bias (assessed by Cochrane authors)
[3] Downgraded 1 level - at a 95% confidence interval, data are consistent with no meaningful difference or appreciable harm with ampicillin

Table 33: GRADE profile – sulfonamide versus penicillin in adults 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	Sulfonamide	Penicillin	Relative (95% CI)	Absolute		
Adverse events (ITT analysis)												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[2]	none	8/44 (18.2%)	6/43 (14%)	OR 1.37 (95% CI 0.43 to 4.34) NICE analysis: RR 1.30 (95% CI 0.49 to 3.44)	42 more per 1000 (from 74 fewer to 274 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI, Confidence interval; OR, Odds ratio; RR, Relative risk; ITT, Intention to treat												

[1] van Driel et al. (2016)
[2] Downgraded 2 levels - at a 95% confidence interval, data are consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 34: GRADE profile – penicillin V once daily versus penicillin V three or four times daily in adults and 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	Penicillin V once daily	Penicillin V 3 or 4 times daily			
Bacteriological cure at follow-up (follow-up 1 to 14 days)											
2[1]	randomised trials	serious[2]	no serious inconsistency[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).	⊕⊕OO LOW	CRITICAL
2[1]	randomised trials	serious[2]	no serious inconsistency[5]	no serious indirectness	serious[6]	none	111/122	95/122	NICE analysis: RR 1.17 (95% CI 1.05 to 1.30, p=0.006, I^2=46%)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI, Confidence interval; RR, Relative risk											

[1] Lan and Colford (2008)
[2] Downgraded 1 level - not assessable, authors did not report on bias for included studies
[3] Not downgraded - the authors reported significant heterogeneity, however in the NICE reanalysis the I^2=38% (random effects model used)
[4] Downgraded 1 level – authors analysis not assessable
[5] Not downgraded – Heterogeneity (I^2) >50%, fixed effect model used
[6] Downgraded 1 level – at a default minimal important difference (MID) of 25% data are consistent with no meaningful difference or appreciable benefit with penicillin V once daily

Table 35: GRADE profile – penicillin V twice daily versus penicillin V three or four times daily in adults and 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	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 in adults and 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	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]	serious[3]	no serious indirectness	no serious imprecision	none	205/236 (86.9%)	250/264 (94.7%)	OR 0.36 (95% CI 0.13 to 0.99) NICE analysis: RR 0.92 (95% CI 0.82 to 1.04)	82 fewer per 1000 (from 1 fewer to 248 fewer)	⊕OOO LOW	CRITICAL
Clinical cure												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	55/67 (82%)	66/70 (94%)	NICE analysis: RR 0.87 (95% CI 0.77 to 0.99, p=0.03)	-	⊕⊕OO MODERATE	CRITICAL
Recurrence												
1[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	6/66 (9%)	1/68 (1%)	NICE analysis: RR 6.18 (95% CI 0.76 to 49.97, p=0.09)	-	⊕OOO VERY LOW	CRITICAL
Relapse												
2[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[5]	none	43/163 (26.4%)	20/165 (12.1%)	NICE analysis: RR 2.48 (95% CI 0.83 to 7.39, p=0.10)	-	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI, Confidence interval; MD, Mean difference; N/A, Not applicable; OR, Odds ratio; RCT, Randomised controlled trial; RR, Relative risk; SD, Standard deviation												

[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 – Heterogeneity in RR NICE analysis (I^2 >50%)
[4] Downgraded 2 levels – at a 95% confidence interval, data are consistent with no meaningful difference or appreciable harm with penicillin V 5 to 7 days; very wide 95% CI
[5] Downgraded 2 levels – at a default minimal important difference (MID) of 25% data are consistent with no meaningful difference or appreciable harm with penicillin V for 5 to 7 days

H.7 Identifying people more likely to benefit from an antibiotic

Table 37: GRADE profile – FeverPAIN score plus rapid antigen testing versus back-up antibiotic prescription in adults and children over 3 years

