National Institute for Health and Care Excellence

Otitis media (acute): antimicrobial prescribing guideline

Evidence review

March 2022

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1 Context

1.1 Background

Acute otitis media is a self-limiting upper respiratory tract infection (Respiratory tract infections (self-limiting): prescribing antibiotics [2008] NICE guideline CG69) mainly affecting children. In children who are not treated with antibiotics, 60% will have improved symptoms within 24 hours, and in over 80% symptoms will settle spontaneously within 3 days (Venekamp et al. 2015). An additional systematic review which sought to determine the duration of symptoms of earache found that symptoms had resolved in 50% of children at day 3 and in 90% by days 7 to 8 (Thompson et al. 2013).

Acute otitis media is defined as the presence of inflammation in the middle ear, associated with an effusion and accompanied by the rapid onset of symptoms and signs of an ear infection. This is to be differentiated from otitis media with effusion, which is defined as the presence of fluid in the middle ear without symptoms and signs of an ear infection. Diagnosing acute otitis media is done clinically by the presence of symptoms (ear pain or suspected ear pain) and examination with otoscopy to detect inflammation and fluid (NICE clinical knowledge summary: otitis media – acute).

Acute otitis media is diagnosed if there is:

- Acute onset of symptoms, including:
  - earache (in older children)
  - pulling, tugging, or rubbing of the ear, or non-specific symptoms such as fever, irritability, crying, poor feeding, restlessness at night, cough, or rhinorrhoea (in younger children).
- On examination signs of:
  - a distinctly red, yellow, or cloudy tympanic membrane
  - a moderate to severe bulging of the tympanic membrane, with loss of normal landmarks
  - an air-fluid level behind the tympanic membrane
  - a perforation of the tympanic membrane or discharge in the external auditory canal.

In very young children (under 3 or 6 months of age) diagnosis can be difficult because of non-specific symptoms or coexisting systemic illness, such as bronchiolitis or bacteraemia. 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 (2017).

Acute otitis media can be caused by both viruses and bacteria, and commonly both are present at the same time. Middle ear fluid from people with acute otitis media often contains both viruses and bacteria, and it is difficult to distinguish clinically between a viral and a bacterial infection. Children who have spontaneous resolution of acute otitis media, may be more likely to have viral infections alone or bacterial pathogens that are less virulent. Whereas, a progressively or severely ill child may be more likely to have a bacterial process that may not resolve spontaneously. Clinical factors that have been suggested to be more associated with a bacterial cause are as follows (Canadian Pediatric Society position statement [2016]):

- a bulging tympanic membrane
- an acute perforated tympanic membrane with purulent discharge.

Individual patient data has also been used to try and identify subgroups of children who may be more likely to benefit from antibiotics (see Clinical effectiveness).

In bacterial infections, the most common causative pathogens are *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pyogenes.* Since the introduction of the pneumococcal conjugate vaccine, the most common bacterial pathogen may be changing from *Streptococcus pneumoniae* to *Haemophilus influenzae* and *Moraxella catarrhalis* (Canadian Pediatric Society position statement).

Respiratory tract infections, including acute otitis media, 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 [2008]). 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 otitis media specifically accounted for 6% of all respiratory tract infection consultations, but the median practice issued an antibiotic prescription for 60% of these (varying between 22% in the lowest prescribing practices to 100% in the highest prescribing practices). However, these data were from an adult population.

1.2 Managing self-limiting infections

Acute otitis media is largely 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 prescribing or immediate prescribing). For acute otitis media, a no antibiotic prescribing strategy or a back-up antibiotic prescribing strategy is recommended. This should be accompanied with advice about the usual natural history of acute otitis media, which can last 4 days, and advice about managing symptoms, including fever. Depending on clinical assessment of severity, children younger than 2 years with bilateral acute otitis media or children with otorrhoea (discharge following perforation of the tympanic membrane) can also be considered for immediate antibiotic prescribing. An immediate antimicrobial prescription or further appropriate investigation and management should also be offered to people who are systemically very unwell, have ‘red flags’ (signs or symptoms of a more serious illness or condition), or are at high risk of serious complications because of pre-existing comorbidity. This includes people with significant heart, lung, renal, liver or neuromuscular disease, immunosuppression, cystic fibrosis, and young children who were born prematurely.

The NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (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 Non-antimicrobial treatments

The NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population (2017) 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 pain and fever in acute otitis media include paracetamol and ibuprofen. Other non-antimicrobial treatment options such as ear drops containing an anaesthetic and an analgesic, decongestants and antihistamines have been used. 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 acute otitis media recommends that routine follow-up is not required in people with acute otitis media unless they have persistent or recurrent symptoms.

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

Red flags that require admission to hospital are acute otitis media symptoms and signs associated with:

- a severe systemic infection (see the NICE guideline on sepsis)
- symptoms and signs suggestive of acute complications, including mastoiditis, meningitis, intracranial abscess, sinus thrombosis, and facial nerve paralysis.

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 (2017).

However, these acute complications are rare. UK primary care data from 1990 to 2006 (Thompson et al. 2009) found the incidence of mastoiditis remained stable at about 1.2 cases per 10,000 child-years. The risk of mastoiditis after otitis media was 1.8 per 10,000 episodes after antibiotics compared with 3.8 per 10,000 episodes without antibiotics. A number needed to treat of 4831 to prevent 1 child from developing mastoiditis.

Other more common complications of acute otitis media include recurrence of infection, hearing loss (which is usually conductive and temporary) and tympanic membrane perforation (burst ear drum). In a European epidemiological study (Liese et al. 2014), spontaneous tympanic membrane perforation occurred in about 2% of acute otitis media cases in the UK. Further complications such as chronic suppurative otitis media, where a persistent perforation can lead to permanent hearing loss and problems with language development, and cholesteatoma can occur with recurrent episodes of acute otitis media.

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 Review question

What pharmacological (antimicrobial and non-antimicrobial) and non-pharmacological interventions are effective in managing acute uncomplicated otitis media?

2.2 Literature search

A literature search was developed to identify evidence for the effectiveness and safety of interventions for managing acute otitis media (see appendix C: literature search strategy for full details). The literature search identified 7,193 references. These references were screened using their titles and abstracts and 243 full text references were obtained and assessed for relevance. Fifty-nine 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%.

The methods for identifying, selecting and prioritising the best available evidence are described in the interim process guide. Ten of the 59 references were prioritised by the committee as the best available evidence and were included in this evidence review (see appendix F: included studies).

The 49 references that were not prioritised for inclusion are listed in appendix I: not prioritised studies, with reasons for not prioritising the studies. Studies that assessed herbal and alternative medicines were not prioritised by the committee as the treatments were not available in the UK. Also see appendix E: evidence prioritisation for more information on study selection.

The remaining 184 references were excluded. These are listed in appendix J: excluded studies with reasons for their exclusion.

See also appendix D: study flow diagram.

2.3 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-antimicrobial pharmacological interventions

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Oral analgesia					
Sjoukes et al. 2016 Systematic review and meta-analysis. Multiple countries. Follow-up at 7 days	n=392 (3 RCTs)	Children with acute otitis media	4 comparisons: Paracetamol vs. placebo Ibuprofen vs. placebo Paracetamol vs. ibuprofen Paracetamol plus Ibuprofen vs. paracetamol		Pain Adverse events
Ear drops containing an anaesthetic and an analgesic					
Foxlee et al. 2011 Systematic review and meta-analysis. Multiple countries. Follow-up at 14 to 15 days	n=391 (5 RCTs)	Children presenting at primary care settings with acute otitis media without perforation	Ear preparations with an analgesic effect (excluding antibiotics)	Placebo or an ear preparation with an analgesic effect (excluding antibiotics)	Severity and duration of pain
Decongestants and antihistamines					
Coleman et al. 2008[1] Systematic review. Multiple countries. Follow up to over 2 months	n=2,695 (15 RCTs)	Children less than 18 years of age with acute otitis media	3 interventions: Decongestant Antihistamine Decongestant plus antihistamine	No medication or placebo	Failure for acute otitis media to resolve
Corticosteroids					
Chonmaitree et al. 2003 RCT. USA. Follow-up to 6 months	n=179	Children aged 3 months to 6 years with acute otitis media (with 2 or more previous episodes; 1 before the age of 1 year)	Prednisolone for 5 days	Placebo	Rate of treatment failure
Abbreviations: RCT, Randomised controlled trial					

Table 2: Summary of included studies: antimicrobials

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Antibiotic prescribing strategies (including back-up antibiotics)					
Spurling et al. 2013 Systematic review and meta-analysis Multiple countries Follow-up 12 months	n=683 (3 RCTs)	Children with acute otitis media	Back-up antibiotic	No antibiotic Immediate antibiotic	Clinical outcomes Symptom severity Antibiotic use Patient satisfaction Antibiotic resistance
Venekamp et al. 2015[2] Systematic review and meta-analysis Multiple countries Follow-up to 3 months	n=1,007 (4 RCTs)	Children aged 15 years or less with acute otitis media	Immediate antibiotic	Expectant observation (also known as 'wait and see' or 'watchful waiting' or 'observation therapy') with or without an antibiotic prescription	Proportion of children with pain at various time points Adverse effects
Antibiotics versus placebo					
Venekamp et al. 2015[2] Systematic review and meta-analysis Multiple countries Follow-up to 3 months	n=3,401 (13 RCTs)	Children aged 2 months to 15 years with acute otitis media (from high income countries)	Antibiotic (different antibiotics were used in the RCTs)	Placebo	Proportion of children with pain at various time points Adverse effects
Rovers et al. 2006 Systematic review and individual patient data meta-analysis Multiple countries Follow-up at 3 to 7 days	n=1,643 (6 RCTs)	Children aged 6 months to 12 years with acute otitis media (from high income countries)	Amoxicillin or co-amoxiclav	Placebo	Proportion of children with pain, fever, or both at 3 to 7 days Adverse effects
Antibiotics versus other antibiotics					
Shekelle et al. 2010 Systematic review and meta-analysis Multiple countries. Follow up to 16 days	n=3,082 (21 RCTs)	Children aged less than 18 years with acute otitis media	Antibiotics of different classes	Other antibiotics	Treatment success
	n-950 (5 RCTs)	Children aged less than 18 years with			

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
		recurrent and/or persistent acute otitis media			
Frequency of antibiotic dosing					
Thanaviratananich et al. 2016 Systematic review and meta-analysis. Multiple countries. Follow-up to 15 days	n=1,601 (5 RCTs)	Children aged 12 years or less with acute otitis media diagnosed by acute ear pain (otalgia) and an inflamed ear drum (confirmed by positive tympanocentesis or tympanogram of type B or C)	Amoxicillin or co-amoxiclav once or twice a day	Amoxicillin or co-amoxiclav three or four times a day	Clinical cure rates at the end of antibiotic treatment
Antibiotic course length					
Kozyrskyj et al. 2010 Systematic review and meta-analysis. Multiple countries. Follow up to 19 days	n=12,045 (49 RCTs)	Children aged one month to 18 years with a clinical diagnosis of acute otitis media	Antibiotic (short course for less than 7 days)	Antibiotic (long course for 7 days or more)	Treatment failure Clinical resolution Relapse or recurrence
Abbreviations: RCT, Randomised controlled trial					
[1] Coleman et al. (2008) was withdrawn as the review authors were unable to update the review, but the content of the review remains valid [2] Venekamp et al. (2015) is 1 systematic review that considered 2 separate review questions					

3 Clinical effectiveness

Full details of clinical effectiveness are shown in appendix H: GRADE profiles. The main results are summarised below for children with acute otitis media. No systematic reviews of randomised controlled trials (RCTs) or RCTs were identified that included data in adults.

3.1 Non-pharmacological interventions

No systematic reviews or RCTs were identified.

3.2 Non-antimicrobial pharmacological interventions

3.2.1 Oral analgesia

The evidence review for oral analgesia is based on 1 systematic review and meta-analysis (Sjoukes et al. 2016), which included 3 RCTs of paracetamol and non-steroidal anti-inflammatory drugs (NSAID) used alone or in combination for pain relief in children with acute otitis media. The age of the children in the 3 RCTs varied: 1 to 6.75 years, 0.5 to 6 years and over 3 years. The dosages of oral analgesia used in the studies were often less than the maximum recommended dosage in the British National Formulary for Children (BNF-C). The authors were unable to carry out pre-specified subgroup analyses (for example, by age group and concurrent use of antibiotics) because there were too few studies and insufficient data.

Paracetamol compared with placebo

One double blind RCT provided data on paracetamol compared with placebo in children aged 1 to 6.75 years with acute otitis media. Diagnosis was based on a tympanic score of 3 or more in at least 1 ear (range of scores 0 to 6). All children received an antibiotic. The dosage of paracetamol used (10 mg/kg three times a day for 48 hours) was lower than the recommended dosage in the BNF-C and considered by the authors to be suboptimal. There was a significant reduction in pain at 48 hours with paracetamol compared with placebo (n=148: 9.6% versus 25.3%; relative risk [RR] 0.38, 95% confidence interval [CI] 0.17 to 0.85, number needed to treat [NNT] 7 [95% CI 4 to 27]; low quality evidence). There was no significant difference between groups in fever at 48 hours (very low quality evidence).

NSAID compared with placebo

The RCT described above also compared ibuprofen (10 mg/kg three times a day for 48 hours) with placebo. There was a significant reduction in pain at 48 hours with ibuprofen compared with placebo (n=146: 7.0% versus 25.3%; RR 0.28, 95% CI 0.11 to 0.70, NNT 6 [95% CI 4 to 16]; moderate quality evidence). There was no significant difference between groups in fever at 48 hours (very low quality evidence).

NSAID compared with paracetamol

Sjoukes et al. (2016) found no significant differences between ibuprofen and paracetamol in pain and fever at various time points (24 hours, 48 to 72 hours and 4 to 7 days; very low to low quality evidence). There were also no significant differences in re-consultations and back-up antibiotic prescriptions between groups (very low to low quality evidence).

NSAID plus paracetamol compared with paracetamol alone

Sjoukes et al. (2016) also compared ibuprofen plus paracetamol with paracetamol alone. It found no significant differences between groups in pain and fever at various time points (24 hours, 48 to 72 hours and 4 to 7 days; very low to low quality evidence). There were also no significant differences in re-consultations, back-up antibiotic prescriptions and serious complications between groups (very low to low quality evidence). The author's state that firm conclusions on the effects of ibuprofen plus paracetamol compared with paracetamol alone could not be drawn because of the very limited number of children in this analysis (total n=56).

3.2.2 Ear drops containing an anaesthetic and an analgesic

Note: this evidence was updated in March 2022 following an exceptional surveillance review as a licensed preparation is now available in the UK. It includes new evidence on ear drops containing an anaesthetic and an analgesic – see appendix K.

The evidence review for ear drops containing an anaesthetic and an analgesic is based on 1 systematic review and meta-analysis of 5 double-blind RCTs (Foxlee et al. 2011) in 391 children aged 3 to 18 years with acute otitis media without perforation. 1 RCT included ear drops only containing an anaesthetic. All children received some form of oral analgesia.

Ear drops containing an anaesthetic and an analgesic compared with placebo

Two RCTs (n=117) provided data on ear drops containing an anaesthetic and an analgesic compared with placebo. There was a significant increase in the proportion of children with a 50% reduction in pain with anaesthetic ear drops 10 minutes after instillation (43.1% versus 20.3%; RR 2.13, 95% CI 1.19 to 3.80, NNT 5 [95% CI 3 to 16]; low quality evidence) and 30 minutes after instillation (84.5% versus 59.3%; RR 1.43, 95% CI 1.12 to 1.81; low quality evidence) on the day acute otitis media was diagnosed, compared with placebo. However, there was no significant difference between groups 20 minutes after installation (low quality evidence). For the outcome of 25% reduction in pain, there was a significant difference in favour of anaesthetic ear drops at all time points (10 minutes, 20 minutes and 30 minutes after installation) compared with placebo (low quality evidence).

Ear drops containing an anaesthetic and an analgesic compared with herbal ear drops

Three RCTs (n=274) compared ear drops containing an anaesthetic and an analgesic with herbal ear drops. In 1 of these studies (n=84) all children were also given amoxicillin. There were no significant differences in mean pain scores between groups on days 1 and 2 after acute otitis media was diagnosed (15 and 30 minutes after instillation; very low quality evidence). There was a significant reduction with herbal ear drops 30 minutes after installation on day 3 (2 RCTs, n=189: mean difference 0.60, 95% CI 0.01 to 1.19) but this is not likely to be clinically relevant (very low quality evidence).

3.2.3 Decongestants and antihistamines

The evidence review for decongestants and antihistamines is based on 1 systematic review and meta-analysis of 15 RCTs (Coleman et al. 2008) in children less than 18 years with acute otitis media. Most studies were conducted in the 1970s and 1980s. Nasal corticosteroids were not considered a decongestant treatment. The use of

other medicines, such as antibiotics and analgesia was accepted. Overall, no significant benefits were found with decongestants or antihistamines in children with acute otitis media who were taking antibiotics (used in 14 of the 15 RCTs) (very low quality evidence).

Decongestants compared with control

Eight RCTs provided data on decongestants (oral in 7 RCTs; nasal in 1 RCT) compared with no treatment or placebo. There were no significant differences between groups in the rate of persistent acute otitis media at 2 weeks (low quality evidence), or after 2 weeks (very low quality evidence). There were also no significant differences in otalgia, hearing loss, fever, prolonged otitis media, recurrence after 2 weeks or the need for surgery (very low to low quality evidence).

Antihistamines compared with control

Eight RCTs provided data on oral antihistamines compared with no treatment or placebo. There were no significant differences between groups in the rate of persistent acute otitis media at 2 weeks and at less than 7 days (low quality evidence). However, it was significantly higher after 2 weeks with an antihistamine compared with control, but this result was not significant when the relative risk was calculated (moderate quality evidence). There were no significant differences in otalgia, hearing loss, prolonged otitis media, persistence after 2 weeks, recurrence, need for surgery and mastoiditis or meningitis (very low to low quality evidence).

Decongestant plus antihistamine compared with control

Five RCTs provided data on oral decongestant plus antihistamine compared with no treatment or placebo. There was a small but significant reduction in the rate of persistent acute otitis media at 2 weeks with a combination of decongestant plus antihistamine, compared with control (5 RCTs, n=482: 31.1% versus 40.5% [calculated by NICE]; RR 0.76, 95% CI 0.60 to 0.96, NNT 11 [95% CI 6 to 104]; low quality evidence). However, sub-group analysis of higher quality studies only found no benefit with treatment (results not presented). There were no significant differences in the rate of persistent acute otitis media at less than 7 days or over 2 weeks, or in recurrence after 2 weeks (low quality evidence).

3.2.4 Oral corticosteroids

This evidence review for oral corticosteroids is based on 1 double-blind placebo controlled RCT (Chonmaitree et al. 2003; n=91) in children aged 3 months to 6 years with acute otitis media, who had 2 or more previous episodes of acute otitis media (1 being before the age of 1 year). This study was included in the systematic review on decongestants and antihistamines (Coleman et al. 2011), but data on corticosteroids were not presented. All children received 1 dose of intramuscular ceftriaxone. Prednisolone was given for 5 days at a dose of 2 mg/kg per day in 3 divided doses.

There were no significant differences between prednisolone and placebo groups in treatment failure during the first 2 weeks (failure at days 5 or 14 that required antibiotic treatment) (15.6% versus 21.7% respectively; very low quality evidence), median duration of effusion (23 days versus 25 days respectively; very low quality evidence) or recurrence at 1, 2, 3 and 4 to 6 months (very low quality evidence).

3.3 Antimicrobials

The evidence review for antimicrobials in children is based on 6 systematic reviews of RCTs (Kozyrskyj et al. 2010, Rovers et al. 2006, Shekelle et al. 2010, Spurling et al. 2013, Thanaviratananich et al. 2013 and Venekamp et al. 2015). The included studies cover back-up antibiotic strategies, antibiotics versus placebo, antibiotics versus other antibiotics, and the frequency and duration of antibiotic treatment.

The age of children ranged from 1 month to up to 18 years, but most were younger children. The diagnosis of acute otitis media varied, with some studies specifying the use of tympanometry or otoscopes, with others allowing a clinical diagnosis based on symptoms alone. Some studies included in the systematic reviews allowed the use of other medicines in addition to an antibiotic, such as oral analgesia.

The evidence base within this evidence review is for the treatment of uncomplicated acute otitis media. Recurrent otitis media was not a specific inclusion or exclusion criteria in most of the studies. Most studies excluded children who had received antibiotics within the past few days or weeks, so would have excluded children with persistent acute otitis media. However, children may or may not have been included if they had an acute episode of recurrent acute otitis media separated by a period of time.

One systematic review (Shekelle et al. 2010) did differentiate between treating children with uncomplicated acute otitis media; and treating children with recurrent or persistent acute otitis media.

3.3.1 Antibiotic prescribing strategies

Two systematic reviews (Spurling et al. 2013 and Venekamp et al. 2015) assessed the evidence on antibiotic prescribing strategies, including back-up antibiotics in children with acute otitis media. Spurling et al. (2013) (3 RCTs) compared back-up antibiotics (to be used more than 48 hours after the initial consultation, if there was no improvement or symptoms got worse) with no antibiotic prescription and immediate antibiotics. Venekamp et al. (2015) (4 RCTs) compared immediate antibiotics with expectant observation, with or without an antibiotic prescription.

Back-up antibiotics compared with no antibiotics

Spurling et al. (2013) found no significant differences between back-up antibiotics and no antibiotics for the outcomes of pain on day 3 (1 RCT, n=206: 25% versus 29%; odds ratio [OR] 0.80, 95% CI 0.43 to 1.48; very low quality evidence) or fever on day 3 (1 RCT, n=206: 17% versus 8%; OR 2.35, 95% CI 0.97 to 5.69; low quality evidence). Patient satisfaction was high in both groups (95.2% versus 91.0%) with no significant difference between back-up antibiotics (given at the time of consultation) and no antibiotics (low quality evidence). However, there was significantly greater antibiotic use in the back-up antibiotics group compared with the no antibiotic group (1 RCT, n=206: 38% versus 13%; OR 4.06, 95% CI 2.01 to 8.19; high quality evidence).

Back-up antibiotics compared with immediate antibiotics

Spurling et al. (2013) found no significant differences between back-up antibiotics and immediate antibiotics for the outcomes of pain on day 3 (1 RCT, n=212: 25% versus 15%; OR 1.93, 95% CI 0.96 to 3.88; moderate quality evidence), pain on days 4 to 6 (1 RCT, n=165: 64% versus 67%; OR 0.89, 95% CI 0.54 to 1.48; high quality

evidence) and pain on day 7 (1 RCT, n=212: 3% versus 0%; OR 6.55, 95% CI 0.33 to 128.35; low quality evidence).

Back-up antibiotics were significantly less effective in reducing pain severity on day 3 (assessed on a scale of 1 to 10 with a lower score indicating less pain) compared with immediate antibiotics (1 RCT, n=213: mean difference 0.75, 95% CI 0.26 to 1.24; moderate quality evidence), but there was no significant difference by day 7 (1 RCT, n=213: mean difference 0.12, 95% CI −0.04 to 0.28; moderate quality evidence). An improvement of less than 1 point at day 3 may not be clinically meaningful.

There was significantly more pain relief used with back-up antibiotics compared with immediate antibiotics (measured by spoons of paracetamol each day), although the clinical relevance of this is unclear (1 RCT, n=282: mean difference 0.59, 95% CI 0.25 to 0.93; moderate quality evidence). No significant difference was observed between back-up and immediate antibiotics for the use of paracetamol plus ibuprofen (1 RCT, n=265: 93% versus 90%; OR 1.48, 95% CI 0.61 to 3.59; high quality evidence).

Malaise on day 3 was significantly increased with back-up antibiotics compared with immediate antibiotics (1 RCT, n=285: 30% versus 10%; OR 2.62, 95% CI 1.44 to 4.76; high quality evidence). There was also a significant increase in malaise severity on day 3 but not on day 7 (except when a proxy measure of 'last day of crying' was used; moderate quality evidence). The clinical relevance of a statistically significant improvement on day 3 or the proxy measure of 'last day crying' is not clear. No significant differences were seen between groups for fever at days 4 to 6 (low quality evidence).

Spurling et al. (2013) also found significantly lower antibiotic use with back-up antibiotics compared with immediate antibiotics, both when the back-up prescription was given at the time of consultation (1 RCT, n=265: 38% versus 87%: OR 0.09, 95% CI 0.05 to 0.17; moderate quality evidence) and when the prescription had to be collected at a separate visit (1 RCT, n=301; 24% versus 87%; OR 0.05, 95% CI 0.02 to 0.08; high quality evidence). There was no significant difference between groups in re-consultation rates (low quality evidence). However, patient satisfaction was significantly lower with back-up antibiotics when participants had to return for a prescription, compared with immediate antibiotics (1 RCT, n=185: 77% versus 91%; OR 0.32, 95%CI 0.16 to 0.65; high quality evidence). No studies were identified that assessed this outcome when a prescription was given at the time of the consultation.

Immediate antibiotics compared with expectant observation

Venekamp et al. (2015) looked at an expectant observation approach, where an antibiotic prescription was or was not provided, using strategies such as back-up prescribing or watchful waiting. The study found no significant differences in pain between immediate antibiotics and expectant observation at days 3 to 7 (4 RCTs, n=959: 29% versus 36% respectively; RR 0.75, 95% CI 0.50 to 1.12; moderate quality evidence) or at days 11 to 14 (1 RCT, n=247: 61% versus 67%; RR 0.91, 95% CI 0.75 to 1.10; high quality evidence). There were also no significant differences between groups for abnormal tympanometry at 4 weeks, tympanic membrane perforation, recurrence of acute otitis media or parent-reported ear pain episodes at 1 year after randomisation (very low to moderate quality evidence).

3.3.2 Antibiotics compared with placebo

One systematic review and meta-analysis of 13 RCTs (Venekamp et al. 2015; n=3,401) assessed the evidence for oral antibiotics compared with placebo in children with acute otitis media. Only RCTs from high-income countries were included. A range of antibiotics were included in the studies, most commonly penicillins and macrolides. No systematic reviews or RCTs of topical antibiotics were identified.

Antibiotics did not significantly reduce pain at 24 hours compared with placebo (6 RCTs, n=1,394: 38% versus 43%; RR 0.89 95% CI 0.78 to 1.01; high quality evidence); around 60% of children were pain free at 24 hours regardless of whether they had an antibiotic or not. Antibiotics did significantly reduce pain at 2 to 3 days (7 RCTs, n=2,320: 11.6% versus 15.9%; RR 0.70, 95% CI 0.57 to 0.86; NNT 24 [95% CI 15 to 70]; moderate quality evidence), although 84% of children in the placebo group had no pain at 2 to 3 days. There was also a significant reduction in pain at 4 to 7 days (8 RCTs, n=1,347: 17.5% versus 24.1%; RR 0.76, 95% CI 0.63 to 0.91; NNT 16 [95% CI 10 to 44]; moderate quality evidence), and at 10 to 12 days (1 RCT, n=278: 7.2% vs. 21.6%; RR 0.33, 95% CI 0.17 to 0.66; NNT 7 [95% CI 5 to 16]; high quality evidence) compared with placebo. However, the absolute differences between antibiotics and placebo were small.

Antibiotics significantly reduced the number of children with abnormal tympanometry compared with placebo at 2 to 4 weeks (7 RCTs, n=2,138: 39.2% versus 48.1%; RR 0.82, 95% CI 0.74 to 0.90; NNT 12 [95% CI 8 to 21]; low quality evidence). However, the absolute differences between antibiotics and placebo were small. There was no significant difference between antibiotics and placebo in the number of children with abnormal tympanometry at 6 to 8 weeks (low quality evidence) or at 3 months (high quality evidence).

The incidence of tympanic membrane perforation (burst ear drum) was significantly lower with antibiotics compared with placebo (5 RCTs, n=1,075: 1.7% versus 4.8%; RR 0.37, 95% CI 0.18 to 0.76; NNT 33 [95% CI 20 to 100]; moderate quality evidence). However, the absolute difference between groups was very small and 95% of children in the placebo group did not experience tympanic membrane perforation.

The number of children who developed acute otitis media in both ears from a presentation in 1 ear was significantly lower with antibiotics compared with placebo (4 RCTs, n=906: 10.6% versus 18.8%; RR 0.49, 95% CI 0.25 to 0.95; low quality evidence). However, the majority of children (81%) in the placebo group did not develop acute otitis media in both ears. There were no significant differences between groups in the risk of late acute otitis media recurrence at 3.5 years follow-up (moderate quality evidence).

3.3.3 Identifying children more likely to benefit from antibiotics

Two systematic reviews (Rovers et al. 2006 and Shekelle et al. 2013) provided additional sub-group analysis that compared the effect of antibiotics by age, laterality (acute otitis media in one ear or both ears) and the presence of otorrhoea (ear discharge) in children with acute otitis media. However, the literature search was not designed specifically to identify prognostic evidence.

