National Institute for Health and Care Excellence

APG Otitis media (acute): draft for consultation

Otitis media (acute): antimicrobial prescribing guideline

Evidence review

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Draft for consultation

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ISBN:

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1 Context

1.1 Background

Acute 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.

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):

- 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). 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 has recommendations for managing self-limiting respiratory tract infections relating to the use of 3 antibiotic prescribing strategies (either no prescribing, delayed prescribing or immediate prescribing). For acute otitis media, a no antibiotic prescribing strategy or a delayed 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 also has recommendations to not issue immediate antimicrobial prescriptions to people who are likely to have a self-limiting condition. Instead other options such as self-care with over the counter preparations, back-up or delayed prescribing, or other non-pharmacological interventions should be discussed alongside the natural history of the condition and safety netting advice.

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

1.2.1 Self-care

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

Self-care options that have been used to relieve pain and fever in acute otitis media include paracetamol and ibuprofen. Other self-care options such as topical analgesics (anaesthetic ear drops), 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 recommends that when a no antibiotic prescribing strategy is adopted, patients should be offered:

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

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

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

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

1.2.3 Antibiotic prescribing strategies

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

- Consider supplying antimicrobials in pack sizes that correspond to local (where available) and national guidelines on course lengths.
- Follow local (where available) or national guidelines on prescribing the shortest effective course, the most appropriate dose, and route of administration.
- Undertake a clinical assessment and document the clinical diagnosis (including symptoms) in the patient's record and clinical management plan.
- Document in the patient's records (electronically wherever possible):
  - the reason for prescribing an antimicrobial
  - the plan of care as discussed with the patient, their family member or carer (as appropriate), including the planned duration of any treatment.
- Take into account the benefits and harms for an individual patient associated with the particular antimicrobial, including:

  - possible interactions with other medicines or any food and drink
  - the patient's other illnesses, for example, the need for dose adjustment in a patient with renal impairment
  - any drug allergies (these should be documented in the patient's record)
  - the risk of selection for organisms causing healthcare associated infections, for example, *Clostridium difficile*.
- Document in the patient's records the reasons for the decision to prescribe outside local (where available) or national guidelines.

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

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

1.3 Safety netting advice

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

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

The NICE clinical knowledge summary on 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.

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

2.1 Literature search

A literature search identified 7,193 references (see appendix B: literature search strategy for full details). These references were screened using their titles and abstracts and 231 full text references were obtained and assessed for relevance. 53 full text references of systematic reviews and randomised controlled trials (RCTs) were assessed as relevant to the guideline review question (see appendix A: review protocol). Ten percent of studies were screened to establish inter-rater reliability.

Nine references were prioritised by the committee as the best available evidence and were included in this evidence review (see appendix D: included studies). Studies that assessed herbal and alternative medicines were not prioritised by the committee. The methods for identifying, selecting and prioritising the best available evidence are described in the interim process guide. The 44 references that were not prioritised for inclusion are listed in appendix G: not prioritised studies.

The remaining 178 references were excluded. These are listed in appendix H: excluded studies with reasons for their exclusion.

See also appendix C: study flow diagram.

2.2 Summary of included studies

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

Table 1: Summary of included studies: non-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
Topical analgesia					
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 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 delayed 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	Delayed antibiotic	No antibiotic Immediate antibiotic	Clinical outcomes Symptom severity Antibiotic use Patient satisfaction Antibiotic resistance
Venekamp et al. 2015[1] 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[1] 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
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 recurrent and/or persistent acute otitis media			
Frequency of antibiotic dosing					
Thanaviratananich et al. 2016	n=1,601 (5 RCTs)	Children aged 12 years or less with acute otitis media diagnosed by	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

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Systematic review and meta-analysis. Multiple countries. Follow-up to 15 days		acute ear pain (otalgia) and an inflamed ear drum (confirmed by positive tympanocentesis or tympanogram of type B or C)			
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] 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 F: GRADE profiles. The main results are summarised below for children with acute otitis media. No systematic reviews or RCTs were identified that included data in adults.

3.1 Non-pharmacological interventions

No systematic reviews or RCTs were included that compared non-pharmacological interventions in adults or children with acute otitis media.

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 randomised controlled trials (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.

Overall, the systematic review (n=392) found both paracetamol and ibuprofen were effective in reducing pain in children with acute otitis media, compared with placebo (very low to low quality evidence). There did not appear to be any significant differences in clinical effectiveness between paracetamol and ibuprofen (very low to low quality evidence). The addition of ibuprofen to paracetamol was no more effective than using paracetamol alone, although this is based on very small numbers of children in the analysis (very low to low quality evidence).

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%; risk ratio [RR] 0.38, 95% confidence interval [CI] 0.17 to 0.85, number needed to treat [NNT] 7; very 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; low 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 delayed antibiotic prescriptions between groups (very 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, delayed antibiotic prescriptions and serious complications between groups (very 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).

312.2 Topical analgesia

The evidence review for topical analgesia 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. All children received some form of oral analgesia.

Anaesthetic ear drops compared with placebo

Two RCTs (n=117) provided data on anaesthetic ear drops compared with placebo. No antibiotics were used in these studies. 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 4; 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).

Anaesthetic ear drops compared with herbal ear drops

Three RCTs (n=274) compared anaesthetic ear drops 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

8 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 (very 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 quality evidence).

Antihistamines compared with control

8 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, less than 7 days or after 2 weeks (very low quality evidence). There were also no significant differences in otalgia, hearing loss, prolonged otitis media, persistence after 2 weeks, recurrence, need for surgery and mastoiditis or meningitis (very low quality evidence).

Decongestant plus antihistamine compared with control

5 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: absolute numbers not reported; RR 0.76 95% CI 0.60 to 0.96, NNT 10; very 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 (very 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 Antimicrobials

The evidence review for antimicrobials in children is based on 5 systematic reviews of RCTs (Kozyrskyj et al. 2010, Shekelle et al 2010, Spurling et al. 2013, Thanaviratananich et al. 2013 and Venekamp et al. 2015). The included studies cover delayed 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.

3.1 Antibiotic prescribing strategies

Two systematic reviews (Spurling et al. 2013 and Venekamp et al. 2015) assessed the evidence on antibiotic prescribing strategies, including delayed antibiotics in children with acute otitis media. Spurling et al (2013) (3 RCTs) compared delayed 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.

Delayed antibiotics compared with no antibiotics

Spurling et al (2013) found no significant differences between delayed 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; very low quality evidence). There was also no significant difference between delayed antibiotics and no antibiotics in patient satisfaction when the delayed prescription was given at the time of consultation (very low quality evidence). However, as would be expected, there was significantly greater antibiotic use in the delayed 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; moderate quality evidence).

Delayed antibiotics compared with immediate antibiotics

Spurling et al (2013) found no significant differences between delayed 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; low 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; very low quality evidence) and pain on day 7 (1 RCT, n= 212: 3% versus 0%; OR 6.55, 95% CI 0.33 to 128.35; very low quality evidence).

Delayed 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; low 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; low quality evidence). The clinical relevance of an improvement of less than 1 point at day 3 is not clear.

There was significantly more pain relief used with delayed 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 delayed 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; very low quality evidence).

Malaise on day 3 was significantly increased with delayed antibiotics compared with immediate antibiotics (1 RCT, n=285: 30% versus 10%; OR 2.62, 95% CI 1.44 to 4.76; moderate 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). 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 (very low quality evidence).

Spurling et al (2013) also found significantly lower antibiotic use with delayed antibiotics compared with immediate antibiotics, both when the delayed 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; high 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 (very low quality evidence). However, patient satisfaction was significantly lower with delayed 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; moderate 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 delayed 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; relative risk [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; moderate 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 low 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 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.