Quality assessment							Effect			Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FeverPAIN plus Rapid antigen testing (n=213)	Back-up prescription (control) (n=207)	Absolute		
Mean score of sore throat and difficulty swallowing for the 2 to 4 days after the consultation, 7 point score: 0= no problem, 6= as bad as could be (standard deviation)											
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	serious[3]	none	2.83 (1.62)	3.11 (1.49)	Adjusted mean difference[4] -0.30 (95% CI -0.61 to 0.004)	⊕⊕OO LOW	CRITICAL
Median duration of symptoms rated moderately bad or worse, days (interquartile range)											
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	serious[5]	none	4 (2 to 7)	5 (3 to 7)	Hazard ratio: 1.11[4] (95% CI 0.88 to 1.40; p=0.37)	⊕⊕OO LOW	CRITICAL
Antibiotic use											
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	serious[5]	none	58/164 (35%)	75/164 (46%)	Risk ratio: 0.73[4] (95% CI 0.52 to 0.98; p=0.03)	⊕⊕OO LOW	CRITICAL
Belief in need to see doctor in future (slightly likely or less)											
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	serious[6]	none	64/161 (40%)	62/163 (38%)	Risk ratio: 1.03[4] (95% CI 0.76 to 1.32, p=0.86)	⊕⊕OO LOW	IMPORTANT
Return within 1 month with sore throat											
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	very serious[7]	none	13/212 (6%)	17/207 (8%)	Risk ratio: 1.06[4] (95% CI 0.66 to 1.63, p=0.81)	⊕OOO VERY LOW	CRITICAL
Suppurative complications											
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	very serious[7]	none	1/211 (0.5%)	0/207 (0%)	NICE analysis: risk ratio: 2.94 (95% CI 0.12 to 71.84)	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI, Confidence interval; N/A, Not applicable; RR, Relative risk

[1] Little et al. 2013
[2] Downgraded 1 level – risk of recruitment bias
[3] Downgraded 1 level – at a default minimal important difference (MID) of 0.5 SD of control for continuous data are consistent with no meaningful difference or appreciable harm with back-up prescription
[4] Adjusted for baseline symptom severity

[5] Downgraded 1 level – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable harm with back-up prescription
[6] Downgraded 1 level – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit with FeverPAIN plus Rapid antigen testing
[7] Downgraded 2 levels – at a default minimal important difference (MID) of 25% data are consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 38: GRADE profile – FeverPAIN score versus back-up antibiotic prescription in adults and children over 3 years

Quality assessment							Effect			Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	FeverPAIN (n=211)	Back-up prescription (control) (n=207)	Absolute		
Mean score of sore throat and difficulty swallowing for the 2 to 4 days after the consultation, 7 point score: 0= no problem, 6= as bad as could be (standard deviation)											
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	no serious imprecision	none	2.88 (1.52)	3.11 (1.49)	Adjusted mean difference[3] -0.33 (95% CI -0.64 to -0.02, p=0.04)	⊕⊕⊕O MODERATE	CRITICAL
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	no serious imprecision	none	2.88 (1.52)	3.11 (1.49)	Adjusted mean difference[3, 4] -0.33 (95% CI -0.64 to -0.02, p=0.04)	⊕⊕⊕O MODERATE	CRITICAL
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	no serious imprecision	none	2.88 (1.52)	3.11 (1.49)	Adjusted mean difference[3, 5] -0.33 (95% CI -0.74 to -0.05, p=0.08)	⊕⊕⊕O MODERATE	CRITICAL
Median duration of symptoms rated moderately bad or worse, days (interquartile range)											
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	serious[3]	none	4 (2 to 6)	5 (3 to 7)	Hazard ratio: 1.30[4] (95% CI 1.03 to 1.63; p=0.03)	⊕⊕OO LOW	CRITICAL
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	serious[3]	none	4 (2 to 6)	5 (3 to 7)	Hazard ratio: 1.29[4, 5] (95% CI 1.02 to 1.63, p=0.03)	⊕⊕OO LOW	CRITICAL
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	serious[3]	none	4 (2 to 6)	5 (3 to 7)	Hazard ratio: 1.30[4, 6] (95% CI 1.07 to 1.57, p=0.01)	⊕⊕OO LOW	CRITICAL
Antibiotic use											
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	serious[3]	none	60/161 (37%)	75/164 (46%)	Risk ratio: 0.71[4] (95% CI 0.50 to 0.95; p=0.02)	⊕⊕OO LOW	CRITICAL
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	serious[3]	none	60/161 (37%)	75/164 (46%)	Risk ratio: 0.[4, 5] (95% CI 0.48 to 0.94, p=0.02)	⊕⊕OO LOW	CRITICAL
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	serious[3]	none	60/161 (37%)	75/164 (46%)	Risk ratio: 0.71[4, 6] (95% CI 0.51 to 1.00, p=0.01)	⊕⊕OO LOW	CRITICAL
Belief in need to see doctor in future (slightly likely or less)											
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	very serious[7]	none	54/155 (35%)	62/163 (38%)	Risk ratio: 0.97[4] (95% CI 0.71 to 1.27, p=0.85)	⊕OOO VERY LOW	IMPORTANT
Return within 1 month with sore throat											
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	very serious[7]	none	17/210 (8%)	17/207 (8%)	Risk ratio: 0.91[4] (95% CI 0.47 to 1.72, p=0.78)	⊕OOO VERY LOW	CRITICAL
Adverse events (skin rash or diarrhoea)											
1[1]	randomised trials	serious[2]	N/A	no serious indirectness	very serious[7]	none	2/210 (1.0%)	0/207 (0%)	NICE analysis: risk ratio: 4.93 (95% CI 0.24 to 102.05)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI, Confidence interval; N/A, Not applicable											