The systematic review and individual patient data meta-analysis by Rovers et al. (2006) included data from 6 RCTs of 1,643 children aged 6 months to 12 years. Co-amoxiclav for 7 days (1 RCT) or amoxicillin for 7 days (2 RCTs) or 10 days (3

RCTs) was compared with placebo. The analysis was limited to short term outcomes, either pain, fever, or both at 3 to 7 days or pain alone at 3 to 7 days.

In children under 2 years there was a significant reduction in pain, fever, or both at 3 to 7 days with antibiotics compared with placebo (6 RCTs, n=567, 33% versus 48%, RR 0.77, 95% CI 0.68 to 0.89, NNT 7; low quality evidence) and in pain alone at 3 to 7 days (6 RCTs, n=567: 28% versus 40%, RR 0.83, 95% CI 0.73 to 0.93, NNT 9; low quality evidence). In children aged 2 years and over there was also a significant reduction in pain, fever, or both at 3 to 7 days with antibiotics compared with placebo (6 RCTs, n=1,076: 20% versus 31%, RR 0.86, 95% CI 0.80 to 0.93, NNT 10; moderate quality evidence) and pain alone at 3 to 7 days (6 RCTs, n=1,076: 16% versus 26%, RR 0.88, 95% CI 0.82 to 0.93, NNT 10; moderate quality evidence). However, the authors report that the effects of antibiotics were not significantly modified by age alone.

Similarly, in children with bilateral acute otitis media there was a significant reduction in pain, fever, or both at 3 to 7 days with antibiotics compared with placebo (6 RCTs, n=456: 27% versus 47%, RR 0.72, 95% CI 0.62 to 0.84, NNT 5; low quality evidence) and in pain alone at 3 to 7 days (6 RCTs, n=456: 20% versus 40%, RR 0.75, 95% CI 0.66 to 0.85, NNT 5; low quality evidence). In children without bilateral acute otitis media there was no significant reduction in pain, fever, or both or pain alone at 3 to 7 days with antibiotics compared to placebo (moderate quality evidence). The authors reported that the effects of antibiotic treatment were not significantly modified by bilateral acute otitis media alone.

In children under 2 years with bilateral acute otitis media, pain, fever, or both at 3 to 7 days was significantly reduced with antibiotics compared with placebo (6 RCTs, n=273: 30% versus 55%: RR 0.64, 95% CI 0.62 to 0.80, NNT 4; low quality evidence) and in pain alone (6 RCTs, n=273: 23% versus 46%, RR 0.70, 95% CI 0.58 to 0.84, NNT 5; low quality evidence). In children aged 2 years and over with bilateral acute otitis media and children there was no significant difference between antibiotics and placebo for the outcome of pain, fever, or both (low quality evidence).

In children with otorrhoea, the outcome of pain, fever, or both at 3 to 7 days was significantly lower with antibiotics compared with placebo (6 RCTs, n=116: 24% versus 60%, RR 0.52, 95% CI 0.37 to 0.73, NNT 3; moderate quality evidence). In children without otorrhoea, the difference was still statistically significant, but the absolute benefit of antibiotics compared with placebo was lower (6 RCTs, n=439: 28% versus 42% with placebo, RR 0.80, 95% CI 0.70 to 0.92, NNT 8; low quality evidence). The outcome of pain alone at 3 to 7 days was not assessed in this population.

The Shekelle et al. (2015) systematic review and meta-analysis of 4 RCTs compared the rate difference for spontaneous recovery (measured by middle ear effusion or inflammation) for different antibiotics in sub-groups of children with uncomplicated acute otitis media. It suggested that children over 2 years were more likely to spontaneously recover from acute otitis media without treatment compared with children under 2 years. In general, the results of individual trials and meta-analyses showed that children with bilateral acute otitis media responded as well to antibiotics as those with unilateral acute otitis media. However, if left untreated, children with acute otitis media in 1 ear did better than those with acute otitis media in both ears. Furthermore, the effect of antibiotics (compared with placebo) was greater in children with otorrhoea than in those without otorrhoea.

3.3.4 Choice of antibiotic

Overall, evidence from 1 systematic review and meta-analysis (Shekelle et al. 2010) did not suggest major differences in treatment success between classes of antibiotics, including penicillins, cephalosporins and macrolides, for treating children with uncomplicated acute otitis media. Meta-analyses for treatment efficacy was undertaken when 3 or more RCTs could be identified.

Penicillins compared with cephalosporins

In children aged 5 months to 12 years, Shekelle et al. (2010) found no significant difference in treatment success (definition varied across studies) at 14 days between ampicillin or amoxicillin compared with a single intramuscular dose of ceftriaxone (4 RCTs, n=518: 93% versus 93%, risk difference 0%, 95% CI −7% to 7%; moderate quality evidence). There was also no significant difference in treatment success in children aged 3 months to 10 years at days 3 to 16 between co-amoxiclav (for 7 to 10 days) and a single intramuscular dose of ceftriaxone (4 RCTs, n=1,362: 77% versus 80%, risk difference 3%, 95% CI −2% to 7%; moderate quality evidence).

Penicillins compared with macrolides

In children aged 6 months to 12 years, Shekelle et al. (2010) found no significant difference in treatment success (definition varied across studies) at days 3 to 14 between co-amoxiclav (7 to 10 days) and azithromycin (5 days or less) (9 RCTs, n=1,826: 86% versus 86%, risk difference 0%, 95% CI −7% to 6%; low quality evidence).

Cephalosporins compared with macrolides

In children aged 6 months to 13 years, Shekelle et al. (2010) found no significant difference in treatment success (definition varied across studies) at days 10 to 14 between cefaclor and azithromycin (duration of treatment not stated) (3 RCTs, n=427; 94% versus 93% respectively; risk difference 1%, 95% CI −4% to 3%; moderate quality evidence).

Choice of antibiotic in children with recurrent or persistent acute otitis media

Shekelle et al. (2010) also considered evidence for treating children with recurrent or persistent acute otitis media. None of the studies found a significant benefit in treatment success (not defined) for any particular antibiotic (moderate quality evidence). There were 5 individual RCTs which compared different antibiotic treatments:

- Co-amoxiclav compared with gatifloxacin: treatment success rate at 3 to 10 days: 1 RCT, n=367: 84% versus 90%; mean difference –5.9%, 95% CI –12.9% to 1.1% treatment; treatment success rate at day 10: 1 RCT, n=141; 79% versus 85%; mean difference –6.1%, 95% CI –15.9% to 3.7%.
- Co-amoxiclav compared with levofloxacin: treatment success rate at day 2 to 5: 1 RCT, n=1,305: 91% versus 94%; mean difference –3.2%, 95% CI –6.2% to –0.2% (this result was not statistically significant when the RR was calculated).
- Co-amoxiclav compared with azithromycin: treatment success rate at day 12 to 16: 1 RCT, n=294: 84% versus 86%; mean difference −1.8%, 95% CI –10% to 6.4%.
- Cefaclor compared with cefuroxime: treatment success rate at day 10: 1 RCT, n=148: 93.6% versus 92.9%; mean difference 0.7%, 95% CI –7% to 9%;

treatment success rate at day 20 to 26: 1 RCT, n=148: 85.9% versus 87.1%; mean difference –1.2%, 95% CI –12% to 10%.

3.3.5 Frequency of antibiotic dosing

One systematic review and meta-analysis of 5 RCTs (Thanaviratananich et al. 2013) in 1,601 children under 12 years with acute otitis media (diagnosed by otalgia and positive tympanocentesis or type B or C tympanogram) compared amoxicillin or co-amoxiclav given once or twice a day with amoxicillin or co-amoxiclav given three or four times a day. The duration of treatment was 10 days in most studies, and the dose of amoxicillin or co-amoxiclav varied. No evidence was identified for a dose given four times a day.

There was no significant difference in clinical cure rates (resolution of otalgia and/or fever, and bacteriological cure rate) at the end of treatment (day 7 to 14) for amoxicillin or co-amoxiclav given once or twice a day compared with three times a day doses (5 RCTs, n=1,601: 89% versus 86%; RR 1.03 95% CI 0.99 to 1.07; high quality evidence). There were also no significant differences in clinical cure rates during treatment, clinical cure rates at 1 to 3 months after treatment and recurrence (very low to high quality evidence).

Subgroup analyses were undertaken to assess any differences between the dose frequency of amoxicillin and co-amoxiclav individually. For amoxicillin only studies, there were no significant differences between once or twice a day doses and three times a day doses in clinical cure at the end of treatment, clinical cure after treatment and recurrence after completion of treatment (low to high quality evidence). There was however a significantly higher clinical cure rate during treatment with amoxicillin given once or twice a day compared with three times a day (1 RCT, n=63: 100% versus 85%; RR 1.17, 95% CI 1.01 to 1.37; moderate quality evidence), but this is based on small numbers of children

For co-amoxiclav only studies, there were no significant differences between once or twice a day doses and three times a day doses in clinical cure during treatment (low quality evidence), clinical cure at the end of treatment (high quality evidence), clinical cure after treatment (high quality evidence) and recurrence (very low quality evidence).

3.3.6 Duration of antibiotic treatment

One systematic review and meta-analysis of 49 RCTs (Kozyrskyj et al. 2010) in children with acute otitis media (n=12,045) compared a short course of antibiotics (more than 48 hours but less than 7 days, unless otherwise stated) with a longer course (7 days or more, unless otherwise stated).

All antibiotics

Kozyrskyj et al. (2010) found that the odds of treatment failure (a lack of clinical resolution, relapse or recurrence within 1 month after the start of treatment) was significantly higher with a short course of antibiotics compared with a longer course at 8 to 19 days (11 RCTs, n=3,932: 18.0% versus 14.4% respectively; OR 1.37, 95% CI 1.15 to 1.64; NNT 28 [95% CI 17 to 77]; very low quality evidence) and at 1 month or less (16 RCTs, n=5,093: 20.5% versus 17.5%; OR 1.34, 95% CI 1.15 to 1.55; NNT 34 [95% CI 20 to 124]; low quality evidence). However, the absolute differences between groups were small and most children did not have treatment failure regardless of whether a short course or longer course was used. There were no significant differences in the odds of treatment failure at 20 to 30 days, 30 to 45

days, 3 months or less, and at 90 days for a short course compared with a longer course of antibiotics (low to moderate quality evidence).

Sub group analyses were undertaken to compare the odds of treatment failure with a short course compared with a longer course of antibiotics in children less than 2 years, children 2 years and over, children with perforated eardrums and children with non-perforated eardrums. No significant differences were identified (low to moderate quality evidence).

When a 5 day course was compared with a 10 day course (excluding co-amoxiclav – see below), the odds of treatment failure at 1 month were significantly higher with the 5 day course (14 RCTs, n=4,151: 19.0% versus 17.7%; OR 1.20, 1.02 to 1.42; low quality evidence), although the absolute difference was very small. A very short course of antibiotics (less than 48 hours) also significantly increased the odds of treatment failure compared with a longer course (2 RCTs, n=118: 20.8% versus 7.7%; OR 2.99, 95% CI 1.04 to 8.54; moderate quality evidence). However, this result was not statistically significant when the RR was calculated.

Antibiotic compared with the same antibiotic

Sensitivity analyses found that there was a significant increase in the odds of treatment failure at 8 to 19 days (6 RCTs, n=2,153: 18.6% versus 11.6%; OR 1.97, 95% CI 1.54 to 2.52; moderate quality evidence) and at 1 month (10 RCTs, n=3,321: 17.4% versus 14.0%; OR 1.65, 95% CI 1.35 to 2.01; moderate quality evidence) with a short course of antibiotic compared with a longer course of the same antibiotic (moderate quality evidence). There was no significant difference between groups at all other time points measured (low to moderate quality evidence).

Additional analyses compared short and longer courses of specific antibiotics. There was a significant increase in the odds of treatment failure with a 5 day course of co-amoxiclav compared with a 10 day course of co-amoxiclav (2 RCTs, n=942: 27.8% versus 16.6%; OR 1.99, 95% CI 1.44 to 2.74; high quality evidence). There was no significant differences in the odds of treatment failure for a short course of ceftriaxone at 1 month or less or 3 months or less, compared with a longer course of ceftriaxone (low to high quality evidence). There was no significant difference in the odds of treatment failure at 25 to 32 days with a short course of azithromycin (single dose) (moderate quality evidence) or at 1 month or less with a 3 to 5 day short course of azithromycin (moderate quality evidence), compared with a longer course of azithromycin. There was a significant increase in the odds of treatment failure at 8 to 19 days with a short course of azithromycin (for 3 to 5 days) compared with a longer course (18 RCTs, n=4,347: 11.4% versus 9.5%; OR 1.27, 95% CI 1.04 to 1.55; low quality evidence). However, the absolute difference between treatments was small.

4 Safety and tolerability

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

See the summaries of product characteristics, British National Formulary (BNF) and BNF for children (BNF-C) for information on contraindications, cautions and adverse effects of individual medicines, and for appropriate use and dosing in specific populations, for example, hepatic impairment, renal impairment, pregnancy and breastfeeding.

4.1 Non-pharmacological interventions

No systematic reviews or randomised controlled trials (RCTs) were identified.

4.2 Non-antimicrobial pharmacological interventions

4.2.1 Oral analgesia

Paracetamol is widely used to treat pain and fever in children. It is generally well tolerated. However, liver damage (and less frequently renal damage) can occur following overdose. Paracetamol doses should not exceed those recommended, and should not be repeated more frequently than every 4 to 6 hours, with a maximum of 4 doses in 24 hours (BNF-C November 2017).

The non-steroidal anti-inflammatory drug, ibuprofen is also widely used to treat pain and fever in children, but paracetamol is now often preferred (BNF-C November 2017). All NSAIDs should be used with caution in the elderly; in allergic disorders; in people with coagulation defects, uncontrolled hypertension, heart failure, and cardiovascular disease; and in people with a history of gastro-intestinal ulceration or bleeding, or inflammatory bowel disease. Side effects include gastro-intestinal disturbances, hypersensitivity reactions (particularly rashes, angioedema, and bronchospasm), and fluid retention (BNF-C November 2017).

The NICE guideline on fever in under 5s: assessment and initial management (2017) recommends that either paracetamol or ibuprofen can be considered in children with fever who appear distressed. However, these should not be used with the sole aim of reducing body temperature in children with fever. Paracetamol or ibuprofen should be continued only as long as the child appears distressed. Considering a change to the other agent is recommended if the child's distress is not alleviated, but giving both agents simultaneously is not recommended. Alternating these agents should only be considered if the distress persists or recurs before the next dose is due.

One systematic review in children with acute otitis media (Sjoukes et al. 2016) found no significant differences in adverse events between paracetamol, ibuprofen and placebo (very low to low quality evidence). However, the authors state that this finding should be interpreted cautiously, given there were few participants, and infrequent occurrence of adverse events.

4.2.2 Ear drops containing an anaesthetic and an analgesic

One systematic review of 5 RCTs (Foxlee et al. 2011) found that only 1 RCT measured adverse effects with ear drops containing an anaesthetic and an analgesic and none were found (low quality evidence).

4.2.3 Decongestants and antihistamines

Nasal decongestants for administration by mouth, such as pseudoephedrine, may not be as effective as preparations for local application but they do not give rise to rebound nasal congestion on withdrawal (BNF November 2017). Pseudoephedrine hydrochloride has few sympathomimetic effects, and is commonly combined with other ingredients (including antihistamines) in preparations intended for the relief of cough and cold symptoms (BNF-C November 2017). Children under 6 years should not be given over the counter cough and cold medicines containing ephedrine, oxymetazoline, phenylephrine, pseudoephedrine, and xylometazoline (MHRA Drug Safety Update April 2009).

Antihistamines differ in their duration of action, incidence of drowsiness, and antimuscarinic effects (such as urinary retention, dry mouth, blurred vision, and gastro-intestinal disturbances); the response to an antihistamine may vary from child to child (BNF-C November 2017). The risk of sedation and psychomotor impairment is greater with sedating antihistamines, such as chlorphenamine. Non-sedating antihistamines such as cetirizine and loratadine cause less sedation and psychomotor impairment than the older antihistamines because they penetrate the blood brain barrier only to a slight extent (BNF November 2017).

In Coleman et al. (2008), 5 of the 15 RCTs reported data on adverse effects. There was a significant increase in adverse effects (excluding drowsiness and hyperactivity) with decongestants compared with placebo (Peto odds ratio [OR] 7.91, 95% confidence interval [CI] 2.36 to 26.54; very low quality evidence). No significant differences in adverse effects were observed with antihistamines or a combination of decongestant plus antihistamine, compared with placebo (very low to low quality evidence). However, there is considerable uncertainty about these results. The estimate of effect for drowsiness, hyperactivity and other adverse effects was about an 8 fold increase (with very wide 95% CIs around these estimates).

4.2.4 Oral corticosteroids

Oral corticosteroids have known systemic effects (mineralocorticoid side effects, for example hypertension, sodium and water retention, and potassium and calcium loss; and glucocorticoid side effects, for example diabetes and osteoporosis). A range of psychological or behavioural effects may also occur including psychomotor hyperactivity, sleep disorders, anxiety, depression and aggression (particularly in children) (MHRA Drug Safety Update, September 2007).

1 RCT (Chonmaitree et al. 2003; n=91) found no significant difference in adverse effects or discontinuations due to adverse effects between oral prednisolone for 5 days and placebo, although the study was very small and full data were not reported (low quality evidence).

4.3 Antimicrobials

Acute otitis media is a self-limiting 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-C 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. See the NICE guideline on drug allergy: diagnosis and management for more information.

Cholestatic jaundice can occur either during or shortly after the use of co-amoxiclav. It is more common in people above the age of 65 years and in men; and has only rarely been reported in children. Jaundice is usually self-limiting and very rarely fatal (BNF-C November 2017).

Macrolides, including clarithromycin and erythromycin, are an alternative to penicillins in people with penicillin allergy (BNF-C November 2017). 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.

4.3.1 Antibiotic prescribing strategies

One systematic review (Spurling et al. 2013) identified 2 RCTs that considered the adverse effects of back-up antibiotics compared with immediate antibiotics. No significant differences were identified between groups for vomiting (1 RCT, n=165) or rash (1 RCT, n=285; very low quality evidence). There was significantly less diarrhoea with back-up antibiotics compared with immediate antibiotics (data pooled by NICE, 2 RCTs, n=550: 8.5% versus 20.9%; relative risk [RR] 0.41, 95% CI 0.26 to 0.64; number needed to harm [NNH] 8 [95% CI 5 to 15]; high quality evidence. No data were available on back-up antibiotics compared with no antibiotics.

A systematic review and meta-analysis (Venekamp et al. 2015) found that immediate antibiotics were associated with an increased risk of vomiting, diarrhoea or rash compared with expectant observation (2 RCTs, n=450: 29% versus 17%; relative risk [RR] 1.71, 95% CI 1.24 to 2.36; NNH 8 [95% CI 5 to 19]; moderate quality evidence).

4.3.2 Antibiotics

A systematic review and meta-analysis of 8 RCTs (Venekamp et al. 2015) found a significantly increased risk of adverse events (vomiting, diarrhoea or rash) with antibiotics compared with placebo (8 RCTs, n=2,107: 27.1% versus 19.6% respectively; RR 1.38, 95% CI 1.19 to 1.59; NNH 13 [95% CI 9 to 25]; moderate quality evidence).

An individual patient data meta-analysis (Rovers et al. 2006) reported that in 6 RCTs of children with uncomplicated acute otitis media the proportion of children who took antibiotics and had diarrhoea varied from 4% to 21%, while those who took a placebo varied from 2% to 14% (low quality evidence). The proportion of children who took antibiotics and who developed a skin rash varied from 1% to 8%, while those who took a placebo varied from 2% to 6%. There was 1 episode of meningitis reported at day 3 of treatment in the placebo group (6 RCTs, n=1643, 0% versus 0.12%, RR

0.34, 95% CI 0.01 to 8.22; low quality evidence), but there were no reports of mastoiditis or other serious complications in the included studies.

A systematic review (Shekelle et al. 2010) in children with uncomplicated acute otitis media reported that overall conclusions regarding clinically important differences in adverse effects between antibiotics could not be reached, but significant differences were seen in single RCTs. Co-amoxiclav was associated with more adverse events overall than cefdinir taken once a day (1 RCT, n=256: rate difference 28%, 95% CI 17% to 39%; moderate quality evidence), cefdinir taken twice a day: (1 RCT, n=256: rate difference 19%, 95% CI 8% to 31%; very low quality evidence); and ceftriaxone (1 RCT, n=513: rate difference 16%, 95% CI 9% to 24%; moderate quality evidence).

Shekelle et al. (2010) also found a significant increase in adverse effects (3 RCT, n=1,366: rate difference 19%, 95% CI 9% to 29%; moderate quality evidence) and gastrointestinal adverse effects (3 RCT, n=1,366: rate difference 18%, 95% CI 8% to 28%; moderate quality evidence) with co-amoxiclav for 7 to 10 days compared with azithromycin for 5 days. There was also a significantly increased risk of diarrhoea with cefixime compared with ampicillin or amoxicillin (5 RCT, n=654: rate difference 8%, 95% CI −13% to −4%; moderate quality evidence).

A systematic review (Thanaviratananich et al. 2013) did not identify any significant differences in adverse events between once or twice a day doses of amoxicillin or co-amoxiclav compared with three times a day doses (3 RCTs, n=878: 31% versus 30%; RR 0.92, 95% CI 0.52 to 1.63; very low quality evidence).

A systematic review (Kozyrskyj et al. 2010) found there were significantly fewer gastrointestinal adverse events with a short course of antibiotics (more than 48 hours but less than 7 days) compared with a longer course (7 days or more) (13 RCTs, n=4,918: 9.0% versus 13.7%; OR 0.72, 95% CI 0.60 to 0.87; very low quality evidence). However, this result was not statistically significant when the RR was calculated. There were significantly more gastrointestinal adverse effects with a short course of ceftriaxone compared with a longer course (1 RCT, n=402: 23.6% versus 9.2%; OR 2.89, 95% CI 1.70 to 4.91; low quality evidence). However, a short course of azithromycin was associated with significantly fewer adverse events compared with a longer course (single dose short course in 2 RCTs, n=658: 16.6% versus 23.2%; OR 0.66, 95% CI 0.45 to 0.96; moderate quality evidence; 3 to 5 day short course in 14 RCTs, n=3,719: 4.7% versus 11.6%; OR 0.36, 95% CI 0.28 to 0.46; moderate quality evidence).

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 (2015) recommends that the risk of antimicrobial resistance for individual patients and the population as a whole should be taken into account when deciding whether or not to prescribe an antimicrobial.

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

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

In bacterial acute otitis media, the most common causative pathogens are *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* and *Streptococcus pyogenes*. Since the introduction of the pneumococcal conjugate vaccine, the most common bacterial pathogen may be changing from *Streptococcus pneumoniae* to *Haemophilus influenza* and *Moraxella catarrhalis* (Canadian Pediatric Society position statement [2016]). Data from the ESPAUR report 2016 on the antibiotic susceptibility of pathogens causing bacteraemia show that for *Streptococcus pneumoniae* the proportion of bloodstream isolates that are not susceptible to penicillins was about 5% in 2015, with a corresponding 8% not susceptible to macrolides. These figures have stayed relatively stable for the past 5 years.

6 Other considerations

6.1 Resource impact

6.1.1 Antibiotics

In a 2011 survey of UK primary care data for adults (Gulliford et al. 2014), consultations for otitis media accounted for 6% of all respiratory tract infection consultations, but the median practice issued an antibiotic prescription for 60% of these. However, these data on antibiotic prescribing are in adults not children.

There is potential for resource savings if a no antibiotic or a back-up antibiotic prescription strategy is used. In 1 systematic review (Spurling et al. 2013), there was significantly lower antibiotic use with a back-up antibiotic prescribing strategy compared with immediate antibiotics, both when the back-up antibiotic prescription was given at the time of consultation (38% versus 87%; 1 randomised controlled trial [RCT]; moderate quality evidence) and when the prescription had to be collected on a separate visit (24% versus 87%; 1 RCT; high quality evidence). There was no significant difference between groups in re-consultation rates (low quality evidence).

Recommended antibiotics are amoxicillin, clarithromycin, erythromycin and co-amoxiclav. All these antibiotics are available as generic formulations, see Drug Tariff for costs.

6.1.2 Ear drops containing an anaesthetic and an analgesic

Ear drops containing an anaesthetic and an analgesic (Otigo ear drops) are a prescription only medicine, 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 [2009]). Longer treatment durations for an acute illness (for example, antibiotics) may also cause problems with medicines adherence for some people.

One systematic review (Thanaviratananich et al. 2013) in children under 12 years with acute otitis media (diagnosed by otalgia and positive tympanocentesis or type B or C tympanogram) compared once or twice a day doses of amoxicillin or co-amoxiclav with three times a day doses of amoxicillin or co-amoxiclav. It found no significant difference in compliance rates between doses (2 RCTs, n=1,520: relative risk [RR] 1.04, 95% confidence interval [CI] 0.98 to 1.10; moderate quality evidence).

7 Terms used in the guideline

7.1.1 Expectant observation

Expectant observation is an observational approach in which an antibiotic prescription may or may not be provided. Examples of this approach include back-up antibiotic prescribing and 'watchful waiting' (when a person is not given a prescription but is offered advice on when to seek further treatment).

