National Institute for Health and Care Excellence

Final

Cough (acute): antimicrobial prescribing guideline

Evidence review

NICE guideline NG120

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Contents

1 Context

1.1 Background

A cough is a reflex response to airway irritation used to clear the upper airways. Acute cough is defined as one which lasts less than 3 weeks, but may last up to 3 or 4 weeks. From published literature, the mean duration of acute cough is 17.8 days (range 15.3 to 28.6 days; Ebell et al. 2013).

Acute cough is most commonly caused by an upper respiratory tract infection, such as a common cold or flu, which are viral infections. An acute cough caused by an upper respiratory tract infection is most commonly suggested by a cough with or without sputum, general malaise and fever. Pain and discharge may be localised to the nose, ears, throat, or sinuses (NICE clinical knowledge summaries: cough).

Other causes of acute cough include lower respiratory tract infections, such as acute bronchitis (or tracheo-bronchitis), pneumonia, acute exacerbations of asthma or chronic obstructive pulmonary disease (COPD), and viral-induced wheeze or bronchiolitis in children. See the NICE antimicrobial prescribing guidelines on community-acquired pneumonia [in development], hospital-acquired pneumonia [in development], acute exacerbation of COPD and acute exacerbation of bronchiectasis.

Acute bronchitis is a transient inflammation of the trachea and major bronchi associated with oedema and mucus production that leads to cough and phlegm production lasting for up to 3 weeks. It is usually caused by a viral infection, but may be caused by a bacterial infection. Acute bronchitis is suggested by a cough with or without sputum, breathlessness, wheeze, or general malaise. Crackles, if present, should clear with coughing. Acute bronchitis is usually self-limiting and should resolve without treatment within 3 to 4 weeks. (NICE clinical knowledge summaries: chest infections – adult).

Less commonly, a cough can be a sign of something serious like lung cancer, a foreign body, bronchiectasis, interstitial lung disease, pneumothorax, pulmonary embolism or heart failure, which will require hospital admission or further investigation (NICE clinical knowledge summaries: cough).

1.2 Managing self-limiting infections

An acute cough lasting less than 3 to 4 weeks caused by an upper respiratory tract infection or acute bronchitis is largely a self-limiting condition, and complications are likely to be rare if antibiotics are withheld. The NICE guideline on respiratory tract infections (self-limiting): prescribing antibiotics (2008) has recommendations for managing self-limiting respiratory tract infections relating to the use of 3 antibiotic prescribing strategies (either no prescribing, back-up prescribing or immediate prescribing).

For acute cough (including acute bronchitis), a no antibiotic prescribing strategy or a back-up antibiotic prescribing strategy is recommended. This should be accompanied with advice about the usual natural history of acute cough, which can last 3 weeks, and advice about managing symptoms, including fever.

An immediate antibiotic prescription or further appropriate investigation and management should be offered to people who:

- are systemically very unwell

- have ‘red flags’ (signs or symptoms of a more serious illness or condition), such as pneumonia
- are at high risk of serious complications because of pre-existing comorbidity, such as significant heart, lung, renal, liver or neuromuscular disease, immunosuppression, cystic fibrosis, and young children who were born prematurely
- are older than 65 years with acute cough and 2 or more of the following criteria, or older than 80 years with acute cough and 1 or more of the following criteria:
  - hospitalisation in previous year
  - type 1 or type 2 diabetes
  - history of congestive heart failure
  - current use of oral glucocorticoids.

The NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) also has recommendations to not issue immediate antimicrobial prescriptions to people who are likely to have a self-limiting condition. Instead other options such as self-care with over the counter preparations, back-up or delayed prescribing, or other non-pharmacological interventions should be discussed alongside the natural history of the condition and safety netting advice.

The NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population (2017) recommends that resources should be available for healthcare professionals to use with the public to provide information about self-limiting infections, to encourage people to manage their infection themselves at home with self-care if it is safe to do so.

1.2.1 Self-care

The NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population (2017) recommends that people should be given verbal advice and written information that they can take away about how to manage their infection themselves at home with self-care if it is safe to do so.

Self-care options that have been used to relieve pain and fever that is causing distress in acute cough include paracetamol and ibuprofen. Other self-care options such as decongestants, mucolytics and antitussives have been used (see Evidence summary).

1.2.2 No antibiotic prescribing strategies

The NICE guideline on respiratory tract infections (self-limiting): prescribing antibiotics (2008) recommends that when a no antibiotic prescribing strategy is adopted, people should be offered reassurance that antibiotics are not needed immediately and offered a clinical review if the condition worsens or becomes prolonged.

When a back-up antibiotic prescribing strategy is adopted, people should be offered reassurance that antibiotics are not needed immediately. They should also be offered advice about using the back-up antibiotic prescription if symptoms are not starting to settle in accordance with the expected course of the illness or if a significant worsening of symptoms occurs. Furthermore, they should be given advice about re-consulting if there is a significant worsening of symptoms despite using the back-up antibiotic prescription. Back up antibiotic prescriptions can be given to the person at the time of consultation or left at an agreed location to be collected at a later date.

1.2.3 Antibiotic prescribing strategies

The NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) provides recommendations for prescribers for prescribing antimicrobials. The recommendations guide prescribers in decisions about antimicrobial prescribing and include recommending that prescribers follow local and national guidelines, use the shortest effective course length and record their decisions, particularly when these decisions are not in line with guidelines. The recommendations also advise that prescribers take into account the benefits and harms for a person when prescribing an antimicrobial, such as possible interactions, co-morbidities, drug allergies and the risks of healthcare associated infections.

The NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population (2017) recommends that resources and advice should be available for people who are prescribed antimicrobials to ensure they are taken as instructed at the correct dose, via the correct route, for the time specified. Verbal advice and written information that people can take away about how to use antimicrobials correctly should be given, including not sharing prescription-only antimicrobials with anyone other than the person they were prescribed or supplied for, not keeping them for use another time and returning unused antimicrobials to the pharmacy for safe disposal and not flushing them down toilets or sinks.

1.3 Safety information

1.3.1 Safety netting

Most coughs resolve within 3 to 4 weeks and don't require medical intervention. The NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population (2017) recommends that people with self-limiting infections should be given explicit advice on when to seek medical help, which symptoms should be considered 'red flags' and safety-netting advice, such as how long symptoms are likely to last with and without antimicrobials, what to do if symptoms get worse, what to do if they experience adverse effects from the treatment and when to ask again for medical advice.

People with acute cough should see their GP if (NHS – cough, December 2018):

- they've had a cough for more than 3 weeks (persistent cough)
- their cough is very bad or quickly gets worse, for example if they have a hacking cough or can't stop coughing
- they have chest pain
- they're losing weight for no reason
- the side of their neck feels swollen and painful (swollen glands)
- they're finding it hard to breathe
- they have a weakened immune system, for example because of chemotherapy or diabetes
- they are coughing up blood (where an urgent appointment is required).

Emergency admission is required for people with acute cough with (NICE clinical knowledge summaries: cough):

- clinical features of suspected pulmonary embolism or pneumothorax
- signs or symptoms of serious illness
- clinical features of foreign body aspiration.

People with a severe systemic infection should be assessed and managed as outlined in the NICE guideline on sepsis.

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.

1.3.2 Medicines safety

Non-pharmacological and non-antimicrobial interventions

Honey should not be given to children until they're over 1 year of age because of concerns about infant botulism. It is also a sugar, and there are concerns about tooth decay (NHS – foods to avoid giving babies and young children).

Safety data for herbal medicines is not always available. Herbal products for minor health conditions where medical supervision is not required can be granted a traditional herbal registration with the MHRA if scientific evidence relating to the safety, quality and traditional use of the herbal product is submitted and approved (MHRA traditional herbal registration, December 2018).

Over the counter cough and cold medicines containing the following active ingredients: antitussives (dextromethorphan and pholcodine); expectorants (guaifenesin and ipecacuanha); nasal decongestants (ephedrine, oxymetazoline, phenylephrine, pseudoephedrine, and xylometazoline); and antihistamines (brompheniramine, chlorphenamine, diphenhydramine, doxylamine, promethazine, and triprolidine) are subject to MHRA advice on how to use these medicines safely for children under 12 years (Drug Safety Update, April 2009).

Cough medicines containing codeine also have restricted use in children (Drug Safety Update, April 2015). Cough suppressants, such as dextromethorphan, should not be given to people with chronic or persistent cough, such as in asthma, or where cough is accompanied by excessive secretions (Benilyn Dry Cough summary of product characteristics).

Paracetamol is widely used to manage pain and fever that is causing distress. It is generally well tolerated, but liver damage (and less frequently renal damage) can occur following over dosage. 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 (British National Formulary [BNF], December 2018).

The non-steroidal anti-inflammatory drug (NSAID), ibuprofen is also widely used to treat pain and fever, but paracetamol is now often preferred. All NSAIDs should be used with caution in the elderly; in allergic disorders; in people with coagulation defects, uncontrolled hypertension, heart failure, and cardiovascular disease; and in people with a history of gastrointestinal ulceration or bleeding, or inflammatory bowel disease. Side effects include gastrointestinal disturbances, hypersensitivity reactions (particularly rashes, angioedema, and bronchospasm), and fluid retention (BNF, December 2018).

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

Inhaled corticosteroids can have systemic (mineralocorticoid and glucocorticoid) effects, including a range of psychological or behavioural effects (particularly in children) (Drug Safety Update, September 2010).

Antimicrobial interventions

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).

About 10% of the general population claim to have a penicillin allergy; this has often been because of a skin rash that occurred during a course of penicillin in childhood. Fewer than 10% of people who think they are allergic to penicillin are truly allergic. People with a history of immediate hypersensitivity to penicillins may also react to cephalosporins and other beta lactam antibiotics (BNF, December 2018). See the NICE guideline on drug allergy: diagnosis and management (2014) for more information.

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, December 2018).

Tetracyclines, including doxycycline, can deposit in growing bone and teeth (by binding to calcium) causing staining and occasionally dental hypoplasia. They should not be given to children under 12 years, or to pregnant or breast-feeding women. The absorption of tetracyclines is reduced by antacids, milk, and aluminium, calcium, iron, magnesium and zinc salts. Common side effects include nausea, vomiting, diarrhoea, dysphagia, and oesophageal irritation (BNF, December 2018).

1.4 Antimicrobial resistance

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

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

The NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) recommends that the risk of antimicrobial resistance for individual patients and the population as a whole should be taken into account when deciding whether or not to prescribe an antimicrobial.

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

The ESPAUR report 2018 reported that antimicrobial prescribing declined significantly between 2013 and 2017, with the total consumption of antibiotics in primary and secondary

care declining by 4.5%. This reflected a 13.2% decrease in primary care and a 7.7% increase in secondary care prescribing. The peak of antibiotic consumption over the last 20 years occurred in 2014, with levels falling since then. The most commonly used antibiotics in England remained stable between 2013 and 2017, and were: penicillins (44.6% in 2017), tetracyclines (22.2% in 2017) and macrolides (14.7% in 2017).

Over the 5-year period, significant declining trends of use were seen for penicillins (inhibitor combinations only), first and second-generation cephalosporins, sulfonamides and trimethoprim, and anti-*C. difficile* agents. In contrast, use of third, fourth and fifth-generation cephalosporins and other antibacterials (including nitrofurantoin) significantly increased.

In the 5-year period from 2013 to 2017, primary care use of penicillins declined by 10.9%, with use of penicillins in the dental setting remaining largely the same. In the hospital setting, prescribing of penicillins was higher in 2017 for both inpatients (2.4%) and outpatients (14.7%) compared with 2013. Prescribing of co-amoxiclav and amoxicillin between 2013 and 2017 decreased by 11.3% and 7.4%, respectively.

Overall use of tetracyclines was unchanged between 2013 and 2017, with doxycycline (49.7% in 2017) and lymecycline (36.3% in 2017) most commonly used. Macrolide use declined by 5.8% from 2013 to 2017. Azithromycin use continued to increase in 2017, with overall use rising by 31.3% since 2013. In contrast, erythromycin use declined over the same period by 40.7%.

Most upper respiratory tract infections (nose, sinuses and sore throat) are caused by viruses (see the NICE antimicrobial prescribing guidelines for sinusitis and sore throat), but they can be caused by bacteria (NHS – respiratory tract infections, October 2018). Acute bronchitis is also usually caused by a viral infection, but may be caused by bacteria. The proportions of viral and bacterial causes of acute bronchitis are unclear because in a high proportion of people in studies no viral or bacterial pathogen can be identified, despite thorough investigation. Also commensal bacteria isolated from the upper respiratory tract, may not or may not have a pathogenic role in a particular infection (NICE clinical knowledge summaries: chest infections – adult).

Acute bronchitis has been estimated to be viral in 85% to 95% of cases. Organisms found in samples are usually commensal organisms from the oropharynx, but may cause harm in people with underlying health conditions *Mycoplasma pneumoniae, Streptococcus pneumoniae, Haemophilus influenzae, Moraxella catarrhalis,* and *Bordetella pertussis* are most commonly involved (Worrall 2008).

Data from the ESPAUR report 2018 on the antibiotic susceptibility of pathogens causing bacteraemia show that, for *Streptococcus pneumoniae,* the proportion of bloodstream isolates that are not susceptible to penicillins is 3−4%, with a corresponding 5−8% not susceptible to macrolides. These figures have stayed relatively stable for the past 5 years.

A systematic review and meta-analysis of observational studies and randomised controlled trials (Costelloe et al. 2010) has shown that individuals prescribed an antibiotic for a respiratory tract infection, including amoxicillin which is often used as a first-line, are more likely to develop resistance to that antibiotic in respiratory and urinary tract bacteria. Resistance rates are likely to be highest in the month following antibiotic use, however may last up to 12 months. Longer and multiple courses of antibiotics are also associated with higher risks of resistance.

1.5 Other considerations

1.5.1 Medicines adherence

Medicines adherence may be a problem for some people with medicines that require frequent dosing or longer treatment durations (for example, some antibiotics) (NICE guideline on medicines adherence [2009]).

1.5.2 Resource impact

Antibiotics for cough or acute bronchitis

In a 2011 survey of UK primary care data for adults (Gulliford et al. 2014), consultations for cough and bronchitis accounted for 39% of all respiratory tract infection consultations, and the median practice issued an antibiotic prescription for 48% of these.

There is potential for resource savings if a no antibiotic or a back-up antibiotic prescription strategy is used. In 1 systematic review (Spurling et al. 2017), there was significantly lower antibiotic use in a population with upper respiratory tract infections (not cough alone) with a back-up antibiotic prescribing strategy compared with immediate antibiotics, both when the back-up antibiotic prescription was given at the time of consultation (38.4% versus 86.8%; 3 randomised controlled trials (RCTs); very low quality evidence) and when the prescription had to be collected on a separate visit (27.3% versus 95.3%; 5 RCTs; very low quality evidence).

Recommended antibiotics are available as generic formulations, see Drug Tariff for costs.

2 Evidence selection

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

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

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

2.1 Literature search

A literature search was developed to identify evidence for the effectiveness and safety of interventions for managing acute cough (including acute bronchitis) (see appendix C: literature search strategy for full details). The literature search identified 16,293 references. These references were screened using their titles and abstracts and 141 full text references were obtained and assessed for relevance. Thirty three full text references of systematic reviews and randomised controlled trials (RCTs) were assessed as relevant to the guideline review question (see appendix B: review protocol). Ten percent of studies were screened to establish inter-rater reliability, and this was within the required threshold of 90%.

The methods for identifying, selecting and prioritising the best available evidence are described in the interim process guide. Twelve of the 33 references were prioritised by the committee as the best available evidence and were included in this evidence review (see appendix F: included studies).

The 21 references that were not prioritised for inclusion are listed in appendix I: not prioritised studies, with reasons for not prioritising the studies. Also see appendix E: evidence prioritisation for more information on study selection.

The remaining 108 references were excluded. These are listed in appendix J: excluded studies with reasons for their exclusion.

See also appendix D: study flow diagram.

2.2 Summary of included studies

A summary of the included studies is shown in tables 1, 2 and 3. Details of the study citation can be found in appendix F: included studies. An overview of the quality assessment of each included study is shown in appendix G: quality assessment of included studies.

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

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Honey					
Oduwole et al. 2014 Systematic review and meta-analysis Multiple countries Follow-up at 1 night only	n=568 (3 RCTs, including 2 DB RCTs)	Children (aged 1 to 18 years) with acute cough	Honey, alone or in combination with antibiotics	Placebo No treatment Over-the-counter medicines	Clinical outcomes
Herbal medicines					
Wagner et al. 2015 Systematic review and meta-analysis Multiple countries Follow-up varied by intervention	n=7,083 (16 RCTs, including 15 DB RCTs)	Adults and children (aged over 1 year) with acute cough	*Echinacea* *Andrographis Paniculata* Ivy/primrose/thyme (various combined or single preparations)	Placebo or other control (not described)	Clinical outcomes
Timmer et al. 2013 Systematic review and meta-analysis Multiple countries Follow-up to day 10	n=1,771 (8 DB RCTs)	Adults and children (aged over 1 year) with acute respiratory tract infection	*Pelargonium sidoides*	Placebo Other treatment	Clinical outcomes
Abbreviations: RCT, Randomised controlled trial; DB, Double blind					

Table 2: Summary of included studies: non-antimicrobial pharmacological interventions

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Oral analgesia					
Kim et al. 2015 Systematic review and meta-analysis Multiple countries	n=1,069 (9 DB RCTs)	Adults and children with common cold (7 RCTs that reported ages were in adults, 2	Non-steroidal anti-inflammatory drugs (NSAIDs)	Placebo Other treatment	Clinical outcomes

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Follow-up at 3 to 7 days		RCTs did not report population ages)			
Expectorants					
Smith et al. 2014 Systematic review and meta-analysis Multiple countries Follow-up at up to 10 days	n=4,835 (29 DB RCTs)	Adults and children (aged over 6 weeks) with acute cough	Guaifenesin	Placebo	Clinical outcomes
Antitussives					
Smith et al. 2014 Systematic review and meta-analysis Multiple countries Follow-up at up to 10 days	n=4,835 (29 DB RCTs)	Adults and children (aged over 6 weeks) with acute cough	Codeine Dextromethorphan Dextromethorphan plus salbutamol	Placebo Other treatment	Clinical outcomes
Antihistamines and decongestants					
Smith et al. 2014 Systematic review and meta-analysis Multiple countries Follow-up at up to 10 days	n=4835 (29 DB RCTs)	Adults and children (aged over 6 weeks) with acute cough	Loratadine Clemastine Diphenhydramine Promethazine	Placebo Other treatment	Clinical outcomes
Mucolytics					
Chalumeau and Duijvestjin 2013 Systematic review and meta-analysis Multiple countries Follow-up at 28 days	n=497 (6 RCTs, including 5 DB RCTs)	Children (under 18 years, with no lower age limit) with a respiratory tract infection (or where studies included adults at least 50% were under 18 years)	Acetylcysteine or carbocisteine (oral, IM, IV or inhaled)	Placebo Active treatment No treatment	Clinical outcomes

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Bronchodilators					
Becker et al. 2015 Systematic review and meta-analysis Multiple countries Follow-up at 7 days	n=552 (7 DB RCTs)	Adults and children with cough / acute bronchitis (older than 24 months of age)	Beta-2 agonist (oral or inhaled)	Placebo Active treatment No treatment	Clinical outcomes Activity General wellbeing
Corticosteroids					
El-Gohary et al. 2013 Systematic review (no meta-analysis) Multiple countries Follow-up period not adequately described	n=335 (4 RCTs)	Adults (aged >16 years) with acute (<3 weeks) or subacute (3 to 8 weeks) respiratory tract infection	Corticosteroids (inhaled or oral)	Placebo	Clinical outcomes
Abbreviations: IM, Intramuscular; IV, Intravenous; DB, Double blind; RCT, Randomised controlled trial;					

Table 3: Summary of included studies: antimicrobials

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Back-up antibiotics					
Spurling et al. 2017 Systematic review and meta-analysis Multiple countries Follow-up 12 months	n=3,555 (11 RCTs [3 RCTs in cough], including 7 RCTs with some element of blinding)	Adults and children (aged 3 years and over in 1 RCT; in adults in a second RCT and unclear in a 3rd RCT for RCTs in cough population) with respiratory tract infections	Back-up antibiotic	No antibiotic Immediate antibiotic	Clinical outcomes Antibiotic use Patient satisfaction Antibiotic resistance
Antibiotics versus placebo					
Smith et al. 2017 Systematic review and meta-analysis	n=5,099 (17 RCTs, including 15 DB RCTs)	Adults and children (aged 3 years and	Antibiotics: • amoxicillin	Placebo No treatment	Clinical outcomes

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Multiple countries Follow-up varied up to 18 days		over) with acute bronchitis	• azithromycin • cefuroxime • co-amoxiclav • demethyl chlortetracycline • doxycycline • erythromycin • trimethoprim-sulfamethoxazole		
Alves et al. 2016 Systematic review and meta-analysis Multiple countries Follow-up varied up to 14 days	n=1,314 (4 RCTs, including 3 DB RCTs)	Children (aged 2 to 59 months) with undifferentiated acute respiratory infection	Antibiotic: • ampicillin • co-amoxiclav	Placebo No treatment	Serious sequelae Side effects
Marchant et al. 2005 Systematic review and meta-analysis Multiple countries Follow-up varied up to 3 months	n=140 (2 RCTs, including 1 DB RCT)	Children (aged 7 years or less) with a moist cough lasting longer than 10 days	Antibiotic: • co-amoxiclav • erythromycin	Placebo No treatment	Clinical outcomes

Abbreviations: RCT, Randomised controlled trial; DB, Double blind

3 Evidence summary

Full details of the evidence are shown in appendix H: GRADE profiles.