[1] Little et al. 2013
[2] Downgraded 1 level – risk of recruitment bias
[3] Downgraded 1 level – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable harm with back-up prescription
[4] Adjusted for baseline symptom severity
[5] Adjusted for practice as covariate
[6] Adjusted for clustering by practice
[7] Downgraded 2 levels – at a minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm

Appendix I: Studies not-prioritised

Study reference	Reason
Adam D, Scholz H, and Helmerking M (2000) Short-course antibiotic treatment of 4782 culture-proven cases of group A streptococcal tonsillopharyngitis and incidence of poststreptococcal sequelae. The Journal of infectious diseases 182(2), 509-16	RCT included in a systematic review that has been prioritised.
Aguilar A, Tinoco J C, Macias M, Huicho L, Levy J, Trujillo H, Lopez P, Pereira M, Maqbool S, Bhutta Z A, Sacy R A, and Deacon S (2000) Clinical and bacteriologic efficacy of amoxycillin b.d. (45 mg/kg/day) Versus Amoxycillin t.d.s (40 mg/kg/day) in children with group A beta-hemolytic streptococcal tonsillopharyngitis. Journal of Chemotherapy 12(5), 396-405	Systematic review has been prioritised.
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	More recent systematic review has been prioritised.
Aspley Sue, Shephard Adrian, Schachtel Emily, Sanner Kathleen, Savino Laurie, and Schachtel Bernard (2016) Efficacy of flurbiprofen 8.75mg lozenge in patients with a swollen and inflamed sore throat. Current medical research and opinion 32(9), 1529-38	Secondary analysis of a primary RCT that has been prioritised.
Berezin E N, Garcia de Quevedo, S , Nicolla L, Viegas D, Eizenberg B, Pedrosa F, and Santos A G (2003) Comparative study of cefaclor versus amoxicillin in the treatment of acute pharyngitis and/or tonsillitis. Antibiotiques 5(2), 83-87	Systematic review has been prioritised.
Block Stan L (2006) Comparative tolerability, safety and efficacy of tablet formulations of twice-daily clarithromycin 250 mg versus once-daily extended-release clarithromycin 500 mg in pediatric and adolescent patients. Clinical pediatrics 45(7), 641-8	Systematic review has been prioritised.
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	Systematic review has been prioritised.
Bulloch Blake, Kabani Amin, and Tenenbein Milton (2003) Oral dexamethasone for the treatment of pain in children with acute pharyngitis: a randomized, double-blind, placebo-controlled trial. Annals of emergency medicine 41(5), 601-8	RCT included in a systematic review that has been prioritised.
Casey J R, and Pichichero M E (2004) Meta-analysis of cephabsporins versus penicillin for treatment of group a streptococcal tonsillopharyngitis in adults. Clinical Infectious Diseases 38(11), 1526-1534	More recent systematic review has been prioritised.
Casey Janet R, and Pichichero Michael E (2004) Meta-analysis of cephalosporin versus penicillin treatment of group A streptococcal tonsillopharyngitis in children. Pediatrics 113(4), 866-82	More recent systematic review has been prioritised.
Casey Janet R, and Pichichero Michael E (2005) Higher dosages of azithromycin are more effective in treatment of group A streptococcal tonsillopharyngitis. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 40(12), 1748-55	Systematic review has been prioritised.
Casey Janet R, and Pichichero Michael E (2005) Metaanalysis of short course antibiotic treatment for group a streptococcal	More recent systematic review has been prioritised.