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; number needed to treat [NNT] 24; 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; 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; moderate 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; 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 (moderate 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; 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; NNT 13; moderate 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 (Venekamp et al. 2015 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.

The Venekamp et al (2015) systematic review identified an individual patient data meta-analysis of 6 RCTs in 1,643 children (Rovers et al. 2006) that was included in the review. Overall, antibiotics appeared to be most beneficial in 2 pre-defined

subgroups: children under 2 years with bilateral acute otitis media, and children of any age with otorrhoea.

No significant differences were observed between antibiotics and placebo based on age alone. However, in children under 2 years with bilateral acute otitis media, pain and/or fever at 3 to 7 days was significantly lower with antibiotics compared with placebo (6 RCTs, n=273: 31% versus 54%; NNT 5; very low quality evidence). In children aged 2 years or older with bilateral acute otitis media, there was no significant difference between groups (6 RCTs, n=183: 23% versus 35%; low quality evidence).

In children with otorrhoea, pain and/or fever at 3 to 7 days was significantly lower with antibiotics compared with placebo (6 RCTs, n=116: 20% versus 67%; NNT 3; very low 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=440: 28% versus 43%; NNT 8; low quality evidence).

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.

3.6.4 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 (low 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 not reported: 91% versus 94%; mean difference –3.2%, 95% CI –6.2% to –0.2%.
- 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%.

326.5 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 moderate 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 (very low to moderate 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; low 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 (very 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; 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; 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 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; NNT 78; 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; NNT 8; moderate quality evidence).

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 moderate 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) (low 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 F: GRADE profiles. The main results are summarised below.

4.1 Non-pharmacological interventions

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

4.2 Non-antimicrobial pharmacological interventions

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

4.2.1 Oral analgesia

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 August 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 August 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 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 August 2017).

The NICE guideline on fever in under 5s: assessment and initial management 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 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 Topical analgesia

One systematic review of 5 RCTs (Foxlee et al. 2011) found that only 1 RCT measured adverse effects with topical analgesia and none were found.

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. Pseudoephedrine has few sympathomimetic effects. However, decongestants should be used with caution in people with diabetes, hypertension, hyperthyroidism, susceptibility to angle-closure glaucoma, prostatic hypertrophy, and ischaemic heart disease (BNF June 2017).

All older antihistamines, such as chlorphenamine, cause sedation. They have significant antimuscarinic activity and children and the elderly are more susceptible to side effects. These include psychomotor impairment, and antimuscarinic effects such as urinary retention, dry mouth, blurred vision, and gastro-intestinal disturbances. Other rare side effects of antihistamines include arrhythmias, dizziness, sleep disturbances, and QT-interval prolongation with some agents. 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 April 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 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) (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 (very 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).

Allergic reactions to penicillins occur in 1 to 10% of treated people and anaphylactic reactions occur in less than 0.05%. People with a history of atopic allergy (for example, asthma, eczema, and hayfever) are at a higher risk of anaphylactic reactions to penicillins. People with a history of immediate hypersensitivity to penicillins may also react to cephalosporins and other beta-lactam antibiotics. The

most common side effect with penicillins is diarrhoea, which can also cause antibiotic-associated colitis. Diarrhoea is most common with broad-spectrum penicillins (such as amoxicillin and co-amoxiclav) (BNF, June 2017). Co-amoxiclav also has a warning that cholestatic jaundice can occur either during or shortly after its use, more commonly in people over 65 years and men. The risk of acute liver toxicity is about 6 times greater with co-amoxiclav than with amoxicillin and the duration of treatment should be appropriate to the indication, not usually exceeding 14 days (BNF, June 2017).

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

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

413.1 Antibiotic prescribing strategies

One systematic review (Spurling et al. 2013) identified 2 RCTs that considered the adverse effects of delayed antibiotics compared with immediate antibiotics. No significant differences were identified between groups for vomiting (1 RCT, n=165: 11% versus 11%; odds ratio OR 1.01,95% CI 0.47 to 2.16; very low quality evidence) or rash (1 RCT, n=285: 5% versus 4%; OR 1.21 95% CI 0.41 to 3.58; very low quality evidence) There was significantly less diarrhoea with delayed antibiotics compared with immediate antibiotics (data not pooled – 1 RCT, n=285: 9% versus 19%; OR, 0.45, 95% CI 0.22 to 0.91; number needed to harm [NNH] 10; low quality evidence; 1 RCT, n=265: 8% versus 23%; OR 0.27, 95% CI 0.13 to 0.58; NNH 6; moderate quality evidence). No data were available on delayed 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 9; moderate quality evidence).

432.2 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; moderate quality evidence).

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%; NNH 3; very low quality evidence), cefdinir taken twice a day: (1 RCT, n=256: rate difference 19%, 95% CI 8% to 31%; NNH 5; very low quality evidence); and ceftriaxone (1 RCT, n=513: rate difference 16%, 95% CI 9% to 24%; NNH 6; very low 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%; NNH 5; moderate quality

evidence) and gastrointestinal adverse effects (3 RCT, n=1,366: rate difference 18%, 95% CI 8% to 28%; NNH 6; 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%; NNH 12; 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; NNH 21; low quality evidence). 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; NNH 7; 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; NNH 15; 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; NNH 14; moderate quality evidence).

5 Resistance

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

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

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

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

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

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). 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 delayed antibiotic prescription strategy is used. In 1 systematic review (Spurling et al. 2013), there was significantly lower antibiotic use with a delayed antibiotic prescribing strategy compared with immediate antibiotics, both when the delayed prescription was given at the time of consultation (38% versus 87%; 1 RCT; high 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 (very low quality evidence).

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

6.2 Medicines adherence

Medicines adherence may be a problem for some people with medicines that require frequent dosing (for example, some antibiotics) (NICE guideline on medicines adherence). Longer treatment durations for an acute illness (for example, 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: RR 1.04, 95% CI 0.98 to 1.10; moderate quality evidence).

6.3 Regulatory status

There are no anaesthetic ear drops licensed for use in the UK.

7 Terms used in the guideline

7.1 Expectant observation

Expectant observation is an observational approach in which an antibiotic prescription may or may not be provided. Examples of this approach include delayed antibiotic prescribing (when a person is given a prescription or advised to collect a prescription at a later date if needed) and 'watchful waiting' (when a person is not given a prescription but is offered advice on when to seek further treatment).

Appendices

Appendix A: Review protocol for acute otitis media

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 delayed antimicrobial • indications for non-antimicrobial interventions

			• antimicrobial choice, optimal dose, duration (specifically length of treatment) and route for specified antimicrobial(s) • the natural history of the condition
IV	Eligibility criteria – population/disease/condition/issue/domain	Population: Adults and children (aged 72 hours and older) with acute uncomplicated otitis media of any severity. Studies that use for example clinical diagnosis, imaging or microbiological methods of diagnosing the condition.	Subgroups of interest, those: • 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 –	Any other plausible strategy or comparator, including: • Placebo or no treatment	Placebo or no treatment, previous studies have demonstrated that acute otitis media

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

	comparator(s)/control or reference (gold) standard	• Non-pharmacological interventions • Non-antimicrobial pharmacological interventions • Antimicrobial pharmacological interventions	(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 • 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 have agreed that the following outcomes are critical: • reduction in symptoms (duration or severity) for example difference in time to substantial improvement • time to clinical cure (mean or median time to resolution of illness) • rate of complications (including mortality) with or without treatment, including escalation of treatment • health and social care utilisation (including length of stay, ITU stays, planned and unplanned contacts). • thresholds or indications for antimicrobial treatment (which people are most, or least likely to benefit from antimicrobials) The committee have agreed that the following outcomes are important: • patient-reported outcomes, such as medicines adherence, patient experience