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) • NICE clinical knowledge summary on otitis media - acute • Canadian Pediatric Society position statement (2016) • ESPAUR report (2016) • Venekamp et al. (2015) • Thompson et al. (2013) • 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: NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population (2017) • NICE clinical knowledge summary on otitis media - acute • Committee experience
Red flags	• What symptoms and signs suggest a more serious illness or condition (red flags)?	• NICE guideline CG160: Fever in under 5s: assessment and initial management (2017) • Thompson et al. 2009

Key area	Key question(s)	Evidence sources
		• Liese et al. (2014) • Committee experience
Non-pharmacological interventions	• What is the clinical effectiveness and safety of non-pharmacological interventions for managing the infection or symptoms?	• No evidence identified (studies that assessed herbal and alternative medicines were not prioritised by the committee)
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 for Children (BNF-C) (November 2017) • Sjoukes et al. (2016) • Foxlee et al. (2011) • Coleman et al. (2008) • Chonmaitree et al. (2003) • MHRA Drug Safety Update, September 2007 • MHRA Drug Safety Update, April 2009
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-C (November 2017)
	• Which people are most likely to benefit from an antimicrobial?	• Evidence review – see appendix F for included studies

Key area	Key question(s)	Evidence sources
	• 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 • British National Formulary for Children (BNF-C) (November 2017) • Summary of product characteristics
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) • Canadian Pediatric Society position statement (2016)
Resource impact	• What is the resource impact of interventions (such as escalation or de-escalation of treatment)?	• Gulliford et al. (2014) • Spurling et al. (2013)
Medicines adherence	• What are the problems with medicines adherence (such as when longer courses of treatment are used)?	• NICE guideline NG76: Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence (2009) • Thanaviratananich et al. (2013)
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 uncomplicated otitis media?	• antimicrobial includes antibiotics • non-antimicrobial includes analgesia • search will include terms for acute uncomplicated otitis media
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 uncomplicated otitis media to address antimicrobial resistance in line with the major goals of antimicrobial stewardship. This includes interventions that lead prescribers to: • optimise therapy 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 or rapid diagnostics) • indications for no or back-up 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 condition
IV	Eligibility criteria – population/diseas	Population: Adults and children (aged 72 hours and older) with acute uncomplicated otitis media of any severity.	Subgroups of interest, those:

	e/condition/issue/ domain	Studies that use for example clinical diagnosis, imaging or microbiological methods of diagnosing the condition.	• with protected characteristics under the Equality Act 2010 • with chronic conditions (such as high blood pressure, diabetes or heart 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 uncomplicated otitis media 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	Placebo or no treatment, previous studies have demonstrated that acute otitis media (AOM) can be caused by both viruses and bacteria, and commonly both are present at the same time therefore we reasonably anticipate that some studies may have placebo or no treatment arms.
VII	Outcomes and prioritisation	a) Clinical outcomes such as: • mortality	The committee have agreed that the following outcomes are critical:

[1] Non-pharmacological interventions include: watchful waiting, no intervention, smoking cessation
[2] Non-antimicrobial pharmacological interventions include: analgesics (paracetamol, ibuprofen)
[3] Antimicrobial pharmacological interventions include: (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, ITU stay, planned and unplanned contacts). The Committee considered which outcomes should be prioritised when multiple outcomes are reported (critical and important outcomes). Additionally, the Committee were asked to consider what clinically important features of study design may be important for this condition (for example length of study follow-up, treatment failure/recurrence, important outcomes of interest such as sequela or progression to more severe illness).	• reduction in symptoms (duration or severity) for example difference in time to substantial improvement • time to clinical cure (mean or median time to resolution of illness) • rate of complications (including mortality) with or without treatment, including escalation of treatment • health and social care utilisation (including length of stay, ITU stays, planned and unplanned contacts). • thresholds or indications for antimicrobial treatment (which people are most, or least likely to benefit from antimicrobials) The committee have agreed that the following outcomes are important: • patient-reported outcomes, such as medicines adherence, patient experience • changes in antimicrobial resistance patterns, trends and levels as a result of treatment
VIII	Eligibility criteria – study design	The search will look for: • Systematic review of randomised controlled trials (RCTs) • RCTs If insufficient evidence is available progress to: • Controlled trials	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 Process; 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, cost effectiveness studies 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-apg10001 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 please 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 outcome/study level	Standard study checklists will be used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual.The risk of bias across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/	
XXI	Criteria for quantitative synthesis (where suitable)	For details please see the interim process guide (2017).	
XXII	Methods for analysis – combining studies and exploring (in)consistency	For details please see the interim process guide (2017).	
XXIII	Meta-bias assessment – publication bias, selective reporting bias	For details please see the interim process guide (2017).	
XXIV	Assessment of confidence in cumulative evidence	For details please see the interim process guide (2017).	
XXV	Rationale/context – Current management	For details please see the introduction to the evidence review in the full 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 section 3 of Developing NICE guidelines: the manual. 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: Ovid MEDLINE(R) <1946 to December Week 1 2016>
Search Strategy: Acute otitis media

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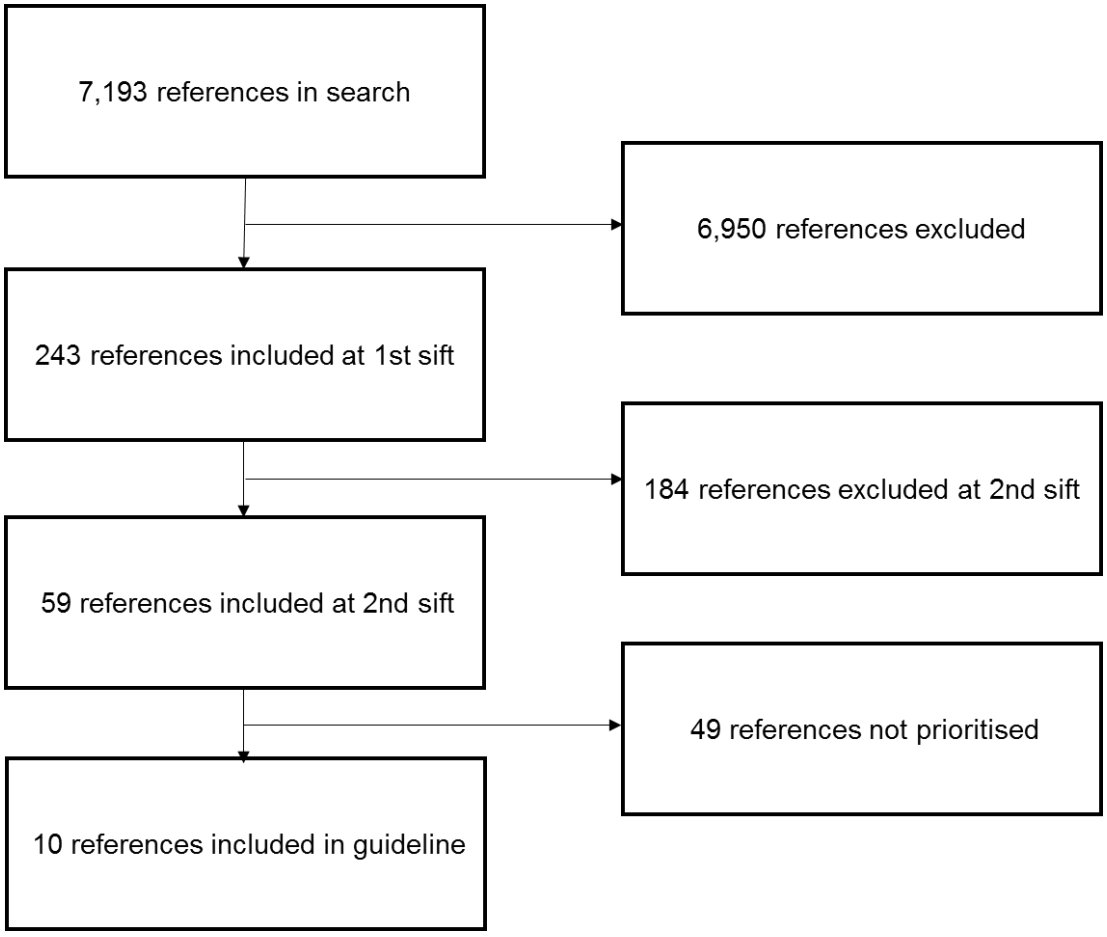
1 exp Otitis Media/ (24481)
2 ((acute adj4 otitis media) or AOM).tw. (6659)
3 (middle and (ear* adj4 (inflam* or infect* or effus*))).tw. (4093)
4 ("glue ear*" or otorrh?ea).tw. (2180)
5 Earache/ (726)
6 (earache* or ((ear or ears) adj3 (pain* or ache* or aching))).tw. (979)
7 exp Hearing Loss/ (65582)
8 ((hearing adj2 (loss* or dull* or problem* or reduc*)) or deafness).tw. (51694)
9 or/1-8 (108836)
10 limit 9 to (english language and yr="2000 -Current") (47918)
11 Animals/ not (Animals/ and Humans/) (4782110)
12 10 not 11 (41874)
13 limit 12 to (letter or historical article or comment or editorial or news) (2359)
14 12 not 13 (39515)
15 amoxicillin/ or cefuroxime/ or erythromycin/ or azithromycin/ or Clarithromycin/ or Amoxicillin-Potassium Clavulanate Combination/ (33932)
16 (amoxicillin* or amix or amoram or amoxident or galenamox or rimoxallin or amoxil).tw. (11743)
17 (cefuroxime* or zinacef or zinnat).tw. (3881)
18 (erythromycin* or tiloryth or primacine or erymax or erythrocin or erythroped or erythroped A).tw. (19358)
19 (azithromycin* or zithromax or zedbac).tw. (6278)
20 (clarithromycin* or klaricid or mycifor XL or coamoxiclav or "co-amoxiclav" or augmentin).tw. (8581)
21 (moxifloxacin or avelox).tw. (3446)
22 Trimethoprim, Sulfamethoxazole Drug Combination/ or (Cotrimoxazole or "Co-trimoxazole" or Septrin).tw. (10102)
23 exp Macrolides/ (108095)
24 macrolide*.tw. (13693)
25 exp penicillins/ (81945)
26 penicillin*.tw. (51572)
27 exp cephalosporins/ (43510)
28 cephalosporin*.tw. (19467)
29 or/15-28 (264618)
30 Acetaminophen/ or Ibuprofen/ (24516)
31 (paracetamol or acetaminophen or panadol or perfalgan or calpol).tw. (20032)
32 (ibuprofen or arthrofen or ebufac or rimafen or brufen or calprofen or feverfen or nurofen or orbifen).tw. (10718)
33 analgesics/ or analgesics, non-narcotic/ or analgesics, short-acting/ (56215)
34 (analgesi* or pain relief* or pain reliev*).tw. (115901)
35 or/30-34 (169424)
36 watchful waiting/ (2487)
37 "no intervention*".tw. (6026)
38 (watchful* adj2 wait*).tw. (1910)
39 (wait adj2 see).tw. (1120)
40 (active* adj2 surveillance*).tw. (5307)
41 (expectant* adj2 manage*).tw. (2579)
42 ((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. (20502)

43 ((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. (1422)
44 ((delay* or defer*) adj3 (treat* or therap* or interven*)).tw. (25472)
45 or/36-44 (64781)
46 anti-infective agents/ or exp anti-bacterial agents/ or exp anti-infective agents, local/ (909765)
47 (antibacter* or anti-bacter* or antibiot* or anti-biot* or antimicrobial* or anti-microbial*).tw. (388436)
48 (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. (3623227)
49 (46 or 47) and 48 (153008)
50 Self Care/ (30993)
51 ((self or selves or themsel*) adj4 (care or manag*)).tw. (30483)
52 or/50-51 (48453)
53 Smoking Cessation/ (28156)
54 "tobacco use cessation"/ (1084)
55 Smoking/pc (18945)
56 "Tobacco Use Disorder"/pc (1997)
57 ((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. (42388)
58 (antismok* or anti smok* or anti-smok*).ti,ab. (1899)
59 or/53-58 (60989)
60 29 or 35 or 45 or 49 or 52 or 59 (717962)
61 14 and 60 (1963)
62 Meta-Analysis.pt. (82995)
63 Network Meta-Analysis/ (0)
64 Meta-Analysis as Topic/ (17210)
65 Review.pt. (2320492)
66 exp Review Literature as Topic/ (10079)
67 (metaanaly$ or metanaly$ or (meta adj3 analy$)).tw. (96923)
68 (review$ or overview$).ti. (346705)
69 (systematic$ adj5 (review$ or overview$)).tw. (91207)
70 ((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw. (6489)
71 ((studies or trial$) adj2 (review$ or overview$)).tw. (33870)
72 (integrat$ adj3 (research or review$ or literature)).tw. (7886)
73 (pool$ adj2 (analy$ or data)).tw. (21161)
74 (handsearch$ or (hand adj3 search$)).tw. (7572)
75 (manual$ adj3 search$).tw. (4282)
76 or/62-75 (2526281)
77 animals/ not humans/ (4782110)
78 76 not 77 (2367664)
79 61 and 78 (515)
80 Randomized Controlled Trial.pt. (484826)
81 Controlled Clinical Trial.pt. (97360)
82 Clinical Trial.pt. (541353)
83 exp Clinical Trials as Topic/ (330838)
84 Placebos/ (36245)
85 Random Allocation/ (97146)
86 Double-Blind Method/ (152304)
87 Single-Blind Method/ (25436)
88 Cross-Over Studies/ (43685)
89 ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw. (968408)
90 (random$ adj3 allocat$).tw. (26149)
91 placebo$.tw. (187659)
92 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. (149201)
93 (crossover$ or (cross adj over$)).tw. (69656)
94 or/80-93 (1727713)

95 animals/ not humans/ (4782110)
96 94 not 95 (1609130)
97 61 and 96 (567)
98 97 not 79 (349)
99 Observational Studies as Topic/ (2081)
100 Observational Study/ (31898)
101 Epidemiologic Studies/ (8042)
102 exp Case-Control Studies/ (897333)
103 exp Cohort Studies/ (1765445)
104 Cross-Sectional Studies/ (259191)
105 Controlled Before-After Studies/ (218)
106 Historically Controlled Study/ (94)
107 Interrupted Time Series Analysis/ (273)
108 Comparative Study.pt. (1942671)
109 case control$.tw. (102918)
110 case series.tw. (45013)
111 (cohort adj (study or studies)).tw. (127553)
112 cohort analy$.tw. (5210)
113 (follow up adj (study or studies)).tw. (44112)
114 (observational adj (study or studies)).tw. (62610)
115 longitudinal.tw. (183312)
116 prospective.tw. (437110)
117 retrospective.tw. (344442)
118 cross sectional.tw. (224959)
119 or/99-118 (4089365)
120 61 and 119 (816)
121 120 not (79 or 97) (496)
122 61 not (79 or 97 or 120) (603)
123 exp Drug Resistance, Bacterial/ (77692)
124 exp Drug Resistance, Multiple/ (30993)
125 ((bacter$ or antibacter$ or anti-bacter$ or "anti bacter$") adj4 (resist$ or tolera$)).tw. (32082)
126 ((antibiot$ or anti-biot$ or "anti biot$") adj4 (resist$ or tolera$)).tw. (39843)
127 (multi$ adj4 drug$ adj4 (resist$ or tolera$)).tw. (11535)
128 (multidrug$ adj4 (resist$ or tolera$)).tw. (36858)
129 (multiresist$ or multi-resist$ or "multi resist$").tw. (5782)
130 ((microb$ or antimicrob$ or anti-microb$ or "anti microb$") adj4 (resist$ or tolera$)).tw. (20343)
131 (superbug$ or super-bug$ or "super bug$").tw. (405)
132 Superinfection/ (1829)
133 (superinvasion$ or super-invasion$ or "super invasion$" or superinfection$ or super-infection$ or "super infection$").tw. (5484)
134 R Factors/ (4481)
135 "r factor$".tw. (3726)
136 (resist$ factor$ or "r plasmid$" or resist$ plasmid$).tw. (5234)
137 or/123-136 (178791)
138 29 and 137 (40351)
139 limit 138 to (english language and yr="2000 -Current") (21130)
140 animals/ not humans/ (4782110)
141 139 not 140 (18705)

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?				
No evidence identified	-	-	-	-
Which non-antimicrobial pharmacological interventions are effective?				
Oral analgesia	Sjoukes et al. 2016	-	-	-
Ear drops containing an anaesthetic and an analgesic	Foxlee et al. 2011	-	Wood et al. 2012	Bolt et al. 2007
Decongestants and antihistamines	Coleman et al. 2008	-	-	-
Oral corticosteroids	-	Chonmaitree et al. 2003	Espositio et al. 2013 Principi et al. 2013	-
Which antibiotic prescribing strategies are effective (including back-up antibiotics)?				
Back-up antibiotics	Spurling et al. 2013 Venekamp et al. 2015	-	Voulomanou et al. 2009 Arroll et al. 2003	Little et al. 2001 Little et al. 2006 McCormick et al. 2005 Worrall et al. 2010 Chao et al. 2008 Spiro et al. 2006
Is an antibiotic effective?				
Antibiotics versus placebo	Venekamp et al. 2015	-	Coker et al. 2010 Takata et al. 2001 Gisselsson-Solen (2014)	Damoiseaux et al. 2000 Hoberman et al. 2011 Le Saux et al. 2005 Neumark et al. 2007 Tahtinen et al. 2011
Which people are most likely to benefit from an antibiotic?				

Key questions	Included studies[1]		Studies not prioritised[2]	
	Systematic reviews	RCTs	Systematic reviews	RCTs
Sub-group analyses of antibiotics versus placebo	Rovers et al. 2006 Shekelle et al. 2010	-	-	-
Antibiotics versus different antibiotics	Thanaviratananich et al. 2016 Shekelle et al. 2010	-	Easton et al. 2003 Ioannidis et al. 2001 Scott et al. 2001 Courter et al. 2010 Law and Amsden 2004 Pacifico and Chiesa 2002	Damrikarnlert et al. 2000 Garrison et al. 2004 Dunne et al. 2003 Dagen et al. 2000a Dagen et.al 2000b Biner et al. 2007
What is the optimal dosage, duration and route of administration of antibiotic?				
Dosage	-	-	-	-
Course length	Kozyrskyj et al. 2010		Gulani et al. 2010 Ovetchline and Cohen 2003 Takata et al. 2001	Adam et al. 2000 Arguedas et al. 2003 Arguedas et al. 2005 Block et al. 2003 Hoberman et al. 2016 Catania and Gallo 2004 Cohen et al. 2000 Guven et al. 2006 Hoberman et al. 2005 Oguz et al. 2003
Route of administration	-	-	-	-

[1] See appendix F for full references of included studies
[2] See appendix I for full references of not-prioritised studies, with reasons for not prioritising these studies

Appendix F: Included studies

Chonmaitree T, Saeed K, Uchida T, Hekknen T, Baldwin C D, Freeman D H, and McCormick D P. (2003) A randomised, placebo-controlled trial of the effect of antihistamine or corticosteroid treatment in acute otitis media. The Journal of Pedatrics. September 2003

Coleman C, and Moore M (2008) Decongestants and antihistamines for acute otitis media in children. Cochrane Database of Systematic Reviews (online) 3, CD001727

Foxlee R, Johansson A, Wejfalk J, Dawkins J, Dooley L, Del Mar , and C (2006) Topical analgesia for acute otitis media. Cochrane database of systematic reviews (online) 3, CD005657

Kozyrskyj A, Klassen T P, Moffatt M, and Harvey K (2010) Short-course antibiotics for acute otitis media. Cochrane database of systematic reviews (Online) 9, CD001095

Shekelle G, Takata G, Newberry S J, Coker T, Limbos MA, Chan LS, Timmer M M, Suttorp M J, Carter J, Motala A, Valentine D, Johnsen B, and Shanman R (2010) Management of Acute Otitis Media: update. Evidence report/technology assessment (198), 1-426

Sjoukes A, Venekamp RP, van de Pol, A C, Hay A D, Little P, Schilder A G, and Damoiseaux R A (2016) Paracetamol (acetaminophen) or non-steroidal anti-inflammatory drugs, alone or combined, for pain relief in acute otitis media in children. The Cochrane database of systematic reviews (online) 12, CD011534

Spurling GKP, Del Mar, CB, Dooley L, Foxlee R, and Farley R (2013) Delayed antibiotics for respiratory infections. The Cochrane database of systematic reviews (online) 4, CD004417

Rovers M M, Glasziou P, Appelman C L, Burke P, McCormick D P, Damoiseaux R A, Gaboury I, Little P, and Hoes A W (2006) Antibiotics for acute otitis media: a meta-analysis with individual patient data. Lancet 368(9545), 1429-1435

Thanaviratananich S, Laopaiboon M, and Vatanasapt P (2013) Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media. Cochrane database of systematic reviews (online) 12, CD004975

Venekamp RP, Sanders SHL, Glasziou PIP, Del Mar, CB, and Rovers MM (2015) Antibiotics for acute otitis media in children. Cochrane database of systematic reviews (online) 6, CD000219

Appendix G: Quality assessment of included studies

G.1 Oral analgesia

Table 3: Overall risk of bias/quality assessment – systematic reviews (SR checklist)

Study reference	Sjoukes et al. 2016
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?	Yes
Were all important outcomes considered?	Yes
Are the benefits worth the harms and costs?	See GRADE profiles

G.2 Ear drops containing an anaesthetic and an analgesic

Table 4: Overall risk of bias/quality assessment – systematic reviews (SR checklist)

Study reference	Foxlee et al. 2011
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

Study reference	Foxlee et al. 2011
Can the results be applied to the local population?	Unclear[a]
Were all important outcomes considered?	Yes
Are the benefits worth the harms and costs?	See GRADE profiles
[a] 3 of the 5 RCTs were conducted in Israel and compared ear drops containing an anaesthetic and an analgesic with a herbal ear drop preparation. It is not clear how this applies to a UK population	

G.3 Decongestants and antihistamines

Table 5: Overall risk of bias/quality assessment – systematic reviews (SR checklist)

Study reference	Coleman et al. 2008
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?	Yes
Were all important outcomes considered?	Yes
Are the benefits worth the harms and costs?	See GRADE profiles

G.4 Oral corticosteroids

Table 6: Overall risk of bias/quality assessment – randomised controlled trials (RCT checklist)

Study reference	Chonmaitree at al. 2003
Did the trial address a clearly focused issue?	Yes
Was the assignment of patients to treatments randomised?	Unclear[a]
Were patients, health workers and study personnel blinded?	Unclear[b]
Were the groups similar at the start of the trial?	Yes

Study reference	Chonmaitree at al. 2003
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[c]
Were all clinically important outcomes considered?	Yes
Are the benefits worth the harms and costs?	See GRADE profiles

[a] The study was randomised but the methods of randomisation and allocation concealment are not described
[b] The study was stated to be double-blind, but the methods of blinding are not described
[c] All children in the study were given a single intramuscular dose of an antibiotic. This does not reflect usual UK practice

G.5 Antibiotic prescribing strategies

Table 7: Overall risk of bias/quality assessment – systematic reviews (SR checklist)

Study reference	Spurling et al. 2013	Venekamp et al. 2015
Did the review address a clearly focused question?	Yes	Yes
Did the authors look for the right type of papers?	Yes	Yes
Do you think all the important, relevant studies were included?	Yes	Yes
Did the review's authors do enough to assess the quality of the included studies?	Yes	Yes
If the results of the review have been combined, was it reasonable to do so?	Yes	Yes
What are the overall results of the review?	See GRADE profiles	See GRADE profiles
How precise are the results?	See GRADE profiles	See GRADE profiles
Can the results be applied to the local population?	Yes	Yes
Were all important outcomes considered?	Yes	Yes
Are the benefits worth the harms and costs?	See GRADE profiles	See GRADE profiles

G.6 Antimicrobials

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

Study reference	Rovers et al. 2006[1]	Venekamp et al. 2015	Shekelle et al. 2010	Kozyrskyj et al. 2010	Thanaviratananich et al. 2009
Did the review address a clearly focused question?	Yes	Yes	Yes	Yes	Yes
Did the authors look for the right type of papers?	Yes	Yes	Yes	Yes	Yes
Do you think all the important, relevant studies were included?	No[2]	Yes	Yes	Yes	Yes
Did the review's authors do enough to assess the quality of the included studies?	Yes	Yes	Yes	Yes	Yes
If the results of the review have been combined, was it reasonable to do so?	Yes	Yes	Yes	Yes	Not applicable
What are the overall results of the review?	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
Can the results be applied to the local population?	Yes	Yes	Yes	Yes	Yes
Were all important outcomes considered?	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

[1] Additional questions from PRISMA-IPD checklist were incorporated into the above checklist

[2] The authors report that 4 eligible studies were not included in the individual patient data analysis as they failed to provide requested study data, aggregate data from published studies was not used (this is reported as publication bias in the GRADE profiles)

Appendix H: GRADE profiles

H.1 Oral analgesia

Table 9: 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[1,2]	Placebo[1]	Relative (95% CI)	Absolute		
Pain at 48 hours												
1[3]	randomised trials	serious[4]	not applicable	no serious indirectness	serious[5]	none	7/73 (9.6%)	19/75 (25.3%)	RR 0.38 (95% CI 0.17 to 0.85)	157 fewer per 1000 (from 38 fewer to 210 fewer)	⊕⊕OO LOW	CRITICAL
Fever at 48 hours												
1[3]	randomised trials	serious[4]	not applicable	no serious indirectness	very serious[6]	none	1/73 (1.4%)	1/75 (1.3%)	RR 1.03 (95% CI 0.07 to 16.12)	0 more per 1000 (from 12 fewer to 202 more)	⊕OOO VERY LOW	CRITICAL
Adverse events												
1[3]	randomised trials	serious[4]	not applicable	no serious indirectness	very serious[6]	none	3/73 (4.1%)	3/75 (4%)	RR 1.03 (95% CI 0.21 to 4.93)	1 more per 1000 (from 32 fewer to 157 more)	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI, Confidence interval; RR, Rate ratio

[1] All children were also taking an antibiotic
[2] The dosage of paracetamol was 10mg/kg three times a day. The authors state that this would now be considered a suboptimal dosage
[3] Sjoukes et al. (2016)
[4] Downgraded 1 level - methodology not fully described. Children with fever above 39°C could be given paracetamol (30 mg to 60 mg) in addition to the studied treatments. Cochrane authors state this may have substantially influenced the study findings
[5] Downgraded 1 level - at a default minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit with paracetamol
[6] 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 10: GRADE profile – ibuprofen versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ibuprofen[1,2]	Placebo[1]	Relative (95% CI)	Absolute		
Pain (follow-up 48 hours)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ibuprofen[1,2]	Placebo[1]	Relative (95% CI)	Absolute		
1[3]	randomised trials	serious[4]	not applicable	no serious indirectness	no serious imprecision	none	5/71 (7.0%)	19/75 (25.3%)	RR 0.28 (95% CI 0.11 to 0.70)	182 fewer per 1000 (from 76 fewer to 225 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Fever (follow-up 48 hours)												
1[3]	randomised trials	serious[4]	not applicable	no serious indirectness	very serious[5]	none	1/71 (1.4%)	1/75 (1.3%)	RR 1.06 (95% CI 0.07 to 16.57)	1 more per 1000 (from 12 fewer to 208 more)	⊕OOO VERY LOW	CRITICAL
Adverse events (follow-up 48 hours)												
1[3]	randomised trials	serious[4]	not applicable	no serious indirectness	very serious[5]	none	5/71 (7%)	3/75 (4%)	RR 1.76 (95% CI 0.44 to 7.10)	30 more per 1000 (from 22 fewer to 244 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI, Confidence interval; RR, Rate ratio												

[1] All children were also taking an antibiotic
[2] The dosage of ibuprofen was 10mg/kg three times a day
[3] Sjoukes et al. (2016)
[4] Downgraded 1 level - methodology not fully described. Children with fever above 39°C could be given paracetamol (30 mg to 60 mg) in addition to the studied treatments. Cochrane authors state this may have substantially influenced the study findings.
[5] 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 11: GRADE profile – ibuprofen versus paracetamol

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ibuprofen	Paracetamol	Relative (95% CI)	Absolute		
Pain at 24 hours												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	12/21 (57.1%)[4]	14/18 (77.8%)[4]	RR 0.83 (95% CI 0.59 to 1.18)	132 fewer per 1000 (from 319 fewer to 140 more)	⊕⊕OO LOW	CRITICAL
Pain at 48 to 72 hours												
2[1]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[6]	none	16/93 (17.2%)[4]	16/90 (17.8%)[4]	RR 0.91 (95% CI 0.54 to 1.54)	16 fewer per 1000 (from 82 fewer to 96 more)	⊕OOO VERY LOW	CRITICAL
Pain at 4 to 7 days												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[6]	none	3/22 (13.6%)[4]	3/16 (18.8%)[4]	RR 0.74 (95% CI 0.17 to 3.23)	49 fewer per 1000 (from 156 fewer to 418 more)	⊕OOO VERY LOW	CRITICAL
Fever at 24 hours												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ibuprofen	Paracetamol	Relative (95% CI)	Absolute		
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[6]	none	4/22 (18.2%)[4]	5/17 (29.4%)[4]	RR 0.69 (95% CI 0.24 to 2.00)	91 fewer per 1000 (from 224 fewer to 294 more)	⊕OOO VERY LOW	CRITICAL
Fever at 48 to 72 hours												
3[1]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[6]	none	4/92 (4.3%)[4]	3/90 (3.3%)[4]	RR 1.18 (95% CI 0.31 to 4.44)	6 more per 1000 (from 23 fewer to 115 more)	⊕OOO VERY LOW	CRITICAL
Fever at 4 to 7 days												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[6]	none	1/22 (4.5%)[4]	0/17 (0%)[4]	RR 2.75 (95% CI 0.12 to 60.70)	-	⊕OOO VERY LOW	CRITICAL
Re-consultations												
1[1]	randomised trials	serious[7]	not applicable	no serious indirectness	serious[9]	none	24/26 (92.3%)[10]	22/27 (81.5%)[10]	RR 1.13 (95% CI 0.92 to 1.40)	106 more per 1000 (from 65 fewer to 326 more)	⊕⊕OO LOW	IMPORTANT
Back-up antibiotic prescription												
1[1]	randomised trials	serious[7]	not applicable	no serious indirectness	very serious[6]	none	14/26 (53.8%)[10]	11/27 (40.7%)[10]	RR 1.32 (95% CI 0.74 to 2.35)	130 more per 1000 (from 106 fewer to 550 more)	⊕OOO VERY LOW	IMPORTANT
Adverse events												
2[1]	randomised trials	serious[2]	serious[8]	no serious indirectness	serious[6]	none	5/97 (5.2%)[4]	3/100 (3%)[4]	RR 1.71 (95% CI 0.43 to 6.90)	21 more per 1000 (from 17 fewer to 177 more)	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI, Confidence interval; RR, Rate ratio,

[1] Sjoukes et al. (2016)
[2] Downgraded 1 level - includes data from an open label study
[3] Downgraded 1 level - at a default minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit with ibuprofen
[4] Varied dosages were used in each RCT
[5] Downgraded 1 level - 2/3 RCTs had methodological issues (1 RCT was an open label study; 1 RCT did not fully describe their methodology)
[6] Downgraded 2 levels - at a default minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm with ibuprofen
[7] Downgraded 1 level - open label study
[8] Downgraded 1 level - not assessable due to no events in 1 trial
[9] Downgraded 1 level - at a default minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit with paracetamol
[10] The dosage was the maximum recommended in the British National Formulary