Study reference	Reason
tonsillopharyngitis. The Pediatric infectious disease journal 24(10), 909-17	
Clegg Herbert W, Ryan Amy G, Dallas Steven D, Kaplan Edward L, Johnson Dwight R, Norton H James, Roddey Oliver F, Martin Edward S, Swetenburg Raymond L, Koonce Elizabeth W, Felkner Mary M, and Giftos P Michael (2006) Treatment of streptococcal pharyngitis with once-daily compared with twice-daily amoxicillin: a noninferiority trial. The Pediatric infectious disease journal 25(9), 761-7	Systematic review has been prioritised.
Del Mar , C B, Glasziou P P, and Spinks A B (2000) Antibiotics for sore throat. The Cochrane database of systematic reviews (4), CD000023	More recent systematic review has been prioritised.
Del Mar , C B, Glasziou P P, and Spinks A B (2004) Antibiotics for sore throat. The Cochrane database of systematic reviews (2), CD000023	More recent systematic review has been prioritised.
Del Mar , C B, Glasziou P P, and Spinks A B (2006) Antibiotics for sore throat. The Cochrane database of systematic reviews (4), CD000023	More recent systematic review has been prioritised.
Esposito S (2000) Comparative Efficacy and Safety of Five-Day Cefaclor and Ten-Day Amoxicillin Treatment of Group A beta-hemolytic Streptococcal Pharyngitis in Children. Interscience Conference on Antimicrobial Agents and Chemotherapy 40, 454	Systematic review has been prioritised.
Gooch W M, Gehanno P, and Harris A M (2000) Cefuroxime axetil in short-course therapy of tonsillopharyngitis. A pooled analysis of 3308 patients receiving 5- or 10-day treatments compared with 10-day oral penicillin V. Clinical Drug Investigation 19(6), 421-430	Systematic review has been prioritised.
Haczynski J, Bardadin J, Gryczynska D, Gryczynski M, Golabek W, Kawalski H, Kazmierczak H, Krecicki T, Kubik P, Namyslowski G, and Popiel L (2001) A comparative study of cefaclor vs. amoxicillin/clavulanate in tonsillopharyngitis. Medical Science Monitor 7(5), 1016-1022	Systematic review has been prioritised.
Haczynski J, Chmielik M, Bien S, Kawalski H, Zawadzka-Glos L, Mierzwa T, Zylka S, Mos M, Szendo-Kita J, Mozejko-Pastewka B, Czarnocki K J, and Rek M (2003) A comparative study of cefaclor vs amoxicillin/clavulanate in pediatric pharyngotonsillitis. Medical Science Monitor 9(3), PI29-PI35	Systematic review has been prioritised.
Hayward Gail, Thompson Matthew, Heneghan Carl, Perera Rafael, Del Mar , Chris , and Glasziou Paul (2009) Corticosteroids for pain relief in sore throat: systematic review and meta-analysis. BMJ (Clinical research ed.) 339, b2976	More recent systematic review has been prioritised.
Ioannidis J P, Contopoulos-Ioannidis D G, Chew P, and Lau J (2001) Meta-analysis of randomized controlled trials on the comparative efficacy and safety of azithromycin against other antibiotics for upper respiratory tract infections. The Journal of antimicrobial chemotherapy 48(5), 677-89	Systematic review has been prioritised.
Kafetzis Dimitris A, Liapi Georgia, Tsolia Mariza, Aoudi Hana, Mathioudakis John, Paraskakis Irene, and Bairamis Theodore (2004) Failure to eradicate Group A beta-haemolytic streptococci (GABHS) from the upper respiratory tract after antibiotic treatment. International journal of antimicrobial agents 23(1), 67-71	RCT included in a systematic review that has been prioritised.
Kaplan E L, and Johnson D R (2001) Unexplained reduced microbiological efficacy of intramuscular benzathine penicillin G and	Systematic review has been prioritised.