The main results are summarised below for adults, young people and children with acute cough (including acute bronchitis).

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

3.1 Non-pharmacological interventions

3.1.1 Honey

The evidence review for honey is based on 1 systematic review and meta-analysis (Oduwole et al. 2014) in children and young people with acute cough caused by an upper respiratory tract infection. The systematic review included 3 randomised controlled trials (RCTs) with a total of 568 children and young people (1 to 17 years) presenting with upper respiratory tract infection and nocturnal symptoms for 7 days or less. Honey was given as a single dose (10 g in 1 RCT, dose not reported in 2 RCTs), and 2 RCTs reported that this was given before bed. A range of types of honey were used, with no studies using the same variety.

Honey compared with no treatment in children with acute cough

Two RCTs included in the systematic review compared honey (buckwheat honey in 1 RCT; natural honey from Iran in 1 RCT) with no treatment. In 1 RCT, all participants were advised to use supportive treatment including saline nose drops, water vapour, cleaning of a blocked nose and paracetamol, if needed.

Honey significantly reduced the frequency of cough (2 RCTs, n=154: mean difference −1.05, 95% confidence interval [CI] −1.48 to −0.62; low quality evidence) and the severity of cough (2 RCTs, n=154: mean difference −1.03, 95% CI −1.59 to −0.47; low quality evidence) at 1 day follow-up on carer-reported 7-point Likert scales (carer responses on cough symptoms ranged from 'extremely' [six points] to 'not at all' [zero points]) compared with no treatment. However, no significant difference in bothersome cough was found between groups (low quality evidence). Measures of combined improvement, and both children's and parents' quality of sleep showed similar significant improvement with honey compared with no treatment at 1 day follow-up (low quality evidence). No adverse effects were reported.

See GRADE profile: table 9.

Honey compared with placebo in children with acute cough

One RCT included in the systematic review compared honey with placebo (silan dates extract). Three types of honey were evaluated, eucalyptus, citrus and labiatae honey, although results were presented together.

Honey significantly improved the frequency of cough (1 RCT, n=300; mean difference −1.85, 95% CI −3.36 to −0.33; moderate quality evidence), the severity of cough (1 RCT, n=300: mean difference −1.83, 95% CI −3.32 to −0.34; moderate quality

evidence) and bothersome cough (1 RCT, n=300: mean difference −2.08, 95% CI −3.97 to −0.19; moderate quality evidence) at 1 day follow-up on 7-point Likert scales compared with placebo. However, no significant differences between groups in children's or parents' sleep quality was seen (moderate quality evidence).

There was no significant difference in gastrointestinal side effects with honey compared with placebo (1 RCT, n=300; 1.8% versus 1.3%; relative risk [RR] 1.33, 95% CI 0.15 to 11.74; low quality evidence).

See GRADE profile: table 10.

Honey compared with antitussives in children with acute cough

Two RCTs included in the systematic review compared honey (buckwheat honey in 1 RCT; natural honey from Iran in 1 RCT) with dextromethorphan (dosage not reported). In 1 RCT, all children were advised to use supportive treatment including saline nose drops, water vapour, cleaning of a blocked nose and paracetamol, if needed.

There was no significant difference between honey and dextromethorphan in the frequency of cough (2 RCTs, n=149: mean difference −0.07, 95% CI −1.07 to 0.94; very low quality evidence), the severity of cough (2 RCTs, n=149: mean difference −0.13, 95% CI −1.25 to 0.99; very low quality evidence) or bothersome cough (1 RCT, n=69: mean difference 0.29, 95% CI −0.56 to 1.14; low quality evidence) at 1 day follow-up on 7-point Likert scales. Measures of combined improvement, and both children's and parents' quality of sleep also showed no significant difference between groups (low quality evidence).

There was no significant difference in gastrointestinal side effects with honey compared with dextromethorphan (2 RCTs, n=149; 2.7% versus 0.0%; RR 4.86, 95% CI 0.24 to 97.69; very low quality evidence). There were also no significant differences in mild adverse effects (including nervousness, insomnia and hyperactivity) or drowsiness (very low quality evidence).

See GRADE profile: table 11.

Honey compared with antihistamines in children with acute cough

One RCT included in the systematic review compared natural honey from Iran with diphenhydramine (dosage not reported). All children were advised to use supportive treatment including saline nose drops, water vapour, cleaning of a blocked nose and paracetamol, if needed.

Honey significantly improved the frequency of cough (1 RCT, n=80; mean difference −0.57, 95% CI −0.90 to −0.24; low quality evidence) and the severity of cough (1 RCT, n=80; mean difference −0.60, 95% CI −0.94 to −0.26; low quality evidence) on 7-point Likert scales compared with diphenhydramine. Measures of parents' and children's quality of sleep also showed similar significant improvement with honey compared with diphenhydramine (low quality evidence).

There was no significant difference in somnolence with honey compared with diphenhydramine (1 RCT, n=80; 0.0% versus 7.5%; RR 0.14, 95% CI 0.01 to 2.68; very low quality evidence).

See GRADE profile: table 12.

3.1.2 Herbal medicines

The evidence review for herbal medicines is based on 2 systematic reviews and meta-analyses (Wagner et al. 2015; and Timmer et al. 2013) in adults, young people and children with acute cough or acute bronchitis. The evidence for many of the herbal medicines was limited by poorly defined populations, outcomes, length of follow-up and a lack of safety data or data on adverse outcomes.

Andrographis paniculata in people with acute cough

One systematic review (Wagner et al. 2015) compared *Andrographis paniculata* (*A. paniculata*) liquid or tablets (6 RCTs, n=807) with placebo for people (population not defined) with acute cough as a symptom of upper respiratory tract infection or common cold. Dosages ranged from 31.5 mg to 200 mg for 3 to 10 days. There is evidence of missing data, with 5 RCTs included in the meta-analysis.

A. paniculata (any preparation) significantly reduced the frequency of cough (3 RCTs, n=493; standardised mean difference [SMD] −1.00, 95% confidence interval [CI] −1.85 to −0.15; very low quality evidence) and the severity of cough (4 RCTs, n=681; SMD −0.57, 95% CI −1.01 to −0.14; very low quality evidence) compared with placebo but there was significant heterogeneity in the original study results.

A. paniculata (liquid) significantly reduced the frequency of cough (1 RCT, n=30; NICE analysis MD −3.20, 95% CI −3.68 to −2.72; moderate quality evidence) and the severity of cough (1 RCT, n=30; NICE analysis MD −2.20, 95% CI −2.87 to −1.53; moderate quality evidence) compared with placebo.

A. paniculata (tablets) significantly reduced the frequency of cough (2 RCTs, n=433; SMD −0.42, 95% CI −0.71 to −0.13; low quality evidence) and the severity of cough (3 RCTs, n=621; SMD −0.36, 95% CI −0.70 to −0.03; low quality evidence) compared with placebo. No safety data were reported.

See GRADE profiles: tables 13-15.

Ivy, primrose or thyme in people with acute cough

One systematic review (Wagner et al. 2015) compared ivy, primrose or thyme as various combined or single preparations (4 RCTs, n=1,428) with placebo for people with acute cough as a symptom of upper respiratory tract infection or common cold. One RCT included adults and children, and 3 RCTs included only adults. Cough was the only outcome reported, which was not defined. There is evidence of missing data, with 3 RCTs included in the meta-analysis.

Ivy, primrose and thyme (any preparation) significantly improved cough (3 RCTs, n= 797; 77.4% versus 54.9%, RR 1.40, 95% CI 1.23 to 1.60; very low quality evidence) compared with placebo, neither the outcome of ‘cough’ nor the follow-up time was not defined.

No safety data were reported. See GRADE profiles: tables 16-18.

Echinacea in people with acute cough

One systematic review (Wagner et al. 2015) compared *Echinacea* (8 RCTs, n=1130) with placebo for people with acute cough as a symptom of upper respiratory tract infection or common cold. One RCT included children, and 7 included adults. Dosages ranged from 300 mg to 6 g daily for 1 to 12 weeks, and included solid and liquid preparations. Cough was the only outcome reported, which was not defined.

There is evidence of missing data, with 2 RCTs included in the meta-analysis. The authors report that most studies did not report any significant reduction in patients' cough symptoms and it is unclear if this statement relates to a paucity of evidence or a paucity of effect of the intervention, but *Echinacea* did diminish their other common cold symptoms in 4 RCTs and in 2 of these RCTs the duration of symptoms was reduced (no data provided).

Echinacea (as liquid) significantly improved cough (2 RCTs; n=200; SMD −0.68, 95% CI −1.32 to −0.04; low quality evidence) compared with placebo in a meta-analysis of overall effect but it is unclear what benefit was measured (for example mean symptom score) or what the follow-up time was. No safety data were reported.

See GRADE profiles: table 19.

Pelargonium sidoides in people with acute bronchitis

The evidence for *Pelargonium sidoides* (*P. sidoides*) comes from 1 systematic review (Timmer et al. 2013; 8 RCTs). Six RCTs including 1,565 adults, young people and children with acute bronchitis less than 48 hours from onset are relevant to this review and have been included. Results were presented for adults, and children and young people, separately. All preparations were given three times a day for 7 days, either as tablets (10, 20 or 30 mg) or liquid (30 drops). All RCTs were conducted in Russia or Ukraine, in either in- or out-patient departments or GP practices, and were initiated and funded by a single manufacturing company.

Pelargonium sidoides compared with placebo in adults

P. sidoides (liquid) significantly reduced 'failure to resolve all symptoms' by day 7 (2 RCTs, n=341; 61.0%% versus 95.3%, RR 0.66, 95% CI 0.52 to 0.83; NNT 3 [3 to 4]; very low quality evidence) and 'failure to resolve cough' by day 7 (2 RCTs, n=341; 55.8% versus 90.5%, RR 0.63, 95% CI 0.47 to 0.85; very low quality evidence), compared with placebo in adults. However, there was significant heterogeneity in the results. Liquid *P. sidoides* also significantly reduced 'failure to resolve sputum' by day 7 compared with placebo (very low quality evidence).

Individually, *P. sidoides* tablets 10 mg, 20 mg or 30 mg did not significantly reduce 'failure to resolve all symptoms' by day 7 compared with placebo (low quality evidence). However, in combined analysis, *P. sidoides* tablets of any dosage significantly reduced 'failure to resolve all symptoms' by day 7 (3 RCTs, n=405; 92.7% versus 99.0%; RR 0.95, 95% CI 0.91 to 0.99; low quality evidence).

P. sidoides tablets of any dosage significantly reduced 'failure to resolve cough' by day 7 (3 RCTs, n=405; 91.7% versus 99.0%; RR 0.94, 95% CI 0.90 to 0.98; NNT 14 [10 to 28]; low quality evidence) compared with placebo in adults. Individually, only *P. sidoides* tablets 30 mg significantly reduced 'failure to resolve cough symptoms' by day 7 (1 RCT, n=134, 91.0% versus 100%, RR 0.92, 95% CI 0.85 to 0.99, low quality evidence) compared with placebo.

Both 20 mg and 30 mg doses of *P. sidoides* tablets significantly reduced 'failure to resolve sputum' by day 7 in adults compared with placebo. No significant effect was found with a 10 mg dose (very low quality evidence).

P. sidoides of any preparation (liquid or tablet) significantly increased the number of people (adults, young people and children) with adverse events, which were mainly gastrointestinal (6 RCTs, n=1565; 19.5% versus 15.1%, RR 1.28, 95% CI 1.01 to 1.62 [NICE analysis]; very low quality evidence) compared with placebo. However, there was no significant difference in the number of people with adverse events

which led to treatment withdrawal (6 RCTs, n=1565; 0.5% versus 1.0%, RR 0.61, 95% CI 0.20 to 1.85 [NICE analysis]; very low quality evidence).

See GRADE profiles: tables 20-26.

Pelargonium sidoides compared with placebo in children

P. sidoides (liquid) significantly reduced 'failure to resolve all symptoms' by day 7 (2 RCTs, n=420; 79.9% versus 97.1%, RR 0.82, 95% CI 0.77 to 0.88; NNT 6 [5 to 9]; low quality evidence) and 'failure to resolve cough' by day 7 (2 RCTs, n=420; 79.4% versus 96.6%, RR 0.82, 95% CI 0.76 to 0.88; low quality evidence) compared with placebo in children. Liquid *P. sidoides* also significantly reduced 'failure to resolve sputum' by day 7 compared with placebo (very low quality evidence).

P. sidoides tablets of any dosage did not significantly reduce 'failure to resolve all symptoms' by day 7 (3 RCTs, n=399, 87.2% versus 91.1%, RR 0.96, 95% CI 0.89 to 1.03; low quality evidence) compared with placebo. Only *P. sidoides* tablets 20 mg significantly reduced 'failure to resolve cough symptoms' by day 7 (1 RCT, n=132, 81.8% versus 93.9%, RR 0.87, 95% CI 0.77 to 0.99, low quality evidence) compared with placebo. *P. sidoides* tablets did not significantly reduce 'failure to resolve sputum' by day 7, at any dosage, compared with placebo (very low quality evidence). For details of safety data, see *pelargonium sidoides* compared with placebo in adults.

See GRADE profiles: tables 27-31.

3.2 Non-antimicrobial pharmacological interventions (self-care medicines)

3.2.1 Oral analgesia

The evidence review for oral analgesia is based on 1 systematic review and meta-analysis of 9 RCTs (Kim et al. 2015) of non-steroidal anti-inflammatory drugs (NSAIDs) in 1,069 mostly adults (and some children) with common cold. The ages of the study population could not be determined as 2 studies did not report the ages of their study population and the remaining studies were in adults. Studies were included in the review if people had symptoms of common cold: runny or stuffy nose (or both), and sneezing, with or without headache or cough (2 RCTs, n=159 assessed using a cough score). The systematic review included different types of NSAIDs with variable doses and routes of administration. The systematic review included RCTs that allowed concurrent use of other medicines as long as they were available to people taking NSAIDs or placebo.

Paracetamol compared with placebo

No systematic reviews or RCTs were identified for paracetamol in adults or children with acute cough.

NSAIDs compared with placebo

NSAIDs (naproxen or ibuprofen) were not significantly different to placebo for a cumulative cough score at follow-up in adults with common cold (2 RCTs, n=159, standardised mean difference (SMD) −0.05, 95% CI −0.66 to 0.56; very low quality evidence). No studies for the outcome of cough in children were identified.

NSAIDs significantly reduced headache score at follow-up in adults with common cold (2 RCTs, n=159, SMD −0.65, 95% CI −1.11 to −0.19; very low quality evidence), joint and muscle pain score in adults (2 RCTs, n=114, SMD −0.40, 95% CI −0.77 to −0.03; low quality evidence), earache score in adults (1 RCT, n=80, MD −0.69, 95% CI −1.18 to −0.20; very low quality evidence) and sneezing score in adults (2 RCTs, n=159, SMD −0.44, 95% CI −0.75 to −0.12; low quality evidence).

The systematic review found no other significant differences with NSAIDs compared with placebo for a range of common cold outcomes, such as symptom severity, duration of illness, throat irritation and malaise. No significant differences in adverse effects were reported.

See GRADE profiles: tables 32-33.

NSAIDs are associated with cardiovascular and gastrointestinal risks (Drug Safety Update, October 2012 and Drug Safety Update, December 2007). See section 1.3.2.

3.2.2 Over-the-counter expectorants

The evidence review for expectorants is based on 1 systematic review (Smith et al. 2014), which included 3 RCTs in 682 adults and young people over 12 years presenting with acute cough or cough related to upper respiratory tract infection. All the included trials compared guaifenesin with placebo. The authors were unable to carry out meta-analyses because the studies were too clinically heterogeneous and provided insufficient data.

Guaifenesin compared with placebo

Guaifenesin significantly reduced patient reported frequency and intensity of cough at 72 hours compared with placebo in 1 RCT of adults and young people over the age of 12 years with acute cough or upper respiratory tract infection (n=239, 75% said guaifenesin was helpful compared with 31% in the placebo group, p<0.01; low quality evidence).

In another RCT, guaifenesin had no significant effect on cough frequency or severity, but significantly reduced sputum thickness compared with placebo (n=65, sputum thickness reduced in 96% of the guaifenesin group compared with 54% of the placebo group, p=0.001; low quality evidence).

In the third RCT, extended-release guaifenesin significantly reduced symptom severity scores at 4 days (n=378, mean score reduction from baseline of 7.1 with guaifenesin compared with 5.7 with placebo, p=0.04; low quality evidence) but not at 7 days (low quality evidence).

In the 2 RCTs reporting adverse events, there was no difference between groups (no p values reported; very low quality evidence).

See GRADE profile: table 34.

Over the counter (OTC) cough medicines containing the expectorant guaifenesin are subject to MHRA advice on how to use cough and cold medicines safely for children under 12 years (Drug Safety Update, April 2009). See section 1.3.2.

3.2.3 Over-the-counter antitussives (cough suppressants)

The evidence review for antitussives is based on 1 systematic review of 11 RCTs in adults, young people and children presenting with acute cough, with or without related upper respiratory tract infection (Smith et al. 2014). The systematic review

included additional studies with antitussives not available in the UK that have not been included in this evidence review. The authors were unable to carry out meta-analyses because the studies were too heterogeneous and provided insufficient data. Codeine was compared with placebo in 2 RCTs, dextromethorphan was compared with placebo in 7 RCTs.