Table 12: GRADE profile – ibuprofen plus paracetamol versus paracetamol alone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ibuprofen + paracetamol	Paracetamol	Relative (95% CI)	Absolute		
Pain (follow-up 24 hours)												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	19/24 (79.2%)[4]	12/17 (70.6%)[4]	RR 1.07 (95% CI 0.78 to 1.47)	49 more per 1000 (from 155 fewer to 332 more)	⊕⊕OO LOW	CRITICAL
Pain (follow-up 48 to 72 hours)												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[5]	none	10/24 (41.7%)[4]	9/17 (52.9%)[4]	RR 0.71 (95% CI 0.42 to 1.20)	154 fewer per 1000 (from 307 fewer to 106 more)	⊕⊕OO LOW	CRITICAL
Pain (follow-up 4 to 7 days)												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[6]	none	8/24 (33.3%)[4]	3/17 (17.6%)[4]	RR 1.65 (95% CI 0.58 to 4.72)	115 more per 1000 (from 74 fewer to 656 more)	⊕OOO VERY LOW	CRITICAL
Fever (follow-up 24 hours)												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[6]	none	12/24 (50%)[4]	5/17 (29.4%)[4]	RR 1.48 (95% CI 0.73 to 2.99)	141 more per 1000 (from 79 fewer to 585 more)	⊕OOO VERY LOW	CRITICAL
Fever (follow-up 48 to 72 hours)												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[6]	none	7/24 (29.2%)[4]	2/17 (11.8%)[4]	RR 2.13 (95% CI 0.60 to 7.60)	133 more per 1000 (from 47 fewer to 776 more)	⊕OOO VERY LOW	CRITICAL
Fever (follow-up 4 to 7 days)												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[7]	none	0/24 (0%)[4]	0/17 (0%)[4]	RR 0.0 (95% CI 0.0 to 0.0)	-	⊕OOO VERY LOW	CRITICAL
Re-consultations												
1[1]	randomised trials	serious[8]	not applicable	no serious indirectness	serious[5]	none	19/29 (65.5%)[9]	22/27 (81.5%)[9]	RR 0.80 (95% CI 0.58 to 1.11)	163 fewer per 1000 (from 342 fewer to 90 more)	⊕⊕OO LOW	IMPORTANT
Back-up antibiotic prescription												
1[1]	randomised trials	serious[8]	not applicable	no serious indirectness	very serious[6]	none	15/29 (51.7%)[9]	11/27 (40.7%)[9]	RR 1.27 (95% CI 0.71 to 2.26)	110 more per 1000 (from 118 fewer to 513 more)	⊕OOO VERY LOW	IMPORTANT
Serious complications												
2[1]	randomised trials	serious[2]	serious[7]	no serious indirectness	serious[7]	none	0/37 (0%)[4]	0/34 (0%)[4]	RR 0.0 (95% CI 0.0 to 0.0)	-	⊕OOO VERY LOW	CRITICAL
Adverse events												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ibuprofen + paracetamol	Paracetamol	Relative (95% CI)	Absolute		
1[1]	randomised trials	serious[8]	not applicable	no serious indirectness	serious[7]	none	0/29 (0%)[9]	0/27 (0%)[9]	RR 0.0 (95% CI 0.0 to 0.0)	-	⊕⊕OO LOW	CRITICAL
Abbreviations: CI, Confidence interval; RR, Rate ratio												

[1] Sjoukes et al. (2016)
[2] Downgraded 1 level - includes data from an open label study
[3] Downgraded 1 level - at a default minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit with paracetamol alone
[4] Varied dosages were used in each RCT
[5] Downgraded 1 level - at a default minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit with ibuprofen plus paracetamol
[6] Downgraded 2 levels - at a default minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[7] Downgraded 1 level - not assessable (no events reported in either group in both RCTs)
[8] Downgraded 1 level - open label study
[9] The dosage was the maximum recommended in the British National Formulary

H.2 Ear drops containing an anaesthetic and an analgesic

Table 13: GRADE profile – ear drops containing an anaesthetic and an analgesic versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anaesthetic/ analgesic ear drops	Placebo	Relative (95% CI)	Absolute		
50% reduction in pain (10 minutes after installation of drops)												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	25/58 (43.1%)	12/59 (20.3%)	RR 2.13 (95% CI 1.19 to 3.8)	230 more per 1000 (from 39 more to 569 more)	⊕⊕OO LOW	CRITICAL
50% reduction in pain (20 minutes after installation of drops)												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	34/58 (58.6%)	28/59 (47.5%)	RR 1.24 (95% CI 0.88 to 1.74)	114 more per 1000 (from 57 fewer to 351 more)	⊕⊕OO LOW	CRITICAL
50% reduction in pain (30 minutes after installation of drops)												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	49/58 (84.5%)	35/59 (59.3%)	RR 1.43 (95% CI 1.12 to 1.81)	255 more per 1000 (from 71 more to 481 more)	⊕⊕OO LOW	CRITICAL
25% reduction in pain (10 minutes after installation of drops)												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	37/58 (63.8%)	25/59 (42.4%)	RR 1.51 (95% CI 1.06 to 2.15)	216 more per 1000 (from 25 more to 487 more)	⊕⊕OO LOW	CRITICAL
25% reduction in pain (20 minutes after installation of drops)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anaesthetic/ analgesic ear drops	Placebo	Relative (95% CI)	Absolute		
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	46/58 (79.3%)	35/59 (59.3%)	RR 1.34 (95% CI 1.04 to 1.71)	202 more per 1000 (from 24 more to 421 more)	⊕⊕OO LOW	CRITICAL
25% reduction in pain (30 minutes after installation of drops)												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	54/58 (93.1%)	41/59 (69.5%)	RR 1.34 (95% CI 1.12 to 1.61)	236 more per 1000 (from 83 more to 424 more)	⊕⊕OO LOW	CRITICAL
Adverse effects												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[4]	none	-	-	1 RCT reported a limited range of adverse effects (tinnitus, dizziness or unsteady gait) and none were found		⊕⊕OO LOW	CRITICAL
Abbreviations: CI, Confidence interval; RR, Rate ratio												

[1] Foxlee et al. (2011)
[2] Downgraded 1 level - allocation concealment not described in both randomised controlled trials (RCTs); randomisation not described and missing data in 1 RCT
[3] Downgraded 1 level - at a default minimal important difference (MID) of 25% data are consistent with no meaningful difference or appreciable benefit with ear drops containing an anaesthetic and an analgesic
[4] Downgraded 1 level - not assessable

Table 14: GRADE profile – ear drops containing an anaesthetic and an analgesic versus herbal ear drops

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anaesthetic/ analgesic ear drops	Herbal ear drops	Relative	Absolute		
Mean pain score at day 1 (15 minutes after installation of ear drops; Better indicated by lower values)												
3[1]	randomised trials	serious[2]	serious[3]	serious[4]	serious[5]	none	127	147	-	MD 0.63 higher (0.45 lower to 1.71 higher)	⊕OOO VERY LOW	CRITICAL
Mean pain score at day 1 (30 minutes after installation of ear drops; Better indicated by lower values)												
3[1]	randomised trials	serious[2]	serious[3]	serious[4]	serious[5]	none	127	147	-	MD 1.02 higher (0.22 lower to 2.27 higher)	⊕OOO VERY LOW	CRITICAL
Mean pain score at day 2 (15 minutes after installation of ear drops; Better indicated by lower values)												
2[1]	randomised trials	serious[2]	serious[3]	serious[4]	serious[5]	none	84	105	-	MD 0.45 higher (0.24 lower to 1.13 higher)	⊕OOO VERY LOW	CRITICAL
Mean pain score at day 2 (30 minutes after installation of ear drops; Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anaesthetic/ analgesic ear drops	Herbal ear drops	Relative	Absolute		
2[1]	randomised trials	serious[2]	serious[3]	serious[4]	serious[5]	none	84	105	-	MD 0.39 higher (0.19 lower to 0.98 higher)	⊕OOO VERY LOW	CRITICAL
Mean pain score at day 3 (15 minutes after installation of ear drops; Better indicated by lower values)												
2[1]	randomised trials	serious[2]	serious[3]	serious[4]	no serious imprecision	none	84	105	-	MD 0.23 higher (0.06 lower to 0.53 higher)	⊕OOO VERY LOW	CRITICAL
Mean pain score at day 3 (30 minutes after installation of ear drops; Better indicated by lower values)												
2[1]	randomised trials	serious[2]	serious[3]	serious[4]	no serious imprecision	none	84	105	-	MD 0.60 higher (0.01 to 1.19 higher)	⊕OOO VERY LOW	CRITICAL
Adverse effects												
No data were reported												CRITICAL
Abbreviations: MD, Mean difference												

[1] Foxlee et al. (2011)
[2] Downgraded 1 level - 3 RCTs did not describe allocation concealment; 1 RCT did not describe randomisation; in 2 RCTs there was incomplete outcome data (assessed by Cochrane authors)
[3] Downgraded 1 level - heterogeneity >50%
[4] Downgraded 1 level - all 3 RCTs were conducted in Israel and the herbal preparation used as the comparator is not known, The relevance of this comparison to the UK is unclear
[5] Downgraded 1 level - at a minimal important difference (MID) of 0.5 median standard deviation (SD) of comparator arm data are consistent with no meaningful difference or appreciable harm with ear drops containing an anaesthetic and an analgesic

H.3 Decongestants and antihistamines

Table 15: GRADE profile – decongestant versus control

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Decongestant	Control	Relative (95% CI)	Absolute		
Persistent acute otitis media at 2 weeks												
5[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	98/480 (20.4%)	94/501 (18.7%)	Peto OR 1.06 (0.73 to 1.54) NICE analysis: RR 1.04 (0.83 to 1.29)	-	⊕⊕OO LOW	CRITICAL
Persistent acute otitis media (before 7 days)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Decongestant	Control	Relative (95% CI)	Absolute		
No data were available												CRITICAL
Persistent acute otitis media (after 2 weeks)												
3[1]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[5]	none	13/146 (8.9%)	12/155 (7.74%)	Peto OR 1.08 (0.45 to 2.55) NICE analysis: RR 1.06 (0.52 to 2.16)	-	⊕OOO VERY LOW	CRITICAL
Otalgia												
2[1]	randomised trials	no serious risk of bias	serious[6]	no serious indirectness	very serious[5]	none	20/85 (23.5%)	26/91 (28.5%)	Peto OR 0.73 (0.36 to 1.51) NICE analysis: RR 0.82 (0.51 to 1.31)	-	⊕OOO VERY LOW	IMPORTANT
Fever												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[5]	none	1/24 (4.16%)	0/26 (0%)	Peto OR 8.03 (95% CI 0.16 to 406.02) NICE analysis: RR 3.24 (0.14 to 75.91)	-	⊕⊕OO LOW	IMPORTANT
Hearing loss												
1[1]	randomised trials	serious[4]	not applicable	no serious indirectness	very serious[5]	none	10/226 (4.42%)	6/236 (2.54%)	Peto OR 1.75 (0.65 to 4.75) NICE analysis: RR 1.74 (0.64 to 4.71	-	⊕OOO VERY LOW	CRITICAL
Complications: prolonged acute otitis media (follow-up 8 to 12 weeks)												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[5]	none	4/38 (10.52%)	5/34 (14.7%)	Peto OR 0.69 (95% CI 0.17 to 2.75) NICE analysis: RR 0.72 (0.21 to 2.45)	-	⊕⊕OO LOW	CRITICAL
Complications: recurrent acute otitis media (after 2 weeks)												
3[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	14/123 (11.38%)	19/125 (15.2%)	Peto OR 0.74 (0.35 to 1.57) NICE analysis: RR 0.78 (0.43 to 1.44)	-	⊕⊕OO LOW	CRITICAL
Complications: need for surgery												
2[1]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[5]	none	7/264 (2.65%)	5/270 (18.51%)	Peto OR 1.38 (0.44 to 4.36) NICE analysis: RR 1.37 (0.45 to 4.16)	-	⊕OOO VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Decongestant	Control	Relative (95% CI)	Absolute		
Hyperactivity												
2[1]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[5]	none	1/75 (1.33%)	2/75 (2.66%)	Peto OR 0.51 (0.05 to 4.95) NICE analysis: RR 0.68 (0.12 to 3.85)	-	⊕OOO VERY LOW	IMPORTANT
Adverse effects (excluding drowsiness or hyperactivity)												
3[1]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[7]	none	11/149 (7.38%)	0/147 (0%)	Peto OR 7.91 (2.36 to 26.54) NICE analysis: RR 11.63 (1.54 to 88.04)	-	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI, Confidence interval; MID, Minimal important difference; OR, Odds ratio; RR, Relative risk												

[1] Coleman et al. (2008)
[2] Downgraded 1 level - This analysis contained 2 studies which Cochrane assessors classed as low quality studies (Cochrane assessed quality score of 2 or less)
[3] Downgraded 1 level - at a default minimal important difference (MID) of 25% data are consistent with no meaningful difference or appreciable benefit with decongestants
[4] Downgraded 1 level - This analysis contained 1 study which Cochrane assessors classed as low quality (Cochrane assessed quality score of 2 or less)
[5] Downgraded 2 levels - at a default minimal important difference (MID) of 25% data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[6] Downgraded 1 level – not assessable (no events in 1 RCT)
[7] Downgraded 2 levels - at a default minimal important difference (MID) of 25% data are consistent with no meaningful difference or appreciable harm with decongestants, the magnitude of the harm is unclear due to the very wide confidence interval

Table 16: GRADE profile – antihistamine versus control

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antihistamine	Control	Relative (95% CI)	Absolute		
Persistent acute otitis media at 2 weeks												
6[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	98/486 (20.16%)	107/501 (21.35%)	Peto OR 0.84 (0.58 to 1.24) NICE analysis: RR 0.92 (0.75 to 1.12)	-	⊕⊕OO LOW	CRITICAL
Persistent acute otitis media (before 7 days)												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[4]	none	5/44 (11.36%)	5/46 (10.87%)	Peto OR 1.05 (0.28 to 3.89) NICE analysis: RR 1.05 (95% CI 0.32 to 3.36)	-	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antihistamine	Control	Relative (95% CI)	Absolute		
Persistent acute otitis media (after 2 weeks)												
2[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	18/53 (33.96%)	11/59 (18.64%)	Peto OR 2.41 (1.02 to 5.68) NICE analysis: RR 1.87 (0.99 to 3.53)	-	⊕⊕⊕O MODERATE	CRITICAL
Otalgia												
2[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	23/85 (27.0%)	26/91 (28.57%)	Peto OR 0.87 (0.43 to 1.76) NICE analysis: RR 0.92 (0.59 to 1.43)	-	⊕⊕OO LOW	IMPORTANT
Hearing loss												
1[1]	randomised trials	serious[6]	not applicable	no serious indirectness	very serious[4]	none	1/250 (0.4%)	2/264 (0.75%)	Peto OR 0.54 (0.06 to 5.22) NICE analysis: RR 0.53 (0.05 to 5.79)	-	⊕OOO VERY LOW	IMPORTANT
Complications: prolonged acute otitis media (follow-up 8 to 12 weeks)												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[4]	none	5/34 (14.7%)	5/34 (14.7%)	Peto OR 1.00 (0.26 to 3.79) NICE analysis: RR 1.00 (0.32 to 3.14)	-	⊕⊕OO LOW	CRITICAL
Complications: recurrent acute otitis media (after 2 weeks)												
5[1]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	very serious[4]	none	31/413 (7.5%)	30/435 (6.9%)	Peto OR 1.10 (0.64 to 1.88) NICE analysis: RR 1.09 (0.68 to 1.73)	-	⊕OOO VERY LOW	CRITICAL
Complications: need for surgery												
3[1]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	very serious[4]	none	17/328 (5.18%)	13/344 (3.78%)	Peto OR 1.40 (0.66 to 2.97) NICE analysis: RR 1.36 (0.68 to 2.69)	-	⊕OOO VERY LOW	CRITICAL
Complications: mastoiditis or meningitis												
No data were available												CRITICAL
Adverse effects (excluding drowsiness or hyperactivity)												
2[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[7]	none	3/94 (3.19%)	0/98 (0%)	Peto OR 7.60 (0.78 to 74.26) NICE analysis: RR 7.0 (0.37 to 133.12)	-	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antihistamine	Control	Relative (95% CI)	Absolute		
Abbreviations: CI, Confidence interval; MID, Minimal important difference; OR, Odds ratio; RR, Relative risk.												

[1] Coleman et al. (2008)
[2] Downgraded 1 level - This analysis contained 2 studies which Cochrane classed as low quality studies (Cochrane assessed quality score of 2 or less)
[3] Downgraded 1 level - at a default minimal important difference (MID) of 25% data are consistent with no meaningful difference or appreciable benefit with antihistamines
[4] Downgraded 2 levels - at a default MID of 25% data are consistent with no meaningful difference, appreciable benefit or appreciable harm with antihistamines
[5] Downgraded 1 level - at a default MID of 25% data are consistent with no meaningful difference or appreciable harm with antihistamines
[6] Downgraded 1 level – This analysis contained 1 study which Cochrane classed as low quality (Cochrane assessed score 1 out of 5)
[7] Downgraded 2 levels - at a default minimal important difference (MID) of 25% data are consistent with no meaningful difference or appreciable harm with antihistamines. The magnitude of the harm is uncertain due to the very wide confidence interval

Table 17: GRADE profile – decongestant plus antihistamine versus control

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Decongestant plus antihistamine	Control	Relative (95% CI)	Absolute		
Persistent acute otitis media at 2 weeks												
5[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	74/238 (31.1%)	99/244 (40.5%)	Peto OR 0.63 (0.43 to 0.93) NICE analysis: RR 0.76 (0.60 to 0.96)	-	⊕⊕OO LOW	CRITICAL
Persistent acute otitis media (before 7 days)												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[4]	none	13/25 (52%)	17/28 (60.7%)	Peto OR 0.71 (0.24 to 2.07) NICE analysis: RR 0.86 (0.53 to 1.38)	-	⊕⊕OO LOW	CRITICAL
Persistent acute otitis media (after 2 weeks)												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[4]	none	5/24 (20.8%)	4/25 (16%)	Peto OR 1.37 (0.33 to 5.74) NICE analysis: RR 1.30 (0.40 to 4.28)	-	⊕⊕OO LOW	CRITICAL
Complications: prolonged acute otitis media												
No data were reported												CRITICAL
Complications: recurrent acute otitis media (after 2 weeks)												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[4]	none	0/26 (0%)	2/26 (7.69%)	Peto OR 0.13 (0.01 to 2.14)	-		CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Decongestant plus antihistamine	Control	Relative (95% CI)	Absolute		
									NICE analysis: RR 0.2 (0.01 to 3.97)		⊕⊕OO LOW	
Hyperactivity												
2[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	1/51 (1.96%)	0/54 (0%)	Peto OR 8.33 (0.16 to 422.51) NICE analysis: RR 3.35 (0.14 to 78.6)	-	⊕⊕OO LOW	IMPORTANT
Drowsiness												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[4]	none	2/25 (8%)	0/28 (0%)	Peto OR 8.68 (0.53 to 143.30) NICE analysis: RR 5.58 (0.28 to 110.89)	-	⊕⊕OO LOW	IMPORTANT
Adverse effects (excluding drowsiness or hyperactivity)												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[4]	none	2/26 (7.69%)	0/26 (0%)	Peto OR 7.69 (0.47 to 126.39) NICE analysis: RR 5.0 (0.25 to 99.34)	-	⊕⊕OO LOW	CRITICAL

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

[1] Coleman et al. (2008)
[2] Downgraded 1 level - This analysis included 1 study Cochrane classed as low quality (Cochrane assessed score 1 out of 5)
[3] Downgraded 1 level - Downgraded 1 level - at a default minimal important difference (MID) of 25% data are consistent with no meaningful difference or appreciable benefit with decongestant plus antihistamine
[4] Downgraded 2 levels - at a default minimal important difference (MID) of 25% data are consistent with no meaningful difference, appreciable benefit or appreciable harm

H.4 Oral corticosteroids

Table 18: GRADE profile – oral corticosteroid versus placebo[1]

Quality assessment							No of patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral corticosteroid	Placebo	Relative (95% CI)		
Treatment failure at day 5											

Quality assessment							No of patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral corticosteroid	Placebo	Relative (95% CI)		
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	very serious[4]	none	4/45 (8.9%)	5/46 (10.9%)	NICE analysis: RR 0.82 (0.23 to 2.85)	⊕OOO VERY LOW	CRITICAL[5]
Treatment failure at day 14											
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	very serious[4]	none	4/45 (8.9%)	5/46 (10.9%)	NICE analysis: RR 0.82 (0.23 to 2.85)	⊕OOO VERY LOW	CRITICAL[5]
Treatment failure during the first 2 weeks											
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	very serious[4]	none	7/45[6] (15.6%)	10/46 (21.7%)	NICE analysis: RR 0.72 (0.30 to 1.71)	⊕OOO VERY LOW	CRITICAL[5]
Presence of middle ear effusion (follow-up 1 month)											
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	very serious[4]	none	20/45 (45%)	22/46 (48%)	NICE analysis: RR 0.93 (0.6 to 1.45)	⊕OOO VERY LOW	CRITICAL
Presence of middle ear effusion (follow-up 2 months)											
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	very serious[4]	none	12/45 (27%)	16/46[7] (34%)	NICE analysis: RR 0.77 (0.41 to 1.43)	⊕OOO VERY LOW	CRITICAL
Presence of middle ear effusion (follow-up 3 months)											
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	very serious[4]	none	9/45[7] (19%)	10/46 (22%)	NICE analysis: RR 0.92 (0.41 to 2.05)	⊕OOO VERY LOW	CRITICAL
Recurrence (follow-up 1 month)											
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	very serious[4]	none	9/45[7] (20%)	7/46 (16%)	NICE analysis: RR 1.31 (95% CI 0.54 to 3.23)	⊕OOO VERY LOW	CRITICAL
Recurrence (follow-up 2 months)											
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	very serious[4]	none	10/45[7] (23%)	12/46[7] (27%)	NICE analysis: RR 0.85 (0.41 to 1.77)	⊕OOO VERY LOW	CRITICAL
Recurrence (follow-up 3 months)											
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	very serious[4]	none	10/45[7] (23%)	15/46[7] (32%)	NICE analysis; RR 0.68 (0.34 to 1.35)	⊕OOO VERY LOW	CRITICAL
Recurrence (follow-up 4 to 6 months)											

Quality assessment							No of patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral corticosteroid	Placebo	Relative (95% CI)		
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	very serious[4]	none	15/45[7] (33%)	17/46[7] (38%)	NICE analysis: RR 0.90 (0.52 to 1.58)	⊕OOO VERY LOW	CRITICAL
Adverse effects											
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	serious[8]	none	-	-	Adverse effects were similar across groups (no analysis reported, data not reported for individual groups)	⊕⊕OO LOW	CRITICAL

Abbreviations: CI, Confidence interval; RR, Relative risk

[1] All children received a single dose of intramuscular ceftriaxone
[2] Chonmaitree et al. (2003)
[3] Downgraded 1 level - allocation concealment, randomisation and blinding not described
[4] Downgraded 2 levels - at a default minimal important difference (MID) of 25% data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[5] Treatment failure was defined as failure that required additional antibiotics
[6] Treatment failure occurred at both visits (day 5 and day 14) in one person
[7] The NICE calculated values from the proportions given in the paper could be either slightly higher or lower, as the authors reported value lies between the two, this makes little difference in the subsequent relative risk
[8] Downgraded 1 level – not assessable

H.5 Antibiotic prescribing strategies

Table 19: GRADE profile – back-up antibiotics 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 antibiotics	No antibiotics	Relative (95% CI)	Absolute		
Pain at day 3												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	26/106 (24.5%)	29/100 (29%)	OR 0.80 (0.43 to 1.48) NICE analysis: RR 0.85 (0.54 to 1.33)	44 fewer per 1000 (from 141 fewer to 87 more)	⊕OOO VERY LOW	CRITICAL
Fever at day 3												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[4]	none	18/106 (17%)	8/100 (8%)	OR 2.35 (0.97 to 5.69) NICE analysis: RR 2.12 (0.97 to 4.66)	90 more per 1000 (from 2 fewer to 251 more)	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Back-up antibiotics	No antibiotics	Relative (95% CI)	Absolute		
Antibiotic use												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	no serious imprecision	strong association[5]	40/106 (37.7%)	13/100 (13%)	OR 4.06 (2.01 to 8.19) NICE analysis: RR 2.90 (1.65 to 5.10)	248 more per 1000 (from 101 more to 420 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Patient satisfaction												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[4]	none	101/106 (95.2%)	91/100 (91.0%)	OR 2.00 (0.65 to 6.18) NICE analysis: RR 1.05 (0.97 to 1.13)	43 more per 1000 (from 42 fewer to 74 more)	⊕⊕OO LOW	IMPORTANT
Abbreviations: CI, Confidence interval; OR, Odds ratio; RR, Relative risk												

[1] Spurling et al. 2013
[2] Downgraded 1 level - high risk of performance and selection bias (as assessed by Cochrane authors)
[3] Downgraded 2 levels - at a default minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[4] Downgraded 1 level - at a default minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit with antibiotic
[5] Upgraded 1 level – RR >2

Table 20: GRADE profile – back-up antibiotics versus immediate antibiotics

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Back-up antibiotics	Immediate antibiotics	Relative (95% CI)	Absolute		
Pain at day 3												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	serious[2]	none	28/111 (25.2%)	15/101 (14.9%)	OR 1.93 (0.96 to 3.88) NICE analysis: RR 1.70 (0.96 to 2.99)	103 more per 1000 (from 5 fewer to 255 more)	⊕⊕⊕O MODERATE	CRITICAL
Pain at days 4 to 6												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	no serious imprecision	none	85/132 (64.4%)	89/133 (66.9%)	OR 0.89 (0.54 to 1.48) NICE analysis: RR 0.96 (0.81 to 1.15)	26 fewer per 1000 (from 147 fewer to 80 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Pain at day 7												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Back-up antibiotics	Immediate antibiotics	Relative (95% CI)	Absolute		
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[3]	none	3/111 (2.7%)	0/101 (0%)	OR 6.55 (0.33 to 128.35) NICE analysis: RR 6.38 (0.33 to 121.9)	-	⊕⊕OO LOW	CRITICAL
Pain severity at day 3[4]												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	serious[2]	none	111	102	-	MD 0.75 higher (0.26 to 1.24 higher)	⊕⊕⊕O MODERATE	CRITICAL
Pain severity at day 7[4]												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	serious[2]	none	111	101	-	MD 0.12 higher (0.04 lower to 0.28 higher)	⊕⊕⊕O MODERATE	CRITICAL
Malaise at day 3												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	no serious imprecision	none	45/150 (30%)	19/135 (14.1%)	OR 2.62 (1.44 to 4.76) NICE analysis: RR 2.13 (1.31 to 3.46)	122 more per 1000 (from 37 more to 240 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Malaise severity at day 3[4]												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	serious[2]	none	150	134	-	MD 0.43 higher (0.11 to 0.75 higher)	⊕⊕⊕O MODERATE	CRITICAL
Malaise severity at day 7 (assessed by 'last day crying'[4,5])												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	serious[2]	none	150	135	-	MD 0.69 higher (0.31 to 1.07 higher)	⊕⊕⊕O MODERATE	CRITICAL
Fever at days 4 to 6[6]												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[3]	none	42/132 (31.8%)	46/133 (34.6%)	OR 0.88 (0.53 to 1.47) NICE analysis: RR 0.92 (0.65 to 1.30)	28 fewer per 1000 (from 127 fewer to 91 more)	⊕⊕OO LOW	CRITICAL
Supplementary spoons of paracetamol/day												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Back-up antibiotics	Immediate antibiotics	Relative (95% CI)	Absolute		
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	serious[2]	none	149	133	-	MD 0.59 higher (0.25 to 0.93 higher)	⊕⊕⊕O MODERATE	CRITICAL
Supplementary use of paracetamol plus ibuprofen												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	no serious imprecision	none	123/132 (93.2%)	120/133 (90.2%)	OR 1.48 (0.61 to 3.59) NICE analysis: RR 1.03 (0.96 to 1.11)	30 more per 1000 (from 53 fewer to 68 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Antibiotic use (back-up antibiotics: prescription at time of visit)												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	no serious imprecision	none	50/132 (37.9%)	116/133 (87.2%)	OR 0.09 (0.05 to 0.17) NICE analysis: RR 0.43 (0.35 to 0.55)	492 fewer per 1000 (from 335 fewer to 618 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Antibiotic use (back-up antibiotics: return for prescription)												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	no serious imprecision	strong association[7]	36/150 (24.0%)	132/151 (87.4%)	OR 0.05 (95% CI 0.02 to 0.08) NICE analysis: RR 0.27 (0.21 to 0.37)	616 fewer per 1000 (from 517 fewer to 752 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Re-consultation rates												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[3]	none	13/132 (9.8%)	11/133 (8.3%)	OR 1.21 (0.52 to 2.81) NICE analysis: RR 1.19 (0.55 to 2.56)	16 more per 1000 (from 38 fewer to 119 more)	⊕⊕OO LOW	CRITICAL
Patient satisfaction (back-up antibiotics: return for prescription)												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	no serious imprecision	none	115/150 (76.7%)	123/135 (91.1%)	OR 0.32 (0.16 to 0.65) NICE analysis: RR 0.84 (0.76 to 0.93)	145 fewer per 1000 (from 42 fewer to 290 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
Diarrhoea (2 RCTs: data pooled by NICE)												
2[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	24/282 (8.5%)	56/268 (20.9%)	NICE analysis: RR 0.41 (0.26 to 0.64)	-	⊕⊕⊕⊕ HIGH	CRITICAL
Vomiting												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Back-up antibiotics	Immediate antibiotics	Relative (95% CI)	Absolute		
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[3]	none	15/132 (11.4%)	15/133 (11.3%)	OR 1.01 (0.47 to 2.16) NICE analysis: RR 1.01 (0.51 to 1.98)	1 more per 1000 (from 56 fewer to 103 more)	⊕⊕OO LOW	CRITICAL
Skin rash												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[3]	none	8/150 (5.3%)	6/135 (4.4%)	OR 1.21 (0.41 to 3.58) NICE analysis: RR 1.20 (0.43 to 3.37)	9 more per 1000 (from 26 fewer to 98 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI, Confidence interval; MD, Mean difference; OR, Odds ratio; RR, Relative Risk												