Study reference	Reason
of oral penicillin V in eradication of group a streptococci from children with acute pharyngitis. Pediatrics 108(5), 1180-6	
Kenealy Tim (2007) Sore throat. BMJ clinical evidence 2007,	More recent systematic review has been prioritised.
Kenealy Tim (2014) Sore throat. BMJ clinical evidence 2014,	More recent systematic review has been prioritised.
Kiderman A, Yaphe J, Bregman J, Zemel T, and Furst A L (2005) Adjuvant prednisone therapy in pharyngitis: A randomised controlled trial from general practice. British Journal of General Practice 55(512), 218-221	RCT included in a systematic review that has been prioritised.
Korb Katrin, Scherer Martin, and Chenot Jean-Francois (2010) Steroids as adjuvant therapy for acute pharyngitis in ambulatory patients: a systematic review. Annals of family medicine 8(1), 58-63	Lower quality systematic review (includes lower quality RCTs).
Kuroki Haruo, Ishiwada Naruhiko, Inoue Nobue, Ishikawa Nobuyasu, Suzuki Hiroshi, Himi Kyoko, and Kurosaki Tomomichi (2013) Comparison of clinical efficacy between 3-day combined clavulanate/amoxicillin preparation treatment and 10-day amoxicillin treatment in children with pharyngolaryngitis or tonsillitis. Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy 19(1), 12-9	Systematic review has been prioritised.
Leelarasamee A, Leowattana W, Tobunluepop P, Chub-upakarn S, Artavetakun W, Jarupoonphol V, Varangphongsri K, and Leelarasamee I (2000) Amoxicillin for fever and sore throat due to non-exudative pharyngotonsillitis: Beneficial or harmful?. International Journal of Infectious Diseases 4(2), 70-74	RCT included in a systematic review that has been prioritised.
Lennon D R, Farrell E, Martin D R, and Stewart J M (2008) Once-daily amoxicillin versus twice-daily penicillin V in group A beta-haemolytic streptococcal pharyngitis. Archives of disease in childhood 93(6), 474-8	Systematic review has been prioritised.
Llor C, Madurell J, Balague-Corbella M, Gomez M, and Cots J M (2011) Impact on antibiotic prescription of rapid antigen detection testing in acute pharyngitis in adults: A randomised clinical trial. British Journal of General Practice 61(586), e244-e251	Low relevance to current UK practice (Spanish study; insufficient details of standard care)
Mahakit Prasit, Vicente Jose Gil, Butt D Iqbal, Angeli German, Bansal Sanjay, and Zambrano David (2006) Oral clindamycin 300 mg BID compared with oral amoxicillin/clavulanic acid 1 g BID in the outpatient treatment of acute recurrent pharyngotonsillitis caused by group a beta-hemolytic streptococci: an international, multicenter, randomized, investigator-blinded, prospective trial in patients between the ages of 12 and 60 years. Clinical therapeutics 28(1), 99-109	Systematic review has been prioritised.
Marvez-Valls Eduardo G, Stuckey Ashley, and Ernst Amy A (2002) A randomized clinical trial of oral versus intramuscular delivery of steroids in acute exudative pharyngitis. Academic emergency medicine : official journal of the Society for Academic Emergency Medicine 9(1), 9-14	RCT included in a systematic review that has been prioritised.
McCarty J, Hedrick J A, and Gooch W M (2000) Clarithromycin suspension vs penicillin V suspension in children with streptococcal pharyngitis. Advances in therapy 17(1), 14-26	RCT included in a systematic review that has been prioritised.
Mullarkey C (2011) Soothing a sore throat: the efficacy and safety of steroids in acute pharyngitis. Irish journal of medical science 180(4), 837-40	More recent systematic review has been prioritised.