		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).	• changes in antimicrobial resistance patterns, trends and levels as a result of treatment
VIII	Eligibility criteria – study design	The search will look for: • Systematic review of randomised controlled trials (RCTs) • RCTs If insufficient evidence is available progress to: • Controlled trials • Systematic reviews of non-randomised controlled trials • Non-randomised controlled trials • Observational and cohort studies • Pre and post intervention studies (before and after) • Time series studies	Committee to advise the NICE project team on the inclusion of information from other condition specific guidance and on whether to progress due to insufficient evidence.
IX	Other inclusion exclusion criteria	The scope sets out what the guidelines will and will not include (exclusions). Further exclusions specific to this guideline include: • non-English language papers, studies that are only available as abstracts • for antimicrobial resistance non-UK papers.	
X	Proposed sensitivity/sub-group analysis, or meta-regression	The search may identify studies in population subgroups (for example adults, older adults, children (those aged under 18 years of age), and people with co-morbidities or characteristics that are protected under the Equality Act 2010 or in the NICE equality impact assessment). These will be analysed within these categories to enable the production of management recommendations.	
XI	Selection process – duplicate	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	

	screening/selection/analysis	recorded, and if it is over 90% then remaining references will screened by one reviewer only. Disagreement will be resolved through discussion. Where abstracts meet all the criteria, or if it is unclear from the study abstract whether it does, the full text will be retrieved. If large numbers of papers are identified and included at full text, the Committee may consider prioritising the evidence for example, evidence of higher quality in terms of study type or evidence with critical or highly important outcomes.	
XII	Data management (software)	Data management will be undertaken using EPPI-reviewer software. Any pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome.	
XIII	Information sources – databases and dates	Medline; Medline in Process; Embase; PubMed; Cochrane database of systematic reviews (CDSR); Database of abstracts of effectiveness (DARE) (legacy); Cochrane Central Register of Controlled Trials (CENTRAL); Health Technology Assessment (HTA) database; Clinicaltrials.gov • All the above to be searched from 2000 to present day. • Filters for systematic reviews; RCTS, 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-ng10050/consultation/html-content Email: infections@nice.org.uk	
XVI	Highlight if amendment to previous protocol	For details please see the interim process guide (2017).	
XVII	Search strategy – for one database	For details please see appendix B	
XVIII	Data collection process – forms/ duplicate	GRADE profiles will be used, for details see appendix F.	
XIX	Data items – define all variables to be collected	GRADE profiles will be used, for details see appendix F.	
XX	Methods for assessing bias at outcome/study level	Standard study checklists will be used to critically appraise individual studies. For details please see 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	

1

Appendix B: Literature search strategy

Database: Ovid MEDLINE(R) <1946 to December Week 1 2016>
Search Strategy: Acute otitis media
---

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)

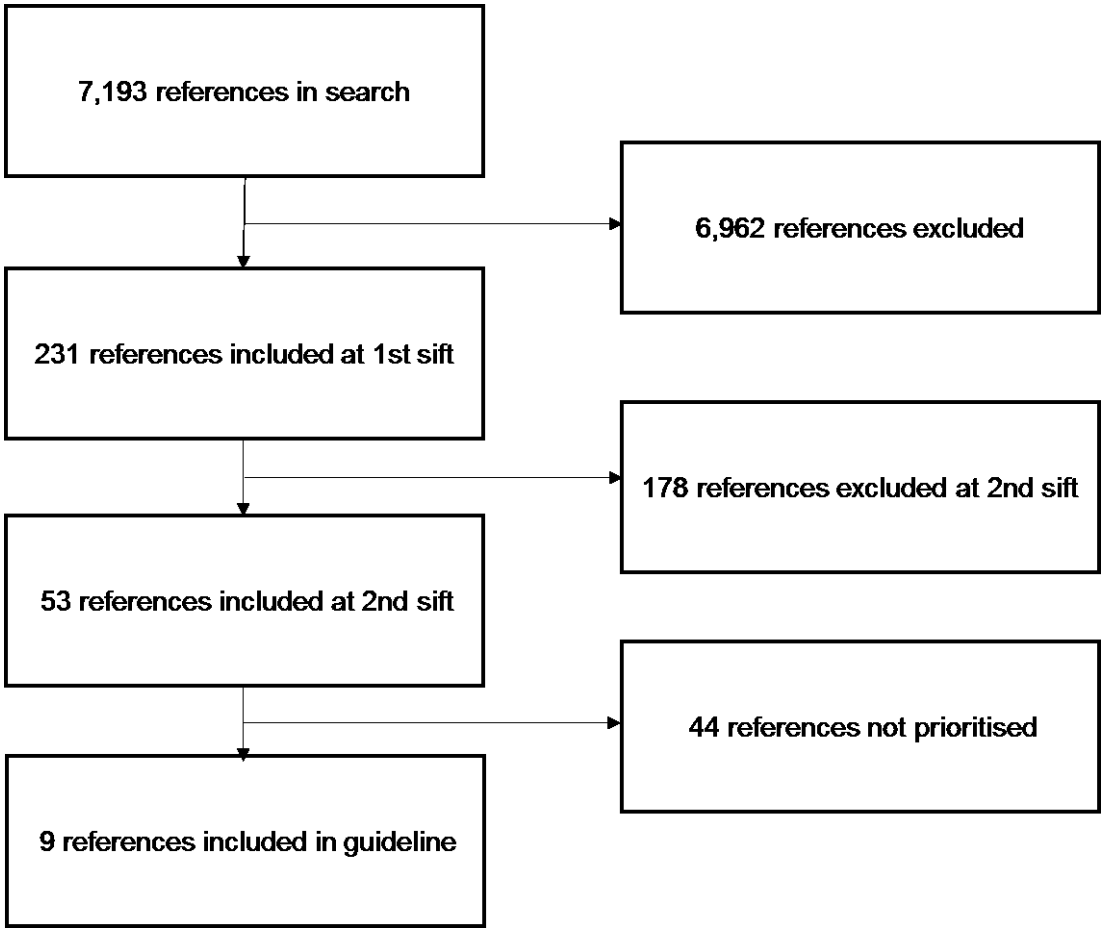
138 29 and 137 (40351)

139 limit 138 to (english language and yr="2000 -Current") (21130)

140 animals/ not humans/ (4782110)

141 139 not 140 (18705)

Appendix C: Study flow diagram



Appendix D: Included studies

Chronmaitree 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

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 E: Quality assessment of included studies

E.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

E.2 Topical analgesia

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 anaesthetic ear drops with a herbal ear drop preparation. It is not clear how this applies to a UK population	

E.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

E.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

E.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

E.6 Antimicrobials

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

Study reference	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
Did the authors look for the right type of papers?	Yes	Yes	Yes	Yes
Do you think all the important, relevant studies were included?	Yes	Yes	Yes	Yes
Did the review's authors do enough to assess the quality of the included studies?	Yes	Yes	Yes	Yes
If the results of the review have been combined, was it reasonable to do so?	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
How precise are the results?	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
Were all important outcomes considered?	Yes	Yes	Yes	Yes
Are the benefits worth the harms and costs?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles

Appendix F: GRADE profiles

F.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[3]	serious[4]	no serious indirectness	serious[5]	none	7/73 (9.6%)	19/75 (25.3%)	RR 0.38 (0.17 to 0.85)	157 fewer per 1000 (from 38 fewer to 210 fewer)	⊕OOO VERY LOW	CRITICAL
Fever at 48 hours												
1[3]	randomised trials	serious[3]	serious[4]	no serious indirectness	very serious[7]	none	1/73 (1.4%)	1/75 (1.3%)	RR 1.03 (0.07 to 16.12)	0 more per 1000 (from 12 fewer to 202 more)	⊕OOO VERY LOW	CRITICAL
Adverse events												
1[1]	randomised trials	serious[3]	serious[4]	no serious indirectness	very serious[7]	none	3/73 (4.1%)	3/75 (4%)	RR 1.03 (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 - not assessable
[6] Downgraded 1 level - at a default minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit with paracetamol
[7] Downgraded 2 levels - at a default 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)												
1[3]	randomised trials	serious[4]	serious[5]	no serious indirectness	no serious imprecision	none	5/71 (7.0%)	19/75 (25.3%)	RR 0.28 (0.11 to 0.70)	182 fewer per 1000 (from 76 fewer to 225 fewer)	⊕⊕OO LOW	CRITICAL