Codeine compared with placebo in adults with acute cough

Codeine was no more effective than placebo, either as a single dose of 30 mg dose or in a total daily dose of 120 mg (30 mg four times daily), in reducing cough symptoms (1 RCT, n=81, p=0.23; low quality evidence). There was no significant difference in cough symptoms at 90 minutes with codeine (as a single 50 mg dose) compared with placebo (1 RCT, n=82, p=0.8; low quality evidence). No safety data were reported.

See GRADE profile: table 35.

Cough medicines containing codeine have restricted use in children (Drug Safety Update April 2015).

Codeine compared with placebo in children with acute cough

Codeine (10 mg in 5 ml, also contained guaifenesin 100 mg in 5 ml as a single dose at bedtime for 3 nights) cough score reduction of 2.2) was no more effective than placebo (1 [3 arm] RCT, n=49: cough score reduction of 2.2) for reducing cough score on day 3 in children with acute cough (p= 0.70, low quality evidence). Adverse effects (mainly drowsiness, diarrhoea and hyperactivity) were not significantly different between 7 of 13 children taking placebo, and 5 of 17 children taking codeine (1 RCT, 54% versus 29%; relative risk [RR] 0.55 (95% CI 0.22 to 1.33), very low quality evidence).

See GRADE profile: table 36.

Dextromethorphan compared with placebo in adults with acute cough

Dextromethorphan (as a single 30 mg dose) was not significantly different for 'decline in cough frequency at 180 minutes' (1 RCT, n=44, p=0.38; very low quality evidence), or 'decline in cough severity at 180 minutes (p=0.08; very low quality evidence) compared with placebo in adults with acute cough.

Dextromethorphan (as single 30 mg dose) significantly reduced cough counts (1 RCT, n=451, differences in mean changes of cough counts between dextromethorphan and placebo varied from 19% to 36%, p< 0.05) and subjective visual analogue scales (data and p value not reported; very low quality evidence) compared with placebo in adults with acute cough.

Dextromethorphan (as a single 30 mg dose) reduced coughing bouts (12% compared with 17% in favour of dextromethorphan, p=0.004), cough components (p=0.003), cough effort (p=0.001) and cough latency (p=0.002) over 3 hours compared with placebo in adults with acute cough in 1 RCT (n=710; very low quality evidence). No safety data were reported in any of the studies.

See GRADE profile: table 37.

Dextromethorphan compared with placebo or other treatment in children

There was no significant difference in parent-recorded symptom scores at 3 days with dextromethorphan 1.5 mg/ml compared with placebo in children with upper

respiratory tract infection (1 RCT, n=50; p value not reported; low quality evidence). Dosages were 5 ml (7.5 mg) three times a day for children under 7 years and 10 ml (15 mg) three times a day for older children. There were no differences between the groups in adverse effects, which were generally mild.

Dextromethorphan (15 mg in 5 ml as a single dose, also contained guaifenesin 100 mg in 5 ml) for 3 nights was no more effective than placebo in reducing composite cough scores at day 1, 2 or 3 in children aged 18 months to 12 years with night cough due to an upper respiratory tract infection (1 RCT, n=57, p=0.41; low quality evidence). Adverse effects (mainly drowsiness, diarrhoea and hyperactivity) were reported in 7 of 13 children taking placebo and 6 of 19 taking dextromethorphan (1 RCT: 54% versus 32%, RR, 0.88 (95% CI 0.44 to 1.76; very low quality evidence).

There was no significant difference in composite symptom scores, cough frequency, or child or parental sleep disturbance with dextromethorphan (as a single dose at night, dosage varied according to age) compared with placebo or diphenhydramine in children or young people aged 2 to 18 years with acute cough due to an upper respiratory tract infection (1 RCT, n=100, p values not reported; low quality evidence). No safety data was reported.

There was no significant difference in composite symptom scores at day 3 with dextromethorphan (5 mg three or four times daily for 3 days) compared with placebo in children and young people (1 to 22 years) with cough due to an upper respiratory tract infection (1 RCT, n=80, p value not reported; low quality evidence). Adverse events (mainly gastrointestinal and dizziness) were reported in 34% of participants in the dextromethorphan group compared with 5% of participants in the placebo group (p value not reported, low quality evidence).

See GRADE profile: table 38.

Dextromethorphan plus salbutamol compared with placebo or dextromethorphan alone in adults

There was no significant difference in cough frequency or daytime cough severity with dextromethorphan 30 mg in combination with salbutamol 2 mg given three times daily for 4 days compared with placebo or dextromethorphan alone in adults with acute cough (1 RCT, n=108, p value not reported; low quality evidence). Dextromethorphan plus salbutamol significantly improved cough relief at night compared with placebo or dextromethorphan alone (mean symptom score 0.19 versus 0.67 and 0.44, respectively on day 4, $p<0.01$; low quality evidence). However, more tremors were reported in the dextromethorphan with salbutamol group than in the placebo group (no figures given, $p<0.05$; low quality evidence).

See GRADE profile: table 39.

OTC cough medicines containing the cough suppressant dextromethorphan are subject to MHRA advice on how to use cough and cold medicines safely for children under 12 years (Drug Safety Update, April 2009).

3.2.4 Over-the-counter antihistamines and decongestants

The evidence review for antihistamines and decongestants (alone or in combination) is based on 1 systematic review of 4 RCTs in adults, young people and children with cough related to a common cold or upper respiratory tract infection (Smith et al. 2014). The systematic review included additional trials with antihistamines and decongestants not available in the UK that have not been included in this evidence

review. The authors were unable to carry out meta-analyses because the studies were too heterogeneous and provided insufficient data.

Loratadine plus pseudoephedrine compared with placebo

Loratadine 5 mg in combination with pseudoephedrine 120 mg twice a day for 5 days was not significantly more effective in reducing a composite cough symptom score compared with placebo in adults with a common cold (1 RCT, n=283, p value not reported; very low quality evidence). Adverse effects (including dry mouth, headache and insomnia) were reported in 30% of the loratadine plus pseudoephedrine group compared with 21% of the placebo group (RR 1.42, 95% CI 0.95 to 2.13, very low quality evidence).

Clemastine compared with placebo or chlorpheniramine

There was no significant difference in cough scores at day 3 with clemastine 0.05 mg/kg/day compared with chlorpheniramine 0.35 mg/kg/day or placebo in children under 5 years with a common cold (1 RCT, n=143, p=0.2; very low quality evidence). Drowsiness and sleepiness was reported in 20% of children, with no difference between groups (p values not reported).

Diphenhydramine compared with placebo

Diphenhydramine (as a single dose at night of 1.25 mg/kg) was no more effective than placebo in reducing composite symptom scores, cough frequency, or child or parental sleep disturbance at 1 to 2 days in children and young people aged 2 to 18 years with acute cough due to an upper respiratory tract infection (1 RCT, n=100, p value not reported; low quality evidence). No safety data were reported.

Promethazine compared with placebo

Promethazine (0.5 mg/kg three times a day for 3 days) was no more effective than placebo in reducing composite cough symptom scores at day 3 in children and young people (1 to 22 years) with acute cough due to an upper respiratory tract infection (1 RCT, n=120, p value not reported; low quality evidence). Adverse events were reported in 32% of participants in the promethazine group compared with 5% of participants in the placebo group (p value not reported; low quality evidence).

See GRADE profiles: tables 40-43.

OTC cough medicines containing the antihistamines diphenhydramine and promethazine are subject to MHRA advice on how to use cough and cold medicines safely for children under 12 years (Drug Safety Update, April 2009).

3.3 Non-antimicrobial pharmacological interventions (prescribed medicines)

3.3.1 Mucolytics

The evidence review for mucolytics (acetylcysteine and carbocisteine) is based on 1 systematic review and meta-analysis of 6 RCTs (Chalumeau and Duijvestijn 2013) in 497 children and young people with acute upper and lower respiratory tract infections. Studies from any setting were included if the children were aged less than 18 years (when studies also included adults they were required to have a minimum of 50% children) with acute bronchitis, acute bronchiolitis, acute pneumonia or acute

cough and a duration of illness less than 4 weeks. Studies involving children or young people with asthma or tuberculosis were included. The systematic review included RCTs that allowed concurrent use of other medicines provided they were available to all people taking mucolytics or placebo.

Mucolytics (oral acetylcysteine and oral carbocisteine) were significantly better than placebo for cough (not defined) at 6 to 7 days in children with acute upper and lower respiratory tract infection (3 RCTs, n=139, 4.1% versus 13.8%, RR 0.29, 95% CI 0.09 to 0.94, NNT 11 [95% CI 6 to 174]; very low quality evidence). Mucolytics (oral acetylcysteine) were not significantly better than placebo for cough at the end of treatment (28 days) (1 RCT, n=100, 6% versus 8%, RR 0.67, 95% CI 0.16 to 2.76; very low quality evidence).

There were no significant differences for the outcomes of productive cough and expectoration at end of treatment (at 7 days), pulmonary function at day 3, febrile state at 6 days, dyspnoea at 6 to 7 days, bad general condition after 6 to 7 days, and appetite trouble at the end of treatment (5 to 9 days) (very low quality evidence). There was also no significant difference for the outcome of abnormal chest signs (for example wheezing or rattling) after 5 days, but there was a significant difference for this outcome at the end of treatment (28 days) (2 RCTs, n=100, 2% versus 16%, RR 0.17, 95% CI 0.03 to 0.99; very low quality evidence). No safety data were reported.

See GRADE profile: table 44.

3.3.2 Bronchodilators

The evidence review for bronchodilators is based on 1 systematic review and meta-analysis of 7 RCTs (Becker et al. 2015) in 552 adults and children with an acute cough or acute bronchitis. Studies were included if participants had acute bronchitis or acute cough (unless clearly due to pneumonia or sinusitis) although the authors were aware that clinical definitions may vary. Studies including those aged less than 24 months, with a pre-existing pulmonary disease (for example asthma, chronic obstructive pulmonary disease or cystic fibrosis) and people known to have another acute respiratory illness (sinusitis, pertussis or pneumonia) were excluded. The systematic review included RCTs that allowed concurrent use of other medicines provided they were available to people taking bronchodilators or a placebo.

Beta-2 agonists compared with placebo or other treatment in adults

Beta-2 agonists (salbutamol tablets, salbutamol inhaler or fenoterol inhaler [not available in the UK]) were not significantly different to placebo for the presence of cough at 7 days in adults with acute cough or acute bronchitis (3 RCTs, n=220, 63.6% versus 70.9%, RR 0.86, 95% CI 0.63 to 1.18; very low quality evidence). There were no significant differences in productive cough after 7 days, night cough after 7 days, not working by day 7 or mean cough score at days 1, 2, 3, 4, 5, 6 or 7 in adults treated with beta-2 agonists compared with placebo or other treatment (very low to moderate quality evidence).

There was a significant increase in adverse effects (shaking, tremor or nervousness) with beta-2 agonists compared with placebo or other treatment (3 RCTs, n=211, 55.2% versus 11.3%, RR 7.94, 95% CI 1.17 to 53.94, NNH 2 [95% CI 1 to 3]; very low quality evidence), but not in other adverse effects.

See GRADE profile: table 45.

Beta-2 agonists compared with placebo or other treatment in children

Beta-2 agonists (salbutamol syrup) were not significantly different to placebo for the presence of cough at 7 days in children with acute cough or acute bronchitis (1 RCT, n=59, 36.7% versus 41.4%, RR 0.89, 95% CI 0.47 to 1.68; very low quality evidence). There were no significant differences in mean cough score at days 1, 2, 3, 4, 5, 6 or 7 in children treated with beta-2 agonists (oral salbutamol) compared with placebo or other treatment (very low to moderate quality evidence).

There were no significant differences in adverse effects (shaking or tremor, or other adverse effects) between beta-2 agonists (oral salbutamol) and placebo or other treatment (very low quality evidence).

See GRADE profile: table 46.

Beta-2 agonists compared with erythromycin in adults

Beta-2 agonists (salbutamol syrup) were significantly better than erythromycin ethylsuccinate syrup for cough after 7 days in adults with acute cough or acute bronchitis (1 RCT, n=34, 41.2% versus 88.2%, RR 0.47, 95% CI 0.26 to 0.85, NNT 3 [95% CI 2 to 6]; low quality evidence), productive cough after 7 days (n=31, 35.7% versus 76.5%, RR 0.47, 95% CI 0.22 to 0.99, NNT 2 (95% CI 2 to 12); low quality evidence), but not night cough after 7 days (n=24, 50% versus 58.3%, RR 0.86, 95% CI 0.39 to 1.88; very low quality evidence). However, this was based on 1 very small study. No data on adverse events were reported.

See GRADE profile: table 47.

3.3.3 Corticosteroids

The evidence review for corticosteroids is based on 1 systematic review of 4 RCTs (El-Gohary et al. 2013) in 335 adults with acute (<3 weeks) or subacute (3 to 8 weeks duration) cough following a respiratory tract infection. All 4 included RCTs compared inhaled corticosteroids with placebo; no studies of oral corticosteroids were found. No meta-analysis was undertaken due to significant heterogeneity.

Only 1 included RCT reported the number of people with acute (n=31) as opposed to subacute (n=99) cough, and this study also included 13 people with chronic cough. Of the other 3 RCTs, 1 RCT reported that the majority of participants had acute cough, 1 RCT reported that the participants had acute and subacute cough and 1 RCT reported that participants had subacute cough only. Studies that included people with underlying asthma or another underlying respiratory tract infection were excluded, as were studies in which there was recent corticosteroid, antibiotic or beta-2 agonist use or an underlying immune-compromising illness. The systematic review included RCTs that allowed concurrent use of other medicines provided they were available to people taking corticosteroids or placebo.

Inhaled corticosteroids compared with placebo in adults

Inhaled corticosteroids (fluticasone proprionate 500 micrograms twice a day) significantly reduced the mean cough score at the end of the second week of treatment compared with placebo in adults with acute or subacute cough following respiratory tract infection in 1 RCT (n=133, mean difference −0.50, 95% CI −0.55 to −0.45; very low quality evidence), but not at 4 weeks. In a sub-group analysis of this RCT, fluticasone proprionate significantly reduced the mean cough score by at least 50% reduction at the end the second week in non-smoking adults compared with

placebo (n=84, 53.5% versus 80.5%, RR 0.66, 95% CI 0.48 to 0.91, NNT 4 [95% CI 3 to 13]; very low quality evidence). The mean difference in the average daily cough score in the second week in non-smoking adults with fluticasone proprionate compared with placebo was −0.9 (95% CI −1.3 to −0.4; 1 RCT, n=133; very low quality evidence). There was no significant difference in smokers. This RCT also found that additional treatment sought after 2 weeks of study treatment was significantly lower in adults taking fluticasone proprionate compared with placebo (n=132, 43.1% versus 62.7%, RR 0.69, 95% CI 0.49 to 0.96, NNT 6 [95% CI 3 to 35]; very low quality evidence).

There were no significant differences across the 4 RCTs found for mean symptom scores (cough, cough frequency, symptoms associated with cough, night-time cough or the frequency of taking cough medicines), and the outcomes of 'little or no improvement at 7 to 14 days', 'severe symptoms at 11 days' and adverse effects (hoarseness) during the treatment period (very low quality evidence).

See GRADE profile: table 48.

Systemic effects (mineralocorticoid and glucocorticoid) may occur with inhaled corticosteroids, including a range of psychological or behavioural effects (particularly in children) (Drug Safety Update, September 2010). See section 1.3.2.

3.4 Antimicrobials

3.4.1 Back-up antibiotics

The evidence review for back-up antibiotics is based on 1 systematic review and meta-analysis of RCTs in people with a range of different respiratory tract infections (acute otitis media, pharyngitis, sore throat, common cold and other respiratory tract infections) in adults and children. Three RCTs were in people with acute cough; 2 of these RCTs included children (Spurling et al. 2017). Studies were included if they compared a back-up antibiotic prescribing strategy (for example a delayed prescription collection or post-dated prescription) compared with an immediate or no antibiotic strategy.

Back-up antibiotics versus immediate or no antibiotics for acute cough

Two RCTs (n=191 and n=807) included in the systematic review included adults and children with acute cough (1 RCT included children aged over 3 years, the second RCT only reported that they included adults and children; ages not reported) These 2 RCTs had collected but not reported data on clinical outcomes for back-up versus immediate antibiotics. The systematic review states that both RCTs reported that there was no difference between back-up antibiotics and immediate antibiotics in reported clinical outcomes.

One RCT (n=405) included in the systematic review compared a back-up antibiotic prescription (either at the time of the visit or requiring collection) with immediate antibiotics and a no antibiotic strategy in adults with acute cough. A back-up antibiotic prescription was not significantly different to an immediate antibiotic or no antibiotics for the outcomes of cough duration, pain duration or fever duration (low quality evidence).

See GRADE profile: table 49.

Back-up antibiotics versus immediate or no antibiotics for all respiratory tract infections

For some outcomes the analysis covered all respiratory tract infections and was not limited to people with acute cough.

A back-up antibiotics prescription significantly reduced antibiotic use compared with an immediate antibiotic prescription in people with all respiratory infections (7 RCTs [4 RCTs in adults and children, 1 RCT in just adults and 2 RCTs in just children], n=1,963, 30.5% versus 93%, RR 0.34, 95% CI 0.27 to 0.44; very low quality evidence). Two different strategies for a back-up prescription both had significant reductions in antibiotic use: a back-up prescription given at the time of the visit compared with immediate antibiotics (3 RCTs, n=547, 38.4% versus 86.8%, RR 0.45, 95% CI 0.38 to 0.58; very low quality evidence) and a back-up prescription with delayed collection compared with immediate antibiotics (5 RCTs, n=1416, 27.3% versus 95.3%, RR 0.29, 95% CI 0.22 to 0.39; very low quality evidence).

Back-up antibiotic prescriptions significantly increased antibiotic use compared with a no antibiotic strategy (4 RCTs [2 RCTs in adults and children, 1 RCT in just adults and 1 RCT in just children], n=1,241, 27.9% versus 13.7%, RR 2.09, 95% CI 1.46 to 2.99; low quality evidence). Significant increases in antibiotic use were found in back-up antibiotic prescriptions given at the time of the visit compared with a no antibiotic strategy (2 RCTs, n=353, 35.3% versus 12.8%, RR 2.81, 95% CI 1.77 to 4.47; low quality evidence) and in back-up prescriptions with delayed collection (3 RCTs, n=888, 24.7% versus 14%, RR 1.79, 95% CI 1.10 to 2.90; very low quality evidence).

Back-up antibiotic prescriptions were not significantly different to immediate antibiotics for patient satisfaction (6 RCTs [4 RCTs in adults and children, 1 RCT in just adults and 1 RCT in just children], n=1,633; very low quality evidence). However back-up antibiotic prescriptions were significantly better than no antibiotics for patient satisfaction (4 RCTs [2 RCTs in adults and children, 1 RCT in just adults and 1 RCT in just children], n=1235, 86.9% versus 82.4%, RR 1.06, 95% CI 1.01 to 1.11, NNT 23 [95% CI 12 to 232]; low quality evidence).

Vomiting was significantly increased in the back-up antibiotic prescription group compared with the immediate antibiotic prescription group (3 RCTs, n=888: very low quality evidence). However, none of these studies were in people with acute cough. There were no significant differences for other adverse events (diarrhoea, rash or re-consultation rates) when back-up antibiotics were compared with immediate antibiotics (very low quality evidence).