Study reference	Reason
Olympia R P, Khine H, and Avner J R (2005) Effectiveness of oral dexamethasone in the treatment of moderate to severe pharyngitis in children. Archives of Pediatrics and Adolescent Medicine 159(3), 278-282	RCT included in a systematic review that has been prioritised.
Pichichero Michael E, and Casey Janet R (2007) Bacterial eradication rates with shortened courses of 2nd- and 3rd-generation cephalosporins versus 10 days of penicillin for treatment of group A streptococcal tonsillopharyngitis in adults. Diagnostic microbiology and infectious disease 59(2), 127-30	More recent systematic review has been prioritised.
Portier Henri, Filipecki Jamila, Weber Philippe, Goldfarb Gerard, Lethuaire Denis, and Chauvin Jean-Pierre (2002) Five day clarithromycin modified release versus 10 day penicillin V for group A streptococcal pharyngitis: a multi-centre, open-label, randomized study. The Journal of antimicrobial chemotherapy 49(2), 337-44	Systematic review has been prioritised.
Rimoin Anne W, Hoff Nicole A, Fischer Walker, Christa L, Hamza Hala S, Vince Adriana, Abdel Rahman, Naglaa , Andrasevic Sasa, Emam Soha, Vukelic Dubravka, Elminawi Nevine, Abdel Ghafar, Hadeer , da Cunha , Antonia L A, Qazi Shamim, Gardovska Dace, and Steinhoff Mark C (2011) Treatment of streptococcal pharyngitis with once-daily amoxicillin versus intramuscular benzathine penicillin G in low-resource settings: a randomized controlled trial. Clinical pediatrics 50(6), 535-42	Systematic review has been prioritised.
Schaad Urs B, Kellerhals Patricia, Altwegg Martin, Swiss Pharyngitis Study, and Group (2002) Azithromycin versus penicillin V for treatment of acute group A streptococcal pharyngitis. The Pediatric infectious disease journal 21(4), 304-8	RCT included in a systematic review that has been prioritised.
Schachtel Bernard P, Shephard Adrian, Shea Timothy, Sanner Kathleen, Savino Laurie, Rezuke Jeanne, Schachtel Emily, and Aspley Sue (2016) Flurbiprofen 8.75 mg lozenges for treating sore throat symptoms: a randomized, double-blind, placebo-controlled study. Pain management 6(6), 519-529	More recent RCT has been prioritised.
Scholz Horst (2004) Streptococcal-A tonsillopharyngitis: a 5-day course of cefuroxime axetil versus a 10-day course of penicillin V. results depending on the children's age. Chemotherapy 50(1), 51-4	RCT included in a systematic review that has been prioritised.
Shephard A, Smith G, Aspley S, and Schachtel B P (2015) Randomised, double-blindlacebo-controlled studies on flurbiprofen 8.75 mg lozenges in patients with/without group A or C streptococcal throat infection, with an assessment of clinicians' prediction of 'strep throat'. International Journal of Clinical Practice 69(1), 59-71	Secondary analysis of a primary RCT that has been prioritised.
Spurling G K. P, Del Mar , C B, Dooley L, and Foxlee R (2004) Delayed antibiotics for symptoms and complications of respiratory infections. The Cochrane database of systematic reviews (4), CD004417	More recent systematic review has been prioritised.
Spurling G K. P, Del Mar , C B, Dooley L, and Foxlee R (2007) Delayed antibiotics for respiratory infections. The Cochrane database of systematic reviews (3), CD004417	More recent systematic review has been prioritised.
Syrogiannopoulos George A, Bozdogan Bulent, Grivea Ioanna N, Ednie Lois M, Kritikou Dimitra I, Katopodis George D, Beratis Nicholas G, Applebaum Peter C, Hellenic Antibiotic-Resistant Respiratory Pathogens Study, and Group (2004) Two dosages of clarithromycin for five days, amoxicillin/clavulanate for five days or penicillin V for ten days in acute group A streptococcal	RCT included in a systematic review that has been prioritised.

Study reference	Reason
tonsillopharyngitis. The Pediatric infectious disease journal 23(9), 857-65	
Takker Urmas, Dzyublyk Oleksandr, Busman Todd, and Notario Gerard (2003) Comparison of 5 days of extended-release clarithromycin versus 10 days of penicillin V for the treatment of streptococcal pharyngitis/tonsillitis: results of a multicenter, double-blind, randomized study in adolescent and adult patients. Current medical research and opinion 19(5), 421-9	Systematic review has been prioritised.
Tasar Ali, Yanturali Sedat, Topacoglu Hakan, Ersoy Gurkan, Unverir Pinar, and Sarikaya Sezgin (2008) Clinical efficacy of dexamethasone for acute exudative pharyngitis. The Journal of emergency medicine 35(4), 363-7	RCT included in a systematic review that has been prioritised.
Uysal S, Sancak R, and Sunbul M (2000) A comparison of the efficacy of cefuroxime axetil and intramuscular benzathine penicillin for treating streptococcal tonsillopharyngitis. Annals of tropical paediatrics 20(3), 199-202	Systematic review has been prioritised.
van Driel , Mieke L, De Sutter , An I M, Keber Natalija, Habraken Hilde, and Christiaens Thierry (2013) Different antibiotic treatments for group A streptococcal pharyngitis. The Cochrane database of systematic reviews 4, CD004406	More recent systematic review has been prioritised.
van Driel , Mieke L, De Sutter , An Im, Keber Natalija, Habraken Hilde, and Christiaens Thierry (2010) Different antibiotic treatments for group A streptococcal pharyngitis. The Cochrane database of systematic reviews (10), CD004406	More recent systematic review has been prioritised.
Wei Julie L, Kasperbauer Jan L, Weaver Amy L, and Boggust Andrew J (2002) Efficacy of single-dose dexamethasone as adjuvant therapy for acute pharyngitis. The Laryngoscope 112(1), 87-93	RCT included in a systematic review that has been prioritised.
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	Lower quality systematic review (includes lower quality RCTs).
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	More recent RCT has been prioritised.
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	RCT included in a systematic review that has been prioritised.
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	RCT included in a systematic review that has been prioritised.