Fever (follow-up 48 hours)											
1[3]	randomised trials	serious[4]	serious[5]	no serious indirectness	very serious[6]	none	1/71 (1.4%)	1/75 (1.3%)	RR 1.06 (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]	serious[5]	no serious indirectness	very serious[6]	none	5/71 (7%)	3/75 (4%)	RR 1.76 (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 1 level - not assessable
[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 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 (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 (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 (0.17 to 3.23)	49 fewer per 1000 (from 156 fewer to 418 more)	⊕OOO VERY LOW	CRITICAL
Fever at 24 hours												
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 (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 (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 (0.12 to 60.70)	-	⊕OOO VERY LOW	CRITICAL
Re-consultations												
1[1]	randomised trials	serious[7]	serious[8]	no serious indirectness	serious[9]	none	24/26 (92.3%)[10]	22/27 (81.5%)[10]	RR 1.13 (0.92 to 1.40)	106 more per 1000 (from 65 fewer to 326 more)	⊕OOO VERY LOW	IMPORTANT
Delayed antibiotic prescription												
1[1]	randomised trials	serious[7]	serious[8]	no serious indirectness	very serious[6]	none	14/26 (53.8%)[10]	11/27 (40.7%)[10]	RR 1.32 (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 (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 MID of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[7] Downgraded 1 level - open label study
[8] Downgraded 1 level - not assessable
[9] Downgraded 1 level - at a default 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 (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 (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 (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 (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 (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]	serious[7]	no serious indirectness	serious[7]	none	0/24 (0%)[4]	0/17 (0%)[4]	RR 0.0 (0.0 to 0.0)	-	⊕OOO VERY LOW	CRITICAL
Re-consultations												
1[1]	randomised trials	serious[8]	serious[9]	no serious indirectness	serious[5]	none	19/29 (65.5%)[10]	22/27 (81.5%)[10]	RR 0.80 (0.58 to 1.11)	163 fewer per 1000 (from 342 fewer to 90 more)	⊕OOO VERY LOW	IMPORTANT
Delayed antibiotic prescription												
1[1]	randomised trials	serious[8]	serious[9]	no serious indirectness	serious[3]	none	15/29 (51.7%)[10]	11/27 (40.7%)[10]	RR 1.27 (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[9]	no serious indirectness	serious[7]	none	0/37 (0%)[4]	0/34 (0%)[4]	RR 0.0 (0.0 to 0.0)	-	⊕OOO VERY LOW	CRITICAL
Adverse events												
1[1]	randomised trials	serious[8]	serious[7]	no serious indirectness	serious[7]	none	0/29 (0%)[10]	0/27 (0%)[10]	RR 0.0 (0.0 to 0.0)	-	⊕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 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 MID of 25%, data are consistent with no meaningful difference or appreciable benefit with ibuprofen plus paracetamol
[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 (no events reported in either group in both RCTs)
[8] Downgraded 1 level - open label study
[9] Downgraded 1 level - not assessable
[10] The dosage was the maximum recommended in the British National Formulary

F.2 Topical analgesia

Table 13: GRADE profile – anaesthetic ear drops versus placebo

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Anaesthetic 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 (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 (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 (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 (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)												
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 (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 (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]	serious[4]	no serious indirectness	serious[4]	none	-	-	1 RCT reported a limited range of adverse effects (tinnitus, dizziness or unsteady gait) and none were found		⊕OOO VERY LOW	CRITICAL
Abbreviations: CI, Confidence interval; RR, Rate ratio												

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

Table 14: GRADE profile – anaesthetic ear drops 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 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]	no serious imprecision	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[6]	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)												
2[1]	randomised trials	serious[2]	serious[3]	serious[4]	serious[6]	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]	serious[7]	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]	serious[7]	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; MID, Minimal important 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 an MID of 25% reduction in mean pain score from before installation on day 1 (approximately 2 points), data are consistent with no meaningful difference or appreciable benefit with herbal ear drops
[6] Downgraded 1 level - at an MID of 25% reduction in mean pain score from before installation on day 2 (approximately 0.7 points), data are consistent with no meaningful difference or appreciable benefit with herbal ear drops
[7] Downgraded 1 level - at an MID of 25% reduction in mean pain score from before installation on day 3 (approximately 0.4 points), data are consistent with no meaningful difference or appreciable benefit with herbal ear drops

F.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]	serious[3]	no serious indirectness	very serious[4]	none	981	Peto OR 1.06 (0.73 to 1.54)	-	⊕OOO VERY LOW	CRITICAL
Persistent acute otitis media (before 7 days)											
No data were available											CRITICAL
Persistent acute otitis media (after 2 weeks)											
3[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[4]	none	301	Peto OR 1.08 (0.45 to 2.55)	-	⊕OOO VERY LOW	CRITICAL
Otalgia											
2[1]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	very serious[4]	none	176	Peto OR 0.73 (0.36 to 1.51)	-	⊕OOO VERY LOW	IMPORTANT
Fever											
1[1]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	very serious[5]	none	50	Peto OR 8.03 (0.16 to 406.02)	-	⊕OOO VERY LOW	IMPORTANT
Hearing loss											
1[1]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	very serious[4]	none	462	Peto OR 1.75 (0.65 to 4.75)	-	⊕OOO VERY LOW	CRITICAL
Complications: prolonged acute otitis media (follow-up 8 to 12 weeks)											
1[1]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	very serious[4]	none	72	Peto OR 0.69 (0.17 to 2.75)	-	⊕OOO VERY LOW	CRITICAL
Complications: recurrent acute otitis media (after 2 weeks)											
3[1]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	very serious[4]	none	248	Peto OR 0.74 (0.35 to 1.57)	-	⊕OOO VERY LOW	CRITICAL
Complications: need for surgery											
2[1]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	very serious[4]	none	534	Peto OR 1.38 (0.44 to 4.36)	-	⊕OOO VERY LOW	CRITICAL
Hyperactivity											
2[1]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	very serious[4]	none	150	Peto OR 0.51 (0.05 to 4.95)	-	⊕OOO VERY LOW	IMPORTANT
Adverse effects (excluding drowsiness or hyperactivity)											
3[1]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	very serious[5]	none	296	Peto OR 7.91 (2.36 to 26.54)	-	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI, Confidence interval; MID, Minimal important difference; OR, Odds ratio											