[1] Spurling et al. (2013)
[2] Downgraded 1 level - at a default minimal important difference (MID) of 25% (or 0.5 standard deviation [SD] of control arm for continuous data), data are consistent with no meaningful difference or appreciable benefit with immediate antibiotic
[3] Downgraded 2 levels - at a default MID of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[4] Severity was measured on a 10 point Likert scale with lower values indicating lower pain
[5] Malaise severity at day 7 was also reported directly (not by proxy) in the primary study, but not reported in the main finding or analysis of Spurling et al. (2013)
[6] Fever at day 3 was reported in the primary study, but not reported in the main finding or analysis of Spurling et al. (2013)
[7] Upgraded 1 level - large effect (point estimate and 95% confidence intervals show >60% reduction in antibiotic use)

Table 21: GRADE profile – immediate antibiotics versus expectant observation

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate antibiotics	Expectant observation[1]	Relative (95% CI)	Absolute		
Pain at days 3 to 7												
4[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	141/478 (29.5%)	171/481 (35.6%)	RR 0.75 (0.50 to 1.12)	89 fewer per 1000 (from 178 fewer to 43 more)	⊕⊕⊕O MODERATE	CRITICAL
Pain at days 11 to 14												
1[2]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	no serious imprecision	none	75/123 (61%)	83/124 (66.9%)	RR 0.91 (0.75 to 1.10)	60 fewer per 1000 (from 167 fewer to 67 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Abnormal tympanometry at 4 weeks												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate antibiotics	Expectant observation[1]	Relative (95% CI)	Absolute		
1[2]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	serious[4]	none	55/108 (50.9%)	49/99 (49.5%)	RR 1.03 (0.78 to 1.35)	15 more per 1000 (from 109 fewer to 173 more)	⊕⊕⊕O MODERATE	CRITICAL
Tympanic membrane perforation												
1[2]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	serious[5]	none	0/92 (0%)	0/87 (0%)	-	-	⊕⊕⊕O MODERATE	CRITICAL
Recurrence of acute otitis media												
1[2]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[6]	none	20/109 (18.3%)	13/100 (13%)	RR 1.41 (0.74 to 2.69)	53 more per 1000 (from 34 fewer to 220 more)	⊕⊕OO LOW	CRITICAL
Parent-reported ear pain episodes at 1 year												
1[2]	randomised trials	no serious risk of bias	serious[5]	no serious indirectness	serious[7]	none	-	-	OR 1.03 (0.60 to 1.78)	-	⊕⊕OO LOW	CRITICAL
Vomiting, diarrhoea or rash												
2[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	77/268 (28.7%)	47/282 (16.7%)	RR 1.71 (1.24 to 2.36)	118 more per 1000 (from 40 more to 227 more)	⊕⊕⊕O MODERATE	CRITICAL

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

[1] See Terms used in the guideline for definition of expectant observation (includes watchful waiting and back-up prescribing)
[2] Venekamp et al. (2015)
[3] Downgraded 1 level - at a default minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit with immediate antibiotic
[4] Downgraded 1 level - at a default MID of 25%, data are consistent with no meaningful difference or appreciable benefit with expectant observation
[5] Downgraded 1 level - not assessable
[6] Downgraded 2 levels - at a default MID of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[7] Downgraded 1 level – not assessable

H.6 Antibiotics

Table 22: GRADE profile – antibiotic versus placebo

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		
Pain at 24 hours												

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		
5[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	267/709 (37.7%)	292/685 (42.6%)	RR 0.89 (0.78 to 1.01)	47 fewer per 1000 (from 94 fewer to 4 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Pain at 2 to 3 days												
7[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	138/1186 (11.6%)	180/1134 (15.9%)	RR 0.70 (0.57 to 0.86)	48 fewer per 1000 (from 22 fewer to 68 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Pain at 4 to 7 days												
8[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	119/680 (17.5%)	161/667 (24.1%)	RR 0.76 (0.63 to 0.91)	58 fewer per 1000 (from 22 fewer to 89 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Pain at 10 to 12 days												
1[2]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	no serious imprecision	none	10/139 (7.2%)	30/139 (21.6%)	RR 0.33 (0.17 to 0.66)	145 fewer per 1000 (from 73 fewer to 179 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Abnormal tympanometry at 2 to 4 weeks												
7[2]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[3]	none	419/1070 (39.2%)	514/1068 (48.1%)	RR 0.82 (0.74 to 0.90)	87 fewer per 1000 (from 48 fewer to 125 fewer)	⊕⊕OO LOW	CRITICAL
Abnormal tympanometry at 6 to 8 weeks												
3[2]	randomised trials	serious[5]	serious[4]	no serious indirectness	no serious imprecision	none	222/478 (46.4%)	249/475 (52.4%)	RR 0.88 (0.78 to 1.00)	63 fewer per 1000 (from 115 fewer to 0 more)	⊕⊕OO LOW	CRITICAL
Abnormal tympanometry at 3 months												
3[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	96/411 (23.4%)	96/398 (24.1%)	RR 0.97 (0.76 to 1.24)	7 fewer per 1000 (from 58 fewer to 58 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Tympanic membrane perforation												
5[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	9/533 (1.7%)	26/542 (4.8%)	RR 0.37 (0.18 to 0.76)	30 fewer per 1000 (from 12 fewer to 39 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Contralateral otitis media in unilateral cases												
4[2]	randomised trials	no serious risk of bias	serious[4]	no serious indirectness	serious[3]	none	48/453 (10.6%)	85/453 (18.8%)	RR 0.49 (0.25 to 0.95)	96 fewer per 1000 (from 9 fewer to 141 fewer)	⊕⊕OO LOW	CRITICAL
Late recurrence of acute otitis media at 3.5 years after randomisation												
6[2]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	208/1138 (18.3%)	213/1062 (20.1%)	RR 0.93 (0.78 to 1.10)	14 fewer per 1000 (from 44 fewer to 20 more)	⊕⊕⊕O MODERATE	IMPORTANT

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		
Vomiting, diarrhoea or rash												
8[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	283/1044 (27.1%)	208/1063 (19.6%)	RR 1.38 (1.19 to 1.59)	74 more per 1000 (from 37 more to 115 more)	⊕⊕⊕O MODERATE	CRITICAL

Abbreviations: CI, Confidence interval; RR, Relative risk

[1] Antibiotics included co-amoxiclav, ampicillin, pheneticillin, amoxicillin, penicillin and phenoxymethylpenicillin
[2] Venekamp et al. (2015)
[3] Downgraded 1 level - at a default minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit with antibiotic
[4] Downgraded 1 level - heterogeneity ≥50%
[5] Downgraded 1 level - unclear risk of selection, performance, attrition bias and/or other bias in included studies
[6] Downgraded 1 level - at a default minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable harm with placebo

Table 23: GRADE profile – antibiotics versus placebo (sub-group analyses)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic	Placebo	Relative (95% CI)	Absolute		
Pain, fever or both												
Children under 2 years – pain, fever, or both at 3 to 7 days[2]												
6[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[5]	91/280 (32.5%)[6]	137/287 (47.7%)[6]	RR 0.77 (0.68 to 0.89)	110 fewer per 1000 (from 53 fewer to 153 fewer)	⊕⊕OO LOW	CRITICAL
Children aged 2 years and over – pain, fever, or both at 3 to 7 days[2]												
6[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[5]	107/536 (20%)[6]	166/540 (30.7%)[6]	RR 0.86 (0.80 to 0.93)	43 fewer per 1000 (from 22 fewer to 61 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Children with bilateral AOM – pain, fever, or both at 3 to 7 days[2]												
6[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[5]	64/237 (27%)[6]	104/219 (47.5%)[6]	RR 0.72 (0.62 to 0.84)	133 fewer per 1000 (from 76 fewer to 180 fewer)	⊕⊕OO LOW	CRITICAL
Children without bilateral AOM – pain, fever, or both at 3 to 7 days[2]												
6[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[5]	104/433 (24%)[6]	132/439 (30.1%)[6]	RR 0.92 (0.85 to 1.00)	24 fewer per 1000 (from 45 fewer to 0 more)	⊕⊕⊕O MODERATE	CRITICAL
Children under 2 years with bilateral AOM – pain, fever, or both at 3 to 7 days[2]												
6[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[5]	42/140 (30%)[6]	74/133 (55.6%)[6]	RR 0.64 (0.62 to 0.80)	200 fewer per 1000 (from 111 fewer to 211 fewer)	⊕⊕OO LOW	CRITICAL
Children aged 2 years and over with bilateral AOM – pain, fever, or both at 3 to 7 days[2]												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic	Placebo	Relative (95% CI)	Absolute		
6[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[5]	20/87 (23%)[6]	30/85 (35.3%)[7]	RR 0.84 (0.70 to 1.02)	56 fewer per 1000 (from 106 fewer to 7 more)	⊕⊕OO LOW	CRITICAL
Children under 2 years with unilateral AOM – pain, fever, or both at 3 to 7 days[2]												
6[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[5]	45/129 (34.9%)[6]	53/132 (40.2%)[6]	RR 0.92 (0.76 to 1.11)	32 fewer per 1000 (from 96 fewer to 44 more)	⊕⊕⊕O MODERATE	CRITICAL
Children aged 2 years and over with unilateral AOM – pain, fever, or both at 3 to 7 days[2]												
6[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[5]	59/310 (19%)[6]	79/301 (26.2%)[6]	RR 0.92 (0.85 to 1.01)	21 fewer per 1000 (from 39 fewer to 3 more)	⊕⊕⊕O MODERATE	CRITICAL
Children with otorrhoea (assessed with: ear discharge present at baseline) – pain, fever, or both at 3 to 7 days[2]												
6[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[5]	12/50 (24%)[6]	39/66 (59.1%)[6]	RR 0.52 (0.37 to 0.73)	284 fewer per 1000 (from 160 fewer to 372 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Children without otorrhoea (assessed with: ear discharge present at baseline) – pain, fever, or both at 3 to 7 days[2]												
6[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[5]	61/218 (28%)[6]	94/221 (42.5%)[6]	RR 0.80 (0.70 to 0.92)	85 fewer per 1000 (from 34 fewer to 128 fewer)	⊕⊕OO LOW	CRITICAL
Pain												
Children under 2 years – pain at 3 to 7 days[8]												
6[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[5]	77/275 (28%)[6]	115/292 (39.4%)[6]	RR 0.83 (0.73 to 0.93)	67 fewer per 1000 (from 28 fewer to 106 fewer)	⊕⊕OO LOW	CRITICAL
Children aged 2 years and over – pain at 3 to 7 days[8]												
6[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[5]	86/539 (16%)[6]	142/537 (26.4%)[6]	RR 0.88 (0.82 to 0.93)	32 fewer per 1000 (from 19 fewer to 48 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Children with bilateral AOM – pain at 3 to 7 days[8]												
6[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[5]	48/240 (20%)[6]	88/216 (40.7%)[6]	RR 0.75 (0.66 to 0.85)	102 fewer per 1000 (from 61 fewer to 139 fewer)	⊕⊕OO LOW	CRITICAL
Children without bilateral AOM – pain at 3 to 7 days[8]												
6[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[5]	85/424 (20%)[6]	102/448 (22.8%)[6]	RR 0.96 (0.89 to 1.03)	9 fewer per 1000 (from 25 fewer to 7 more)	⊕⊕⊕O MODERATE	CRITICAL
Children under 2 years with bilateral AOM – pain at 3 to 7 days[8]												
6[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[5]	32/139 (23%)[6]	62/134 (46.3%)[6]	RR 0.70 (0.58 to 0.84)	139 fewer per 1000 (from 74 fewer to 194 fewer)	⊕⊕OO LOW	CRITICAL
Children aged 2 years and over with bilateral AOM – pain at 3 to 7 days[8]												
6[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	reporting bias[5]	16/94 (17%)[6]	26/89 (29.2%)[6]	RR 0.83 (0.71 to 0.99)	50 fewer per 1000 (from 3 fewer to 85 fewer)	⊕⊕OO LOW	CRITICAL
Children under 2 years with unilateral AOM – pain at 3 to 7 days[8]												
6[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[5]	41/133 (30.8%)[6]	42/128 (32.8%)[6]	RR 0.99 (0.84 to 1.17)	3 fewer per 1000 (from 53 fewer to 56 more)	⊕⊕⊕O MODERATE	CRITICAL
Children aged 2 years and over with unilateral AOM – pain at 3 to 7 days[8]												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic	Placebo	Relative (95% CI)	Absolute		
6[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[5]	44/294 (15%)[6]	59/317 (18.6%)[6]	RR 0.95 (0.88 to 1.02)	9 fewer per 1000 (from 22 fewer to 4 more)	⊕⊕⊕O MODERATE	CRITICAL
Adverse effects												
Diarrhoea												
6[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[9]	reporting bias[5]	n=819	n=824	Not assessable	4% to 21% (antibiotics) 2% to 14% (placebo)	⊕⊕OO LOW	CRITICAL
Skin rash												
6[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[9]	reporting bias[5]	n=819	n=824	Not assessable	1% to 8% (antibiotics) 2% to 6% (placebo)	⊕⊕OO LOW	CRITICAL
Meningitis at day 3												
6[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[10]	reporting bias[5]	0/819 (0%)	1/824 (0.12%)	NICE analysis: RR 0.34 (0.01 to 8.22)	1 case reported in a placebo group at day 3[11]	⊕⊕OO LOW	CRITICAL
Mastoiditis or other serious complications												
6[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[9]	reporting bias[5]	0/819 (0%)	0/824 (0%)	not estimable	No study reported mastoiditis or other serious complications	⊕⊕OO LOW	CRITICAL
Abbreviations: AOM, Acute otitis media; CI, Confidence interval; RR, Relative risk												

[1] Antibiotics in the included studies were co-amoxiclav for 7 days in 1 study, or amoxicillin for 7 days (2 studies) or 10 days (3 studies)
[2] Pain assessed by parents and recorded in diary form (either yes or no), fever was a temperature above 38°C
[3] Rovers et al. (2006)
[4] Downgraded 1 level - at a default minimal important difference (MID) of 25% data are consistent with no meaningful difference or appreciable benefit with antibiotics
[5] Downgraded 1 level - the author's note that 10 RCTs were identified as relevant, but only 6 RCTs provided study data
[6] Denominators are estimated to match numerator/percentages in published study
[7] The calculated denominator (85) does not match that predicted from the authors numerator/percentage (96)
[8] Pain assessed by parents and recorded in diary form (either yes or no)
[9] Downgraded 1 level - not assessable
[10] Downgraded 2 levels – at a default minimal important difference (MID) of 25% data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[11] Patient reported to have received antibiotics at day 2 because of deterioration

Table 24: GRADE profile – penicillin versus cephalosporin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Penicillin	Cephalosporin	Relative (95% CI)	Absolute		
Treatment success at day 5 to 14[1]												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Penicillin	Cephalosporin	Relative (95% CI)	Absolute		
4[2]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	no serious imprecision	none	242/260 (93.1%)	241/258 (93.4%)	Risk difference 0% (-7% to 7%) NICE analysis: RR 1.00 (0.93 to 1.08)	-	⊕⊕⊕O MODERATE	CRITICAL
Treatment success at days 3 to 16[4]												
5[2]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	539/676 (79.7%) NICE analysis[6] 513/676 (75.88%)	531/686 (77.4%) NICE analysis[6] 497/686 (72.44%)	Risk difference 0% (-2 % to 7%) NICE analysis: RR 1.04 (0.99 to 1.10)	-	⊕⊕⊕O MODERATE	CRITICAL
Any adverse events[7]												
1[2]	randomised trials	serious[5]	not applicable	no serious indirectness	no serious imprecision	none	54/128 (42.2%)	18/128 (14.1%)	Rate difference 28% (17% to 39%) NICE analysis: RR 3.00 (1.87 to 4.82)	-	⊕⊕⊕O MODERATE	CRITICAL
Any adverse events[8]												
1[2]	randomised trials	serious[5]	not applicable	no serious indirectness	no serious imprecision	none	54/128 (42.2%)	29/128 (22.7%)	Rate difference 20% (8% to 31%) NICE analysis: RR 1.86 (1.27 to 2.72)	-	⊕⊕⊕O MODERATE	CRITICAL
Any adverse events[9]												
1[2]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	no serious imprecision	none	79/258 (30.6%)	36/255 (14.1%)	Rate difference 16% (9% to 24%) NICE analysis: RR 2.17 (1.52 to 3.09)	-	⊕⊕⊕⊕ HIGH	CRITICAL
Diarrhoea[10]												
5[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[11]	none	53/374 (14.2%)	80/380 (21.1%)	Rate difference 8% (4% to 13%) NICE analysis: RR 1.69 (1.22 to 2.35)	-	⊕⊕⊕O MODERATE	CRITICAL

Abbreviations: CI, Confidence interval; RR, Relative risk.

[1] Ampicillin or amoxicillin versus ceftriaxone
[2] Shekelle et al. (2010)

[3] Downgraded 1 level - I^2 score >50%
[4] Co-amoxiclav for 7 to 10 days versus ceftriaxone (single dose)
[5] Downgraded 1 level - Jadad scores <3 indicating low quality studies
[6] The authors reported overall numerators and proportions do not match the individual study numerators and proportions in the meta-analysis, with treatment success for both study arms
[7] Co-amoxiclav versus cefdinir (once daily)
[8] Co-amoxiclav versus cefdinir (twice daily)
[9] Co-amoxiclav versus ceftriaxone
[10] Ampicillin or amoxicillin versus cefixime
[11] Downgraded 1 level - at a default minimal important difference (MID) of 25% data are consistent with no meaningful difference or appreciable harm with cephalosporin

Table 25: GRADE profile – penicillin versus macrolide

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Co-amoxiclav for 7 to 10 days	Azithromycin for 5 days or less	Relative (95% CI)	Absolute		
Treatment success at days 3 to 14												
9[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	no serious imprecision	none	822/951 (86.4%)	753/875 (86.1%)	Risk difference 0% (-7% to 6%) NICE analysis: RR 1.01 (0.95 to 1.08)	-	⊕⊕OO LOW	CRITICAL
Overall adverse events												
3[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	no serious imprecision	none	51/688 (7.41%)	173/678 (25.5%)	Risk difference: -19.2 (-29.2 to -9.2) NICE analysis: RR 0.29 (0.18 to 0.47)	-	⊕⊕OO LOW	CRITICAL
Gastrointestinal adverse events												
3[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	no serious imprecision	none	45/688 (6.54%)	161/678 (23.7%)	Risk difference: -18.0 (-28 to -8.0) NICE analysis: 0.28 (0.18 to 0.43)	-	⊕⊕OO LOW	CRITICAL
Abbreviations: CI, Confidence interval; RR, Relative risk.												

[1] Shekelle et al. (2010)
[2] Downgraded 1 level - Jadad scores <3 indicating low quality studies
[3] Downgraded 1 level - I^2 score >50%

Table 26: GRADE profile – cephalosporin versus macrolide

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cefaclor	Azithromycin	Relative (95% CI)	Absolute		
Treatment success at days 10 to 14												
3[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	199/212 (93.9%)	200/215 (93%)	Risk difference 1% (-4% to 3%) NICE analysis: RR 1.00 (0.95 to 1.05)	-	⊕⊕⊕O MODERATE	CRITICAL
Abbreviations: CI, confidence interval; RR, Relative risk.												

[1] Shekelle et al. (2010)
[2] Downgraded 1 level - Jadad score <3 indicating a low quality studies

Table 27: GRADE profile – penicillin versus quinolone in children with recurrent or persistent acute otitis media

Quality assessment							No of patients		Effect (95% CI)	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Penicillin	Quinolone			
Treatment success at days 3 to 10[1,2]											
1[3]	randomised trials	serious[4]	not applicable	no serious indirectness	no serious imprecision	none	102/121 (84.3%)	222/246 (90.2%)	Mean difference -5.9% (-12.9% to 1.1%) NICE analysis: RR 0.93 (0.86 to 1.02)	⊕⊕⊕O MODERATE	CRITICAL
Treatment success at day 10[1,2]											
1[3]	randomised trials	serious[4]	not applicable	no serious indirectness	no serious imprecision	none	92/117 (78.6%)	105/124 (84.7%)	Mean difference -6.1% (-15.9% to 3.7%) NICE analysis: RR 0.93 (0.82 to 1.05)	⊕⊕⊕O MODERATE	CRITICAL
Treatment success at days 2 to 5[2,5]											
1[3]	randomised trials	serious[4]	not applicable	no serious indirectness	no serious imprecision	none	592/630 (94%)	613/675 (90.1%)	Mean difference -3.2% (-6.2% to -0.2%)[6] NICE analysis: RR 1.03 (1.00 to 1.07)	⊕⊕⊕O MODERATE	CRITICAL
Abbreviations: CI, confidence interval; RR, Relative risk.											

[1] Co-amoxiclav versus gatifloxacin
[2] Treatment success not defined in Shekelle et al. (2010)
[3] Shekelle et al. (2010)
[4] Downgraded 1 level - not assessable
[5] Co-amoxiclav versus levofloxacin
[6] Original mean difference not reproducible (NICE calculated mean difference 0.03, 95% CI 0.00 to 0.06)

Table 28: GRADE profile – penicillin versus macrolide in children with recurrent or persistent acute otitis media

Quality assessment							No of patients		Effect (95% CI)	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Co-amoxiclav	Azithromycin			
Treatment success at days 12 to 16[1]											
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	no serious imprecision	none	122/145 (84.1%)	128/149 (85.9%)	Mean difference -1.8% (-10% to 6.4%) NICE analysis: RR 0.98 (0.89 to 1.08)	⊕⊕⊕O MODERATE	CRITICAL
Abbreviations: CI, confidence interval; RR, Relative risk.											

[1] Treatment success not defined in Shekelle et al. (2010)
[2] Shekelle et al. (2010)
[3] Downgraded 1 level - not assessable

Table 29: GRADE profile – cephalosporin versus another cephalosporin in children with recurrent or persistent acute otitis media

Quality assessment							No of patients		Effect (95% CI)	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cefaclor	Cefuroxime			
Treatment success at day 10[1]											
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	no serious imprecision	none	73/78 (93.6%)	65/70 (92.9%)	Mean difference 0.7% (-7% to 9%) NICE analysis: RR 1.01 (0.92 to 1.10)	⊕⊕⊕O MODERATE	CRITICAL
Treatment success at days 20 to 26[1]											
1[2]	randomised trials	serious[3]	not applicable	no serious indirectness	no serious imprecision	none	67/78 (85.9%)	61/70 (87.1%)	Mean difference -1.2% (-12% to 10%) NICE analysis: RR 0.99 (0.87 to 1.12)	⊕⊕⊕O MODERATE	CRITICAL
Abbreviations: CI, Confidence interval; RR, Relative risk											

[1] Treatment success not defined in Shekelle et al. (2010)
[2] Shekelle et al. (2010)
[3] Downgraded 1 level - not assessable

Table 30: GRADE profile – frequency of antibiotic dosing (amoxicillin or co-amoxiclav): once or twice a day versus three times a day

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Amoxicillin or co-amoxiclav once or twice a day	Amoxicillin or co-amoxiclav three times a day	Relative (95% CI)	Absolute		
Clinical cure at the end of treatment (days 7 to 15)												
5[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	716/805 (88.9%)	688/796 (86.4%)	RR 1.03 (0.99 to 1.07)	26 more per 1000 (from 9 fewer to 61 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Clinical cure during treatment												
2[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[2]	none	78/229 (34.1%)	73/219 (33.3%)	RR 1.06 (0.85 to 1.33)	20 more per 1000 (from 50 fewer to 110 more)	⊕⊕⊕O MODERATE	CRITICAL
Clinical cure post treatment (1 to 3 months after treatment)												
4[1]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	no serious imprecision	none	567/733 (77.4%)	557/743 (75%)	RR 1.02 (0.95 to 1.09)	15 more per 1000 (from 37 fewer to 67 more)	⊕⊕⊕O MODERATE	CRITICAL
Recurrence after completion of treatment												
3[1]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	very serious[4]	none	62/516 (12%)	47/513 (9.2%)	RR 1.21 (0.52 to 2.81)	19 more per 1000 (from 44 fewer to 166 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects: skin and diarrhoea												
3[1]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	very serious[4]	none	136/440 (30.9%)	131/438 (29.9%)	RR 0.92 (0.52 to 1.63)	24 fewer per 1000 (from 144 fewer to 188 more)	⊕OOO VERY LOW	CRITICAL
Compliance												
2[1]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	no serious imprecision	none	655/760 (86.2%)	622/760 (81.8%)	RR 1.04 (0.98 to 1.10)	33 more per 1000 (from 16 fewer to 82 more)	⊕⊕⊕O MODERATE	CRITICAL

Abbreviations: CI, Confidence interval; RR, Relative risk

[1] Thanaviratananich et al. (2013)
[2] Downgraded 1 level - at a default minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit with once or twice a day doses
[3] Downgraded 1 level - I^2 score >50%
[4] 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 31: GRADE profile – frequency of antibiotic dosing (amoxicillin): once or twice a day versus three times a day

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Amoxicillin once or twice a day	Amoxicillin three times a day	Relative (95% CI)	Absolute		
Clinical cure at the end of treatment												
2[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	76/88 (86.4%)	74/89 (83.1%)	RR 1.05 (0.82 to 1.34)	42 more per 1000 (from 150 fewer to 283 more)	⊕⊕OO LOW	CRITICAL
Clinical cure during treatment												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	serious[3]	none	30/30 (100%)	28/33 (84.8%)	RR 1.17 (1.01 to 1.37)	144 more per 1000 (from 8 more to 314 more)	⊕⊕⊕O MODERATE	CRITICAL
Clinical cure post treatment												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	no serious imprecision	none	42/46 (91.3%)	48/49 (98%)	RR 0.93 (0.85 to 1.03)	69 fewer per 1000 (from 147 fewer to 29 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Recurrence after completion of treatment												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[4]	none	4/49 (8.2%)	1/51 (2%)	RR 4.16 (0.48 to 35.95)	62 more per 1000 (from 10 fewer to 685 more)	⊕⊕OO LOW	CRITICAL
Adverse events: diarrhoea												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[4]	none	1/55 (1.8%)	1/55 (1.8%)	RR 1.00 (0.06 to 15.59)	0 fewer per 1000 (from 17 fewer to 265 more)	⊕⊕OO LOW	CRITICAL
Adverse events: skin												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[4]	none	3/55 (5.5%)	3/55 (5.5%)	RR 1.00 (0.21 to 4.74)	0 fewer per 1000 (from 43 fewer to 204 more)	⊕⊕OO LOW	CRITICAL
Compliance												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	no serious imprecision	none	33/33 (100%)	34/34 (100%)	RR 1.00 (0.94 to 1.06)	0 fewer per 1000 (from 60 fewer to 60 more)	⊕⊕⊕⊕ HIGH	CRITICAL

Abbreviations: RR, relative risk; CI, Confidence interval

[1] Thanaviratananich et al. (2013)
[2] Downgraded 1 level - I^2 score >50%
[3] Downgraded 1 level - at a default minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit with once or twice a day doses
[4] Downgraded 2 level - at a default minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 32: GRADE profile – frequency of antibiotic dosing (co-amoxiclav): once or twice a day versus three times a day

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Co-amoxiclav once or twice daily	Co-amoxiclav three times daily	Relative (95% CI)	Absolute		
Clinical cure at the end of treatment												
3[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	640/717 (89.3%)	614/707 (86.8%)	RR 1.03 (0.99 to 1.07)	26 more per 1000 (from 9 fewer to 61 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Clinical cure during treatment												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[2]	none	48/199 (24.1%)	45/186 (24.2%)	RR 1.00 (0.70 to 1.42)	0 fewer per 1000 (from 73 fewer to 102 more)	⊕⊕OO LOW	CRITICAL
Clinical cure post treatment												
3[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	525/687 (76.4%)	509/694 (73.3%)	RR 1.04 (0.98 to 1.10)	29 more per 1000 (from 15 fewer to 73 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Recurrence after completion of treatment												
2[1]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	very serious[2]	none	58/467 (12.4%)	46/462 (10.0%)	RR 1.01 (0.39 to 2.60)	1 more per 1000 (from 61 fewer 159 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI, Confidence interval; RR, Relative risk												