Appendix J: 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
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	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
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

Study reference	Reason for exclusion
Anonymous (2000) WHO model prescribing information: Streptococcal pharyngitis and prevention of rheumatic fever. WHO Drug Information 14(2), 99-104	Publication/study type
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	Population
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 Bp, Berry P, Shephard A, Sanner Km, Savino L, Rezuke J, Shea T, and Smith G (2012) Treatment of odynophagia and dysphagia by flurbipro fen 8.75 mg lo zenges. 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
Billings K R, and Maddalozzo J (2013) Complementary and Integrative Treatments: Adenotonsillar Disease. Otolaryngologic Clinics of North America 46(3), 329-334	Intervention
Bird J H, Biggs T C, and King E V (2014) Controversies in the management of acute tonsillitis: an evidence-based review. Clinical	Publication/study type

Study reference	Reason for exclusion
otolaryngology : official journal of ENT-UK, and official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery 39(6), 368-74	
Bisno A L (2001) Primary care: Acute pharyngitis. New England Journal of Medicine 344(3), 205-211	Publication/study type
Bisno A L, Gerber M A, Gwaltney Jr, J M, Kaplan E L, and Schwartz R H (2002) Practice guidelines for the diagnosis and management of group A streptococcal pharyngitis. Clinical Infectious Diseases 35(2), 113-125	Publication/study type
Bisno Alan L, Peter Garnet S, and Kaplan Edward L (2002) Diagnosis of strep throat in adults: are clinical criteria really good enough?. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 35(2), 126-9	Publication/study type
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

Study reference	Reason for exclusion
Brook Itzhak (2002) Anaerobic bacteria in upper respiratory tract and other head and neck infections. The Annals of otology, rhinology, and 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 (2007) Cephalosporins in overcoming beta-lactamase-producing bacteria and preservation of the interfering bacteria in the treatment of otitis, sinusitis and tonsillitis. Expert review of anti-infective therapy 5(6), 939-50	Publication/study type
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 J J, and Cohen S J (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
Chenot Jean-Francois, Weber Peter, and Friede Tim (2014) Efficacy of Ambroxol lozenges for pharyngitis: a meta-analysis. BMC family practice 15, 45	Intervention
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
Chiappini Elena, Regoli Marta, Bonsignori Francesca, Sollai Sara, Parretti Alessandra, Galli Luisa, de Martino , and Maurizio (2011) Analysis of different recommendations from international guidelines for	Publication/study type

Study reference	Reason for exclusion
the management of acute pharyngitis in adults and children. Clinical therapeutics 33(1), 48-58	
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 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	Publication/study type
Cohen Jeremie F, Cohen Robert, Levy Corinne, Thollot Franck, Benani Mohamed, Bidet Philippe, and Chalumeau Martin (2015) Selective testing strategies for diagnosing group A streptococcal infection in children with pharyngitis: a systematic review and prospective multicentre external validation study. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 187(1), 23-32	Publication/study type
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
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
Cots Josep M, Alos Juan-Ignacio, Barcena Mario, Boleda Xavier, Canada Jose L, Gomez Niceto, Mendoza Ana, Vilaseca Isabel, and Llor Carles (2015) Recommendations for management of acute pharyngitis in adults. Acta otorrinolaringologica espanola 66(3), 159-70	Publication/study type
Coxeter Peter, Del Mar Chris B, McGregor Leanne, Beller Elaine M, and Hoffmann Tammy C (2015) Interventions to facilitate shared decision making to address antibiotic use for acute respiratory infections in primary care. Cochrane Database of Systematic Reviews (11),	Population
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

Study reference	Reason for exclusion
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 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
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Reveiz Ludovic, and Cardona Andres Felipe (2013) Antibiotics for acute laryngitis in adults. The Cochrane database of systematic reviews 3, CD004783	Population
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