[1] Coleman et al (2008)
[2] Downgraded 1 level - it is not clear which RCTs contributed to the analysis. The overall systematic review includes some low quality studies (Cochrane assessed quality score of 2 or less), all of

which assessed persistence of acute otitis media (time of outcome measurement not known)
[3] Downgraded 1 level - not assessable
[4] Downgraded 2 levels - at a default MID of 25% data are consistent with no meaningful difference, appreciable benefit or appreciable harm with decongestants
[5] Downgraded 2 levels - at a default 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]	serious[3]	no serious indirectness	serious[4]	none	987		Peto OR 0.84 (0.58 to 1.24)	-	⊕OOO VERY LOW	CRITICAL
Persistent acute otitis media (before 7 days)												
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	very serious[5]	none	90		Peto OR 1.05 (0.28 to 3.89)	-	⊕OOO VERY LOW	CRITICAL
Persistent acute otitis media (after 2 weeks)												
2[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[6]	none	112		Peto OR 2.41 (1.02 to 5.68)	-	⊕OOO VERY LOW	CRITICAL
Otalgia												
2[1]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	very serious[5]	none	176		Peto OR 0.87 (0.43 to 1.76)	-	⊕OOO VERY LOW	IMPORTANT
Hearing loss												
1[1]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	very serious[5]	none	514		Peto OR 0.54 (0.06 to 5.22)	-	⊕OOO VERY LOW	IMPORTANT
Complications: prolonged acute otitis media (follow-up 8 to 12 weeks)												
1[1]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	very serious[5]	none	68		Peto OR 1.00 (0.26 to 3.79)	-	⊕OOO VERY LOW	CRITICAL
Complications: recurrent acute otitis media (after 2 weeks)												
5[1]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	very serious[5]	none	848		Peto OR 1.10 (0.64 to 1.88)	-	⊕OOO VERY LOW	CRITICAL
Complications: need for surgery												
3[1]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	very serious[5]	none	672		Peto OR 1.40 (0.66 to 2.97)	-	⊕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	serious[3]	no serious indirectness	very serious[7]	none	192	Peto OR 7.60 (0.78 to 74.26)		⊕OOO VERY LOW	CRITICAL
Abbreviations: CI, Confidence interval; MID, Minimal important difference; OR, Odds ratio											

[1] Coleman et al (2008)
[2] Downgraded 1 level - it is not clear which RCTs contributed to the analysis. The overall systematic review includes some low quality studies (Cochrane assessed quality score of 2 or less), all of which assessed persistence of acute otitis media (time of outcome measurement not known)
[3] Downgraded 1 level - not assessable
[4] Downgraded 1 level - at a default MID of 25% data are consistent with no meaningful difference or appreciable benefit with antihistamines
[5] Downgraded 2 levels - at a default MID of 25% data are consistent with no meaningful difference, appreciable benefit or appreciable harm with antihistamines
[6] Downgraded 1 level - at a default MID of 25% data are consistent with no meaningful difference or appreciable harm with antihistamines
[7] Downgraded 2 levels - at a default 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]	serious[3]	no serious indirectness	serious[4]	none	482		Peto OR 0.63 (0.43 to 0.93)	-	⊕OOO VERY LOW	CRITICAL
Persistent acute otitis media (before 7 days)												
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	very serious[5]	none	53		Peto OR 0.71 (0.24 to 2.07)	-	⊕OOO VERY LOW	CRITICAL
Persistent acute otitis media (after 2 weeks)												
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	very serious[5]	none	49		Peto OR 1.37 (0.33 to 5.74)	-	⊕OOO VERY 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	serious[3]	no serious indirectness	very serious[5]	none	52		Peto OR 0.13 (0.01 to 2.14)	-	⊕OOO VERY LOW	CRITICAL
Hyperactivity												

2[1]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	very serious[5]	none	105	Peto OR 8.33 (0.16 to 422.51)	-	⊕OOO VERY LOW	IMPORTANT
Drowsiness											
1[1]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	very serious[5]	none	53	Peto OR 8.68 (0.53 to 143.30)	-	⊕OOO VERY LOW	IMPORTANT
Adverse effects (excluding drowsiness or hyperactivity)											
1[1]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	very serious[5]	none	52	Peto OR 7.69 (0.47 to 126.39)	-	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI, Confidence interval; MID, Minimal important difference; OR, Odds ratio											

[1] Coleman et al (2008)
[2] Downgraded 1 level - it is not clear which RCTs contributed to the analysis. The overall systematic review includes some low quality studies (Cochrane assessed quality score of 2 or less), all of which assessed persistence of acute otitis media (time of outcome measurement not known)
[3] Downgraded 1 level - not assessable
[4] Downgraded 1 level - at a default MID of 25% data are consistent with no meaningful difference or appreciable benefit with decongestant plus antihistamine
[5] Downgraded 2 levels - at a default MID of 25% data are consistent with no meaningful difference, appreciable benefit or appreciable harm

F.4 Oral corticosteroids

Table 18: GRADE profile – oral corticosteroid versus placebo

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Oral corticosteroid**	**Placebo**	**Relative**	**Absolute**		
Treatment failure at day 5												
1[2]	randomised trials	serious[3]	serious[4]	no serious indirectness	serious[4]	none	4/45 (8.9%)	5/46 (10.9%)	No analysis of corticosteroid vs. placebo reported		⊕OOO VERY LOW	CRITICAL[5]
Treatment failure at day 14												
1[2]	randomised trials	serious[3]	serious[4]	no serious indirectness	serious[4]	none	4/45 (8.9%)	5/46 (10.9%)	No analysis of corticosteroid vs. placebo reported		⊕OOO VERY LOW	CRITICAL[5]
Treatment failure during the first 2 weeks												
1[2]	randomised trials	serious[3]	serious[4]	no serious indirectness	serious[4]	none	7/45[6] (15.6%)	10/46 (21.7%)	No analysis of corticosteroid vs. placebo reported		⊕OOO VERY LOW	CRITICAL[5]
Presence of middle ear effusion (follow-up 1 month)												
1[2]	randomised trials	serious[3]	serious[4]	no serious indirectness	serious[4]	none	45%	48%	No analysis of corticosteroid vs. placebo reported		⊕OOO VERY LOW	CRITICAL

Presence of middle ear effusion (follow-up 2 months)											
1[2]	randomised trials	serious[3]	serious[4]	no serious indirectness	serious[4]	none	27%	34%	No analysis of corticosteroid vs. placebo reported	⊕OOO VERY LOW	CRITICAL
Presence of middle ear effusion (follow-up 3 months)											
1[2]	randomised trials	serious[3]	serious[4]	no serious indirectness	serious[4]	none	19%	22%	No analysis of corticosteroid vs. placebo reported	⊕OOO VERY LOW	CRITICAL
Recurrence (follow-up 1 month)											
1[2]	randomised trials	serious[3]	serious[4]	no serious indirectness	serious[4]	none	20%	16%	No analysis of corticosteroid vs. placebo reported	⊕OOO VERY LOW	CRITICAL
Recurrence (follow-up 2 months)											
1[2]	randomised trials	serious[3]	serious[4]	no serious indirectness	serious[4]	none	23%	27%	No analysis of corticosteroid vs. placebo reported	⊕OOO VERY LOW	CRITICAL
Recurrence (follow-up 3 months)											
1[2]	randomised trials	serious[3]	serious[4]	no serious indirectness	serious[4]	none	23%	32%	No analysis of corticosteroid vs. placebo reported	⊕OOO VERY LOW	CRITICAL
Recurrence (follow-up 4 to 6 months)											
1[2]	randomised trials	serious[3]	serious[4]	no serious indirectness	serious[4]	none	33%	38%	No analysis of corticosteroid vs. placebo reported	⊕OOO VERY LOW	CRITICAL
Adverse effects											
1[2]	randomised trials	serious[3]	serious[4]	no serious indirectness	serious[4]	none	-	-	Adverse effects were similar across groups (no analysis reported)	⊕OOO VERY LOW	CRITICAL

[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 1 level - not assessable
[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

F.5 Antibiotic prescribing strategies

Table 19: GRADE profile – delayed antibiotics versus no antibiotics

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Delayed antibiotics**	**No antibiotics**	**Relative (95% CI)**	**Absolute**		
Pain at day 3												

1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[4]	none	26/106 (24.5%)	29/100 (29%)	OR 0.80 (0.43 to 1.48)	44 fewer per 1000 (from 141 fewer to 87 more)	⊕OOO VERY LOW	CRITICAL
Fever at day 3												
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[4]	none	18/106 (17%)	8/100 (8%)	OR 2.35 (0.97 to 5.69)	90 more per 1000 (from 2 fewer to 251 more)	⊕OOO VERY LOW	CRITICAL
Antibiotic use												
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	no serious imprecision	strong association[5]	40/106 (37.7%)	13/100 (13%)	OR 4.06 (2.01 to 8.19)	248 more per 1000 (from 101 more to 420 more)	⊕⊕⊕O MODERATE	CRITICAL
Patient satisfaction												
1[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	very serious[6]	none	98/106 (92.5%)	91/100 (91%)	OR 2.00 (0.65 to 6.18)	43 more per 1000 (from 42 fewer to 74 more)	⊕OOO VERY LOW	IMPORTANT
Abbreviations: CI, Confidence interval; OR, Odds ratio												