[1] Thanaviratananich et al. (2013)
[2] Downgraded 2 level - at a default minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[3] Downgraded 1 level - I^2 score >50%

Table 33: GRADE profile – short course antibiotic versus longer course antibiotic: different antibiotics

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short course (>48 hours but <7 days)	Longer course (7 days or more)	Relative (95% CI)	Absolute		
Treatment failure at 8 to 19 days[1]												
11[2]	randomised trials	serious[3]	serious[4]	no serious indirectness	serious[5]	none	340/1892 (18.0%)	293/2040 (14.4%)	Peto OR 1.37 (1.15 to 1.64) NICE analysis: RR 1.28 (1.02 to 1.62)	43 more per 1000 (from 18 more to 72 more)	⊕OOO VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short course (>48 hours but <7 days)	Longer course (7 days or more)	Relative (95% CI)	Absolute		
Treatment failure at 1 month or less[1,6]												
16[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[5]	none	486/2376 (20.5%)	475/2717 (17.5%)	Peto OR 1.34 (95% CI 1.15 to 1.55) NICE analysis: RR 1.24 (1.11 to 1.39)	46 more per 1000 (from 21 more to 72 more)	⊕⊕OO LOW	CRITICAL
Treatment failure at 20 to 30 days[1]												
9[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[5]	none	238/1141 (20.9%)	271/1335 (20.3%)	Peto OR 1.16 (95% CI 0.94 to 1.42) NICE analysis: RR 1.11 (0.96 to 1.29)	25 more per 1000 (from 10 fewer to 63 more)	⊕⊕OO LOW	CRITICAL
Treatment failure at 30 to 45 days[1]												
5[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	355/873 (40.7%)	364/988 (36.8%)	Peto OR 1.18 (0.97 to 1.43) NICE analysis: RR 1.10 (0.99 to 1.24)	39 more per 1000 (from 7 fewer to 86 more)	⊕⊕⊕O MODERATE	CRITICAL
Treatment failure at 3 months or less[1]												
7[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	391/973 (40.2%)	399/1095 (36.4%)	Peto OR 1.18 (0.98 to 1.41) NICE analysis: RR 1.10 (0.99 to 1.23)	39 more per 1000 (from 5 fewer to 83 more)	⊕⊕⊕O MODERATE	CRITICAL
Treatment failure at 90 days[1]												
2[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	36/100 (36%)	35/107 (32.7%)	Peto OR 1.16 (95% CI 0.65 to 2.06) NICE analysis: RR 1.10 (0.76 to 1.60)	33 more per 1000 (from 87 fewer to 173 more)	⊕⊕⊕O MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short course (>48 hours but <7 days)	Longer course (7 days or more)	Relative (95% CI)	Absolute		
Gastrointestinal adverse effects												
13[2]	randomised trials	serious[3]	serious[4]	no serious indirectness	serious[7]	none	206/2221 (9.27%)	369/2697 (13.7%)	Peto OR 0.72 (95% CI 0.60 to 0.87) NICE analysis: RR 0.81 (0.61 to 1.07)	34 fewer per 1000 (from 16 fewer to 50 fewer)	⊕OOO VERY LOW	CRITICAL
Sub-group analyses												
Children under 2 years: treatment failure at 1 month or less[1]												
5[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	99/296 (33.4%)	85/274 (31%)	Peto OR 1.09 (0.76 to 1.57) NICE analysis: RR 1.06 (0.84 to 1.34)	19 more per 1000 (from 55 fewer to 104 more)	⊕⊕⊕O MODERATE	CRITICAL
Children 2 years and over: treatment failure at 1 month or less[1]												
6[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	74/530 (14%)	86/534 (16.1%)	Peto OR 0.85 (0.60 to 1.21) NICE analysis: RR 0.88 (0.67 to 1.16)	21 fewer per 1000 (from 58 fewer to 27 more)	⊕⊕⊕O MODERATE	CRITICAL
Children with perforated eardrum: treatment failure at 1 month or less[1]												
1[2]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	serious[5]	none	10/15 (66.7%)	4/12 (33.3%)	Peto OR 3.62 (0.81 to 16.06) NICE analysis: RR 2.0 (0.83 to 4.81)	311 more per 1000 (from 45 fewer to 556 more)	⊕⊕⊕O MODERATE	CRITICAL
Children with non-perforated eardrum: treatment failure at 1 month or less[1]												
1[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[8]	none	10/47 (21.3%)	11/54 (20.4%)	Peto OR 1.02 (0.40 to 2.75) NICE analysis: RR 1.04 (0.49 to 2.24)	3 more per 1000 (from 111 fewer to 209 more)	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short course (>48 hours but <7 days)	Longer course (7 days or more)	Relative (95% CI)	Absolute		
Abbreviations: CI, Confidence interval; OR, Odds ratio; RR, Relative risk												

[1] Treatment failure is defined as a lack of clinical resolution, relapse or recurrence of acute otitis media within 1 month after the start of treatment
[2] Kozyrskyj et al. (2010)
[3] Downgraded 1 level – the majority of studies had at least one high risk or unclear risk of bias for adequate sequence generation, allocation concealment, incomplete outcome data and adequate blinding
[4] Downgraded 1 level – I^2 >50%
[5] Downgraded 1 level - at a default minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit with longer course antibiotic
[6] Additional sensitivity analysis to account for identified risk of bias (blinding and concealment) did not change the direction of effect
[7] Downgraded 1 level - at a default MID of 25%, data are consistent with no meaningful difference or appreciable benefit with short course antibiotic
[8] Downgraded 2 levels - at a default MID of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 34: GRADE profile – short course antibiotic (5 days) versus longer course antibiotic (10 days)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short course (5 days)	Longer course (10 days)	Relative (95% CI)	Absolute		
Treatment failure at 1 month[1] (excluding co-amoxiclav)												
14[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	378/1987 (19.0%)	383/2164 (17.7%)	Peto OR 1.20 (1.02 to 1.42) NICE analysis: RR 1.15 (1.01 to 1.30)	28 more per 1000 (from 3 more to 57 more)	⊕⊕OO LOW	CRITICAL
Treatment failure at 1 month[1] (co-amoxiclav only)												
2[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	108/389 (27.8%)	92/553 (16.6%)	Peto OR 1.99 (1.44 to 2.74) NICE analysis: RR 1.70 (1.32 to 2.18)	118 more per 1000 (from 57 more to 187 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Abbreviations: CI, Confidence interval; OR, odds ratio; RR, Relative risk												

[1] Treatment failure is defined as a lack of clinical resolution, relapse or recurrence of acute otitis media within 1 month after the start of treatment
[2] Kozyrskyj et al. (2010)
[3] Downgraded 1 level - majority of studies had at least one high risk or unclear risk of bias for adequate sequence generation, allocation concealment, incomplete outcome data and adequate blinding
[4] Downgraded 1 level - at a default minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit with longer course antibiotic

Table 35: GRADE profile – very short course antibiotic (<48 hours) versus longer course antibiotic (7 days or more)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short course (<48 hours)	Longer course (7 days or more)	Relative (95% CI)	Absolute		
Treatment failure at 1 month or less[1,2]												
2[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	11/53 (20.8%)	5/65 (7.7%)	Peto OR 2.99 (95% CI 1.04 to 8.54) NICE analysis: RR 2.55 (95% CI 0.99 to 6.58)	123 more per 1000 (from 3 more to 339 more)	⊕⊕⊕O MODERATE	CRITICAL
Abbreviations: OR, odds ratio; CI, Confidence interval												

[1] Treatment failure is defined as a lack of clinical resolution, relapse or recurrence of acute otitis media within 1 month after the start of treatment
[2] Antibiotics were penicillin V and amoxicillin
[3] Kozyrskyj et al. (2010)
[4] Downgraded 1 level - at a default minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit with longer course antibiotic

Table 36: GRADE profile – short course antibiotic versus longer course antibiotic: same antibiotic

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short course (>48 hours but <7 days)	Longer course (7 days or more)	Relative (95% CI)	Absolute		
Treatment failure at 8 to 19 days[1]												
6[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	185/995 (18.6%)	134/1158 (11.6%)	Peto OR 1.97 (95% CI 1.54 to 2.52) NICE analysis: RR 1.75 (95% CI 1.42 to 2.14)	89 more per 1000 (from 52 more to 132 more)	⊕⊕⊕O MODERATE	CRITICAL
Treatment failure at 20 to 30 days[1]												
4[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	87/561 (15.5%)	129/758 (17.0%)	Peto OR 1.27 (95% CI 0.92 to 1.76) NICE analysis: RR 1.20 (95% CI 0.94 to 1.53)	36 more per 1000 (from 11 fewer to 95 more)	⊕⊕⊕O MODERATE	CRITICAL
Treatment failure at 1 month or less[1]												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short course (>48 hours but <7 days)	Longer course (7 days or more)	Relative (95% CI)	Absolute		
9[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	258/1482 (17.4%)	257/1839 (14.0%)	Peto OR 1.65 (95% CI 1.35 to 2.01) NICE analysis: RR 1.48 (95% CI 1.26 to 1.73)	72 more per 1000 (from 40 more to 106 more)	⊕⊕⊕O MODERATE	CRITICAL
Treatment failure at 30 to 45 days[1]												
3[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	241/577 (41.8%)	258/708 (36.4%)	Peto OR 1.25 (95% CI 1.00 to 1.57) NICE analysis: RR 1.15 (95% CI 1.00 to 1.32)	53 more per 1000 (from 0 more to 109 more)	⊕⊕⊕O MODERATE	CRITICAL
Treatment failure at 90 days[1]												
2[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	36/100 (36%)	35/107 (32.7%)	Peto OR 1.16 (95% CI 0.65 to 2.06) NICE analysis: RR 1.10 (95% CI 0.76 to 1.60)	33 more per 1000 (from 87 fewer to 173 more)	⊕⊕OO LOW	CRITICAL
Treatment failure at 3 months or less[1]												
5[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	277/677 (40.9%)	293/815 (36.0%)	Peto OR 1.24 (95% CI 1.00 to 1.53) NICE analysis: RR 1.14 (95% CI 1.00 to 1.30)	51 more per 1000 (from 0 more to 103 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: OR, odds ratio; CI, Confidence interval; RR, Relative risk.												

[1] Treatment failure is defined as a lack of clinical resolution, relapse or recurrence of acute otitis media within 1 month after the start of treatment
[2] Kozyrskyj et al. 2010
[3] Downgraded 1 level - majority of studies had at least one high risk or unclear risk of bias for adequate sequence generation, allocation concealment, incomplete outcome data and adequate blinding
[4] Downgraded 1 level - at a default minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit with longer course antibiotic

Table 37: GRADE profile – short course antibiotic versus longer course antibiotic: ceftriaxone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftriaxone (single IM dose)	Ceftriaxone (7 days or more)	Relative (95% CI)	Absolute		
Treatment failure at 1 month or less[1]												
8[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	247/838 (29.5%)	235/871 (27%)	Peto OR 1.07 (95% CI 0.86 to 1.33) NICE analysis: RR 1.05 (95% CI 0.91 to 1.21)	14 more per 1000 (from 29 fewer to 60 more)	⊕⊕⊕O MODERATE	CRITICAL
Treatment failure at 3 months or less[1]												
3[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	130/355 (36.6%)	139/346 (40.2%)	Peto OR 0.89 (95% CI 0.66 to 1.21) NICE analysis: RR 0.93 (95% CI 0.78 to 1.13)	28 fewer per 1000 (from 95 fewer to 47 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Gastrointestinal adverse effects												
1[2]	randomised trials	serious[4]	not applicable	no serious indirectness	no serious imprecision	none	46/195 (23.6%)	19/207 (9.2%)	Peto OR 2.89 (95% CI 1.70 to 4.91) NICE analysis: RR 2.57 (95% CI 1.56 to 4.23)	134 more per 1000 (from 55 more to 240 more)	⊕⊕⊕O MODERATE	CRITICAL

Abbreviations: CI, Confidence interval; IM, Intramuscular; OR, odds ratio;

[1] Treatment failure is defined as a lack of clinical resolution, relapse or recurrence of acute otitis media within 1 month after the start of treatment
[2] Kozyrskyj et al. (2010)
[3] Downgraded 1 level - majority of studies had at least one high risk or unclear risk of bias for adequate sequence generation, allocation concealment, incomplete outcome data and adequate blinding
[4] Downgraded 1 level - 2 high risk and 1 unclear criteria on Cochrane risk of bias score

Table 38: GRADE profile – short course antibiotic versus longer course antibiotic: azithromycin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azithromycin (>48 hours but <7 days)	Azithromycin (7 days or more	Relative (95% CI)	Absolute		
Azithromycin (single IM dose short course): treatment failure at 25 to 32 days[1]												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azithromycin (>48 hours but <7 days)	Azithromycin (7 days or more	Relative (95% CI)	Absolute		
2[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	72/303 (23.8%)	72/305 (23.6%)	Peto OR 1.01 (0.69 to 1.47) NICE analysis: RR 1.01 (0.76 to 1.34)	2 more per 1000 (from 60 fewer to 76 more)	⊕⊕⊕O MODERATE	CRITICAL
Azithromycin (short course for 3 to 5 days): treatment failure at 8 to 19 days[1]												
18[2]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[3]	none	253/2225 (11.4%)	201/2122 (9.5%)	Peto OR 1.27 (1.04 to 1.55) NICE analysis: RR 1.22 (1.03 to 1.45)	23 more per 1000 (from 3 more to 45 more)	⊕⊕OO LOW	CRITICAL
Azithromycin (short course for 3 to 5 days): treatment failure at 1 month or less[1]												
19[2]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	412/2237 (18.4%)	392/2117 (18.5%)	Peto OR 1.02 (0.87 to 1.20) NICE analysis: RR 1.02 (0.90 to 1.14)	3 more per 1000 (from 20 fewer to 29 more)	⊕⊕⊕O MODERATE	CRITICAL
Azithromycin (single IM dose short course): gastrointestinal adverse effects												
2[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	55/331 (16.6%)	76/327 (23.2%)	Peto OR 0.66 (0.45 to 0.96) NICE analysis: RR 0.71 (0.52 to 0.97)	66 fewer per 1000 (from 7 fewer to 113 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Azithromycin (short course for 3 to 5 days): gastrointestinal adverse effects												
14[2]	randomised trials	serious[5]	serious[7]	no serious indirectness	no serious imprecision	none	91/1925 (4.7%)	209/1797 (11.6%)	Peto OR 0.36 (0.28 to 0.46) NICE analysis: RR 0.38 (95% CI 0.22 to 0.66)	71 fewer per 1000 (from 59 fewer to 81 fewer)	⊕⊕OO LOW	CRITICAL

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

[1] Treatment failure is defined as a lack of clinical resolution, relapse or recurrence of acute otitis media within 1 month after the start of treatment
[2] Kozyrskyj et al. (2010)
[3] Downgraded 1 level - at a default minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit with longer course antibiotic
[4] Downgraded 1 level - majority of studies had at least one high risk or unclear risk of bias for adequate sequence generation, allocation concealment, incomplete outcome data and adequate blinding
[5] Downgraded 2 levels - at a default MID of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[6] Downgraded 1 level - at a default MID of 25%, data are consistent with no meaningful difference or appreciable benefit with short course antibiotic
[7] Downgraded 1 level - I^2 >50%

Appendix I: Studies not-prioritised

Study reference	Reason
Adam D (2000) Efficacy and tolerability of 5-day vs. 10-day treatment with cefixime suspension in children with acute otitis media. Drugs of Today 36(SUPPL. E), 29-33	RCT included in a systematic review that has been prioritised
Arguedas A, Loaiza C, Perez A, Gutierrez A, Herrera M L, and Rothermel C D (2003) A pilot study of single-dose azithromycin versus three-day azithromycin or single-dose ceftriaxone for uncomplicated acute otitis media in children. Current Therapeutic Research - Clinical and Experimental 64(SUPPL. 1), A16-A29	Pilot study included in a systematic review that has been prioritised
Arguedas Adriano, Emparanza Paz, Schwartz Richard H, Soley Carolina, Guevara Silvia, de Caprariis , Pascal J, and Espinoza Gabriela (2005) A randomized, multicenter, double blind, double dummy trial of single dose azithromycin versus high dose amoxicillin for treatment of uncomplicated acute otitis media. The Pediatric infectious disease journal 24(2), 153-61	RCT included in a systematic review that has been prioritised
Arroll B, Kenealy T, and Kerse N (2003) Do delayed prescriptions reduce antibiotic use in respiratory tract infections? A systematic review. British Journal of General Practice 53(496), 871-877	Lower quality systematic review
Biner Betul, Celtik Coskun, Oner Naci, Kucukugurluoglu Yasemin, Guzel Ahmet, Yildirim Cetin, and Adali Mustafa Kemal (2007) The comparison of single-dose ceftriaxone, five-day azithromycin, and ten-day amoxicillin/clavulanate for the treatment of children with acute otitis media. The Turkish journal of pediatrics 49(4), 390-6	RCT included in a systematic review that has been prioritised
Block S L, Arrieta A, Seibel M, McLinn S, Eppes S, and Murphy M J (2003) Single-dose (30 mg/kg) azithromycin compared with 10-day amoxicillin/clavulanate for the treatment of uncomplicated acute otitis media: A double-blind, placebo-controlled, randomized clinical trial. Current Therapeutic Research - Clinical and Experimental 64(SUPPL. 1), A30-A42	RCT included in a systematic review that has been prioritised
Bolt Penny, Barnett Peter, Babl Franz E, and Sharwood Lisa N (2008) Topical lignocaine for pain relief in acute otitis media: results of a double-blind placebo-controlled randomised trial. Archives of disease in childhood 93(1), 40-4	RCT included in a systematic review that has been prioritised
Boonacker Chantal W. B, Hoes Arno W, Dikhoff Marie-Jose, Schilder Anne G. M, and Rovers Maroeska M (2010) Interventions in health care professionals to improve treatment in children with upper respiratory tract infections. International journal of pediatric otorhinolaryngology 74(10), 1113-21	Excluded on intervention – not about the treatment of AOM
Bornhoft G, Wolf U, Von Ammon , K , Righetti M, Maxion-Bergemann S, Baumgartner S, Thurneysen A, and Matthiessen P F (2006) Effectiveness, safety and cost-effectiveness of homeopathy in general practice - Summarized health technology assessment. Forschende Komplementarmedizin 13(SUPPL. 2), 19-29	Excluded on intervention – treatment not available in the UK
Carr R R, and Nahata M C (2006) Complementary and alternative medicine for upper-respiratory-tract infection in children. American Journal of Health-System Pharmacy 63(1), 33-39	Excluded on intervention – treatment not available in the UK
Chao Jennifer H, Kunkov Sergey, Reyes Lilia B, Lichten Stephanie, and Crain Ellen F (2008) Comparison of two approaches to observation therapy for acute otitis media in the emergency department. Pediatrics 121(5), e1352-6	RCT included in a systematic review that has been prioritised

Study reference	Reason
Cohen R, Levy C, Boucherat M, Langue J, Autret E, Gehanno P, de La Rocque , and F (2000) Five vs. ten days of antibiotic therapy for acute otitis media in young children. The Pediatric infectious disease journal 19(5), 458-63	RCT included in a systematic review that has been prioritised
Coker T R, Chan L S, Newberry S J, Limbos M A, Suttorp M J, Shekelle P G, and Takata G S (2010) Diagnosis, microbial epidemiology, and antibiotic treatment of acute otitis media in children: A systematic review. JAMA - Journal of the American Medical Association 304(19), 2161-2169	Lower quality systematic review
Courter Jd, Baker Wl, Nowak Ks, Smogowicz La, Desjardins Ll, Coleman Ci, and Girotto Je (2010) Increased clinical failures when treating acute otitis media with macrolides: a meta-analysis (Structured abstract). Annals of Pharmacotherapy 44(3), 471-478	Lower quality systematic review
Catania S, and Gallo A (2004) [Clinical efficacy and tolerability of short course therapy with cefaclor compared with long-term therapy for treatment of acute otitis media in children]. Le infezioni in medicina : rivista periodica di eziologia, epidemiologia, diagnostica, and clinica e terapia delle patologie infettive 12(4), 259-65	RCT included in a systematic review that has been prioritised
Dagan R, Johnson C E, McLinn S, Abughali N, Feris J, Leibovitz E, Burch D J, and Jacobs M R (2000a) Bacteriologic and clinical efficacy of amoxicillin/clavulanate vs. azithromycin in acute otitis media. The Pediatric infectious disease journal 19(2), 95-104	RCT included in a systematic review that has been prioritised
Dagan R, Leibovitz E, Fliss D M, Leiberman A, Jacobs M R, Craig W, and Yagupsky P (2000b) Bacteriologic efficacies of oral azithromycin and oral cefaclor in treatment of acute otitis media in infants and young children. Antimicrobial agents and chemotherapy 44(1), 43-50	RCT included in a systematic review that has been prioritised
Damoiseaux R A. M. J, Van Balen , F A M, Hoes A W, Verheij T J. M, De Melker , and R A (2000) Primary care based randomised, double blind trial of amoxicillin versus placebo for acute otitis media in children aged under 2 years. British Medical Journal 320(7231), 350-354	RCT included in a systematic review that has been prioritised
Damrikarnlert L, Jauregui A C, and Kzadri M (2000) Efficacy and safety of amoxycillin/clavulanate (Augmentin) twice daily versus three times daily in the treatment of acute otitis media in children. Journal of Chemotherapy 12(1), 79-87	RCT included in a systematic review that has been prioritised
Dunne Michael W, Latiolais Thomas, Lewis Barnett, Pistorius Bruce, Bottenfield Gerald, Moore William H, Garrett Anne, Stewart Tracy D, Aoki Jeffrey, Spiegel Craig, Boettger David, and Shemer Anne (2003) Randomized, double-blind study of the clinical efficacy of 3 days of azithromycin compared with co-amoxiclav for the treatment of acute otitis media. The Journal of antimicrobial chemotherapy 52(3), 469-72	RCT included in a systematic review that has been prioritised
Easton Jane, Noble Stuart, and Perry Caroline M (2003) Amoxicillin/clavulanic acid: a review of its use in the management of paediatric patients with acute otitis media. Drugs 63(3), 311-40	Lower quality systematic review (studies are covered in another systematic review that has been prioritised)
Esposito S, Bianchini S, Baggi E, Castellazzi L, Fumagalli M, and Principi N (2013) Use of topical or systemic steroids in children with upper respiratory tract infection. European Journal of Inflammation 11(2), 337-344	Lower quality systematic review (studies are covered in another systematic review that has been prioritised)

Study reference	Reason
Garrison Gina Daubney, Sorum Paul C, Hioe Wayne, and Miller Margaret M (2004) High-dose versus standard-dose amoxicillin for acute otitis media. The Annals of pharmacotherapy 38(1), 15-9	RCT included in a systematic review that has been prioritised
Guven Mehmet, Bulut Yunus, Sezer Taner, Aladag Ibrahim, Eyibilen Ahmet, and Etikan Ilker (2006) Bacterial etiology of acute otitis media and clinical efficacy of amoxicillin-clavulanate versus azithromycin. International journal of pediatric otorhinolaryngology 70(5), 915-23	RCT included in a systematic review that has been prioritised
Gulani Anjana, Sachdev H P. S, and Qazi Shamim A (2010) Efficacy of short course (<4 days) of antibiotics for treatment of acute otitis media in children: a systematic review of randomized controlled trials. Indian pediatrics 47(1), 74-87	RCT included in a systematic review that has been prioritised
Gisselsson-Solen M (2014) The importance of being specific-a meta-analysis evaluating the effect of antibiotics in acute otitis media. International Journal of Pediatric Otorhinolaryngology 78(8), 1221-1227	Lower quality systematic review
Hoberman Alejandro, Dagan Ron, Leibovitz Eugene, Rosenblut Andres, Johnson Candice E, Huff Anne, Bandekar Rajesh, and Wynne Brian (2005) Large dosage amoxicillin/clavulanate, compared with azithromycin, for the treatment of bacterial acute otitis media in children. The Pediatric infectious disease journal 24(6), 525-32	RCT included in a systematic review that has been prioritised
Hoberman Alejandro, Paradise Jack L, Rockette Howard E, Shaikh Nader, Wald Ellen R, Kearney Diana H, Colborn D Kathleen, Kurs-Lasky Marcia, Bhatnagar Sonika, Haralam Mary Ann, Zoffel Lisa M, Jenkins Carly, Pope Marcia A, Balentine Tracy L, and Barbadora Karen A (2011) Treatment of acute otitis media in children under 2 years of age. The New England journal of medicine 364(2), 105-15	RCT included in a systematic review that has been prioritised
Hoberman A, Paradise J L, Rockette H E, Kearney D H, Bhatnagar S, Shope T R, Martin J M, Kurs-Lasky M, Copelli S J, Colborn D K, Block S L, Labella J J, Lynch T G, Cohen N L, Haralam M, Pope M A, Nagg J P, Green M D, and Shaikh N (2016) Shortened antimicrobial treatment for acute Otitis media in young children. New England Journal of Medicine 375(25), 2446-2456	Single study deprioritised as did not add to higher quality Systematic review, which 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	Lower quality systematic review (studies are covered in another systematic review that has been prioritised)
Law Constance, and Amsden Guy W (2004) Single-dose azithromycin for respiratory tract infections. The Annals of pharmacotherapy 38(3), 433-9	Lower quality systematic review (studies are covered in another systematic review that has been prioritised)
Le Saux , N , Gaboury I, Baird M, Klassen T P, MacCormick J, Blanchard C, Pitters C, Sampson M, and Moher D (2005) A randomized, double-blind, placebo-controlled noninferiority trial of amoxicillin for clinically diagnosed acute otitis media in children 6 months to 5 years of age. CMAJ 172(3), 335-341	RCT included in a systematic review that has been prioritised
Levi Jessica R, Brody Robert M, McKee-Cole Katie, Pribitkin Edmund, and O'Reilly Robert (2013) Complementary and alternative medicine for pediatric otitis media. International journal of pediatric otorhinolaryngology 77(6), 926-31	Excluded on intervention – treatment not available in the UK
Levi J R, and O'Reilly R (2013) Complementary and Integrative Treatments: Otitis Media. Otolaryngologic Clinics of North America 46(3), 309-327	Excluded on intervention – treatment not available in the UK

Study reference	Reason
Little P, Gould C, Williamson I, Moore M, Warner G, and Dunleavey J (2001) Pragmatic randomised controlled trial of two prescribing strategies for childhood acute otitis media. British Medical Journal 322(7282), 336-342	RCT included in a systematic review that has been prioritised
Little P, Moore M, Warner G, Dunleavy J, and Williamson I (2006) Longer term outcomes from a randomised trial of prescribing strategies in otitis media. British Journal of General Practice 56(524), 176-182	RCT considered in a systematic review that has been prioritised
McCormick David P, Chonmaitree Tasnee, Pittman Carmen, Saeed Kokab, Friedman Norman R, Uchida Tatsuo, and Baldwin Constance D (2005) Nonsevere acute otitis media: a clinical trial comparing outcomes of watchful waiting versus immediate antibiotic treatment. Pediatrics 115(6), 1455-65	RCT included in a systematic review that has been prioritised
Neumark Thomas, Molstad Sigvard, Rosen Christer, Persson Lars-Goran, Torngren Annika, Brudin Lars, and Eliasson Ingvar (2007) Evaluation of phenoxymethylpenicillin treatment of acute otitis media in children aged 2-16. Scandinavian journal of primary health care 25(3), 166-71	RCT included in a systematic review that has been prioritised
Oguz Fatma, Unuvar Emin, Suoglu Yusufhan, Erdamar Burak, Dundar Gulnur, Katircioglu Sami, and Sidal Mujgan (2003) Etiology of acute otitis media in childhood and evaluation of two different protocols of antibiotic therapy: 10 days cefaclor vs. 3 days azitromycin. International journal of pediatric otorhinolaryngology 67(1), 43-51	RCT included in a systematic review that has been prioritised
Ovetchkine P, and Cohen R (2003) Shortened course of antibacterial therapy for acute otitis media. Pediatric Drugs 5(2), 133-140	Lower quality systematic review (studies are covered in another systematic review that has been prioritised)
Pacifico L, and Chiesa C (2002) Azithromycin in children: A critical review of the evidence. Current Therapeutic Research - Clinical and Experimental 63(1), 54-76	Lower quality systematic review (studies are covered in another systematic review that has been prioritised)
Principi N, Bianchini S, Baggi E, and Esposito S (2013) No evidence for the effectiveness of systemic corticosteroids in acute pharyngitis, community-acquired pneumonia and acute otitis media. European Journal of Clinical Microbiology and Infectious Diseases 32(2), 151-160	Lower quality systematic review (studies are covered in another systematic review that has been prioritised)
Scott L J, Ormrod D, and Goa K L (2001) Cefuroxime axetil: An updated review of its use in the management of bacterial infections. Drugs 61(10), 1455-1500	Lower quality systematic review (studies are covered in another systematic review that has been prioritised)
Spiro David M, Tay Khoon-Yen, Arnold Donald H, Dziura James D, Baker Mark D, and Shapiro Eugene D (2006) Wait-and-see prescription for the treatment of acute otitis media: a randomized controlled trial. JAMA 296(10), 1235-41	RCT included in a systematic review that has been prioritised
Tahtinen Paula A, Laine Miia K, Huovinen Pentti, Jalava Jari, Ruuskanen Olli, and Ruohola Aino (2011) A placebo-controlled trial of antimicrobial treatment for acute otitis media. The New England journal of medicine 364(2), 116-26O'Neill Paddy (2002) Acute otitis media. Clinical evidence (8), 251-61	RCT included in a systematic review that has been prioritised