See GRADE profile: table 50.

3.4.2 Antibiotics compared with placebo in adults

The evidence review for antibiotics compared with placebo in adults is based on 1 systematic review and meta-analysis (Smith et al. 2017).

The systematic review by Smith et al (2017) included 17 RCTs (n=5,099) comparing antibiotics with placebo or no active treatment in adults and children. It included RCTs where participants had a clinical syndrome of cough with or without productive sputum, with a diagnosis of acute bronchitis or cough with persistent cold or flu-like illness that was not resolving (or acute lower respiratory tract infection when pneumonia is not suspected). The systematic review excluded people with pre-existing chronic bronchitis (for example, acute exacerbation of chronic bronchitis) and included studies that allowed concurrent use of other medications (for example

analgesics, antitussives, antipyretics or mucolytics) provided they allowed equal access to such medications for people in both groups. The systematic review was limited by unclear timing of follow-up for the outcomes, and the validity of the outcome measures and symptom scales used by the included studies. It was often unclear if a statistically significant differences between groups were clinically meaningful.

Antibiotics for clinical improvement in adults with acute bronchitis

Antibiotics (doxycycline, co-trimoxazole, erythromycin, cefuroxime, azithromycin, amoxicillin and co-amoxiclav) were not significantly better than placebo (or no active treatment) for clinical improvement at follow-up in a meta-analysis of 11 RCTs (9 RCTs in adults and 2 RCTs in adults and children, n=3,841, RR 1.07, 95% CI 0.99 to 1.15, NNT 16 [95% CI 11 to 27], low quality evidence) in people with acute bronchitis. Clinical improvement was measured by a global assessment of improvement by clinicians at follow up.

Antibiotics were also not significantly better than placebo alone for clinical improvement at follow-up (NICE meta-analysis of 10 RCTs [7 RCTs in just adults, 2 RCTs in adults and children and 1 RCT with an unclear population], n=3,652; low quality evidence).

In NICE subgroup analysis there was no significant difference in clinical improvement between doxycycline and placebo (3 RCTs), erythromycin and placebo (2 RCTs) or amoxicillin and placebo (2 RCTs; low to moderate quality evidence). However, cefuroxime significantly increased clinical improvement at follow-up in adults with acute bronchitis compared with placebo (NICE analysis, 1 RCT, n=343, 92.4% versus 79.1%, RR 1.17, 95% CI 1.07 to 1.28; low quality evidence).

Antibiotics (erythromycin, cefuroxime, doxycycline or co-amoxiclav) did not significantly reduce the number of people with acute bronchitis who had no improvement in physician's global assessment at follow-up compared with placebo (6 RCTs [5 RCTs in just adults and 1 RCT in adults and children], n=891, very low quality evidence). However, this analysis included a subgroup from a larger study in people with non-purulent tracheo-bronchitis from an upper respiratory tract infection study. With this study omitted, antibiotics were significantly better than placebo in the number of people who had no improvement in physician's global assessment at follow-up (5 RCTs, n=816, 7.7% versus 17.6%, RR 0.44, 95% CI 0.3 to 0.65, NNT 11 [95% CI 7 to 19]; moderate quality evidence). However, only 1 RCT in this analysis of cefuroxime versus placebo (accounting for 35.5% of the weight in the meta-analysis) had a significant reduction in the antibiotic group for this outcome.

Antibiotics (erythromycin, cefuroxime or doxycycline) were significantly better than placebo for an abnormal lung examination at follow-up in adults with acute bronchitis (5 RCTs, n=613, 18.5% versus 34.8%, RR 0.54, 95% CI 0.41 to 0.7, NNT 7 (95% CI 5 to 11); moderate quality evidence). However, only 1 RCT in this analysis of cefuroxime versus placebo (accounting for 77.8% of the weight in the meta-analysis) had a significant reduction for an abnormal lung examination at follow-up in the antibiotic group.

Antibiotics (erythromycin, doxycycline or amoxicillin) significantly reduced the mean number of days feeling ill compared with placebo or no active treatment (5 RCTs [3 RCTs in adults and children, 2 RCTs in just adults], n=809, mean difference −0.64 days, 95% CI −1.16 to −0.13; moderate quality evidence). However, the significant effect was not maintained when a study with no active treatment (no placebo) was omitted. A NICE subgroup analysis of RCTs of doxycycline versus placebo showed a

significant reduction in the mean number of days feeling ill compared with placebo (3 RCTs, n=383, mean difference −0.64, 95% CI −1.24 to −0.04; high quality evidence).

See GRADE profiles: tables 51-52.

Antibiotics for reduction of cough in adults with acute bronchitis

Antibiotics (erythromycin or doxycycline) significantly reduced cough at follow-up visit in adults with acute bronchitis compared with placebo (4 RCTs, n=275, 32.9% versus 50.8%, RR 0.64, 95% CI 0.49 to 0.85, NNT 6 [95% CI 4 to 16]; moderate quality evidence). This significant reduction in cough was seen in a subgroup of RCTs of doxycycline compared with placebo (2 RCTs, n=210, 22.9% versus 42.6%, RR 0.54, 95% CI 0.36 to 0.81, NNT 6 [95% CI 4 to 14]; moderate quality evidence) but not for erythromycin compared with placebo (low quality evidence).

Antibiotics (erythromycin, cefuroxime or doxycycline) significantly reduced night cough at follow-up in adults with acute bronchitis compared with placebo (4 RCTs, n=538, 29.5% versus 44.6%, RR 0.67, 95% CI 0.54 to 0.83, NNT 7 [95% CI 5 to 15]; low quality evidence). This significant reduction was seen in a subgroup analysis of cefuroxime versus placebo (1 RCT, n=340, 36.8% versus 56.8%, RR 0.65, 95% CI 0.51 0.82; low quality evidence) but not for erythromycin or doxycycline versus placebo (low quality evidence). Antibiotics (erythromycin, doxycycline or demethyl chlortetracycline) did not make any significant difference to the presence of productive cough at follow-up in people with acute bronchitis (7 RCTs [4 RCTs in adults, 2 RCTs in adults and children and 1 RCT with an unclear population], n=713, moderate quality evidence).

See GRADE profile: table 53.

Antibiotics for duration of cough in adults with acute bronchitis

Antibiotics (erythromycin, amoxicillin or doxycycline) significantly reduced the mean number of days of cough compared with placebo or no active treatment (7 RCTs [4 RCTs in adults and children, 3 RCTs in just adults], n=2,776, mean difference −0.46 days, 95% CI −0.87 to −0.04; moderate quality evidence). This significant reduction was also seen in studies that compared antibiotics with placebo only (6 RCTs, n=2,350, MD −0.55, 95% CI −1.00 to −0.10; moderate quality evidence). No significant differences were found for individual antibiotics in subgroup analyses.

Antibiotics made no significant difference to the mean number of days of productive cough (6 RCTs [3 RCTs in adults and children 3 RCTs in just adults]) compared with placebo or no active treatment. This analysis included a subgroup from a larger study in people with non-purulent tracheo-bronchitis from an upper respiratory tract infection study. With this study omitted, antibiotics did significantly reduce the mean number of days of productive cough (5 RCTs, n=535, MD −0.52 days, 95% CI −1.03 to −0.01; moderate quality evidence). The significant difference was maintained in a subgroup of studies comparing doxycycline with placebo (4 RCTs, n=444, MD −0.56 days, 95% CI −1.09 to −0.04; moderate quality evidence) but not in 2 RCTs of amoxicillin or erythromycin compared with placebo or no treatment.

See GRADE profile: table 54.

Adverse effects of antibiotics in adults with acute bronchitis

Antibiotics significantly increased the overall number of adverse effects compared with placebo or no active treatment (12 RCTs, n=3,496, 22.6% versus 18.7%, RR

1.20, 95% CI 1.05 to 1.36, NNH 25 [95% CI 15 to 84]; low quality evidence). There were no significant differences in adverse effects for subgroups of different antibiotics (erythromycin, amoxicillin, co-amoxiclav or doxycycline) versus placebo or no active treatment (very low to low quality evidence).

See GRADE profile: table 55.

3.4.3 Antibiotics compared with placebo in children

The evidence review for antibiotics compared with placebo in children and young people is based on 2 systematic reviews and meta-analyses (see also section 3.4.2).

Antibiotics for moist cough of greater than 10 days duration in children

The first systematic review (Marchant et al. 2005) included 140 children (aged 7 years or less) from 2 RCTs which compared antibiotics with placebo or no treatment for moist cough of greater than 10 days duration. Studies of children with bronchiectasis, cystic fibrosis, *Mycoplasma pneumoniae, Chlamydia*, underlying cardio-respiratory conditions, wheeze or systemic illness were excluded. Included studies could use other concurrent medicines provided they were available to both the intervention and control groups.

Antibiotics (erythromycin or co-amoxiclav) significantly reduced the number of children with clinical failure (not cured or not substantially improved) at follow-up in children with prolonged moist cough compared with placebo or no treatment (2 RCTs, n=140, 34.3% versus 72.6%, RR 0.46, 95% CI 0.32 to 0.65, NNT 3 [95% CI 2 to 5]; moderate quality evidence). However, this became non-significant in NICE analysis (but remained as significant reductions in the Marchant et al. 2005 systematic review using odds ratios) when children with *Bordetella pertussis* were excluded (12 children [8.6% of all children, n=140, in the analysis] from 1 RCT [Gottfarb et al. 1994] included in the meta-analysis) and in an intention-to-treat analysis using those not lost to follow-up (very low quality evidence).

Antibiotics significantly reduced the number of children who needed additional treatment due to illness compared with placebo or no treatment (2 RCTs, n=125, 5.1% versus 36.4%, RR 0.14, 95% CI 0.04 to 0.45, NNT 4 [95% CI 3 to 6]; moderate quality evidence) but there was no significant heterogeneity in the analysis. There was no significant difference between antibiotics and placebo or no treatment for adverse effects (vomiting, rash or diarrhoea).

See GRADE profile: table 56.

Antibiotics for the prevention of complications from undifferentiated acute respiratory tract infection in children

The second systematic review (Alves et al. 2016) included 1,314 children (aged 2 to 59 months) from 4 RCTs, which compared antibiotics with placebo for the prevention of complications (acute otitis media or pneumonia) and antibiotic adverse effects in undifferentiated acute respiratory tract infection. The studies do not report how many of the children had a cough at baseline, although the authors do state that evidence from a systematic review suggests that three-quarters of children with undifferentiated acute respiratory infection present with a cough. The study is limited by population (subacute cough) as in 1 RCT around 50% of the study population had a cough for more than 3 weeks, and in the second RCT the mean length of cough was 3 to 4 weeks.

Antibiotics (co-amoxiclav) had no significant effect on the development of acute otitis media in children with acute undifferentiated respiratory tract infection compared with placebo or no treatment (3 RCTs, n=414; very low quality evidence), or in a subgroup of children from high income countries (2 RCTs, n=318; very low quality evidence). Antibiotics (ampicillin) had no significant effect on the development of pneumonia in children aged under 11 months (1 RCT, n=326; very low quality evidence) or those aged 12 to 58 months with undifferentiated acute respiratory tract infection compared with placebo or no treatment (1 RCT, n=563; very low quality evidence).

See GRADE profile: table 57.

3.4.4 Choice of antibiotic

No systematic reviews and randomised controlled trials met the inclusion criteria.

3.4.5 Antibiotic dosage, duration and route of administration

No systematic reviews and randomised controlled trials met the inclusion criteria.

Antibiotic course length

No systematic reviews and randomised controlled trials met the inclusion criteria.

Antibiotic route of administration

No systematic reviews and randomised controlled trials met the inclusion criteria.

4 Terms used in the guideline

4.1.1 Acute cough

An acute cough is a cough which lasts less than 3 weeks. It is most commonly caused by an upper respiratory tract infection, such as a common cold or flu, which are viral infections. Other causes of acute cough include lower respiratory tract infections, such as acute bronchitis, pneumonia, acute exacerbations of asthma or chronic obstructive pulmonary disease and viral-induced wheeze or bronchiolitis in children (NICE clinical knowledge summary: cough).

4.1.2 Acute bronchitis

Acute bronchitis is a transient inflammation of the trachea and major bronchi associated with oedema and mucus production that leads to cough and phlegm production lasting for up to 3 weeks. It is usually caused by a viral infection, but may be caused by a bacterial infection (NICE clinical knowledge summary: chest infections – adult).

Appendices

Appendix A: Evidence sources

Key area	Key question(s)	Evidence sources
Background	• What is the natural history of the infection? • What is the expected duration and severity of symptoms with or without antimicrobial treatment? • What are the most likely causative organisms? • What are the usual symptoms and signs of the infection? • What are the known complication rates of the infection, with and without antimicrobial treatment?	• Ebell et al. (2013) • NICE clinical knowledge summaries – cough • NICE guideline on fever in under 5s: assessment and initial management (2008)
Safety information	• What safety netting advice is needed for managing the infection? • What symptoms and signs suggest a more serious illness or condition (red flags)?	• NICE guideline NG63: NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population (2017) • NHS – cough, October 2018 • NICE clinical knowledge summaries – cough • NICE guideline CG160: fever in under 5s: assessment and initial management (2017) • NHS – foods to avoid giving your baby, October 2018 • MHRA traditional herbal registration, October 2018 • Drug Safety Update – codeine April 2009, • Benilyn Dry Cough summary of product characteristics • BNF October 2018 • Drug Safety Update – corticosteroids, September 2010

Key area	Key question(s)	Evidence sources
		• NICE clinical knowledge summaries – diarrhoea – antibiotic associated • NICE guideline CG183: drug allergy: diagnosis and management (2014) • Committee experience
Antimicrobial resistance	• What resistance patterns, trends and levels of resistance exist both locally and nationally for the causative organisms of the infection • What is the need for broad or narrow spectrum antimicrobials? • What is the impact of specific antimicrobials on the development of future resistance to that and other antimicrobials?	• NICE guideline NG15: Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) • CMO report (2011) • ESPAUR report (2018) • NHS – respiratory tract infections October 2018 • NICE clinical knowledge summaries: chest infections – adult • Worrall 2008 • Costelloe et al. 2010
Medicines adherence	• What are the problems with medicines adherence (such as when longer courses of treatment are used)?	• NICE guideline NG76: Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence (2009)
Resource impact	• What is the resource impact of interventions (such as escalation or de-escalation of treatment)?	• Gulliford et al. (2014) • Spurling et al. (2013) • NHSBSA Drug Tariff
Regulatory status	• What is the regulatory status of interventions for managing the infection or symptoms?	• Summary of product characteristics
Non-pharmacological interventions	• What is the clinical effectiveness and safety of non-pharmacological interventions for managing the infection or symptoms?	• Evidence review – see appendix F for included studies • NHS – foods to avoid giving your baby, October 2018 • MHRA traditional herbal registration, October 2018

Key area	Key question(s)	Evidence sources
Non-antimicrobial pharmacological interventions	• What is the clinical effectiveness and safety of non-antimicrobial pharmacological interventions for managing the infection or symptoms?	• Evidence review – see appendix F for included studies • NICE guideline on fever in under 5s: assessment and initial management (2017) • Drug Safety Update, April 2009 • Drug Safety Update, September 2010 • Drug Safety Update, April 2015 • Summary of product characteristics • British National Formulary (BNF) October 2018 • BNF for children (BNF-C) October 2018
Antimicrobial prescribing strategies	• What is the clinical effectiveness and safety of antimicrobial prescribing strategies (including back-up prescribing) for managing the infection or symptoms?	• Evidence review – see appendix F for included studies
Antimicrobials	• What is the clinical effectiveness and safety of antimicrobials for managing the infection or symptoms?	• Evidence review – see appendix F for included studies • NICE clinical knowledge summary: diarrhoea – antibiotic associated. • NICE guideline on drug allergy: diagnosis and management (2014) • British National Formulary (BNF) October 2018 • BNF for children (BNF-C) October 2018
	• Which people are most likely to benefit from an antimicrobial?	• Evidence review – see appendix F for included studies
	• Which antimicrobial should be prescribed if one is indicated (first, second and third line treatment, including people with drug allergy)?	• Evidence review – see appendix F for included studies
	• What is the optimal dose, duration and route of administration of antimicrobials?	• Evidence review – see appendix F for included studies • British National Formulary (BNF) October 2018

Key area	Key question(s)	Evidence sources
		• BNF for children (BNF-C) October 2018 • Summary of product characteristics

Appendix B: Review protocol

I	Review question	What pharmacological (antimicrobial and non-antimicrobial) and non-pharmacological interventions are effective in managing acute cough, including acute bronchitis?	• antimicrobials include antibiotics • non-antimicrobials include analgesia, over-the-counter cough preparations, corticosteroids, bronchodilators (e.g. beta-2 agonists, anticholinergics, leukotriene receptor antagonists), and mucolytics. • non-pharmacologicals (e.g. drinking fluids, honey and herbal medicines. • search will include terms for lower respiratory tract infection, chest infection, acute cough and acute bronchitis.
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 interventions in managing acute cough, including acute bronchitis, in line with the major goals of antimicrobial stewardship. This includes interventions that lead prescribers to: • optimise outcomes for individuals • reduce overuse, misuse or abuse of antimicrobials All of the above will be considered in the context of national antimicrobial resistance patterns where available, if not available committee expertise will be used to guide decision-making.	The secondary objectives of the review of studies will include: • indications for prescribing an antimicrobial (individual patient factors [including adverse events] and illness severity) • indications for no or delayed antimicrobials • indications for non-antimicrobial interventions • antimicrobial choice, optimal dose, duration and route for specified antimicrobial(s) • the natural history of the infection
IV	Eligibility criteria – population/	Population: Adults and children (aged 72 hours and older) with an acute cough (duration of symptoms less than 8 weeks), including acute bronchitis.	Subgroups of interest, those:

	disease/ condition/ issue/domain	Studies that use for example symptoms or signs (prognosis), clinical diagnosis, imaging, microbiological methods, or laboratory testing of blood for diagnosing the condition.	• with protected characteristics under the Equality Act 2010. • with chronic conditions (such as high blood pressure, diabetes or heart disease). • at high risk of serious complications because of pre-existing comorbidity[1] • with symptoms and signs suggestive of serious illness and/or complications[2] • <18 years (children) including those with fever and additional intermediate or high risk factors[3] • patient is older than 65 years and older than 80 years[4] • with purulent sputum and exacerbations • with asthma
V	Eligibility criteria – intervention(s) / exposure(s)	The review will include studies which include: • Non-pharmacological interventions[5]. • Non-antimicrobial pharmacological interventions[6]. • Antimicrobial pharmacological interventions[7]. For the treatment of acute cough, including acute bronchitis, as outlined above, 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)

[1] significant heart, lung, renal, liver or neuromuscular disease, immunosuppression, cystic fibrosis, and young children who were born prematurely
[2] Including pneumonia, heart, lung, kidney, liver or neuromuscular disease, or immunosuppression
[3] Outlined in more detail in CG160 Fever in under 5s: assessment and initial management
[4] hospitalisation in previous year; type 1 or type 2 diabetes, history of congestive heart failure, current use of oral glucocorticoids.
[5] Non-pharmacological interventions include: drinking fluids, honey and herbal medicines
[6] Non-antimicrobial pharmacological interventions include: analgesics, corticosteroids (oral or inhaled), bronchodilators (beta-2 agonists, anticholinergics, leukotriene receptor antagonists), mucolytics and over-the-counter cough preparations (e.g. antitussives, expectorants, antihistamines and decongestants),
[7] 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