[1] Spurling et al 2013
[2] Downgraded 1 level - high risk of performance and selection bias (as assessed by Cochrane authors)
[3] Downgraded 1 level - not assessable
[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 – OR >2
[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 20: GRADE profile – delayed antibiotics versus immediate antibiotics

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Delayed antibiotics**	**Immediate antibiotics**	**Relative (95% CI)**	**Absolute**		
Pain at day 3												
1[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	28/111 (25.2%)	15/101 (14.9%)	OR 1.93 (0.96 to 3.88)	103 more per 1000 (from 5 fewer to 255 more)	⊕⊕OO LOW	CRITICAL
Pain at days 4 to 6												
1[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	very serious[4]	none	85/132 (64.4%)	89/133 (66.9%)	OR 0.89 (0.54 to 1.48)	26 fewer per 1000 (from 147 fewer to 80 more)	⊕OOO VERY LOW	CRITICAL
Pain at day 7												
1[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	very serious[4]	none	3/111 (2.7%)	0/101 (0%)	OR 6.55 (0.33 to 128.35)	-	⊕OOO VERY LOW	CRITICAL
Pain severity at day 3[5]												
1[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[6]	none	111	102	-	MD 0.75 higher (0.26 to 1.24 higher)	⊕⊕OO LOW	CRITICAL
Pain severity at day 7[5]												

1[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[6]	none	111	101	-	MD 0.12 lower (0.04 lower to 0.28 higher)	⊕⊕OO LOW	CRITICAL
Malaise at day 3												
1[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	none	45/150 (30%)	13/135 (9.6%)	OR 2.62 (1.44 to 4.76)	122 more per 1000 (from 37 more to 240 more)	⊕⊕⊕O MODERATE	CRITICAL
Malaise severity at day 3[5]												
1[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[6]	none	150	134	-	MD 0.43 higher (0.11 to 0.75 higher)	⊕⊕OO LOW	CRITICAL
Malaise severity at day 7 (assessed by 'last day crying'[5,7])												
1[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[6]	none	150	135	-	MD 0.69 higher (0.31 to 1.07 higher)	⊕⊕OO LOW	CRITICAL
Fever at days 4 to 6[8]												
1[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	very serious[4]	none	42/132 (31.8%)	46/133 (34.6%)	OR 0.88 (0.53 to 1.47)	28 fewer per 1000 (from 127 fewer to 91 more)	⊕OOO VERY LOW	CRITICAL
Supplementary spoons of paracetamol/day												
1[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	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	serious[2]	no serious indirectness	very serious[4]	none	123/132 (93.2%)	120/133 (90.2%)	OR 1.48 (0.61 to 3.59)	30 more per 1000 (from 53 fewer to 68 more)	⊕OOO VERY LOW	CRITICAL
Antibiotic use (delayed antibiotics: prescription at time of visit)												
1[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	strong association[9]	50/132 (37.9%)	116/133 (87.2%)	OR 0.09 (0.05 to 0.17)	492 fewer per 1000 (from 335 fewer to 618 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Antibiotic use (delayed antibiotics: return for prescription)												
1[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	strong association[9]	36/150 (24.0%)	132/151 (87.4%)	OR 0.05 (0.02 to 0.08)	616 fewer per 1000 (from 517 fewer to 752 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Re-consultation rates												
1[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	very serious[4]	none	13/132 (9.8%)	11/133 (8.3%)	OR 1.21 (0.52 to 2.81)	16 more per 1000 (from 38 fewer to 119 more)	⊕OOO VERY LOW	CRITICAL
Patient satisfaction												
1[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	none	115/150 (76.7%)	123/135 (91.1%)	OR 0.32 (0.16 to 0.65)	145 fewer per 1000 (from 42 fewer to 290 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
Diarrhoea (2 RCTs: data not pooled)												
1[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	serious[3]	none	14/150 (9.3%)	25/135 (18.5%)	OR 0.45 (0.22 to 0.91)	92 fewer per 1000 (from 14 fewer to 138 fewer)	⊕⊕OO LOW	CRITICAL

1[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	none	10/132 (7.6%)	31/133 (23.3%)	OR 0.27 (0.13 to 0.58)	157 fewer per 1000 (from 83 fewer to 195 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Vomiting												
1[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	very serious[4]	none	15/132 (11.4%)	15/133 (11.3%)	OR 1.01 (0.47 to 2.16)	1 more per 1000 (from 56 fewer to 103 more)	⊕OOO VERY LOW	CRITICAL
Skin rash												
1[1]	randomised trials	no serious risk of bias	serious[2]	no serious indirectness	very serious[4]	none	8/150 (5.3%)	6/135 (4.4%)	OR 1.21 (0.41 to 3.58)	9 more per 1000 (from 26 fewer to 98 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI, Confidence interval; RR, Relative Risk												

[1] Spurling et al (2013)
[2] Downgraded 1 level - not assessable
[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 2 levels - at a default minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[5] Severity was measured on a 10 point Likert scale with lower values indicating lower pain
[6] Downgraded 1 level - MID not assessable
[7] 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)
[8] Fever at day 3 was reported in the primary study, but not reported in the main finding or analysis of Spurling et al (2013)
[9] Upgraded 1 level - large effect

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	serious[4]	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)	⊕⊕⊕O MODERATE	CRITICAL
Abnormal tympanometry at 4 weeks												
1[2]	randomised trials	no serious risk of bias	serious[4]	no serious indirectness	serious[5]	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)	⊕⊕OO LOW	CRITICAL
Tympanic membrane perforation												
1[2]	randomised trials	no serious risk of bias	serious[4]	no serious indirectness	serious[4]	none	0/92 (0%)	0/87 (0%)	-	-	⊕⊕OO LOW	CRITICAL
Recurrence of acute otitis media												

1[2]	randomised trials	no serious risk of bias	serious[4]	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)	⊕OOO VERY LOW	CRITICAL
Parent-reported ear pain episodes at 1 year												
1[2]	randomised trials	no serious risk of bias	serious[4]	no serious indirectness	very serious[6]	none	-	-	OR 1.03, 95% 0.60 to 1.78	-	⊕OOO VERY LOW	CRITICAL
Vomiting, diarrhoea or rash												
2[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	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; RR, Relative Risk												

1 See Terms used in the guideline for definition of expectant observation (includes watchful waiting and delayed 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 - not assessable
5 Downgraded 1 level - at a default minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit with expectant observation
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