Study reference	Reason
Takata G S, Chan L S, Shekelle P, Morton S C, Mason W, and Marcy S M (2001) Evidence assessment of management of acute otitis media: I. The role of antibiotics in treatment of uncomplicated acute otitis media. Pediatrics 108(2), 239-47	Lower quality systematic review (studies are covered in another systematic review that has been prioritised)
Vouloumanou Evridiki K, Karageorgopoulos Drosos E, Kazantzi Maria S, Kapaskelis Anastasios M, and Falagas Matthew E (2009) Antibiotics versus placebo or watchful waiting for acute otitis media: a meta-analysis of randomized controlled trials. The Journal of antimicrobial chemotherapy 64(1), 16-24	RCT included in a systematic review that has been prioritised
Wood D N, Nakas N, and Gregory C W (2012) Clinical trials assessing ototopical agents in the treatment of pain associated with acute otitis media in children. International Journal of Pediatric Otorhinolaryngology 76(9), 1229-1235	Lower quality systematic review (studies are covered in another systematic review that has been prioritised)
Worrall G J, Kettle A, Graham W, and Hutchinson J (2010) Postdated versus usual delayed antibiotic prescriptions in primary care: Reduction in antibiotic use for acute respiratory infections?. Canadian Family Physician 56(10), 1032-1036	RCT included in a systematic review that has been prioritised

Appendix J: Excluded studies

Study reference	Reason for exclusion
Actrn , and Reath J (2013) A multi-centre open label randomised non-inferiority study to compare the efficacy of antibiotics versus watchful waiting for Acute Otitis Media without perforation in low-risk urban Aboriginal and Torres Strait Islander children. ANZCTR [www.anzctr.org.au]	Excluded on publication/study type – not interventional study
Ables A Z, and Warren P K (2004) High-dose azithromycin or amoxicilin-clavulanate for recurrent otitis media? Journal of Family Practice 53(3), 186	Excluded on population – recurrent AOM
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	Excluded on publication/study type – not interventional study
Aggarwal Anju, and Rath Suman (2004) Cefpodoxime - utility in respiratory tract infections and typhoid fever. Indian journal of pediatrics 71(5), 413-5	Excluded on publication/study type – not interventional study
Ahmed M, Sloan J E, and Clemente E (2001) Clinical efficacy and safety of trimethoprim HC1 oral solution in the treatment of acute otitis media and urinary tract infection in children. Today's Therapeutic Trends 19(2), 63-76	Excluded on publication/study type – not interventional study
Aliphas Avner, Prufer Neil, and Grundfast Kenneth M (2006) Emerging therapies for the treatment and prevention of otitis media. Expert opinion on emerging drugs 11(2), 251-64	Excluded on publication/study type – not interventional study
Anonymous (2003) Acute otitis media in adults - Many unknowns. Prescrire International 12(65), 108-109	Excluded on publication/study type – not interventional study
Anonymous (2003) Acute otitis media in children: Amoxicillin remains the standard antibiotic; but justified in certain situations only. Prescrire International 12(67), 184-189	Excluded on publication/study type – not interventional study
Anonymous (2003) Antibiotics in children with acute otitis media?. Prescrire international 12(66), 148-50	Excluded on publication/study type – not interventional study
Anonymous (2004) Acute otitis media: Update on diagnosis and antibiotic choices. Consultant 44(12), 1546-1548	Excluded on publication/study type – not interventional study
Anonymous (2005) Parent satisfaction OK with no treatment of otitis. Journal of family practice 54(9), 754	Excluded on publication/study type – not interventional study
Anonymous (2005) Parent satisfaction OK with no treatment of otitis. Journal of family practice 54(9), 754	Excluded on publication/study type – not interventional study
Anonymous (2006) Parents prefer shared decision-making for acute otitis media. Journal of Family Practice 55(3), 189	Excluded on publication/study type – not interventional study
Anonymous (2008) Best evidence topic reports. Bet 1. The role of topical analgesia in acute otitis media. Emergency medicine journal : EMJ 25(2), 103-4	Excluded on publication/study type – not interventional study
Anwar A A, and Lalwani A K (2012) Should antibiotics be prescribed for acute otitis media?. Laryngoscope 122(1), 4-5	Excluded on publication/study type – not interventional study
Appelbaum Peter C (2005) Are cephalosporins appropriate for the treatment of acute otitis media in this era of increasing antimicrobial resistance among common respiratory tract pathogens?. Clinical pediatrics 44(2), 95-107	Excluded on publication/study type – not interventional study
Arguedas A, Loaiza C, and Soley C (2004) Single dose azithromycin for the treatment of uncomplicated otitis media. Pediatric infectious disease journal 23(2 Suppl), S108-14	Excluded on publication/study type – not interventional study
Arguedas Adriano, Loaiza Cecilia, and Soley Carolina (2004) Single dose azithromycin for the treatment of uncomplicated otitis	Excluded on publication/study type – not interventional study

Study reference	Reason for exclusion
media. The Pediatric infectious disease journal 23(2 Suppl), S108-14	
Aronovitz G H (2000) Antimicrobial therapy of acute otitis media: review of treatment recommendations. Clinical therapeutics 22(1), 29-39	Excluded on publication/study type – not interventional study
Arrieta Antonio, and Singh Jasjit (2004) Management of recurrent and persistent acute otitis media: new options with familiar antibiotics. The Pediatric infectious disease journal 23(2 Suppl), S115-24	Excluded on publication/study type – not interventional study
Arroll B (2005) Antibiotics for upper respiratory tract infections: an overview of Cochrane reviews. Respiratory medicine 99(3), 255-61	Excluded on publication/study type – not interventional study
Atkinson H, Wallis S, and Coatesworth A P (2015) Acute otitis media. Postgraduate Medicine 127(4), 386-390	Excluded on publication/study type – not interventional study
Aulepp Kristine, Muneerah Aayshah, and Hamm Robert M (2006) Does treatment with antibiotics reduce the duration or severity of symptoms of acute otitis media in children as compared to treatment with analgesics alone?. The Journal of the Oklahoma State Medical Association 99(10), 521-2	Excluded on publication/study type – not interventional study
Bacci C, Galli L, de Martino , M , and Chiappini E (2015) Fluoroquinolones in children: Update of the literature. Journal of Chemotherapy 27(5), 257-265	Excluded on publication/study type – not interventional study
Barberan J, Aguilar L, and Gimenez M J (2012) Update on the clinical utility and optimal use of cefditoren. International Journal of General Medicine 5, 455-464	Excluded on intervention – not interventional study
Barnett E D (2002) Antibiotic resistance and choice of antimicrobial agents for acute otitis media. Pediatric Annals 31(12), 794-799	Excluded on publication/study type – not interventional study
Bascelli L M, and Losh D P (2001) How does a "wait and see" approach to prescribing antibiotics for acute otitis media (AOM) compare with immediate antibiotic treatment?. The Journal of family practice 50(5), 469	Excluded on publication/study type – not interventional study
Benninger M S (2008) Acute bacterial rhinosinusitis and otitis media: Changes in pathogenicity following widespread use of pneumococcal conjugate vaccine. Otolaryngology - Head and Neck Surgery 138(3), 274-278	Excluded on intervention – not about the treatment of AOM
Benninger M S, and Manz R (2010) The impact of vaccination on rhinosinusitis and otitis media. Current Allergy and Asthma Reports 10(6), 411-418	Excluded on publication/study type – not about the treatment of AOM
Bhargava Sumit, Lodha Rakesh, and Kabra S K (2003) Cefprozil: a review. Indian journal of pediatrics 70(5), 395-400	Excluded on intervention – not about the treatment of AOM
Bhetwal Narayan, and McConaghy John R (2007) The evaluation and treatment of children with acute otitis media. Primary care 34(1), 59-70	Excluded on publication/study type – not interventional study
Birman C (2005) Management of otitis media. Medicine Today 6(8), 14-21	Excluded on publication/study type – not interventional study
Blazek-O'Neill B (2005) Complementary and alternative medicine in allergy, otitis media, and asthma. Current Allergy and Asthma Reports 5(4), 313-318	Excluded on publication/study type – not an RCT
Bluestone C D (2004) Studies in otitis media: Children's Hospital of Pittsburgh-University of Pittsburgh Progress Report - 2004. Laryngoscope 114(11 III), 1-26	Excluded on publication/study type – not interventional study

Study reference	Reason for exclusion
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	Excluded on publication/study type – not interventional study
Brook I (2009) Current management of upper respiratory tract and head and neck infections. European Archives of Oto-Rhino-Laryngology 266(3), 315-323	Excluded on publication/study type – not interventional study
Brook Itzhak (2004) Use of oral cephalosporins in the treatment of acute otitis media in children. International journal of antimicrobial agents 24(1), 18-23	Excluded on publication/study type – not interventional study
Brunton S (2006) Current face of acute otitis media: Microbiology and prevalence resulting from widespread use of heptavalent pneumococcal conjugate vaccine. Clinical Therapeutics 28(1), 118-123	Excluded on outcome – not about the treatment of AOM
Canut Blasco, A , Martin-Herrero J E, Maortua H, Labora A, Isla A, and Rodriguez-Gascon A (2009) Impact of acute otitis media pathogen shifts on the clinical efficacy of several antibiotics: A therapeutic outcomes model. Journal of Chemotherapy 21(4), 408-413	Excluded on publication/study type – not interventional study
Chan L S, Takata G S, Shekelle P, Morton S C, Mason W, and Marcy S M (2001) Evidence assessment of management of acute otitis media: II. Research gaps and priorities for future research. Pediatrics 108(2), 248-54	Excluded on outcome – not about the treatment of AOM
Cheong K H, and Hussain S S. M (2012) Management of recurrent acute otitis media in children: systematic review of the effect of different interventions on otitis media recurrence, recurrence frequency and total recurrence time. The Journal of laryngology and otology 126(9), 874-85	Excluded on population – not focused on uncomplicated AOM
Choi S H, Kim E Y, and Kim Y J (2013) Systemic use of fluoroquinolone in children. Korean Journal of Pediatrics 56(5), 196-201	Excluded on population – not focused on AOM
Coates H (2001) Managing acute otitis media what the GP needs to know. Medicine Today 2(11), 43-51	Excluded on publication/study type – not interventional study
Cober M P, and Johnson C E (2005) Otitis media: Review of the 2004 treatment guidelines. Annals of Pharmacotherapy 39(11), 1879-1887	Excluded on intervention – not interventional study
Cohen R (2009) The need for prudent use of antibiotics and routine use of vaccines. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases 15 Suppl 3, 21-3	Excluded on publication/study type excluded – not interventional study
Cohen R, Ovetchkine P, and Gehanno P (2001) Current approaches to otitis media. Current Opinion in Infectious Diseases 14(3), 337-342	Excluded on publication/study type – not interventional study
Corbeel Lucien (2007) What is new in otitis media?. European journal of pediatrics 166(6), 511-9	Excluded on publication/study type – not interventional study
Costelloe C, Metcalfe C, Lovering A, Mant D, and Hay A D (2010) Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: Systematic review and meta-analysis. BMJ (Online) 340(7756), 1120	Excluded on outcome – not about the treatment of AOM specifically – URTI more generally
Cunningham M, Guardiani E, Kim H J, and Brook I (2012) Otitis media. Future Microbiology 7(6), 733-753	Excluded on publication/study type – not interventional study
Dagan R (2004) Antibiotics for acute otitis media in the era of antibiotic resistance - What are the choices?. Advances in Experimental Medicine and Biology 549, 41-45	Excluded on publication/study type – not interventional study

Study reference	Reason for exclusion
Dagan R (2010) Appropriate treatment of acute otitis media in the era of antibiotic resistance. Pediatric Drugs 12(SUPPL. 1), 3-9	Excluded on publication/study type – not interventional study
Dagan R, and Garau J (2004) Appropriate use of antibiotics: Focus on acute otitis media. Clinical Pediatrics 43(4), 313-321	Excluded on publication/study type – not interventional study
Dagan R, and Leibovitz E (2002) Bacterial eradication in the treatment of otitis media. Lancet Infectious Diseases 2(10), 593-604	Excluded on publication/study type – not interventional study
Dagan R, Hoberman A, Johnson C, Leibovitz E L, Arguedas A, Rose F V, Wynne B R, and Jacobs M R (2001) Bacteriologic and clinical efficacy of high dose amoxicillin/clavulanate in children with acute otitis media. The Pediatric infectious disease journal 20(9), 829-37	Excluded on publication/study type – not interventional study
Dagan Ron, Schneider Shira, Givon-Lavi Noga, Greenberg David, Leiberman Alberto, Jacobs Michael R, and Leibovitz Eugene (2008) Failure to achieve early bacterial eradication increases clinical failure rate in acute otitis media in young children. The Pediatric infectious disease journal 27(3), 200-6	Excluded on publication/study type – not interventional study
Dalhoff A (2012) Resistance surveillance studies: A multifaceted problem-the fluoroquinolone example. Infection 40(3), 239-262	Excluded on population - not focused on the treatment of AOM
Damoiseaux R A. M. J (2000) Antibiotics for acute otitis media in infancy: Based on fear or on facts?. Paediatric and Perinatal Drug Therapy 4(2), 58-61	Excluded on publication/study type – not interventional study
Damoiseaux R A. M. J, Van Balen , and F A M (2000) Duration of clinical symptoms in children under two years of age with acute otitis media. European Journal of General Practice 6(2), 48-51	Excluded on outcomes – not about the treatment of AOM
Damoiseaux Roger A. J. M, and Rovers Maroeska M (2011) AOM in children. BMJ clinical evidence 2011	Excluded on publication/study type – review of reviews
Damoiseaux Ramj, Balen Fam, and Melker Ra (2001) Randomised double-blind trial in primary care of amoxicillin versus placebo for acute otitis media in infants. The 4th Extraordinary International Symposium on Recent Advances in Otitis Media , 30	Excluded on publication/study type – not interventional study
Darrow David H, Dash Nariman, and Derkay Craig S (2003) Otitis media: concepts and controversies. Current opinion in otolaryngology & head and neck surgery 11(6), 416-23	Excluded on publication/study type – not interventional study
De Diego , J I, Prim M P, Alfonso C, Sastre N, Rabanal I, and Gavilan J (2001) Comparison of amoxicillin and azithromycin in the prevention of recurrent acute otitis media. International journal of pediatric otorhinolaryngology 58(1), 47-51	Excluded on population – not about the treatment of uncomplicated AOM
Del Mar, Chris , and Glasziou Paul (2002) A child with earache. Are antibiotics the best treatment?. Australian family physician 31(2), 141-4	Excluded on publication/study type – not interventional study
Del-Rio-Navarro B E, Espinosa Rosales, F , Flenady V, and Sienra-Monge J J. L (2006) Immunostimulants for preventing respiratory tract infection in children. Cochrane Database of Systematic Reviews (4), no pagination	Excluded on outcome – not focused on the treatment of AOM
Denneny Iii J. C (2002) Ototopical agents in the treatment of the draining ear. American Journal of Managed Care 8(14 SUPPL.), S353-S360	Excluded on publication/study type – not interventional study
DeRyke C A, Maglio D, and Nicolau D P (2005) Defining the need for new antimicrobials: Clinical and economic implications of resistance in the hospitalised patient. Expert Opinion on Pharmacotherapy 6(6), 873-889	Excluded on publication/study type – not interventional study

Study reference	Reason for exclusion
Ebell Mark H (2011) Short course of antibiotics for acute otitis media treatment. American family physician 83(1), 37	Excluded on publication/study type – not interventional study
Elango S (2003) Reevaluating the use of antibiotics in acute otitis media in children. The Medical journal of Malaysia 58(3), 465-9	Excluded on publication/study type – not interventional study
Ernst E (2000) Complementary and alternative medicine in the practice of otolaryngology. Current Opinion in Otolaryngology and Head and Neck Surgery 8(3), 211-216	Excluded on population – not focused on the treatment of AOM
Erramouspe J, and Heyneman C A (2000) treatment and prevention of otitis media. The Annals of pharmacotherapy 34(12), 1452-68	Excluded on publication/study type – not interventional study
Fay D L, Schellhase K G, and Wujek D (2003) Naturopathic ear drops minimally effective for acute otitis media. Journal of Family Practice 52(9), 673-676	Excluded on publication/study type – not interventional study
Fendrick A M, Saint S, Brook I, Jacobs M R, Pelton S, and Sethi S (2001) Diagnosis and treatment of upper respiratory tract infections in the primary care setting. Clinical therapeutics 23(10), 1683-706	Excluded on publication/study type – not interventional study
Fenn A R, and Fitzgerald M A (2000) Antimicrobial choices in the treatment of acute otitis media. Lippincott's primary care practice 4(5), 515-23	Excluded on publication/study type – not interventional study
Fulton B, and Perry C M (2001) Cefpodoxime proxetil: a review of its use in the management of bacterial infections in paediatric patients. Paediatric drugs 3(2), 137-58	Excluded on publication/study type – not interventional study
Gillies M, Ranakusuma A, Hoffmann T, Thorning S, McGuire T, Glasziou P, and Del C (2015) Common harms from amoxicillin: A systematic review and meta-analysis of randomized placebo-controlled trials for any indication. CMAJ 187(1), E21-E31	Excluded on outcome – not interventional study
Glasziou P P, Del Mar , C B, Hayem M, and Sanders S L (2000) Antibiotics for acute otitis media in children. The Cochrane database of systematic reviews (4), CD000219	Excluded on publication/study type - this systematic review has been updated and prioritised
Glasziou P P, Del Mar , C B, Sanders S L, and Hayem M (2004) Antibiotics for acute otitis media in children. The Cochrane database of systematic reviews (1), CD000219	Excluded on publication/study type - this systematic review has been updated and prioritised
Green R J (2006) Symptomatic treatment of upper respiratory tract symptoms in children. South African Family Practice 48(4), 38-42	Excluded on publication/study type – not interventional study
Groenwold Rolf H. H, Rovers Maroeska M, Lubsen Jacobus, van der Heijden , and Geert Jmg (2010) Subgroup effects despite homogeneous heterogeneity test results. BMC medical research methodology 10, 43	Excluded on outcome – not focused on the treatment of AOM
Guay D R (2000) Cefdinir: an expanded-spectrum oral cephalosporin. The Annals of pharmacotherapy 34(12), 1469-77	Excluded on intervention – not focused on uncomplicated AOM
Guay D R (2000) Short-Course antimicrobial therapy for upper respiratory tract infections. Clinical therapeutics 22(6), 673-84	Excluded on intervention – not focused on uncomplicated AOM
Guay David R. P (2002) Cefdinir: an advanced-generation, broad-spectrum oral cephalosporin. Clinical therapeutics 24(4), 473-89	Excluded on intervention – not interventional study
Gupta B D, and Singh A (2001) Otitis media. Indian journal of pediatrics 68 Suppl 3, S24-31	Excluded on publication/study type – not interventional study

Study reference	Reason for exclusion
Gunasekera Hasantha, Morris Peter S, McIntyre Peter, and Craig Jonathan C (2009) Management of children with otitis media: a summary of evidence from recent systematic reviews. Journal of paediatrics and child health 45(10), 554-3	Excluded on publication/study type – not interventional study
Gutierrez-Castrellon P, Mayorga-Buitron J L, Bosch-Canto V, Solomon-Santibanez G, De Colsa-Ranero , and A (2012) Efficacy and safety of clarithromycin in pediatric patients with upper respiratory infections: A systematic review with meta-analysis. Revista de Investigacion Clinica 64(2), 126-135	Excluded on outcome – not about the treatment of AOM specifically – URTI more generally
Halter R, and Kelsberg G (2004) Is antibiotic prophylaxis effective for recurrent acute otitis media?. Journal of Family Practice 53(12), 999-1000	Excluded on publication/study type – not interventional study
Hang A, and Brietzke S E (2012) Otitis media: Epidemiology and management. Infectious Disorders - Drug Targets 12(4), 261-266	Excluded on publication/study type – not interventional study
Hoberman A, and Paradise J L (2000) Acute otitis media: Diagnosis and management in the year 2000. Pediatric Annals 29(10), 609-620	Excluded on publication/study type – not interventional study
Hoberman Alejandro, Marchant Colin D, Kaplan Sheldon L, and Feldman Sandor (2002) Treatment of acute otitis media consensus recommendations. Clinical pediatrics 41(6), 373-90	Excluded on publication/study type – not interventional study
Husain N, Huang A, and Ramos O (2009) Otitis media: Current diagnosis and treatment. International Pediatrics 24(4), 174-182	Excluded on publication/study type – not interventional study
Jackson R (2001) Antibiotics for otitis media. Emergency Medicine Journal 18(2), 123	Excluded on publication/study type – not interventional study
Jain S K, Tunkel D E, and Bishai W R (2005) Management of acute rhinosinusitis, bronchitis syndromes, and acute otitis media. Advanced Studies in Medicine 5(7), 344-350	Excluded on publication/study type – not interventional study
Johnson C E, and Belman S (2001) The role of antibacterial therapy of acute otitis media in promoting drug resistance. Paediatric drugs 3(9), 639-47	Excluded on publication/study type – not interventional study
Johnson Nicholas C, and Holger Joel S (2007) Pediatric acute otitis media: the case for delayed antibiotic treatment. The Journal of emergency medicine 32(3), 279-84	Excluded on publication/study type – not interventional study
Kaplan S L (2004) New antibiotics and bacterial resistance: Rational prescribing in pediatric infection. Advances in Experimental Medicine and Biology 549, 5-8	Excluded on publication/study type – not interventional study
Kawalski H, Blacha E, Kopacz M, Mos M, Cierpiol-Tracz E, Welniak M, Dudziak B, Bojda S, Kossowska B, Gatniejewska E, and Ligacz M (2001) Azithromycin vs. Clarithromycin and Co-amoxiclav: Clinical and economic comparison in the treatment of acute otitis media in children. New Medicine 4(2), 14-9	Excluded on publication/study type
Klein J O (2000) Management of otitis media with antimicrobial agents. Current clinical topics in infectious diseases 20, 174-88	Excluded on publication/study type – not interventional study
Klein Jerome O (2002) Strategies for decreasing multidrug antibiotic resistance: role of ototopical agents for treatment of middle ear infections. The American journal of managed care 8(14 Suppl), S345-52	Excluded on publication/study type – not interventional study
Klein Jerome O, and Schaad Urs B (2004) [Use of azithromycin in the treatment of acute otitis media and tonsillopharyngitis: summary and conclusions. The Pediatric infectious disease journal 23(2 Suppl), S140-1	Excluded on publication/study type – not interventional study

Study reference	Reason for exclusion
Koopman L, Hoes A W, Glasziou P P, Appelman C L, Burke P, McCormick D P, Damoiseaux R A, Le Saux , N , and Rovers M M (2008) Antibiotic therapy to prevent the development of asymptomatic middle ear effusion in children with acute otitis media: A meta-analysis of individual patient data. Archives of Otolaryngology - Head and Neck Surgery 134(2), 128-132	Excluded on population – not focused on uncomplicated acute otitis media
Kozyrskyj A L, Hildes-Ripstein G E, Longstaffe S E, Wincott J L, Sitar D S, Klassen T P, and Moffatt M E (2000) Short course antibiotics for acute otitis media. The Cochrane database of systematic reviews (2),	Excluded on publication/study type - this systematic review has been updated and prioritised
Leach A J, and Morris P S (2006) Antibiotics for the prevention of acute and chronic suppurative otitis media in children. The Cochrane database of systematic reviews (4), CD004401	Excluded on outcome – the findings for AOM could not be disaggregated
Leach A J, and Morris P S (2009) Antibiotics for the prevention of acute and chronic suppurative otitis media in children. Cochrane Database of Systematic Reviews (4), no pagination	Excluded on outcome - the findings for AOM could not be disaggregated
Lee H, Kim J, and Nguyen V (2013) Ear infections: Otitis externa and otitis media. Primary Care - Clinics in Office Practice 40(3), 671-686	Excluded on publication/study type – not interventional study
Leibovici L, Soares-Weiser K, Paul M, Goldberg E, Herxheimer A, and Garner P (2003) Considering resistance in systematic reviews of antibiotic treatment. Journal of Antimicrobial Chemotherapy 52(4), 564-571	Excluded on intervention – not focused on the treatment of AOM
Leibovitz E (2011) Antibiotic treatment of acute otitis media in children: To wait or not to wait?. Clinical Investigation 1(7), 903-906	Excluded on publication/study type – not an interventional study
Leibovitz E, and Dagan R (2001) Otitis media therapy and drug resistance part 1: Management principles. Infections in Medicine 18(4), 212-216	Excluded on publication/study type – not an interventional study
Leibovitz Eugene, and Greenberg David (2004) Acute otitis media in children: current epidemiology, microbiology, clinical manifestations, and treatment. Chang Gung medical journal 27(7), 475-88	Excluded on publication/study type – not an interventional study
Lieberthal A S, Carroll A E, Chonmaitree T, Ganiats T G, Hoberman A, Jackson M A, Joffe M D, Miller D T, Rosenfeld R M, Sevilla X D, Schwartz R H, Thomas P A, and Tunkel D E (2013) The diagnosis and management of acute otitis media. Pediatrics 131(3), e964-e999	Excluded on population
Little P, Gould C, Moore M, Warner G, Dunleavey J, and Williamson I (2002) Predictors of poor outcome and benefits from antibiotics in children with acute otitis media: Pragmatic randomised trial. British Medical Journal 325(7354), 22-24	Excluded on publication/study type – not an interventional study (secondary data analysis)
Marmor A, and Newman Tb (2011) Amoxicillin-clavulanate improves symptoms, reduces treatment failure in select children with acute otitis media and increases risk of diarrhoea. Evidence-based medicine 16(5), 150-2	Excluded on publication/study type – not an interventional study
Mandel Ellen M, and Casselbrant Margaretha L (2012) Treatment of acute otitis media in young children. Current allergy and asthma reports 12(6), 559-63	Excluded on publication/study type – not an interventional study
Marchisio P, Nazzari E, Torretta S, Esposito S, and Principi N (2014) Medical prevention of recurrent acute otitis media: An updated overview. Expert Review of Anti-Infective Therapy 12(5), 611-620	Excluded on outcome – not about the treatment of uncomplicated AOM