VI	Eligibility criteria – comparator(s)/ control or reference (gold) standard	Any other plausible strategy or comparator, including: • Placebo. • Non-pharmacological interventions. • Non-antimicrobial pharmacological interventions. • Other antimicrobial pharmacological interventions.	
VII	Outcomes and prioritisation	a) Clinical outcomes such as: • mortality • infection cure rates (number or proportion of people with resolution of symptoms at a given time point, incidence of escalation of treatment) • time to clinical cure (mean or median time to resolution of illness) • reduction in symptoms (duration or severity) • rate of complications with or without treatment • safety, tolerability, and adverse effects. b) Changes in antimicrobial resistance patterns, trends and levels as a result of treatment. c) Patient-reported outcomes, such as medicines adherence, patient experience and patient satisfaction. d) Ability to carry out activities of daily living. e) Service user experience. f) Health and social care related quality of life, including long-term harm or disability. g) Health and social care utilisation (including length of stay, planned and unplanned contacts). The Committee considered which outcomes should be prioritised when multiple outcomes are reported (critical and important	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[8] (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). The committee have agreed that the following outcomes are important: • patient-reported outcomes, such as medicines adherence, patient experience, sickness absence • changes in antimicrobial resistance patterns, trends and levels as a result of treatment

[8] These would include but are not limited to more common complications e.g. infective exacerbations and chronic bacterial colonization

		outcomes). Additionally, the Committee were asked to consider what clinically important features of study design may be important for this condition (for example length of study follow-up, treatment failure/recurrence, important outcomes of interest such as sequela or progression to more severe illness).	
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. In order to progress due to insufficient evidence, non-antimicrobial and non-pharmacological interventions were grouped into classes as follows (based on systematic reviews by Oduwole et al. 2014, Wagner et al. 2015, Timmer et al. 2013, Kim et al. 2015, Smith et al. 2014, Becker et al. 2015, El-Gohary et al. 2013 and Chalumeau and Duijvestijn 2013): • Honey • Herbal medicines • Paracetamol • NSAIDs • Over-the-counter expectorants • Over-the-counter antitussives • Over-the-counter antihistamines • Over-the-counter decongestants • Over-the-counter mucolytics • Beta-2 agonists • Anticholinergics • Leukotriene receptor antagonists • Corticosteroids • Mucolytics

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 • in relation to antimicrobial resistance, non-UK papers • Chronic cough (>8 weeks duration) • Cough due to/associated with: chronic bronchitis, pneumonia (community or hospital acquired), exacerbations of chronic obstructive pulmonary disease, congestive heart failure, cystic fibrosis, bronchiectasis, bronchiolitis, whooping cough, pneumothorax, pulmonary embolism, ventilator use, viral-induced wheeze, a non-infective cause, such as cough due to ACE-inhibitor use. • Managing non-cough symptoms of upper respiratory tract infections, such as sinusitis, otitis media and sore throat.	
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 included if studies stratify results by population subgroups, and these categories may enable the production of management recommendations.	
XI	Selection process – duplicate screening/ selection/ analysis	All references from the database searches will be downloaded, de-duplicated and screened on title and abstract against the criteria above. A randomly selected initial sample of 10% of records will be screened by two reviewers independently. The rate of agreement for this sample will be recorded, and if it is over 90% then remaining references will screened by one reviewer only. Disagreement will be resolved through discussion. Where abstracts meet all the criteria, or if it is unclear from the study abstract whether it does, the full text will be retrieved.	

		If large numbers of papers are identified and included at full text, the Committee may consider prioritising the evidence for example, evidence of higher quality in terms of study type or evidence with critical or highly important outcomes.	
XII	Data management (software)	Data management will be undertaken using EPPI-reviewer software. GRADEpro will be used to assess the quality of evidence for each outcome.	
XIII	Information sources – databases and dates	The following sources will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) via Wiley • Cochrane Database of Systematic Reviews (CDSR) via Wiley • Database of Abstracts of Effectiveness (DARE) via Wiley – legacy, last updated April 2015 • Embase via Ovid • Health Technology Assessment (HTA) via Wiley • MEDLINE via Ovid • MEDLINE-in-Process via Ovid The search strategy will be developed in MEDLINE and then adapted or translated as appropriate for the other sources, taking into account their size, search functionality and subject coverage. Database functionality will be used, where available, to exclude: • non-English language papers • animal studies • editorials, letters, news items, case reports and commentaries • conference abstracts and posters • theses and dissertations • duplicates. Date limits will be applied to restrict the search results to: • studies published from 2006 to the present day	

		The results will be downloaded in the following mutually exclusive sets: • Systematic reviews and meta-analysis • Randomised controlled trials • Observational and comparative studies • Other results See appendix B for further details on the search strategy. Duplicates will be removed using automated and manual processes. The de-duplicated file will be uploaded into EPPI-Reviewer for data screening.	
XV	Author contacts	Web: https://www.nice.org.uk/guidance/indevelopment/gid-ng10050/consultation/html-content Email: infections@nice.org.uk	
XVI	Highlight if amendment to previous protocol	For details please see the interim process guide (2017).	
XVII	Search strategy – for one database	For details see appendix C.	
XVIII	Data collection process – forms/duplicate	GRADE profiles will be used, for details see appendix H.	
XIX	Data items – define all variables to be collected	GRADE profiles will be used, for details see appendix H.	
XX	Methods for assessing bias at outcome/ study level	Standard study checklists will be used to critically appraise individual studies. For details please see the interim process guide (2017). The risk of bias across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations	

		Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/	
XXI	Criteria for quantitative synthesis (where suitable)	For details please see the interim process guide (2017).	
XXII	Methods for analysis – combining studies and exploring (in)consistency	For details please see the interim process guide (2017).	
XXIII	Meta-bias assessment – publication bias, selective reporting bias	For details please see the interim process guide (2017).	
XXIV	Assessment of confidence in cumulative evidence	For details please see the interim process guide (2017).	
XXV	Rationale/ context – Current management	For details please see the interim process guide (2017).	
XXVI	Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by NICE and chaired by Dr Tessa Lewis in line with the interim process guide (2017). Staff from NICE undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and	

		drafted the guideline in collaboration with the committee. For details please see the methods chapter of the full guideline.	
XXVII	Sources of funding/support	Developed and funded by NICE.	
XXVIII	Name of sponsor	Developed and funded by NICE.	
XXIX	Roles of sponsor	NICE funds and develops guidelines for those working in the NHS, public health, and social care in England.	

Appendix C: Literature search strategy

	No. of hits in MEDLINE	Position in the strategy
Search with limits and Systematic Reviews	5376	Line 247
Search with limits and RCTs (not SRs)	3431	Line 266
Search with limits and Observational Studies (not SRs or RCTs)	5648	Line 289
Search with limits (without SRs, RCTs, Observational)	10093	Line 290
Total for screening	24548	

Key to search operators

/	Medical Subject Heading (MeSH) term
Exp	Explodes the MeSH terms to retrieve narrower terms in the hierarchy
.ti	Searches the title field
.ab	Searches the abstract field
*	Truncation symbol (searches all word endings after the stem)
adj*n*	Adjacency operator to retrieve records containing the terms within a specified number (*n*) of words of each other

Database(s): Ovid MEDLINE(R) 1946 to October Week 1 2017, Ovid MEDLINE(R) Epub Ahead of Print October 16, 2017, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations October 16, 2017, Ovid MEDLINE(R) Daily Update October 16, 2017

Search Strategy:

#	Searches	Results
1	Cough/	15165
2	cough*.ti,ab.	45432
3	((postnasal* or post nasal*) adj3 drip*).ti,ab.	589
4	Bronchitis/	21093
5	(bronchit* or tracheobronchit*).ti,ab.	22136
6	(bronchial adj2 infect*).ti,ab.	782
7	Respiratory Tract Infections/	37036
8	Respiratory Syncytial Virus Infections/	6243
9	((pulmonary or lung* or airway* or airflow* or bronch* or respirat*) adj3 syncytial virus*).ti,ab.	12118
10	Pneumovirus*.ti,ab.	343
11	(("respiratory tract*" or "acute respiratory" or "lower respiratory" or chest) adj3 (infect* or cough*)).ti,ab.	30623
12	LRTI.ti,ab.	980
13	exp Pneumonia/	88843
14	(pneumon* or bronchopneumon* or pleuropneumon* or tracheobronchit*).ti,ab.	176553
15	or/1-14	323542
16	limit 15 to yr="2006 -Current"	133940
17	limit 16 to english language	120589
18	Animals/ not (Animals/ and Humans/)	4643829
19	17 not 18	108249

20	limit 19 to (letter or historical article or comment or editorial or news or case reports)	18545
21	19 not 20	89704
22	anti-infective agents/ or exp anti-bacterial agents/ or exp anti-infective agents, local/	908739
23	(antibacter* or anti-bacter* or "anti bacter*" or antimicrobial or anti-microbial or "anti microbial" or antibiot* or anti-biot* or "anti biot*").ti,ab.	433955
24	or/22-23	1095907
25	Amoxicillin/	9361
26	(Amoxicillin* or Amoxycillin* or Amoxil*).ti,ab.	16425
27	Ampicillin/	13807
28	Ampicillin*.ti,ab.	22039
29	Azithromycin/	4771
30	(Azithromycin* or Azithromicin* or Zithromax*).ti,ab.	7221
31	Aztreonam/	1437
32	(Aztreonam* or Azactam*).ti,ab.	2951
33	Penicillin G/	9348
34	(Benzylpenicillin* or "Penicillin G").ti,ab.	8206
35	Cefaclor/	881
36	(Cefaclor* or Distaclor* or Keftid*).ti,ab.	1741
37	Cefixime/	772
38	(Cefixime* or Suprax*).ti,ab.	1569
39	Cefotaxime/	5575
40	Cefotaxime*.ti,ab.	8120
41	(Ceftaroline* or Zinforo*).ti,ab.	583
42	Ceftazidime/	3797
43	(Ceftazidime* or Fortum* or Tazidime*).ti,ab.	8387
44	(Ceftobiprole* or Zevtera*).ti,ab.	262
45	(Ceftolozane* or Tazobactam* or Zerbaxa*).ti,ab.	3869
46	Ceftriaxone/	5707
47	(Ceftriaxone* or Rocephin* or Rocefin*).ti,ab.	9632
48	Cefuroxime/	2190
49	(Cefuroxime* or Cephuroxime* or Zinacef* or Zinnat* or Aprokam*).ti,ab.	4248
50	Chloramphenicol/	20280
51	(Chloramphenicol* or Cloranfenicol* or Kemicetine* or Kloramfenikol*).ti,ab.	26700
52	Ciprofloxacin/	12735
53	(Ciprofloxacin* or Ciproxin*).ti,ab.	23629
54	Clarithromycin/	6001
55	(Clarithromycin* or Clarie* or Klaricid* or Xetinin*).ti,ab.	8465
56	Clindamycin/	5646
57	(Clindamycin* or Dalacin* or Zindaclin*).ti,ab.	9899
58	Amoxicillin-Potassium Clavulanate Combination/	2501
59	(Co-amoxiclav* or Coamoxiclav* or Amox-clav* or Amoxicillin-Clavulanic Acid* or Amoxicillin-Potassium Clavulanate Combination* or Amoxi-Clavulanate* or Clavulanate Potentiated Amoxycillin Potassium* or Clavulanate-Amoxicillin Combination* or Augmentin*).ti,ab.	14738
60	Trimethoprim, Sulfamethoxazole Drug Combination/	6860

61	(Septrin* or Co-trimoxazole* or Cotrimoxazole* or Sulfamethoxazole Trimethoprim Comb* or Trimethoprim Sulfamethoxazole Comb*).ti,ab.	6035
62	Colistin/	3468
63	(Colistin* or Colistimethate* or Colimycin* or Coly-Mycin* or Colymycin* or Colomycin* or Promixin*).ti,ab.	4884
64	Doxycycline/	9238
65	(Doxycycline* or Efracea* or Periostat* or Vibramycin*).ti,ab.	12343
66	(Ertapenem* or Invanz*).ti,ab.	1256
67	Erythromycin/	14229
68	Erythromycin Estolate/	154
69	Erythromycin Ethylsuccinate/	522
70	(Erythromycin* or Erymax* or Tiloryth* or Erythrocin* or Erythrolar* or Erythroped*).ti,ab.	20574
71	Fosfomycin/	1839
72	(Fosfomycin* or Phosphomycin* or Fosfocina* or Monuril* or Monurol* or Fomicyt*).ti,ab.	2623
73	Floxacillin/	739
74	(Floxacillin* or Flucloxacillin*).ti,ab.	842
75	Gentamicins/	18583
76	(Gentamicin* or Gentamycin* or Cidomycin*).ti,ab.	25954
77	Imipenem/	4016
78	(Imipenem* or Primaxin*).ti,ab.	9709
79	Levofloxacin/	2965
80	(Levofloxacin* or Evoxil* or Tavanic*).ti,ab.	6626
81	Linezolid/	2599
82	(Linezolid* or Zyvox*).ti,ab.	4911
83	Meropenem*.ti,ab.	5187
84	(Moxifloxacin* or Avelox*).ti,ab.	4045
85	Ofloxacin/	6224
86	(Ofloxacin* or Tarivid*).ti,ab.	6844
87	Piperacillin/	2713
88	(Piperacillin* or Tazobactam* or Tazocin*).ti,ab.	6818
89	Rifampin/	17357
90	(Rifampicin* or Rifampin* or Rifadin* or Rimactane*).ti,ab.	22688
91	Teicoplanin/	2234
92	(Teicoplanin* or Targocid*).ti,ab.	3467
93	(Telavancin* or Vibativ*).ti,ab.	369
94	(Temocillin* or Negaban*).ti,ab.	302
95	(Tigecycline* or Tygacil*).ti,ab.	2562
96	Vancomycin/	12899
97	(Vancomycin* or Vancomicin* or Vancocin*).ti,ab.	24386
98	or/25-97	276644
99	exp Aminoglycosides/	154042
100	Aminoglycoside*.ti,ab.	18162
101	exp Penicillins/	81338
102	Penicillin*.ti,ab.	54151
103	exp beta-Lactamase inhibitors/	7519

104	(("beta Lactamase*" or betaLactamase*) adj3 (antagonist* or agonist* or agent* or inhibitor* or blocker*)).ti,ab.	2897
105	beta-Lactams/	6140
106	("beta-Lactam" or betaLactam or "beta Lactam " or "beta-Lactams" or betaLactams or "beta Lactams").ti,ab.	19809
107	exp Carbapenems/	9627
108	Carbapenem*.ti,ab.	10899
109	exp Cephalosporins/	42255
110	Cephalosporin*.ti,ab.	21163
111	exp Fluoroquinolones/	31349
112	Fluoroquinolone*.ti,ab.	14729
113	exp Macrolides/	105782
114	Macrolide*.ti,ab.	14603
115	exp Polymyxins/	8638
116	Polymyxin*.ti,ab.	6747
117	exp Quinolones/	45007
118	Quinolone*.ti,ab.	13119
119	exp Tetracyclines/	47435
120	Tetracycline*.ti,ab.	34131
121	or/99-120	497907
122	Bronchodilator Agents/	19033
123	(Bronchodilator* or broncholytic* or bronchial dilat* or bronchodilating* or bronchodilatant*).ti,ab.	14064
124	analgesics/	46460
125	exp analgesics, non-narcotic/	322666
126	analgesics, short-acting/	8
127	antipyretics/	2591
128	(analgesic* or antipyretic*).ti,ab.	77553
129	Acetaminophen/	17280
130	(paracetamol* or acetaminophen* or Panadol* or perfalgan* or calpol*).ti,ab.	22807
131	Cholinergic antagonists/	4933
132	(Anticholinergic* or "Anti-cholinergic*" or "Anti cholinergic*" or Antimuscarinic* or Anti muscarinic* or Anti-muscarinic*).ti,ab.	14963
133	(("adrenergic beta" or "beta adrenergic" or beta2 or "beta 2") adj3 (antagonist* or agonist* or agent* or inhibitor* or blocker*)).ti,ab.	23087
134	Adrenergic beta-2 Receptor Agonists/	2581
135	(("adrenergic beta" or "beta adrenergic" or beta2 or "beta 2") adj3 (antagonist* or agonist* or agent* or inhibitor* or blocker*)).ti,ab.	23087
136	Albuterol/	9858
137	(Salbutamol* or Albuterol* or Salbulin* or Ventolin* or Salamol*).ti,ab.	9742
138	exp Codeine/	6616
139	(Codeine* or Pholcodine* or Covonia* or Galenphol* or Pavacol* or Galcodine*).ti,ab.	4854
140	Adrenal Cortex Hormones/	63302
141	(Corticosteroid* or corticoid* or Adrenal Cortex Hormone*).ti,ab.	102411
142	Nonprescription Drugs/	5876
143	(non prescription* or nonprescription* or otc or "over the counter*" or "over-the-counter*").ti,ab.	12255