F.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												
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	serious[4]	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)	⊕⊕⊕O MODERATE	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]	no serious inconsistency	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)	⊕⊕⊕O MODERATE	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	no serious inconsistency	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)	⊕⊕⊕O MODERATE	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
Vomiting, diarrhoea or rash											
8[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	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
Identifying children more likely to benefit from antibiotics – sub-group analyses											
Children under 2 years with bilateral acute otitis media: pain and/or fever at days 3 to 7											
6[2]	randomised trials	serious[6]	serious[4]	no serious indirectness	serious[3]	none	42/136 (30.9%)	74/136 (54.4%)	RR 0.75 (0.64 to 0.76)	136 fewer per 1000 (from 131 fewer to 196 fewer)	⊕OOO VERY LOW	CRITICAL
Children 2 years and over with bilateral acute otitis media: pain and/or fever at days 3 to 7											
6[2]	randomised trials	serious[6]	serious[4]	no serious indirectness	no serious imprecision	none	20/92 (21.7%)	30/92 (32.6%)	RR 0.88 (0.75 to 1.01)	39 fewer per 1000 (from 82 fewer to 3 more)	⊕⊕OO LOW	CRITICAL
Children with otorrhoea: pain and/or fever at days 3 to 7											
6[2]	randomised trials	serious[6]	serious[4]	no serious indirectness	serious[3]	none	12/58 (20.7%)	39/58 (67.2%)	RR 0.64 (0.47 to 0.81)	242 fewer per 1000 (from 128 fewer to 356 fewer)	⊕OOO VERY LOW	CRITICAL
Children without otorrhoea: pain and/or fever at days 3 to 7 days											
6[2]	randomised trials	serious[6]	serious[4]	no serious indirectness	no serious imprecision	none	61/220 (27.7%)	94/220 (42.7%)	RR 0.86 (0.77 to 0.95)	60 fewer per 1000 (from 21 fewer to 98 fewer)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI, Confidence interval; RR, Relative risk												

[1] Antibiotics included co-amoxiclav, ampicillin, pheneticillin, amoxicillin, penicillin and phenomethyl penicillin
[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 - not assessable
[5] Downgraded 1 level - unclear risk of selection, performance, attrition bias and/or other bias in included studies
[6] Downgraded 1 level - not assessable: data derived from individual patient data study (Rovers et al 2006) and not assessed for bias in Venekamp et al (2015)

Table 23: 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 14[1]												
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%)	-	⊕⊕⊕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%)	531/686 (77.4%)	Risk difference 0% (-2 %to 7%)	-	⊕⊕⊕O MODERATE	CRITICAL
Any adverse events[6]												
1[2]	randomised trials	serious[7]	serious[8]	no serious indirectness	serious[9]	none	54/128 (42.2%)	18/128 (14.1%)	Rate difference 28% (17% to 39%)	-	⊕OOO VERY LOW	CRITICAL
Any adverse events[10]												
1[2]	randomised trials	serious[7]	serious[8]	no serious indirectness	serious[9]	none	54/128 (42.2%)	29/128 (22.7%)	Rate difference 19% (8% to 31%)	-	⊕OOO VERY LOW	CRITICAL
Any adverse events[11]												
1[2]	randomised trials	no serious risk of bias	serious[8]	no serious indirectness	serious[9]	none	79/258 (30.6%)	36/255 (14.1%)	Rate difference 16% (9% to 24%)	-	⊕⊕OO LOW	CRITICAL
Diarrhoea[12]												
5[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	53/374 (14.2%)	80/380 (21.1%)	Rate difference 8% (4% to 13%)	-	⊕⊕⊕O MODERATE	CRITICAL
Abbreviations: CI, Confidence interval												

[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] Co-amoxiclav versus cefdinir (once daily)
[7] Downgraded 1 level - Jadad score <3 indicating low quality studies
[8] Downgraded 1 level - not assessable
[9] Downgraded 1 level - at a default minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit with antibiotic
[10] Co-amoxiclav versus cefdinir (twice daily)
[11] Co-amoxiclav versus ceftriaxone
[12] Ampicillin or co-amoxiclav versus cefixime

Table 24: 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%)	-	⊕⊕OO LOW	CRITICAL
Abbreviations: CI, Confidence interval												

[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 25: 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%)	-	⊕⊕⊕O MODERATE	CRITICAL
Abbreviations: CI, confidence interval												

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

Table 26: 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]	serious[4]	no serious indirectness	no serious imprecision	none	102/121 (84.3%)	222/246 (90.2%)	Mean difference -5.9% (-12.9% to 1.1%)	⊕⊕OO LOW	CRITICAL
Treatment success at day 10[1,2]											
1[3]	randomised trials	serious[4]	serious[4]	no serious indirectness	no serious imprecision	none	92/117 (78.6%)	105/124 (84.7%)	Mean difference -6.1% (-15.9% to 3.7%)	⊕⊕OO LOW	CRITICAL
Treatment success at days 2 to 5[2,5]											
1[3]	randomised trials	serious[4]	serious[4]	no serious indirectness	no serious imprecision	none	Not reported		Mean difference -3.2%, (-6.2% to -0.2%)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI, confidence interval											

[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

Table 27: 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]	serious[3]	no serious indirectness	no serious imprecision	none	122/145 (84.1%)	128/149 (85.9%)	Mean difference -1.8% (-10% to 6.4%)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI, confidence interval											

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

Table 28: 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]	serious[4]	no serious indirectness	no serious imprecision	none	73/78 (93.6%)	65/70 (92.9%)	Mean difference 0.7% (-7% to 9%)	⊕⊕OO LOW	CRITICAL
Treatment success at days 20 to 26[1]											
1[,2]	randomised trials	serious[3]	serious[4]	no serious indirectness	no serious imprecision	none	67/78 (85.9%)	61/70 (87.1%)	Mean difference -1.2% (-12% to 10%)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI, confidence interval											

[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 – 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: RR, relative risk; CI, confidence interval											

[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 30: 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	serious[4]	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)	⊕⊕OO LOW	CRITICAL
Clinical cure post treatment												
1[1]	randomised trials	no serious risk of bias	serious[4]	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)	⊕⊕⊕O MODERATE	CRITICAL
Recurrence after completion of treatment												
1[1]	randomised trials	no serious risk of bias	serious[4]	no serious indirectness	very serious[5]	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)	⊕OOO VERY LOW	CRITICAL
Adverse events: diarrhoea												
1[1]	randomised trials	no serious risk of bias	serious[4]	no serious indirectness	very serious[5]	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)	⊕OOO VERY LOW	CRITICAL
Adverse events: skin												
1[1]	randomised trials	no serious risk of bias	serious[4]	no serious indirectness	very serious[5]	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)	⊕OOO VERY LOW	CRITICAL
Compliance												
1[1]	randomised trials	no serious risk of bias	serious[4]	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)	⊕⊕⊕O MODERATE	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 1 level - not assessable
[5] 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 31: 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	serious[2]	no serious indirectness	very serious[3]	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)	⊕OOO VERY 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[4]	no serious indirectness	very serious[3]	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: RR, Relative risk; CI, Confidence interval												

[1] Thanaviratananich et al (2013)
[2] Downgraded 1 level - not assessable
[3] Downgraded 2 level - 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 - I^2 score >50%

Table 32: 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%)	OR 1.37 (1.15 to 1.64)	43 more per 1000 (from 18 more to 72 more)	⊕OOO VERY LOW	CRITICAL
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%)	OR 1.34 (1.15 to 1.55)	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%)	OR 1.16 (0.94 to 1.42)	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	serious[5]	none	355/873 (40.7%)	364/988 (36.8%)	OR 1.18 (0.97 to 1.43)	39 more per 1000 (from 7 fewer to 86 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[5]	none	391/973 (40.2%)	399/1095 (36.4%)	OR 1.18 (0.98 to 1.41)	39 more per 1000 (from 5 fewer to 83 more)	⊕⊕OO LOW	CRITICAL
Treatment failure at 90 days[1]												
2[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[7]	none	36/100 (36%)	35/107 (32.7%)	OR 1.16 (0.65 to 2.06)	33 more per 1000 (from 87 fewer to 173 more)	⊕⊕OO LOW	CRITICAL
Gastrointestinal adverse effects												
13[2]	randomised trials	serious[3]	serious[4]	no serious indirectness	serious[8]	none	201/2221 (9.0%)	369/2697 (13.7%)	OR 0.72 (0.60 to 0.87)	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]												
2[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	99/296 (33.4%)	85/274 (31%)	OR 1.09 (0.76 to 1.57)	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]												
2[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[7]	none	74/530 (14%)	86/534 (16.1%)	OR 0.85 (0.60 to 1.21)	21 fewer per 1000 (from 58 fewer to 27 more)	⊕⊕OO LOW	CRITICAL
Children with 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	serious[5]	none	10/15 (66.7%)	4/12 (33.3%)	OR 3.62 (0.81 to 16.06)	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[7]	none	10/47 (21.3%)	11/54 (20.4%)	OR 1.02 (0.40 to 2.75)	3 more per 1000 (from 111 fewer to 209 more)	⊕⊕OO LOW	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] 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 2 levels - at a default minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[8] Downgraded 1 level - at a default minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit with short course antibiotic