Study reference	Reason for exclusion
McCormick Dp (2001) Pragmatic randomized controlled trial of two prescribing strategies for childhood acute otitis media. Journal of pediatrics 139(3), 468	excluded - could not be located
Meropol Sharon B (2008) Valuing reduced antibiotic use for pediatric acute otitis media. Pediatrics 121(4), 669-73	Excluded on outcome – not about the treatment of AOM
Montgomery Diane (2005) A new approach to treating acute otitis media. Journal of pediatric health care : official publication of National Association of Pediatric Nurse Associates & Practitioners 19(1), 50-2	Excluded on publication/study type – not an interventional study
Morris Peter S, Gadil Gaudencio, McCallum Gabrielle B, Wilson Cate A, Smith-Vaughan Heidi C, Torzillo Paul, and Leach Amanda J (2010) Single-dose azithromycin versus seven days of amoxycillin in the treatment of acute otitis media in Aboriginal children (AATAAC): a double blind, randomised controlled trial. The Medical journal of Australia 192(1), 24-9	Excluded on population
Nesbit Chadd E, and Powers Margaret C (2013) An evidence-based approach to managing acute otitis media. Pediatric emergency medicine practice 10(4), 1-7	Excluded on publication/study type – not an interventional study
O'Neill Paddy (2002) Acute otitis media. Clinical evidence (8), 251-61	Excluded on publication/study type – not an interventional study
O'Neill Paddy, and Roberts Tony (2003) Acute otitis media. Clinical evidence (9), 274-86	Excluded on publication/study type – not an interventional study
O'Neill Paddy, and Roberts Tony (2004) Acute otitis media. Clinical evidence (11), 314-27	Excluded on publication/study type – not an interventional study
O'Neill Paddy, and Roberts Tony (2005) Acute otitis media in children. Clinical evidence (13), 227-38	Excluded on publication/study type – not an interventional study
O'Neill Paddy, Roberts Tony, Bradley Stevenson, and Clare (2006) Otitis media in children (acute). Clinical evidence (15), 500-10	Excluded on publication/study type – not an interventional study
O'Neill Paddy, Roberts Tony, Bradley Stevenson, and Clare (2007) Otitis media in children (acute). BMJ clinical evidence 2007,	Excluded on publication/study type – not an interventional study
Ovetchkine P, Rieder M J, Bernstein M L, Goldman R D, and Moriartey R (2013) Azithromycin use in paediatrics: A practical overview. Paediatrics and Child Health (Canada) 18(6), 311-313	Excluded on publication/study type – not an interventional study
Pappas D, and Owen Hendley J (2003) Otitis media A scholarly review of the evidence. Minerva pediatrica 55(5), 407-14	Excluded on publication/study type – not an interventional study
Pichicero M (2000) Short courses of antibiotic in acute otitis media and sinusitis infections. The Journal of international medical research 28 Suppl 1, 25A-36A	Excluded on publication/study type – not an interventional study
Pichichero M E (2000) Short course antibiotic therapy for respiratory infections: a review of the evidence. The Pediatric infectious disease journal 19(9), 929-37	Excluded on publication/study type – not an interventional study
Pichichero M E (2000) Acute otitis media: part II. Treatment in an era of increasing antibiotic resistance. American family physician 61(8), 2410-6	Excluded on publication/study type – not an interventional study

Study reference	Reason for exclusion
Pichichero M E (2000) Evaluating the need, timing and best choice of antibiotic therapy for acute otitis media and tonsillopharyngitis infections in children. The Pediatric infectious disease journal 19(12 Suppl), S131-40	Excluded on publication/study type– not an interventional study
Pichichero M E, and Brixner D I (2006) A review of recommended antibiotic therapies with impact on outcomes in acute otitis media and acute bacterial sinusitis. American Journal of Managed Care 12(SUPPL. 10), S292-S302	Excluded on publication/study type – not an interventional study
Pichichero M E, and Casey J R (2008) Comparison of study designs for acute otitis media trials. International Journal of Pediatric Otorhinolaryngology 72(6), 737-750	Excluded on outcome – not about the treatment of AOM
Pichichero Michael E (2005) A review of evidence supporting the American Academy of Pediatrics recommendation for prescribing cephalosporin antibiotics for penicillin-allergic patients. Pediatrics 115(4), 1048-57	Excluded on publication/study type – not an interventional study
Pichichero Michael E, and Casey Janet R (2002) Otitis media. Expert opinion on pharmacotherapy 3(8), 1073-90	Excluded on publication/study type – not an interventional study
Pichichero Michael E, Arguedas Adriano, Dagan Ron, Sher Larry, Saez-Llorens Xavier, Hamed Kamal, and Echols Roger (2005) Safety and efficacy of gatifloxacin therapy for children with recurrent acute otitis media (AOM) and/or AOM treatment failure. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 41(4), 470-8	Excluded on intervention – not about the treatment of uncomplicated AOM
Pinto S, Costa J, Vaz Carneiro, A , and Fernandes R (2013) Analysis of the Cochrane review: Antibiotics for acute otitis media in children. Cochrane database syst rev. 2013;1:CD000219. Acta Medica Portuguesa 26(6), 633-636	Excluded on publication/study type – full text not available in English language
Powers John H (2007) Diagnosis and treatment of acute otitis media: evaluating the evidence. Infectious disease clinics of North America 21(2), 409-vi	Excluded on publication/study type – not an interventional study
Principi N (2000) Oral cephalosporins in the treatment of acute otitis media. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases 6 Suppl 3, 61-3	Excluded on publication/study type – not an interventional study
Principi N (2000) Oral cephalosporins in the treatment of acute otitis media. Clinical Microbiology and Infection 6(S3), 61-63	Excluded on publication/study type – not an interventional study
Qureishi Ali, Lee Yan, Belfield Katherine, Birchall John P, and Daniel Matija (2014) Update on otitis media - prevention and treatment. Infection and drug resistance 7, 15-24	Excluded on publication/study type – not interventional study
Rafailidis P I, Pitsounis A I, and Falagas M E (2009) Meta-analyses on the Optimization of the Duration of Antimicrobial Treatment for Various Infections. Infectious Disease Clinics of North America 23(2), 269-276	Excluded on publication/study type – summary of a meta-analysis
Rainsford K D (2009) Ibuprofen: Pharmacology, efficacy and safety. Inflammopharmacology 17(6), 275-342	Excluded on population – not focused on the treatment of AOM
Ramgoolam A, and Steele R (2002) Formulations of antibiotics for children in primary care: Effects on compliance and efficacy. Pediatric Drugs 4(5), 323-333	Excluded on publication/study type – not interventional study
Rawof S, and Upadhye S (2009) Antibiotics for acute otitis media: Which children are likely to benefit?. Canadian Journal of Emergency Medicine 11(6), 553-557	Excluded on publication/study type – not interventional study

Study reference	Reason for exclusion
Rosa-Olivares J, Porro A, Rodriguez-Varela M, Riefkohl G, and Niroomand-Rad I (2015) Otitis media: To treat, to refer, to do nothing: A review for the practitioner. Pediatrics in Review 36(11), 480-486	Excluded on publication/study type – not interventional study
Rosenfeld R M (2004) Antibiotic use for otitis media: Oral, topical, or none?. Pediatric Annals 33(12), 833-842	Excluded on publication/study type – not interventional study
Rosenfeld R M, Casselbrant M L, and Hannley M T (2001) Implications of the AHRQ evidence report on acute otitis media. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery 125(5), 440-439	Excluded on publication/study type – not interventional study
Rothermel C D (2003) Single-dose azithromycin for acute otitis media: A pharmacokinetic/ pharmacodynamic rationale. Current Therapeutic Research - Clinical and Experimental 64(SUPPL. 1), A4-A15	Excluded on publication/study type – not interventional study
Rubin Lorry G (2010) Prevention and treatment of meningitis and acute otitis media in children with cochlear implants. Otology & neurotology : official publication of the American Otological Society, and American Neurotology Society [and] European Academy of Otology and Neurotology 31(8), 1331-3	Excluded on population – not focused on uncomplicated acute otitis media
Schmelzle J, Birtwhistle R V, and Tan A K. W (2008) Acute otitis media in children with tympanostomy tubes. Canadian Family Physician 54(8), 1123-1127	Excluded on population – not focused on uncomplicated acute otitis media
Shaikh Nader, and Hoberman Alejandro (2010) Update: acute otitis media. Pediatric annals 39(1), 28-33	Excluded on publication/study type – not interventional study
Sher L, Arguedas A, Husseman M, Pichichero M, Hamed K A, Biswas D, Pierce P, and Echols R (2005) Randomized, investigator-blinded, multicenter, comparative study of gatifloxacin versus amoxicillin/clavulanate in recurrent otitis media and acute otitis media treatment failure in children. Pediatric Infectious Disease Journal 24(4), 301-308	Excluded on intervention – findings for uncomplicated acute otitis media could not be disaggregated
Siegel R M, and Bien J P (2004) Acute otitis media in children: A continuing story. Pediatrics in Review 25(6), 187-193	Excluded on publication/study type – not interventional study
Siempos I I, Dimopoulos G, and Falagas M E (2009) Meta-analyses on the Prevention and Treatment of Respiratory Tract Infections. Infectious Disease Clinics of North America 23(2), 331-353	Excluded on publication/study type – summary of a meta-analysis
Singer J, Russi C, and Taylor J (2005) Single-use antibiotics for the pediatric patient in the emergency department. Pediatric Emergency Care 21(1), 50-60	Excluded on publication/study type – not interventional study
Soley Carolin A, and Arguedas Adriano (2005) Single-dose azithromycin for the treatment of children with acute otitis media. Expert review of anti-infective therapy 3(5), 707-17	Excluded on publication/study type – not interventional study
Sorum P, Garrison G, Hioe W, Koenig K, Bidot R, Feeney W, Higgins E, Pelnik-Fecko T, Zabinski-Kramer K, Sandler R, Austin M, and Miller M (2001) Should we routinely prescribe high-dose amoxicillin when treating acute otitis media?. Pediatric research 49(4), 164a	Excluded on publication/study type – not interventional study
Spector N D, and Kelly S F (2004) Medical home, obesity, acute otitis media, and otitis media with effusion. Current Opinion in Pediatrics 16(6), 706-722	Excluded on publication/study type – not interventional study
Spiro David M, and Arnold Donald H (2008) The concept and practice of a wait-and-see approach to acute otitis media. Current opinion in pediatrics 20(1), 72-8	Excluded on publication/study type – not interventional study

Study reference	Reason for exclusion
Spurling G K, Del Mar , C B, Dooley L, and Foxlee R (2004) Delayed antibiotics for symptoms and complications of respiratory infections. Cochrane database of systematic reviews (Online) (4), CD004417	Excluded on publication/study type – this systematic review has been updated and prioritised
Stine A R (2000) Is amoxicillin more effective than placebo in treating acute otitis media in children younger than 2 years?. The Journal of family practice 49(5), 465-6	Excluded on publication/study type – not interventional study
Subbotina Mv, Kunitsina Mn, Buksha Ia, Galchenko Mt, and Platonenko Oi (2009) [The use of sinupret in the combined treatment of acute otitis media in children]. Vestnik otorinolaringologii (2), 43-5	Excluded on publication/study type – not in English language
Syggelou A, Fanos V, and Iacovidou N (2011) Acute otitis media in neonatal life: A review. Journal of Chemotherapy 23(3), 123-126	Excluded on publication/study type – not interventional study
Tahtinen Paula A, Laine Miia K, Ruuskanen Olli, and Ruohola Aino (2012) Delayed versus immediate antimicrobial treatment for acute otitis media. The Pediatric infectious disease journal 31(12), 1227-32	Excluded on publication/study type – not interventional study
Taneja M K, and Taneja V (2014) Drug therapy for otitis media. Indian Journal of Otology 20(1), 1-3	Excluded on publication/study type – not interventional study
Teele D W (2000) Acute otitis media: Antimicrobial therapy in an era of. New Zealand Medical Journal 113(1113), 284-286	Excluded on publication/study type – not interventional study
Thanaviratananich Sanguansak, Laopaiboon Malinee, and Vatanasapt Patravoot (2008) Once or twice daily versus three times daily amoxicillin with or without clavulanate for the treatment of acute otitis media. The Cochrane database of systematic reviews (4), CD004975	Excluded on publication/study type - this systematic review has been updated and prioritised
Thomas Nicole M, and Brook Itzhak (2014) Otitis media: an update on current pharmacotherapy and future perspectives. Expert opinion on pharmacotherapy 15(8), 1069-83	Excluded on publication/study type – not interventional study
Thomas J P, Berner R, Zahnert T, and Dazert S (2014) Acute otitis media - A structured approach. Deutsches Arzteblatt International 111(9), 151-160	Excluded on publication/study type – not interventional study
Toll Edward C, and Nunez Desmond A (2012) Diagnosis and treatment of acute otitis media: review. The Journal of laryngology and otology 126(10), 976-83	Excluded on publication/study type – not interventional study
Toltzis Philip (2005) Comparison of amoxicillin with alternative agents for the treatment of acute otitis media in children. Pharmacotherapy 25(12 Pt 2), 124S-129S	Excluded on publication/study type – not interventional study
Troster K (2000) Clinical efficacy, duration of therapy and safety profile of cefixime in daily practice: Results of German postmarketing surveillance studies. Drugs of Today 36(SUPPL. E), 7-12	Excluded on population – not focused on the treatment of AOM
Turnidge J (2001) Responsible prescribing for upper respiratory tract infections. Drugs 61(14), 2065-77	Excluded on publication/study type – not interventional study
Underhill J (2003) Management of common infections in primary care - Sore throat and acute otitis media. Pharmacy in Practice 13(7), 222-225	Excluded on publication/study type – not interventional study
Venekamp Roderick P, Damoiseaux Roger A. M. J, and Schilder Anne G. M (2014) Acute otitis media in children. BMJ clinical evidence 2014,	Excluded on publication/study type – not interventional study
Venekamp Roderick P, Sanders Sharon, Glasziou Paul P, Del Mar , Chris B, and Rovers Maroeska M (2013) Antibiotics for	Excluded on publication/study type – this systematic review

Study reference	Reason for exclusion
acute otitis media in children. The Cochrane database of systematic reviews 1, CD000219	has been updated and prioritised
Vitter J S (2011) Do antibiotics improve the treatment of acute otitis media?. American Family Physician 84(9), no pagination	Excluded on publication/study type – not interventional study
Wall G M, Stroman D W, Roland P S, and Dohar J (2009) Ciprofloxacin 0.3%/dexamethasone 0.1% sterile otic suspension for the topical treatment of ear infections: A review of the literature. Pediatric Infectious Disease Journal 28(2), 141-144	Excluded on population – not focused on the treatment of AOM
Weick M B, and Kane K Y (2003) Children with fever and vomiting benefit from immediate antibiotics for acute otitis media. Journal of Family Practice 52(1), 12	Excluded on publication/study type – not interventional study
Wicker A M, and Mohundro B L (2010) Management of pediatric otitis media. U.S. Pharmacist 35(3), 44-49	Excluded on publication/study type – not interventional study
Wilson E C. F, and Wilson J V (2009) Time to review short courses of antibiotics. Pharmaceutical Journal 282(7552), 590-594	Excluded on publication/study type – not interventional study
Wright S (2001) Delayed prescribing of antibiotics increased duration of acute otitis media symptoms in children but reduced diarrhoea. Evidence-based nursing 4(4), 107	Excluded on publication/study type – not interventional study
Xiao Yy, Shi Y, and Song Y (2004) Amoxicillin/clavulanic acid (14:1) in treatment of respiratory tract and middle ear bacterial infection. Chinese Journal of New Drugs and Clinical Remedies 23(3), 170-3	Excluded on publication/study type – not in English language
Zhang Ym, Dong P, and Lu P (2003) Efficacy and safety of one dose of ceftriaxone vs ten-day oral amoxicillin for treatment of acute otitis media in children [Chinese]. Chinese Journal of Pediatrics 41(2), 135-8	Excluded on publication/study type – not in English language

Appendix K: Update to include new evidence on ear drops containing an anaesthetic and an analgesic

This evidence review was partially updated in March 2022 following an exceptional surveillance review as a licensed preparation is now available in the UK. It includes new evidence on ear drops containing an anaesthetic and an analgesic.

This appendix includes update information only.

K.1 Literature search

A literature search of evidence from 2011 (the date of the Cochrane review included in NG91) on ear drops containing an anaesthetic and an analgesic in acute otitis media identified 704 references. These references were screened using their titles and abstracts and 5 full text references were obtained and assessed for relevance. One study was included as relevant (Hay et al. 2019).

The Cochrane review (Foxlee et al. 2011) included in NG91 has not been updated since the guideline was published.

K.2 Study details

New evidence is included from an RCT (Hay et al. 2019) in 106 children aged 1 to 10 years with acute otitis media in primary care, who did not need immediate antibiotics – see Table 39.

Due to problems with the procurement of placebo ear drops, most participants (n=74) were randomised to a 2-group unblinded trial of ear drops containing an anaesthetic and an analgesic compared with usual care. A smaller number (n=32) were randomised to a 3-group trial of ear drops containing an anaesthetic and an analgesic compared with usual care (unblinded) or placebo ear drops (blinded). The sample size needed to achieve statistical power was not achieved.

See Table 40 for the quality assessment of the new study.

Table 39: Summary of the new study (Hay et al. 2019)

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Hay et al. 2019 RCT UK Follow-up at 8 days	n=106 (2-group trial, n=74; 3-group trial n=32)	Children aged 1-10 years presenting in primary care with acute otitis media who did not need immediate antibiotics. All children had ear pain in previous 24 hours; 88% received oral analgesia	Benzocaine and phenazone ear drops	Usual care (no antibiotic or delayed antibiotic prescription) or placebo ear drops	Antibiotic consumption

Table 40: Overall risk of bias/quality assessment – randomised controlled trials (RCT checklist)

Study reference	Hay et al. 2019
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 – the 2-group trial was unblinded
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 profile
How precise was the estimate of the treatment effect?	See GRADE profile
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 profile

K.3 Clinical effectiveness

K.3.1 Ear drops containing an anaesthetic and an analgesic compared with usual care

Antibiotic consumption

Hay et al. 2019 considered the effectiveness of ear drops containing an anaesthetic and an analgesic compared with NICE guideline recommended management in UK primary care (no antibiotic or delayed antibiotic prescription). Antibiotic consumption in this context is particularly important to assess if there was any reduction in the use of subsequent antibiotics following use of ear drops containing an anaesthetic and an analgesic.

When data were meta-analysed from the 2-group and 3-group trials (Hay et al. 2019; n=77), there was a statistically significant reduction in the primary outcome of antibiotic consumption with ear drops containing an anaesthetic and an analgesic compared with usual care (2.6% versus 29.0%; odds ratio [OR] 0.09, 95% confidence interval [CI] 0.02 to 0.55, p=0.009; moderate quality evidence). When this was adjusted for issuing a delayed antibiotic prescription (a confounder for antibiotic use) the OR was 0.15 (95% CI 0.03 to 0.87), p=0.035; low quality evidence).

There was more uncertainty in the results when the 2-group (n=59) and 3-group (n=18) trials were analysed separately, due to the lower numbers of children. In the 2-group trial there was a statistically significant reduction in the primary outcome of antibiotic consumption with ear drops containing an anaesthetic and an analgesic compared with usual care (moderate quality evidence), but this was no longer statistically significant when adjusted for issuing a delayed antibiotic prescription (low quality evidence). In the 3-group trial, there was no statistically significant difference between groups (very low quality evidence).

See appendix K.4: GRADE profiles.

Ear pain

When data were meta-analysed from the 2-group and 3-group trials (n=81), ear pain scores (range 1-10) at day 2 were statistically significantly better with ear drops containing an anaesthetic and an analgesic compared with usual care (2.88, standard deviation [SD] 2.28 versus. 4.56, SD 2.37, mean difference –1.70 95%CI –2.74 to –0.66, p=0.001; low quality evidence). A 1-point change was prespecified as the minimal clinically important difference. Similar results were seen when this result was adjusted for pain score at consultation (low quality evidence).

There were no statistically significant differences between groups in ear pain scores at day 1 (1 hour after administration), pain duration or overall symptom burden (low to very low quality evidence).

See appendix K.4: GRADE profiles.

Parent satisfaction

In the 2-group trial, 93% (27/29) of parents were satisfied with ear drops containing an anaesthetic and an analgesic and 7% (2/29) were neither satisfied nor dissatisfied. No data were reported for the usual care group (very low quality evidence).

Adverse events

No adverse events related to treatment were reported (very low quality evidence).

K.3.2 Ear drops containing an anaesthetic and an analgesic compared with placebo ear drops

Ear pain

There were no statistically significant differences in ear pain scores at day 2, pain duration or overall symptom burden with ear drops containing an anaesthetic and an analgesic compared with placebo ear drops (Hay et al. 2019; n=17, low quality evidence). However, due to small numbers of children there is considerable uncertainty in the results.

See appendix K.4: GRADE profiles.

Oral analgesia consumption

There was no statistically significant difference in oral analgesia consumption with ear drops containing an anaesthetic and an analgesic compared with placebo ear drops (n=16, low quality evidence). Oral analgesia use was high in both groups (89% versus 86%).

See appendix K.4: GRADE profiles.

Parent satisfaction

In the 3-group trial, 90% (9/10) of parents were satisfied with ear drops containing an anaesthetic and an analgesic and 10% (1/10) were neither satisfied nor dissatisfied. Parent satisfaction was lower with placebo ear drops with 57% (4/7) of parents were satisfied, 29% (2/7) were neither satisfied nor dissatisfied and 14% (1/7) were not satisfied (low quality evidence).

Adverse events

No adverse events related to treatment were reported (low quality evidence).

K.4 GRADE profiles

Table 41: GRADE profile – ear drops containing an anaesthetic and an analgesic compared with usual care

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anaesthetic/ analgesic ear drops	Usual care	Relative (95% CI)	Absolute		
Antibiotic consumption (combined data) (follow-up 8 days)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	no serious imprecision	none	1/39 (2.6%)	11/38 (28.9%)	OR 0.09 (0.02 to 0.55)[3]	254 fewer per 1000 (from 106 fewer to 281 fewer)	⊕⊕⊕O MODERATE	CRITICAL
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[4]	none			Adjusted OR 0.15 (0.03 to 0.87)[5,6]	232 fewer per 1000 (from 28 fewer to 277 fewer)	⊕⊕OO LOW	CRITICAL
Antibiotic consumption (2-group trial) (follow-up 8 days)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	no serious imprecision	none	1/29 (3.4%)	9/30 (30%)	OR 0.08 (0.01 to 0.71)	267 fewer per 1000 (from 67 fewer to 296 fewer)	⊕⊕⊕O MODERATE	CRITICAL
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[4]	none			Adjusted OR 0.12 (0.01 to 1.18)[5]	251 fewer per 1000 (from 296 fewer to 36 more)	⊕⊕OO LOW	CRITICAL
Antibiotic consumption (3-group trial) (follow-up 8 days)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[7]	none	0/10 (0%)	2/8 (25%)	OR 0.11 (0 to 3.17)[8]	215 fewer per 1000 (from 250 fewer to 264 more)	⊕OOO VERY LOW	CRITICAL
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[7]	none			Adjusted OR 0.20 (0.01 to 3.49)[5,8]	188 fewer per 1000 (from 247 fewer to 288 more)	⊕OOO VERY LOW	CRITICAL
Ear pain on day 2 (combined data) (range of scores: 0-10; Better indicated by lower values)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[4]	none	42	39	-	MD 1.70 lower (2.74 to 0.66 lower)[9]	⊕⊕OO LOW	CRITICAL
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[4]	none			-	Adjusted MD 1.99 lower (3.01 to 0.95 lower)[3,9,10]	⊕⊕OO LOW	CRITICAL
Ear pain on day 2 (2-group trial) (range of scores: 0-10; Better indicated by lower values)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[4]	none	32	30	-	MD 1.62 lower (2.86 to 0.39 lower)[9]	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anaesthetic/ analgesic ear drops	Usual care	Relative (95% CI)	Absolute		
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[4]	none			-	Adjusted MD 2.01 lower (3.23 to 0.78 lower)[3,9,10]	⊕⊕OO LOW	CRITICAL
Ear pain on day 2 (3-group trial) (range of scores: 0-10; Better indicated by lower values)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[7]	none	10	9	-	MD 1.90 lower (3.85 lower to 0.05 higher)[9]	⊕OOO VERY LOW	CRITICAL
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[7]	none	10	9	-	Adjusted MD 1.93 lower (3.92 lower to 0.05 higher)[3,9,10]	⊕OOO VERY LOW	CRITICAL
Ear pain on day 1 (approximately 1 hour after administering the drops) (3-group trial) (range of scores: 0-10; Better indicated by lower values)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[7]	none	10	7	-	MD 0.73 lower (2.16 lower to 0.7 higher)[9]	⊕OOO VERY LOW	CRITICAL
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[7]	none	10	7	-	Adjusted MD 0.74 lower (2.32 lower to 0.85 higher)[9,10]	⊕OOO VERY LOW	CRITICAL
Overall symptom burden (2-group trial) (follow-up 8 days; quantified by AUC; Better indicated by higher values)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[11]	none	32 Median 11.5 (IQR 5.8 to 33.5)	28 Median 30.3 (IQR 6.3 to 45.0)	-	Difference of means 1.14 higher (0.20 lower to 2.49 higher)[12]	⊕OOO VERY LOW	CRITICAL
Overall symptom burden (3-group trial) (follow-up 8 days; quantified by AUC; Better indicated by higher values)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[11]	none	10 Median 15.8 (IQR 8.5 to 21.5)	9 Median 28.5 (IQR 14.0 to 42.0)	-	Difference of means 1.35 higher (0.13 lower to 2.84 higher)[12]	⊕OOO VERY LOW	CRITICAL
Overall duration of pain (2-group trial) (Better indicated by lower values)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[4,13]	none	34 Median 3 days (IQR 2 to 5)	31 Median 4 days (IQR 3 to X[13])	HR 0.62 (0.34 to 1.11)	-	⊕OOO VERY LOW	CRITICAL
Overall duration of pain (3-group trial) (Better indicated by lower values)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[7]	none	10 Median 3 days (IQR 3 to 5)	9 Median 3 days (IQR 2 to 6)	HR 0.94 (0.38 to 2.61)	-	⊕OOO VERY LOW	CRITICAL
Parent satisfaction with treatment (2-group trial)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anaesthetic/ analgesic ear drops	Usual care	Relative (95% CI)	Absolute		
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[14]	none	9/10 (90%)	No data reported	-	-	⊕OOO VERY LOW	CRITICAL
Adverse events												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[15]	none	1 adverse event in the control group, but this was not related to treatment				⊕OOO VERY LOW	CRITICAL

Abbreviations: AUC, area under curve; CI, confidence interval; HR, hazard ratio; IQR, interquartile range; MD, mean difference; OR, odds ratio

[1] Hay et al. 2019
[2] Unblinded study
[3] Pooled estimate using inverse variance method, I^2 = 0%
[4] Wide confidence intervals include the possibility of appreciable benefit or no difference
[5] Adjusted for giving a delayed antibiotic prescription, missing for 1 patient in the 3-group trial
[6] Pooled estimate using the inverse variance method, I^2 = 29.1%
[7] Very wide confidence intervals include the possibility of appreciable benefit, no difference, or appreciable harm
[8] Continuity correction of 0.4444
[9] Prespecified 1-point minimum clinically important difference
[10] Adjusted for the parent-reported pain score at consultation
[11] Very wide confidence intervals, high uncertainty due to very small numbers of participants
[12] Difference in means calculated using square root of area under the curve
[13] Missing data due to large proportion of censoring at 8 days
[14] No data reported so unable to determine is appreciable benefit, harm or no difference
[15] No events observed so unable to determine is appreciable benefit, harm or no difference

Table 42: GRADE profile – ear drops containing an anaesthetic and an analgesic compared with placebo ear drops

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anaesthetic/ analgesic ear drops	Placebo ear drops	Relative (95% CI)	Absolute		
Ear pain on day 2 (range of scores: 0-10; Better indicated by lower values)												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[2]	none	10	7	-	MD 0.96 higher (0.99 lower to 2.91 higher)[3]	⊕⊕OO LOW	CRITICAL
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[2]	none			-	Adjusted MD 0.67 higher (1.44 lower to 2.79 higher)[3,4]	⊕⊕OO LOW	CRITICAL
Oral analgesia consumption												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[2]	none	8/9 (88.9%)	6/7 (85.7%)	OR 1.33 (0.07 to 25.91)	31 more per 1000 (from 561 fewer to 136 more)	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Anaesthetic/ analgesic ear drops	Placebo ear drops	Relative (95% CI)	Absolute		
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[2]	none			Adjusted OR 1.21 (0.04 to 34)[3]	22 more per 1000 (from 664 fewer to 138 more)	⊕⊕OO LOW	CRITICAL
Overall symptom burden (follow-up 8 days; quantified by AUC; Better indicated by higher values)												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[2]	none	10 Median 15.8 (IQR 8.5 to 21.5)	7 Median 24.5 (IQR 10.5 to 50.5)	HR 1.81 (-0.28 to 3.90)	-	⊕⊕OO LOW	CRITICAL
Overall duration of pain (Better indicated by lower values)												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[2]	none	10 Median 3 days (IQR 3 to 5)	7 Median 2 days (IQR 2 to 4)	HR 1.70 (0.61 to 4.75)	-	⊕⊕OO LOW	CRITICAL
Parent satisfaction with treatment												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[2]	none	9/10 (90%)	4/7 (57.1%)	-	571 fewer per 1000 (from 571 fewer to 571 fewer)	⊕⊕OO LOW	CRITICAL
Adverse events												
1[1]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[2]	none	1 adverse event in the control group, but this was not related to treatment				⊕⊕OO LOW	CRITICAL

Abbreviations: AUC, area under curve; CI, confidence interval; HR, hazard ratio; IQR, interquartile range; MD, mean difference; OR, odds ratio

[1] Hay et al. 2019
[2] Very wide confidence intervals, high uncertainty due to very small numbers of participants
[3] Prespecified 1-point minimum clinically important difference
[4] Adjusted for the parent-reported score at consultation