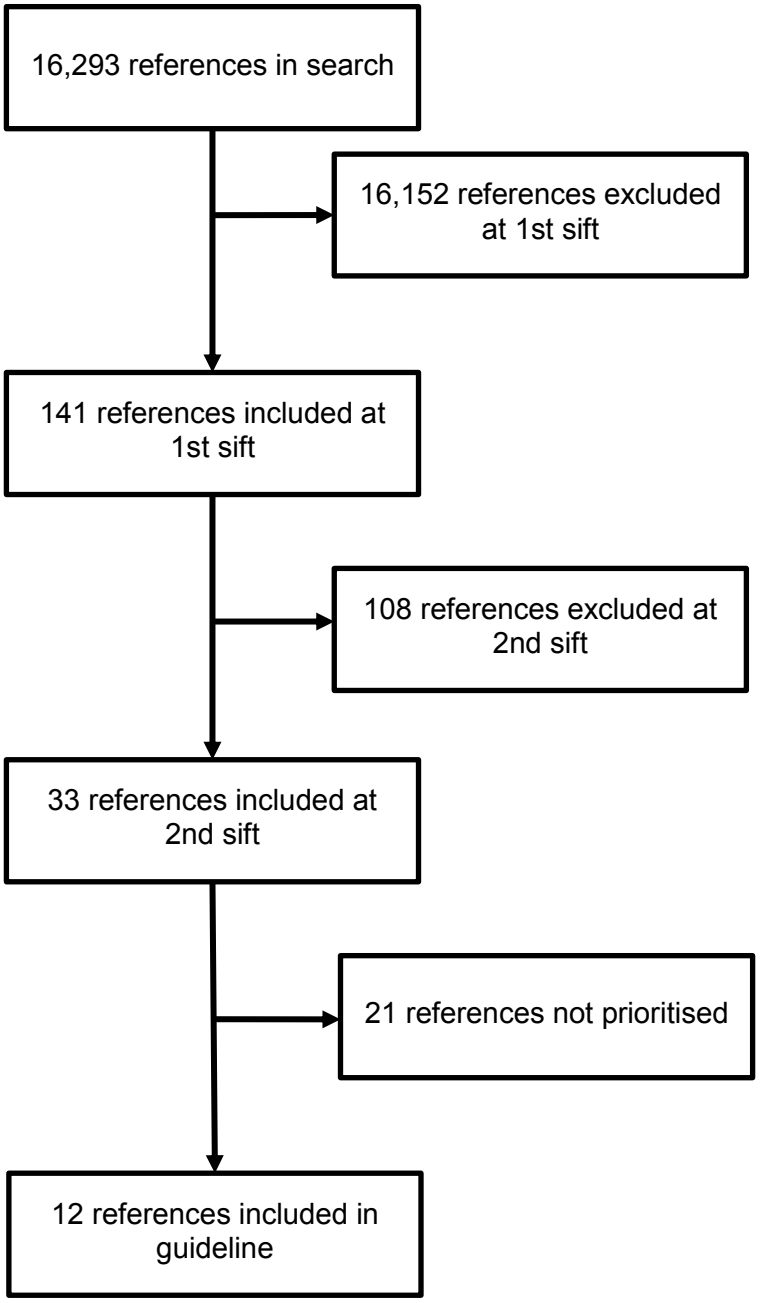
144	Antitussive Agents/	2841
145	Antitussive*.ti,ab.	1887
146	(cough* adj3 (suppressant* or mixture* or syrup* or medicine* or medicinal* or remedy* or remedies* or product or products)).ti,ab.	915
147	exp Histamine Antagonists/	63352
148	Antazoline/	212
149	Brompheniramine/	351
150	Chlorpheniramine/	1989
151	Cinnarizine/	805
152	Cyproheptadine/	2322
153	Diphenhydramine/	4027
154	Doxylamine/	384
155	Ergotamine/	2436
156	Hydroxyzine/	1451
157	Ketotifen/	1175
158	Pizotyline/	283
159	Promethazine/	3130
160	Trimeprazine/	327
161	Triprolidine/	309
162	(histamin* adj3 (antagonist* or agonist* or agent* or inhibitor* or blocker*)).ti,ab.	9260
163	(antihistamin* or anti-histamin* or Alimemazine* or Trimeprazine* or Antazoline* or Brompheniramine* or Chlorpheniramine* or Chlorphenamine* or Cinnarizine* or Stugeron* or Cyproheptadine* or Periactin* or Diphenhydramine* or Doxylamine* or Ergotamine* or Migril* or Hydroxyzine* or Atarax* or Ketotifen* or Zaditen* or Promethazine* or Phenergan* or Sominex* or Pizotifen* or Pizotyline* or Triprolidine* or Acrivastine*).ti,ab.	28590
164	Demulcents/	4
165	(demulcent* or mucoprotective* or muco protective* or Linctus*).ti,ab.	227
166	Glycerol/	25266
167	(Glycerol* or Glycerine*).ti,ab.	48554
168	Menthol/	1800
169	menthol*.ti,ab.	2448
170	exp Prednisolone/	51015
171	(Prednisolone* or Fluprednisolone* or Methylprednisolone* or Deltacortril* or Dilacort* or Pevanti* or Deltastab* or Predsol*).ti,ab.	38273
172	exp Anti-Inflammatory Agents, Non-Steroidal/	193330
173	nsaid*.ti,ab.	23343
174	((nonsteroid* or non steroid*) adj3 (anti inflammator* or antiinflammator*)).ti,ab.	37248
175	Ibuprofen/	8334
176	(ibuprofen* or arthrofen* or ebufac* or rimafen* or brufen* or calprofen* or feverfen* or nurofen* or orbifen*).ti,ab.	12307
177	Dextromethorphan/	1806
178	Dextromethorphan*.ti,ab.	2510
179	Leukotriene Antagonists/	3063
180	(leukotriene* adj3 (antagonist* or agonist* or agent* or inhibitor* or blocker*)).ti,ab.	3798
181	Montelukast*.ti,ab.	1980
182	(Zafirlukast* or Accolate*).ti,ab.	419
183	exp Expectorants/	16597

184	exp Guaifenesin/	776
185	Ipecac/	639
186	(expectorant* or mucolytic* or guaifenesin* or ipecac* or ipecacuanha*).ti,ab.	3101
187	Mannitol/	12719
188	(Mannitol* or Osmohale* or Bronchitol*).ti,ab.	17698
189	(Dornase alfa* or Dornase alpha* or Pulmozyme*).ti,ab.	240
190	or/122-189	850363
191	Honey/	3396
192	Apitherapy/	114
193	(honey* or lemon*).ti,ab.	22587
194	or/191-193	22919
195	Drugs, Chinese Herbal/	37457
196	Plants, Medicinal/	58533
197	exp Geraniaceae/	607
198	Echinacea/	740
199	Fallopia Japonica/	181
200	Thymus Plant/	1219
201	Eucalyptus/	2144
202	Forsythia/	161
203	exp Glycyrrhiza/	2539
204	Andrographis/	392
205	(herb* or Geraniaceae* or Pelargonium* or Geranium* or Kaloba* or Echinacea* or Coneflower* or Japonica* or Knotweed* or Thyme* or Thymus* or Eucalyptus* or Forsythia* or Forsythiae* or Goldenbell* or Lian Qiao* or Glycyrrhiza* or Licorice* or Liquorice* or Andrographis*).ti,ab.	164139
206	((medicine* or medical* or medicinal* or product or products or remedies* or remedy*) adj3 (plant* or plants or root or roots or flower or flowers or bark or barks or seed or seeds or shrub or shrubs or botanic*)).ti,ab.	22856
207	or/195-206	250647
208	Fluid therapy/	19132
209	Drinking/	14141
210	Drinking Behavior/	6828
211	exp Beverages/	124467
212	((water* or fluid* or liquid* or beverage* or drinks) adj3 (consumption* or consume* or consuming* or intake* or drink* or hydrat* or rehydrat* or therap*)).ti,ab.	93975
213	or/208-212	232893
214	watchful waiting/	2801
215	"no intervention*".ti,ab.	6967
216	(watchful* adj2 wait*).ti,ab.	2321
217	(wait adj2 see).ti,ab.	1352
218	(active* adj2 surveillance*).ti,ab.	6517
219	(expectant* adj2 manage*).ti,ab.	3048
220	or/214-219	21495
221	Self Care/	31538
222	Self medication/	4616
223	((self or selves or themsel*) adj4 (care or manag*)).ti,ab.	37143
224	or/221-223	59581
225	Inappropriate prescribing/	2110

226	((delay* or defer*) adj3 (treat* or therap* or interven*)).ti,ab.	29049
227	((prescription* or prescrib*) adj3 ("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* 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 misuse* or "mis-use*" or overuse* or "over-use*" or "over-prescri*" or abuse*)).ti,ab.	24600
228	((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*") adj3 ("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* 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 misuse* or "mis-use*" or overuse* or "over-use*" or "over-prescri*" or abuse*)).ti,ab.	103402
229	or/225-228	154677
230	24 or 98 or 121 or 190 or 194 or 207 or 213 or 220 or 224 or 229	2645544
231	21 and 230	30468
232	Meta-Analysis.pt.	91779
233	Network Meta-Analysis/	220
234	Meta-Analysis as Topic/	17154
235	Review.pt.	2443246
236	exp Review Literature as Topic/	10197
237	(metaanaly* or metanaly* or (meta adj3 analy*)).ti,ab.	130880
238	(review* or overview*).ti.	435300
239	(systematic* adj5 (review* or overview*)).ti,ab.	130897
240	((quantitative* or qualitative*) adj5 (review* or overview*)).ti,ab.	8451
241	((studies or trial*) adj2 (review* or overview*)).ti,ab.	40696
242	(integrat* adj3 (research or review* or literature)).ti,ab.	9912
243	(pool* adj2 (analy* or data)).ti,ab.	25735
244	(handsearch* or (hand adj3 search*)).ti,ab.	8417
245	(manual* adj3 search*).ti,ab.	5300
246	or/232-245	2725485
247	231 and 246	5376
248	98 or 121 or 190 or 194 or 207 or 213 or 220 or 224 or 229	2086858
249	21 and 248	23218
250	Randomized Controlled Trial.pt.	497031
251	Controlled Clinical Trial.pt.	99256
252	Clinical Trial.pt.	548028
253	exp Clinical Trials as Topic/	332203
254	Placebos/	36433
255	Random Allocation/	99660
256	Double-Blind Method/	157533
257	Single-Blind Method/	26574
258	Cross-Over Studies/	45016
259	((random* or control* or clinical*) adj3 (trial* or stud*)).ti,ab.	1115406
260	(random* adj3 allocat*).ti,ab.	31822
261	placebo*.ti,ab.	209215
262	((singl* or doubl* or trebl* or tripl*) adj (blind* or mask*)).ti,ab.	167858
263	(crossover* or (cross adj over*)).ti,ab.	82346

264 or/250-263	1895644
265 249 and 264	4969
266 265 not 247	3431
267 Observational Studies as Topic/	2818
268 Observational Study/	46520
269 Epidemiologic Studies/	7973
270 exp Case-Control Studies/	948245
271 exp Cohort Studies/	1823837
272 Cross-Sectional Studies/	269121
273 Controlled Before-After Studies/	297
274 Historically Controlled Study/	149
275 Interrupted Time Series Analysis/	369
276 Comparative Study.pt.	1908513
277 case control*.ti,ab.	114928
278 case series.ti,ab.	59535
279 (cohort adj (study or studies)).ti,ab.	156605
280 cohort analy*.ti,ab.	6292
281 (follow up adj (study or studies)).ti,ab.	47161
282 (observational adj (study or studies)).ti,ab.	81605
283 longitudinal.ti,ab.	210546
284 prospective.ti,ab.	509033
285 retrospective.ti,ab.	431491
286 cross sectional.ti,ab.	278740
287 or/267-286	4334061
288 249 and 287	7941
289 288 not (247 or 266)	5648
290 249 not (247 or 266 or 289)	10093

Appendix D: Study flow diagram



Appendix E: Evidence prioritisation

Key questions	Included studies[1]		Studies not prioritised[2]	
	Systematic reviews	RCTs	Systematic reviews	RCTs
Which non-pharmacological interventions are effective?				
Herbal medicines	Timmer et al. 2013 Wagner et al. 2015	-	Agbabiaka et al. 2008 Anheyer et al. 2017 Arroll 2010 Cheng et al. 2017 Chenot et al. 2011 Ding et al. 2016 Jiang et al. 2012 Kim et al. 2016 Kligler et al. 2006 Liu et al. 2013 Wei et al. 2016	-
Honey studies in acute cough	Oduwole et al. 2014	-	Nitsche and Carreno 2016 Heppermann et al. 2009 Smith et al. 2014	-
Which non-antimicrobial pharmacological interventions are effective?				
Oral analgesia	Kim et al. 2015	-	Arroll 2010	-
Over-the-counter medicines (expectorants, antitussives, antihistamines and decongestants)	Smith et al. 2014		Arroll 2010 Björnsdóttir et al. 2007 De Blasio et al. 2013 De Sutter et al. 2012 Isbister et al. 2012 Ryan et al. 2008 Zanasi et al. 2015	De Blasio et al. 2012

Key questions	Included studies[1]		Studies not prioritised[2]	
	Systematic reviews	RCTs	Systematic reviews	RCTs
Mucolytics	Chalumeau and Duijvestjin 2013	-	-	-
Bronchodilators	Becker et al. 2015	-	-	-
Corticosteroids	El-Gohary et al. 2013	-	-	-
Which antibiotic prescribing strategy is effective (including back-up antibiotics)?				
Back-up antibiotics	Spurling et al. 2017	-	McDonagh et al. 2016	-
Is an antibiotic effective?				
Antibiotics versus placebo studies	Smith et al. 2017 Alves et al. 2016 Marchant et al. 2005	-	Arroll 2010	-
Which antibiotic is most effective?				
Antibiotics versus different antibiotics studies	-	-	-	-
What is the optimal dose, duration and route of administration of antibiotic?				
Dose and/or frequency studies	-	-	-	-
Course length studies	-	-	-	-
Route of administration studies	-	-	-	-

Abbreviations: SR, Systematic review; RCT, Randomised controlled trial

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

Appendix F: Included studies

Alves Galvao, M G, Rocha Crispino Santos, M A, Alves Da Cunha, and A J L (2009) Antibiotics for undifferentiated acute respiratory tract infections in children under five years of age. Cochrane Database of Systematic Reviews (3), CD007880

Becker Lorne A, Hom Jeffrey, Villasis-Keever Miguel, van der Wouden , and Johannes C (2015) Beta2-agonists for acute cough or a clinical diagnosis of acute bronchitis. The Cochrane database of systematic reviews (9), CD001726

Chalumeau Martin, and Duijvestijn Yvonne C. M (2013) Acetylcysteine and carbocysteine for acute upper and lower respiratory tract infections in paediatric patients without chronic broncho-pulmonary disease. The Cochrane database of systematic reviews (5), CD003124

El-Gohary Magdy, Hay Alastair D, Coventry Peter, Moore Michael, Stuart Beth, and Little Paul (2013) Corticosteroids for acute and subacute cough following respiratory tract infection: a systematic review. Family practice 30(5), 492-500

Kim Soo Young, Chang Yoon-Jung, Cho Hye Min, Hwang Ye-Won, and Moon Yoo Sun (2015) Non-steroidal anti-inflammatory drugs for the common cold. The Cochrane database of systematic reviews (9), CD006362

Marchant JM, Morris PS, Gaffney J, Chang AB (2005) Antibiotics for prolonged moist cough in children. Cochrane Database of Systematic Reviews 2005, Issue 4. Art. No.: CD004822. DOI: 10.1002/14651858.CD004822.pub2.

Oduwole O, Meremikwu M M, Oyo-Ita A, and Udoh E E (2014) Honey for acute cough in children. Evidence-Based Child Health 9(2), 303-346

Smith S M, Schroeder K, and Fahey T (2008) Over-the-counter medications for acute cough in children and adults in ambulatory settings. The Cochrane database of systematic reviews (1), CD001831

Smith Susan M, Fahey Tom, Smucny John, and Becker Lorne A (2017) Antibiotics for acute bronchitis. The Cochrane database of systematic reviews 6, CD000245

Spurling Geoffrey Kp, Del Mar, Chris B, Dooley Liz, Foxlee Ruth, and Farley Rebecca (2017) Delayed antibiotic prescriptions for respiratory infections. The Cochrane database of systematic reviews 9, CD004417

Timmer Antje, Gunther Judith, Motschall Edith, Rucker Gerta, Antes Gerd, and Kern Winfried V (2013) Pelargonium sidoides extract for treating acute respiratory tract infections. The Cochrane database of systematic reviews (10), CD006323

Wagner Luise, Cramer Holger, Klose Petra, Lauche Romy, Gass Florian, Dobos Gustav, and Langhorst Jost (2015) Herbal Medicine for Cough: a Systematic Review and Meta-Analysis. Forschende Komplementarmedizin (2006) 22(6), 359-68

Appendix G: Quality assessment of included studies

G.1 Non-pharmacological interventions

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

Study reference	Oduwole et al. (2014)	Wagner et al. (2015)	Timmer et al. (2013)
Did the review address a clearly focused question?	Yes	No[1]	Yes
Did the authors look for the right type of papers?	Yes	Yes	Yes
Do you think all the important, relevant studies were included?	Yes	Unclear[2]	Yes
Did the review's authors do enough to assess the quality of the included studies?	Yes	Yes	Yes
If the results of the review have been combined, was it reasonable to do so?	Yes	Yes	Yes
What are the overall results of the review?	See GRADE profiles	See GRADE profiles	See GRADE profiles
How precise are the results?	See GRADE profiles	See GRADE profiles	See GRADE profiles
Can the results be applied to the local population?	Yes	Yes	Yes
Were all important outcomes considered?	Yes	Yes	Yes
Are the benefits worth the harms and costs?	See GRADE profiles	See GRADE profiles	See GRADE profiles

[1] Unclear when adults, children, or a mixed population were given the intervention; outcome reporting is not specific

[2] Limited reporting of literature search methods, with no report of reference list follow up, contact with study authors, or searches for unpublished data

G.2 Non-antimicrobial pharmacological interventions (self-care medicines)

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

Study reference	Smith et al. 2014	Kim et al. 2015
Did the review address a clearly focused question?	Yes	Yes
Did the authors look for the right type of papers?	Yes	Partially[3]
Do you think all the important, relevant studies were included?	Yes	Yes

Study reference	Smith et al. 2014	Kim et al. 2015
Did the review's authors do enough to assess the quality of the included studies?	Unclear[1]	Yes[4]
If the results of the review have been combined, was it reasonable to do so?	N/A[2]	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 profile
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?	Yes	See GRADE profile

Abbreviations: N/A; not applicable

[1] The authors were unable to carry out meta-analyses because the studies were clinically heterogeneous and provided insufficient data.

[2] Participant numbers and event rates in intervention and control groups were inadequately reported in the review. It is also unclear whether the authors attempted to access missing data

[3] The review examined studies looking at common cold which included cough, downgraded for indirectness

[4] Cochrane risk of bias tool used, no included studies was assessed as at low risk of bias

G.3 Non-antimicrobial pharmacological interventions (prescribed medicines)

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

Study reference	Becker et al. 2015	Chalumeau & Duijvestijn 2013	El-Gohary et al. 2013
Did the review address a clearly focused question?	Yes	Yes	Yes
Did the authors look for the right type of papers?	Yes	Yes	Yes
Do you think all the important, relevant studies were included?	Yes	Yes	Yes
Did the review's authors do enough to assess the quality of the included studies?	Yes[1]	Yes[1]	Yes[2]
If the results of the review have been combined, was it reasonable to do so?	Yes	Yes	N/A[3]
What are the overall results of the review?	See GRADE profile	See GRADE profile	See GRADE profile
How precise are the results?	See GRADE profile	See GRADE profile	See GRADE profile
Can the results be applied to the local population?	Yes	Yes	Yes

Study reference	Becker et al. 2015	Chalumeau & Duijvestijn 2013	El-Gohary et al. 2013
Were all important outcomes considered?	Yes	Yes	Yes
Are the benefits worth the harms and costs?	See GRADE profile	See GRADE profile	See GRADE profile

[1] Cochrane risk of bias tool used, no included studies was assessed as at low risk of bias

[2] Cochrane risk of bias tool used, only 1 of 4 included studies was assessed by the authors as at low risk of bias (although this study also had unclear allocation concealment)

[3] Narrative presentation of results, no meta-analysis due to high heterogeneity

G.4 Back-up antibiotics

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

Study reference	Spurling et al. 2017
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[1]
If the results of the review have been combined, was it reasonable to do so?	Unclear[2]
What are the overall results of the review?	See GRADE profile
How precise are the results?	See GRADE profile
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 profile

[1] Cochrane risk of bias tool used, only 1 of 11 included studies was assessed as at low risk of bias

[2] The Cochrane authors did not undertake meta-analysis for a number of outcomes due to very high heterogeneity, and in some cases where meta-analysis was undertaken the effects model used was not reflective of the amount of heterogeneity

G.5 Antibiotics

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

Study reference	Alves et al. 2016	Marchant et al. 2005	Smith et al. 2017
Did the review address a clearly focused question?	Yes	Yes	Yes
Did the authors look for the right type of papers?	Yes	Yes	Yes
Do you think all the important, relevant studies were included?	Yes	Yes	Yes
Did the review's authors do enough to assess the quality of the included studies?	Yes[1]	Yes[1]	Yes[1]
If the results of the review have been combined, was it reasonable to do so?	Yes	Yes	Yes
What are the overall results of the review?	See GRADE profile	See GRADE profile	See GRADE profile
How precise are the results?	See GRADE profile	See GRADE profile	See GRADE profile
Can the results be applied to the local population?	Yes	Yes	Yes
Were all important outcomes considered?	Yes	Yes	Yes
Are the benefits worth the harms and costs?	See GRADE profile	See GRADE profile	See GRADE profile
[1] Cochrane risk of bias tool used, only 1 of 11 included studies was assessed as at low risk of bias			