Table 33: 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%)	OR 1.20 (1.02 to 1.42)	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%)	OR 1.99 (1.44 to 2.74)	118 more per 1000 (from 57 more to 187 more)	⊕⊕⊕⊕ HIGH	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] 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 34: 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%)	OR 2.99 (1.04 to 8.54)	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 35: 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%)	OR 1.97 (1.54 to 2.52)	89 more per 1000 (from 52 more to 132 more)	⊕⊕⊕O MODERATE	CRITICAL
Treatment failure at 20 to 30 days[1]												
3[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%)	OR 1.27 (0.92 to 1.76)	36 more per 1000 (from 11 fewer to 95 more)	⊕⊕⊕O MODERATE	CRITICAL
Treatment failure at 1 month or less[1]												
10[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	258/1482 (17.4%)	257/1839 (14.0%)	OR 1.65 (1.35 to 2.01)	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%)	OR 1.25 (1.00 to 1.57)	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	very serious[5]	none	36/100 (36%)	35/107 (32.7%)	OR 1.16 (0.65 to 2.06)	33 more per 1000 (from 87 fewer to 173 more)	⊕OOO VERY 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%)	OR 1.24 (1.00 to 1.53)	51 more per 1000 (from 0 more to 103 more)	⊕⊕OO LOW	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] 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
[5] Downgraded 2 levels - at a default minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable benefit

Table 36: 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	serious[4]	none	247/838 (29.5%)	235/871 (27%)	OR 1.07 (0.86 to 1.33)	14 more per 1000 (from 29 fewer to 60 more)	⊕⊕OO LOW	CRITICAL
Treatment failure at 3 months or less[1]												

3[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	130/355 (36.6%)	139/346 (40.2%)	OR 0.89 (0.66 to 1.21)	28 fewer per 1000 (from 95 fewer to 47 more)	⊕⊕⊕O MODERATE	CRITICAL
Gastrointestinal adverse effects												
1[2]	randomised trials	serious[6]	serious[7]	no serious indirectness	no serious imprecision	none	46/195 (23.6%)	19/207 (9.2%)	OR 2.89 (1.70 to 4.91)	134 more per 1000 (from 55 more to 240 more)	⊕⊕OO LOW	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 - at a default minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit with longer course antibiotic
[6] Downgraded 1 level - 2 high risk and 1 unclear criteria on Cochrane risk of bias score
[7] Downgrade 1 level - not assessable

Table 37: 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]												
2[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	72/303 (23.8%)	72/305 (23.6%)	OR 1.01 (0.69 to 1.47)	2 more per 1000 (from 60 fewer to 76 more)	⊕⊕OO LOW	CRITICAL
Azithromycin (short course for 3 to 5 days): treatment failure at 8 to 19 days[1]												
18[2]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[4]	none	253/2225 (11.4%)	201/2122 (9.5%)	OR 1.27 (1.04 to 1.55)	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 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%)	OR 1.02 (0.87 to 1.20)	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%)	OR 0.66 (0.45 to 0.96)	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%)	OR 0.36 (0.28 to 0.46)	71 fewer per 1000 (from 59 fewer to 81 fewer)	⊕⊕OO LOW	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 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 longer course antibiotic
[5] 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
[6] Downgraded 1 level - at a default minimal important difference (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 G: Studies not-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

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

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

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

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

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

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), 458-63Coker 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

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

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

Dagan R, Johnson C E, McLinn S, Abughali N, Feris J, Leibovitz E, Burch D J, and Jacobs M R (2000) Bacteriologic and clinical efficacy of amoxicillin/clavulanate vs. azithromycin in acute otitis media. The Pediatric infectious disease journal 19(2), 95-104

Dagan R, Leibovitz E, Fliss D M, Leiberman A, Jacobs M R, Craig W, and Yagupsky P (2000) 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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Law Constance, and Amsden Guy W (2004) Single-dose azithromycin for respiratory tract infections. The Annals of pharmacotherapy 38(3), 433-9

McCormick David P, Saeed Kokab, Uchida Tatsuo, Baldwin Constance D, Deskin Ronald, Lett-Brown Michael A, Heikkinen Terho, and Chonmaitree Tasnee (2003) Middle ear fluid histamine and leukotriene B4 in acute otitis media: effect of antihistamine or corticosteroid treatment. International journal of pediatric otorhinolaryngology 67(3), 221-30

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

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

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

Ovetchkine P, and Cohen R (2003) Shortened course of antibacterial therapy for acute otitis media. Pediatric Drugs 5(2), 133-140

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

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

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

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

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

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

Wang CY, Lu CY, Hsieh YC, Lee CY, Huang LM. (2004) Intramuscular ceftriaxone in comparison with oral amoxicillin-clavulanate for the treatment of acute otitis media in infants and children J Microbiol Immunol Infect. 37(1):57-62.

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

Appendix H: Excluded studies

Study reference	Reason for exclusion
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 media. The Pediatric infectious disease journal 23(2 Suppl), S108-14	excluded on publication/study type – not interventional study

Study reference	Reason for exclusion
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
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
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
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
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
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

Study reference	Reason for exclusion
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
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 – 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
Cunningham C, Cleland S, Wilson H, and Barnetson R (2007) Wegener's granulomatosis presenting as polyneuropayhy - A case report and review of the literature. Scottish Medical Journal 52(2), no pagination	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
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

Study reference	Reason for exclusion
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
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
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

Study reference	Reason for exclusion
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
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
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
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
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
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
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
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
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

Study reference	Reason for exclusion
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
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
Kujala T, Alho O P, Luotonen J, Kristo A, Uhari M, Renko M, Kontiokari T, Pokka T, and Koivunen P (2012) Tympanostomy with and without adenoidectomy for the prevention of recurrences of acute otitis media: A randomized controlled trial. Pediatric Infectious Disease Journal 31(6), 565-569	excluded on outcomes – not focused on uncomplicated otitis media
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
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
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

Study reference	Reason for exclusion
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
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) 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
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

Study reference	Reason for exclusion
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
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
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
Rovers M M, Black N, Browning G G, Maw R, Zielhuis G A, and Haggard M P (2005) Grommets in otitis media with effusion: an individual patient data meta-analysis. Archives of disease in childhood 90(5), 480-5	excluded on population – not focused on uncomplicated acute otitis media
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

Study reference	Reason for exclusion
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
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
Somers Th, Declau F, Kuhweide R, and Robillard Th (2007) Otosclerosis. B-ENT 3(SUPPL. 6), 3-10	excluded on population – not focused on the treatment of AOM
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
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
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
Tang L S, Montemayor C, and Pereira F A (2006) Sensorineural hearing loss: Potential therapies and gene targets for drug development. IUBMB Life 58(9), 525-530	excluded on outcome – not about the treatment of AOM
Tannenbaum C, Gray M, Hoffstetter S, and Cardozo L (2013) Comorbidities associated with bladder dysfunction. International Journal of Clinical Practice 67(2), 105-113	excluded on outcome – not about the treatment of AOM
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
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
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
Turnidge J (2001) Responsible prescribing for upper respiratory tract infections. Drugs 61(14), 2065-77	excluded on publication/study type – not interventional study

Study reference	Reason for exclusion
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
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
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