Appendix H: GRADE profiles

H.1 Honey

Table 9: GRADE profile – honey versus no treatment for children with acute cough

Quality assessment							No of patients		Absolute Effect (95% CI)	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Honey[1]	No treatment			
Frequency of cough at 1 day[2] (range of scores: 0-6; Better indicated by lower values)											
2[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	75	79	MD 1.05 lower (1.48 to 0.62 lower)	⊕⊕OO LOW	CRITICAL
Severity of cough at 1 day[2] (range of scores: 0-6; Better indicated by lower values)											
2[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	75	79	MD 1.03 lower (1.59 to 0.47 lower)	⊕⊕OO LOW	CRITICAL
Bothersome cough (not defined) at 1 day[2] (range of scores: 0-6; Better indicated by lower values)											
1[3]	randomised trials	serious[4]	N/A	no serious indirectness	serious[5]	none	36	39	MD 0.93 lower (1.98 lower to 0.12 higher)	⊕⊕OO LOW	CRITICAL
Cough impact on children's' sleep at 1 day[2] (Better indicated by lower values)											
2[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	75	79	MD 1.04 lower (1.57 to 0.51 lower)	⊕⊕OO LOW	IMPORTANT
Cough impact on parents' sleep at 1 day[2] (Better indicated by lower values)											
2[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	75	79	MD 0.88 lower (1.23 to 0.52 lower)	⊕⊕OO LOW	IMPORTANT
Combined improvement (not defined) at 1 day (Better indicated by lower values)											
1[3]	randomised trials	serious[4]	N/A	no serious indirectness	serious[5]	none	35	39	MD 4.31 lower (6.77 to 1.85 lower)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI, confidence interval; MD, mean difference; N/A, not applicable											

[1] In 1 RCT, all children were advised to use supportive treatment including saline nose drops, water vapour, cleaning of a blocked nose and paracetamol, if needed
[2] Measured using a 7-point Likert scale; caregivers' responses to the questionnaire ranged from 'extreme' (6 points) to 'none at all' (0 points)
[3] Oduwole et al. 2014
[4] Downgraded 1 level - authors described included studies as high risk of bias, due to non-blinding of participants and investigators, unclear allocation concealment, the use of supportive treatment for all study arms, and subjective patient reported outcomes
[5] Downgraded 1 level - not assessable

Table 10: GRADE profile – honey versus placebo for children with acute cough

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Honey	Placebo[1]	Relative (95% CI)	Absolute (95% CI)		
Frequency of cough at 1 day[2] (range of scores: 0-6; Better indicated by lower values)												
1[3]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[4]	none	225	75	-	MD 1.85 lower (3.36 to 0.33 lower)	⊕⊕⊕O MODERATE	CRITICAL
Severity of cough at 1 day[2] (range of scores: 0-6; Better indicated by lower values)												
1[3]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[4]	none	225	75	-	MD 1.83 lower (3.32 to 0.34 lower)	⊕⊕⊕O MODERATE	CRITICAL
Bothersome cough (not defined) at 1 day[2] (range of scores: 0-6; Better indicated by lower values)												
1[3]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[4]	none	225	75	-	MD 2.08 lower (3.97 to 0.19 lower)	⊕⊕⊕O MODERATE	CRITICAL
Cough impact on children's' sleep at 1 day[2] (Better indicated by lower values)												
1[3]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[4]	none	225	75	-	MD 1.94 lower (3.93 lower to 0.06 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Cough impact on parents' sleep at 1 day[2] (Better indicated by lower values)												
1[3]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[4]	none	225	75	-	MD 2.05 lower (4.24 lower to 0.13 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Gastrointestinal adverse effects (stomach ache, nausea and vomiting) at 1 day												
1[3]	randomised trials	no serious risk of bias	N/A	no serious indirectness	very serious[5]	none	4/225 (1.8%)	1/75 (1.3%)	RR 1.33 (0.15 to 11.74)	4 more per 1000 (from 11 fewer to 143 more)	⊕⊕OO LOW	CRITICAL

Abbreviations: CI, confidence interval; MD, mean difference; N/A, not applicable; RR, relative risk

[1] Silan dates extract
[2] Measured using a 7-point Likert scale; caregivers' responses to the questionnaire ranged from 'extreme' (6 points) to 'none at all' (0 points)
[3] Oduwole et al. 2014
[4] Downgraded 1 level - not assessable
[5] Downgraded 2 levels: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with honey, and no meaningful difference or appreciable benefit with placebo

Table 11: GRADE profile – honey versus antitussive for children with acute cough

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Honey[1]	Dextromethorphan	Relative (95% CI)	Absolute (95% CI)		
Frequency of cough at 1 day[2] (range of scores: 0-6; Better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Honey[1]	Dextromethorphan	Relative (95% CI)	Absolute (95% CI)		
2[3]	randomised trials	serious[4]	serious[5]	no serious indirectness	serious[6]	none	75	74	-	MD 0.07 lower (1.07 lower to 0.94 higher)	⊕OOO VERY LOW	CRITICAL
Severity of cough at 1 day[2] (range of scores: 0-6; Better indicated by lower values)												
2[3]	randomised trials	serious[4]	serious[5]	no serious indirectness	serious[6]	none	75	74	-	MD 0.13 lower (1.25 lower to 0.99 higher)	⊕OOO VERY LOW	CRITICAL
Bothersome cough (not defined) at 1 day[2] (range of scores: 0-6; Better indicated by lower values)												
1[3]	randomised trials	serious[4]	N/A	no serious indirectness	serious[6]	none	35	34	-	MD 0.29 higher (0.56 lower to 1.14 higher)	⊕⊕OO LOW	CRITICAL
Cough impact on children's' sleep at 1 day[2] (Better indicated by lower values)												
2[3]	randomised trials	serious[4]	serious[5]	no serious indirectness	serious[6]	none	75	74	-	MD 0.03 higher (1.12 lower to 1.19 higher)	⊕OOO VERY LOW	IMPORTANT
Cough impact on parents' sleep at 1 day[2] (Better indicated by lower values)												
2[3]	randomised trials	serious[4]	serious[5]	no serious indirectness	serious[6]	none	75	74	-	MD 0.16 lower (0.84 lower to 0.53 higher)	⊕OOO VERY LOW	IMPORTANT
Combined improvement (not defined) at 1 day (Better indicated by lower values)												
1[3]	randomised trials	serious[4]	N/A	no serious indirectness	serious[6]	none	35	34	-	MD 2.32 higher (1.24 lower to 5.88 higher)	⊕⊕OO LOW	CRITICAL
Mild adverse effects (nervousness, insomnia and hyperactivity) at 1 day												
2[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[7]	none	7/75 (9.3%)	2/74 (2.7%)	RR 2.94 (0.74 to 11.71)	52 more per 1000 (from 7 fewer to 289 more)	⊕OOO VERY LOW	CRITICAL
Gastrointestinal adverse effects (stomach ache, nausea and vomiting) at 1 day												
2[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[7]	none	2/75 (2.7%)	0/74 (0%)	RR 4.86 (0.24 to 97.69)	-	⊕OOO VERY LOW	CRITICAL
Drowsiness at 1 day												
2[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[7]	none	1/75 (1.3%)	0/74 (0%)	RR 2.92 (0.12 to 69.2)	-	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI, confidence interval; MD, mean difference; N/A – not applicable; RR, relative risk

[1] In 1 RCT, all children were advised to use supportive treatment including saline nose drops, water vapour, cleaning of a blocked nose and paracetamol, if needed

[2] Measured using a 7-point Likert scale; caregivers' responses to the questionnaire ranged from 'extreme' (6 points) to 'none at all' (0 points)

[3] Oduwole et al. 2014
[4] Downgraded 1 level - authors described included studies as high risk of bias, due to non-blinding of participants and investigators, unclear allocation concealment, the use of supportive treatment for all study arms, and subjective patient reported outcomes
[5] Downgraded 1 level - heterogeneity >50%
[6] Downgraded 1 level - not assessable
[7] Downgraded 2 levels: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with honey, and no meaningful difference or appreciable benefit with dextromethorphan

Table 12: GRADE profile – honey versus sedating antihistamine for children with acute cough

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Honey[1]	Diphenhydramine	Relative (95% CI)	Absolute (95% CI)		
Frequency of cough at 1 day[2] (range of scores: 0-6; Better indicated by lower values)												
1[3]	randomised trials	serious[4]	N/A	no serious indirectness	serious[5]	none	40	40	-	MD 0.57 lower (0.9 to 0.24 lower)	⊕⊕OO LOW	CRITICAL
Severity of cough at 1 day[2] (range of scores: 0-6; Better indicated by lower values)												
1[3]	randomised trials	serious[4]	N/A	no serious indirectness	serious[5]	none	40	40	-	MD 0.60 lower (0.94 to 0.26 lower)	⊕⊕OO LOW	CRITICAL
Cough impact on children's' sleep at 1 day[2] (Better indicated by lower values)												
1[3]	randomised trials	serious[4]	N/A	no serious indirectness	serious[5]	none	40	40	-	MD 0.55 lower (0.87 to 0.23 lower)	⊕⊕OO LOW	IMPORTANT
Cough impact on parents' sleep at 1 day[2] (Better indicated by lower values)												
1[3]	randomised trials	serious[4]	N/A	no serious indirectness	serious[5]	none	40	40	-	MD 048 lower (0.76 to 0.2 lower)	⊕⊕OO LOW	IMPORTANT
Somnolence at 1 day												
1[3]	randomised trials	serious[4]	N/A	no serious indirectness	very serious[6]	none	0/40 (0%)	3/40 (7.5%)	RR 0.14 (0.01 to 2.68)	65 fewer per 1000 (from 74 fewer to 126 more)	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI, confidence interval; MD, mean difference; N/A – not applicable; RR, relative risk

[1] All children were advised to use supportive treatment including saline nose drops, water vapour, cleaning of a blocked nose and paracetamol, if needed
[2] Measured using a 7-point Likert scale; caregivers' responses to the questionnaire ranged from 'extreme' (6 points) to 'none at all' (0 points)
[3] Oduwole et al. 2014
[4] Downgraded 1 level - authors described included studies as high risk of bias, due to non-blinding of participants and investigators, unclear allocation concealment, the use of supportive treatment for all study arms, and subjective patient reported outcomes
[5] Downgraded 1 level - not assessable
[6] Downgraded 2 levels: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with honey, and no meaningful difference or appreciable harm with diphenhydramine

H.2 Herbal medicines

Table 13: GRADE profile – *Andrographis paniculata* versus placebo in people with acute cough

Quality assessment							No of patients		Absolute Effect (95% CI)	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*Andrographis paniculata*[1]	Placebo			
Frequency of cough (not defined) (Better indicated by lower values)											
3[2]	randomised trials	serious[3]	serious[4]	no serious indirectness	serious[5]	none	244	249	SMD 1.00 lower (1.85 to 0.15 lower)	⊕OOO VERY LOW	CRITICAL
Severity of cough (not defined) (Better indicated by lower values)											
4[2]	randomised trials	serious[3]	serious[4]	no serious indirectness	serious[5]	yes[6]	333	348	SMD 0.57 lower (1.01 to 0.14 lower)	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI, confidence interval; SMD, standard mean difference

[1] KalmCold® capsules, KanJan® tablets or KanJang® oral solution (including extracts of A*ndrographis paniculata* and *Echinacea*). Daily dosages ranged from 31.5mg to 200mg and duration of intake from 3 to 10 days.
[2] Wagner et al. 2015
[3] Downgraded 1 level - missing data, with no explanation provided of reason for lack of reporting
[4] Downgraded 1 level - heterogeneity >50%
[5] Downgraded 1 level - at a minimal important difference of 0.5 of the median standard deviation of the comparator arm, data are consistent with no meaningful difference or appreciable harm with placebo
[6] Downgraded 1 level – data reported for the confidence interval in the meta-analysis figure differs from that reported in the text (SMD 0.57 lower [0.70 lower to 0.03 lower].

Table 14: GRADE profile – *Andrographis paniculata* (liquid) versus placebo in people with acute cough

Quality assessment							No of patients		Absolute Effect (95% CI)	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*Andrographis paniculata* (liquid)[1]	Placebo			
Frequency of cough (not defined) (Better indicated by lower values)											
1[2]	randomised trials	serious[3]	N/A	no serious indirectness	no serious imprecision	none	30	30	SMD 3.33 lower (4.13 to 2.53 lower) NICE analysis MD -3.20 (-3.68 to -2.72)	⊕⊕⊕O MODERATE	CRITICAL
Severity of cough (not defined) (Better indicated by lower values)											
1[2]	randomised trials	serious[3]	N/A	no serious indirectness	no serious imprecision	none	30	30	SMD 1.63 lower (2.22 to 1.04 lower) NICE analysis MD -2.20 (-2.87 to -1.53)	⊕⊕⊕O MODERATE	CRITICAL

Abbreviations: CI, confidence interval; N/A, not applicable; SMD, standard mean difference

[1] KanJang® oral solution including extracts of *Andrographis paniculata* and *Echinacea.* Daily dosages ranged from 31.5mg to 200mg and duration of intake from 3 to 10 days.
[2] Wagner et al. 2015
[3] Downgraded 1 level - missing data, with no explanation provided of reason for lack of reporting

Table 15: GRADE profile – *Andrographis paniculata* (tablets) versus placebo in people with acute cough

Quality assessment							No of patients		Absolute Effect (95% CI)	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*Andrographis paniculata* (tablets)[1]	Placebo			
Frequency of cough (not defined) (Better indicated by lower values)											
2[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	214	219	SMD 0.42 lower (0.71 to 0.13 lower)	⊕⊕OO LOW	CRITICAL
Severity of cough (not defined) (Better indicated by lower values)											
3[2]	randomised trials	serious[3]	serious[5]	no serious indirectness	no serious imprecision	none	303	318	SMD 0.36 lower (0.70 to 0.03 lower)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI, confidence interval; SMD, standard mean difference											

[1] KalmCold® capsules or KanJan® tablets, containing a combination of *Andrographis paniculata* and *Echinacea.* Daily dosages ranged from 31.5mg to 200mg and duration of intake from 3 to 10 days.
[2] Wagner et al. 2015
[3] Downgraded 1 level - missing data, with no explanation provided of reason for lack of reporting
[4] Downgraded 1 level - at a minimal important difference of 0.5 of the median standard deviation of the comparator arm, data are consistent with no meaningful difference or appreciable harm with placebo
[5] Downgraded 1 level - heterogeneity >50%

Table 16: GRADE profile – Ivy, primrose and thyme versus placebo in people with acute cough

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ivy, primrose and thyme	Placebo	Relative (95% CI)	Absolute (95% CI)		
Cough (not defined) (Better indicated by higher values)												
3[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	serious[4]	none	311/402 (77.4%)	217/395 (54.9%)	RR 1.40 (1.23 to 1.60)	220 more per 1000 (from 126 more to 330 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI, confidence interval; RR, relative risk												

[1] Wagner et al. 2015
[2] Downgraded 1 level - missing data, with no explanation provided of reason for lack of reporting
[3] Downgraded 1 level - ivy and primrose are not interventions of interest, but cannot be analysed separately to thyme
[4] Downgraded 1 level: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable benefit with ivy, primrose and thyme

Table 17: GRADE profile - Ivy, primrose and thyme (liquid) versus placebo in people with acute cough

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ivy, primrose and thyme (liquid)	Placebo	Relative (95% CI)	Absolute (95% CI)		
Cough (not defined) (Better indicated by higher values)												
1[1]	randomised trials	serious[2]	N/A	serious[3]	no serious imprecision	none	151/182 (83%)	96/178 (53.9%)	RR 1.54 (1.32 to 1.79)	291 more per 1000 (from 173 more to 426 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI, confidence interval; N/A, not applicable; RR, relative risk												

[1] Wagner et al. 2015
[2] Downgraded 1 level - missing data, with no explanation provided of reason for lack of reporting
[3] Downgraded 1 level - ivy and primrose are not interventions of interest, but cannot be analysed separately to thyme

Table 58: GRADE profile - Ivy, primrose and thyme (tablets) versus placebo in people with acute cough

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ivy, primrose and thyme (tablets)	Placebo	Relative (95% CI)	Absolute (95% CI)		
Cough not defined (Better indicated by higher values)												
2[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	serious[4]	none	160/220 (72.7%)	121/217 (55.8%)	RR 1.30 (1.13 to 1.49)	167 more per 1000 (from 72 more to 273 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI, confidence interval; RR, relative risk												

[1] Wagner et al. 2015
[2] Downgraded 1 level - missing data, with no explanation provided of reason for lack of reporting
[3] Downgraded 1 level - ivy and primrose are not interventions of interest, but cannot be analysed separately to thyme
[4] Downgraded 1 level: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable benefit with ivy, primrose and thyme

Table19: GRADE profile - *Echinacea* versus placebo in people with acute cough

Quality assessment							No of patients		Absolute Effect (95% CI)	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*Echinacea*	Placebo			
Cough (Better indicated by lower values)											
2[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	no serious imprecision	none	101	99	SMD 0.68 lower (1.32 to 0.04 lower)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI, confidence interval; SMD, standard mean difference											

[1] Wagner et al. 2015
[2] Downgraded 1 level - missing data, with no explanation provided of reason for lack of reporting
[3] Downgraded 1 level - heterogeneity >50%

Table 620: GRADE profile - *Pelargonium sidoides* (liquid) versus placebo in adults with acute bronchitis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*Pelargonium sidoides* (liquid)[1]	Placebo	Relative (95% CI)	Absolute (95% CI)		
Failure to resolve all symptoms by day 7												
2[2]	randomised trials	very serious[3]	serious[4]	no serious indirectness	serious[5]	none	105/172 (61%)	161/169 (95.3%)	RR 0.66 (0.52 to 0.83)	324 fewer per 1000 (from 162 fewer to 457 fewer)	⊕OOO VERY LOW	CRITICAL
Failure to resolve cough by day 7												
2[2]	randomised trials	very serious[3]	serious[4]	no serious indirectness	serious[5]	none	96/172 (55.8%)	153/169 (90.5%)	RR 0.63 (0.47 to 0.85)	335 fewer per 1000 (from 136 fewer to 480 fewer)	⊕OOO VERY LOW	CRITICAL
Failure to resolve sputum by day 7												
2[2]	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[5]	none	82/172 (47.7%)	123/169 (72.8%)	RR 0.65 (0.54 to 0.78)	255 fewer per 1000 (from 160 fewer to 335 fewer)	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI, confidence interval; RR, relative risk

[1] 30 drops, 3 times a day for 7 days
[2] Timmer et al. 2013
[3] Downgraded 2 levels – all included studies were initiated and funded by the same manufacturing company; authors report that none of the included studies attempted to examine the success and integrity of blinding, with concerns expressed about the effectiveness of blinding considering the subjective nature of the outcome measures; funnel plot analysis indicates possibility of publication bias
[4] Downgraded 1 level - heterogeneity >50%
[5] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with *Pelargonium sidoides*

Table 7: GRADE profile - *Pelargonium sidoides* (tablet, any dosage) versus placebo in adults with acute bronchitis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*Pelargonium sidoides* tablet (any dosage)[1]	Placebo	Relative (95% CI)	Absolute (95% CI)		
Failure to resolve all symptoms by day 7												
3[2]	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	281/303 (92.7%)	101/102 (99%)	RR 0.95 (0.91 to 0.99)	50 fewer per 1000 (from 10 fewer to 89 fewer)	⊕⊕OO LOW	CRITICAL
Failure to resolve cough by day 7												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*Pelargonium sidoides* tablet (any dosage)[1]	Placebo	Relative (95% CI)	Absolute (95% CI)		
3[2]	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	278/303 (91.7%)	101/102 (99%)	RR 0.94 (0.90 to 0.98)	59 fewer per 1000 (from 20 fewer to 99 fewer)	⊕⊕OO LOW	CRITICAL
Failure to resolve sputum by day 7												
3[2]	randomised trials	very serious[3]	serious[4]	no serious indirectness	serious[5]	none	166/303 (54.8%)	76/102 (74.5%)	RR 0.73 (0.57 to 0.94)	201 fewer per 1000 (from 45 fewer to 320 fewer)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI, confidence interval; RR, relative risk												

[1] 10, 20 or 30mg given 3 times a day for 7 days
[2] Timmer et al. 2013
[3] Downgraded 2 levels – all included studies were initiated and funded by the same manufacturing company; authors report that none of the included studies attempted to examine the success and integrity of blinding, with concerns expressed about the effectiveness of blinding considering the subjective nature of the outcome measures; funnel plot analysis indicates possibility of publication bias
[4] Downgraded 1 level - heterogeneity >50%
[5] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with *Pelargonium sidoides*

Table 22: GRADE profile - *Pelargonium sidoides* (tablet, 10mg) versus placebo in adults with acute bronchitis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*Pelargonium sidoides* tablet (10mg)[1]	Placebo	Relative (95% CI)	Absolute (95% CI)		
Failure to resolve all symptoms by day 7												
1[2]	randomised trials	very serious[3]	N/A	no serious indirectness	no serious imprecision	none	98/102 (96.1%)	34/34 (100%)	RR 0.97 (0.92 to 1.03)	30 fewer per 1000 (from 80 fewer to 30 more)	⊕⊕OO LOW	CRITICAL
Failure to resolve cough by day 7												
1[2]	randomised trials	very serious[3]	N/A	no serious indirectness	no serious imprecision	none	98/102 (96.1%)	34/34 (100%)	RR 0.97 (0.92 to 1.03)	30 fewer per 1000 (from 80 fewer to 30 more)	⊕⊕OO LOW	CRITICAL
Failure to resolve sputum by day 7												
1[2]	randomised trials	very serious[3]	N/A	no serious indirectness	serious[4]	none	69/102 (67.6%)	25/34 (73.5%)	RR 0.92 (0.72 to 1.17)	59 fewer per 1000 (from 206 fewer to 125 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI, confidence interval; RR, relative risk; N/A, not applicable												

[1] Given 3 times a day for 7 days
[2] Timmer et al. 2013
[3] Downgraded 2 levels – all included studies were initiated and funded by the same manufacturing company; authors report that none of the included studies attempted to examine the success and integrity of blinding, with concerns expressed about the effectiveness of blinding considering the subjective nature of the outcome measures; funnel plot analysis indicates possibility of publication

bias
[4] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with *Pelargonium sidoides*

Table 23: GRADE profile - *Pelargonium sidoides* (tablet, 20mg) versus placebo in adults with acute bronchitis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*Pelargonium sidoides* tablet (20mg)[1]	Placebo	Relative (95% CI)	Absolute (95% CI)		
Failure to resolve all symptoms by day 7												
1[2]	randomised trials	very serious[3]	N/A	no serious indirectness	no serious imprecision	none	91/101 (90.1%)	33/34 (97.1%)	RR 0.93 (0.85 to 1.01)	68 fewer per 1000 (from 146 fewer to 10 more)	⊕⊕OO LOW	CRITICAL
Failure to resolve cough by day 7												
1[2]	randomised trials	very serious[3]	N/A	no serious indirectness	no serious imprecision	none	89/101 (88.1%)	33/34 (97.1%)	RR 0.91 (0.83 to 1.00)	87 fewer per 1000 (from 165 fewer to 0 more)	⊕⊕OO LOW	CRITICAL
Failure to resolve sputum by day 7												
1[2]	randomised trials	very serious[3]	N/A	no serious indirectness	serious[4]	none	51/101 (50.5%)	26/34 (76.5%)	RR 0.66 (0.50 to 0.86)	260 fewer per 1000 (from 107 fewer to 382 fewer)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI, confidence interval; RR, relative risk; N/A, not applicable												

[1] Given 3 times a day for 7 days
[2] Timmer et al. 2013
[3] Downgraded 2 levels – all included studies were initiated and funded by the same manufacturing company; authors report that none of the included studies attempted to examine the success and integrity of blinding, with concerns expressed about the effectiveness of blinding considering the subjective nature of the outcome measures; funnel plot analysis indicates possibility of publication bias
[4] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with *Pelargonium sidoides*

Table 84: GRADE profile - *Pelargonium sidoides* (tablet, 30mg) versus placebo in adults with acute bronchitis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*Pelargonium sidoides* tablet (30mg)[1]	Placebo	Relative (95% CI)	Absolute (95% CI)		
Failure to resolve all symptoms by day 7												
1[2]	randomised trials	very serious[3]	N/A	no serious indirectness	no serious imprecision	none	92/100 (92%)	34/34 (100%)	RR 0.93 (0.87 to 1.00)	70 fewer per 1000 (from 130 fewer to 0 more)	⊕⊕OO LOW	CRITICAL
Failure to resolve cough by day 7												
1[2]	randomised trials	very serious[3]	N/A	no serious indirectness	no serious imprecision	none	91/100 (91%)	34/34 (100%)	RR 0.92 (0.85 to 0.99)	80 fewer per 1000 (from 10 fewer to 150 fewer)	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*Pelargonium sidoides* tablet (30mg)[1]	Placebo	Relative (95% CI)	Absolute (95% CI)		
Failure to resolve sputum by day 7												
1[2]	randomised trials	very serious[3]	N/A	no serious indirectness	serious[4]	none	46/100 (46%)	25/34 (73.5%)	RR 0.63 (0.47 to 0.84)	272 fewer per 1000 (from 118 fewer to 390 fewer)	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI, confidence interval; RR, relative risk; N/A, not applicable

[1] Given 3 times a day for 7 days
[2] Timmer et al. 2013
[3] Downgraded 2 levels – all included studies were initiated and funded by the same manufacturing company; authors report that none of the included studies attempted to examine the success and integrity of blinding, with concerns expressed about the effectiveness of blinding considering the subjective nature of the outcome measures; funnel plot analysis indicates possibility of publication bias
[4] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with *Pelargonium sidoides*

Table 95: GRADE profile - *Pelargonium sidoides* (any preparation) versus placebo in people with acute bronchitis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pelargonium sidoides (any preparation)[1]	Placebo	Relative (95% CI)	Absolute (95% CI)		
Patients with adverse events												
6[2]	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	192/987 (19.5%)	87/578 (15.1%)	RR 1.28 (1.01 to 1.62)[5]	42 more per 1000 (from 2 more to 93 more)	⊕OOO VERY LOW	CRITICAL
Adverse events leading to withdrawal												
6[2]	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	very serious[6]	none	5/987 (0.51%)	6/578 (1.0%)	RR 0.61 (0.20 to 1.85)[5]	4 fewer per 1000 (from 8 fewer to 9 more)	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI, confidence interval; RR, relative risk

[1] Given 3 times a day for 7 days (either as 10, 20, or 30mg tablets or 30 drops of liquid per dose)
[2] Timmer et al. 2013
[3] Downgraded 2 levels – all included studies were initiated and funded by the same manufacturing company; authors report that none of the included studies attempted to examine the success and integrity of blinding, with concerns expressed about the effectiveness of blinding considering the subjective nature of the outcome measures; funnel plot analysis indicates possibility of publication bias
[4] Downgraded 1 level: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with *Pelargonium sidoides*
[5] NICE analysis
[6] Downgraded 2 levels: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with *Pelargonium sidoides*, and no meaningful difference or appreciable harm with placebo

Table 26: GRADE profile - *Pelargonium sidoides* (any preparation) versus placebo in adults with acute bronchitis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*Pelargonium sidoides* (any preparation)[1]	Placebo	Relative (95% CI)	Absolute (95% CI)		
Failure to resolve sputum by day 7												
5[2]	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	248/475 (52.2%)	199/271 (73.4%)	RR 0.70 (0.60 to 0.82)	220 fewer per 1000 (from 132 fewer to 294 fewer)	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI, confidence interval; RR, relative risk

[1] Given 3 times a day for 7 days (either as 10, 20 or 30mg tablets or 30 drops of liquid per dose)
[2] Timmer et al. 2013
[3] Downgraded 2 levels – all included studies were initiated and funded by the same manufacturing company; authors report that none of the included studies attempted to examine the success and integrity of blinding, with concerns expressed about the effectiveness of blinding considering the subjective nature of the outcome measures; funnel plot analysis indicates possibility of publication bias
[4] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with *Pelargonium sidoides*

Table 27: GRADE profile – *Pelargonium sidoides* (liquid) versus placebo in children with acute bronchitis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*Pelargonium sidoides* (liquid)[1]	Placebo	Relative (95% CI)	Absolute (95% CI)		
Failure to resolve all symptoms by day 7												
2[2]	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	171/214 (79.9%)	200/206 (97.1%)	RR 0.82 (0.77 to 0.88)	175 fewer per 1000 (from 117 fewer to 223 fewer)	⊕⊕OO LOW	CRITICAL
Failure to resolve cough by day 7												
2[2]	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	170/214 (79.4%)	199/206 (96.6%)	RR 0.82 (0.76 to 0.88)	174 fewer per 1000 (from 116 fewer to 232 fewer)	⊕⊕OO LOW	CRITICAL
Failure to resolve sputum by day 7												
2[2]	randomised trials	very serious[3]	serious[4]	no serious indirectness	serious[5]	none	50/140 (35.7%)	84/132 (63.6%)	RR 0.55 (0.33 to 0.91)	286 fewer per 1000 (from 57 fewer to 426 fewer)	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI, confidence interval; RR, relative risk

[1] 30 drops, 3 times a day for 7 days
[2] Timmer et al. 2013

[3] Downgraded 2 levels – all included studies were initiated and funded by the same manufacturing company; authors report that none of the included studies attempted to examine the success and integrity of blinding, with concerns expressed about the effectiveness of blinding considering the subjective nature of the outcome measures; funnel plot analysis indicates possibility of publication bias
[4] Downgraded 1 level - heterogeneity >50%
[5] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with *Pelargonium sidoides*.

Table 10: GRADE profile - *Pelargonium sidoides* (tablet, any dosage) versus placebo in children with acute bronchitis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*Pelargonium sidoides* tablet (any dosage)[1]	Placebo	Relative (95% CI)	Absolute (95% CI)		
Failure to resolve all symptoms by day 7												
3[2]	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	260/298 (87.2%)	92/101 (91.1%)	RR 0.96 (0.89 to 1.03)	36 fewer per 1000 (from 100 fewer to 27 more)	⊕⊕OO LOW	CRITICAL
Failure to resolve cough by day 7												
3[2]	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	259/298 (86.9%)	91/101 (90.1%)	RR 0.96 (0.86 to 1.07)	36 fewer per 1000 (from 126 fewer to 63 more)	⊕⊕OO LOW	CRITICAL
Failure to resolve sputum by day 7												
3[2]	randomised trials	very serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	158/298 (53%)	62/101 (61.4%)	RR 0.87 (0.71 to 1.06)	80 fewer per 1000 (from 178 fewer to 37 more)	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI, confidence interval; RR, relative risk

[1] 10, 20 or 30mg, given 3 times a day for 7 days
[2] Timmer et al. 2013
[3] Downgraded 2 levels – all included studies were initiated and funded by the same manufacturing company; authors report that none of the included studies attempted to examine the success and integrity of blinding, with concerns expressed about the effectiveness of blinding considering the subjective nature of the outcome measures; funnel plot analysis indicates possibility of publication bias
[4] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with *Pelargonium sidoides*.

Table 29: GRADE profile - *Pelargonium sidoides* (tablet, 10mg) versus placebo in children with acute bronchitis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*Pelargonium sidoides* tablet (10mg)[1]	Placebo	Relative (95% CI)	Absolute (95% CI)		
Failure to resolve all symptoms by day 7												
1[2]	randomised trials	very serious[3]	N/A	no serious indirectness	no serious imprecision	none	91/100 (91.0%)	31/34 (91.2%)	RR 1.00 (0.88 to 1.13)	0 fewer per 1000 (from 109 fewer to 119 more)	⊕⊕OO LOW	CRITICAL
Failure to resolve cough by day 7												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*Pelargonium sidoides* tablet (10mg)[1]	Placebo	Relative (95% CI)	Absolute (95% CI)		
1[2]	randomised trials	very serious[3]	N/A	no serious indirectness	no serious imprecision	none	91/100 (91.0%)	30/34 (88.2%)	RR 1.03 (0.90 to 1.18)	26 more per 1000 (from 88 fewer to 159 more)	⊕⊕OO LOW	CRITICAL
Failure to resolve sputum by day 7												
1[2]	randomised trials	very serious[3]	N/A	no serious indirectness	serious[4]	none	64/100 (64.0%)	21/34 (61.8%)	RR 1.04 (0.77 to 1.40)	25 more per 1000 (from 142 fewer to 247 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI, confidence interval; RR, relative risk; N/A, not applicable												

[1] Given 3 times a day for 7 days
[2] Timmer et al. 2013
[3] Downgraded 2 levels – all included studies were initiated and funded by the same manufacturing company; authors report that none of the included studies attempted to examine the success and integrity of blinding, with concerns expressed about the effectiveness of blinding considering the subjective nature of the outcome measures; funnel plot analysis indicates possibility of publication bias
[4] Downgraded 1 level: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with *Pelargonium sidoides*.

Table 30: GRADE profile - *Pelargonium sidoides* (tablet, 20mg) versus placebo in children with acute bronchitis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*Pelargonium sidoides* tablet (20mg)[1]	Placebo	Relative (95% CI)	Absolute (95% CI)		
Failure to resolve all symptoms by day 7												
1[2]	randomised trials	very serious[3]	N/A	no serious indirectness	no serious imprecision	none	82/99 (82.8%)	30/33 (90.9%)	RR 0.91 (0.79 to 1.05)	82 fewer per 1000 (from 191 fewer to 45 more)	⊕⊕OO LOW	CRITICAL
Failure to resolve cough by day 7												
1[2]	randomised trials	very serious[3]	N/A	no serious indirectness	no serious imprecision	none	81/99 (81.8%)	31/33 (93.9%)	RR 0.87 (0.77 to 0.99)	122 fewer per 1000 (from 9 fewer to 216 fewer)	⊕⊕OO LOW	CRITICAL
Failure to resolve sputum by day 7												
1[2]	randomised trials	very serious[3]	N/A	no serious indirectness	serious[4]	none	49/99 (49.5%)	20/33 (60.6%)	RR 0.82 (0.58 to 1.15)	109 fewer per 1000 (from 255 fewer to 91 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI, confidence interval; RR, relative risk; N/A, not applicable												

[1] Given 3 times a day for 7 days
[2] Timmer et al. 2013
[3] Downgraded 2 levels – all included studies were initiated and funded by the same manufacturing company; authors report that none of the included studies attempted to examine the success and integrity of blinding, with concerns expressed about the effectiveness of blinding considering the subjective nature of the outcome measures; funnel plot analysis indicates possibility of publication bias

[4] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with *Pelargonium sidoides*.

Table 31: **GRADE profile - *Pelargonium sidoides* (tablet, 30mg) versus placebo in children with acute bronchitis**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	*Pelargonium sidoides* tablet (30mg)[1]	Placebo	Relative (95% CI)	Absolute (95% CI)		
Failure to resolve all symptoms by day 7												
1[2]	randomised trials	very serious[3]	N/A	no serious indirectness	no serious imprecision	none	87/99 (87.9%)	31/34 (91.2%)	RR 0.96 (0.85 to 1.10)	36 fewer per 1000 (from 137 fewer to 91 more)	⊕⊕OO LOW	CRITICAL
Failure to resolve cough by day 7												
1[2]	randomised trials	very serious[3]	N/A	no serious indirectness	no serious imprecision	none	87/99 (87.9%)	30/34 (88.2%)	RR 1.00 (0.86 to 1.15)	0 fewer per 1000 (from 124 fewer to 132 more)	⊕⊕OO LOW	CRITICAL
Failure to resolve sputum by day 7												
1[2]	randomised trials	very serious[3]	N/A	no serious indirectness	serious[4]	none	45/99 (45.5%)	21/34 (61.8%)	RR 0.74 (0.52 to 1.04)	161 fewer per 1000 (from 296 fewer to 25 more)	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI, confidence interval; RR, relative risk; N/A, not applicable

[1] Given 3 times a day for 7 days
[2] Timmer et al. 2013
[3] Downgraded 2 levels – all included studies were initiated and funded by the same manufacturing company; authors report that none of the included studies attempted to examine the success and integrity of blinding, with concerns expressed about the effectiveness of blinding considering the subjective nature of the outcome measures; funnel plot analysis indicates possibility of publication bias
[4] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with *Pelargonium sidoides*.

H.3 Oral analgesia

Table 32: GRADE profile – non-steroidal anti-inflammatory drugs versus placebo in adults and children with common cold

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NSAID	Placebo	Relative (95% CI)	Absolute		
Sum of overall symptom score (measured with: total symptom score[1,2]; better indicated by lower values)												
3[3]	randomised trials	serious[4]	serious[5]	serious[6]	no serious imprecision	none	141[7]	152	-	SMD 0.40 lower (1.03 lower to 0.24 higher)	⊕OOO VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NSAID	Placebo	Relative (95% CI)	Absolute		
Moderate to marked severity (assessed with: 2 to 3 points on the symptom severity score [2])												
1[3]	randomised trials	serious[4]	not applicable	serious[6]	very serious[8]	none	3/18 (16.7%)[9]	6/22 (27.3%)	RR 0.61 (0.18 to 2.11)	106 fewer per 1000 (from 224 fewer to 303 more)	⊕OOO VERY LOW	CRITICAL
Duration of illness (measured with: unclear whether hours or days duration[2,10]; better indicated by lower values)												
2[3]	randomised trials	serious[4]	serious[5]	serious[6]	serious[11]	none	102[12]	112	-	MD 0.23 lower (1.75 lower to 1.29 higher)	⊕OOO VERY LOW	CRITICAL
Duration of illness (measured with: days of restricted daily activity[2]; better indicated by lower values)												
1[3]	randomised trials	serious[4]	not applicable	serious[6]	no serious imprecision	none	84[13]	90	-	MD 0.56 lower (1.24 lower to 0.12 higher)	⊕⊕OO LOW	CRITICAL
Throat irritation score (measured with: throat irritation symptom subscale score[1,2]; better indicated by lower values)												
2[3]	randomised trials	serious[4]	no serious inconsistency	serious[6]	no serious imprecision	none	77[14]	82	-	SMD 0.01 lower (0.33 lower to 0.3 higher)	⊕⊕OO LOW	IMPORTANT
Headache score (measured with: headache subscale score[1,2]; better indicated by lower values)												
2[3]	randomised trials	serious[4]	serious[5]	serious[6]	serious[11]	none	77[14]	82	-	SMD 0.65 lower (1.11 to 0.19 lower)	⊕OOO VERY LOW	IMPORTANT
Joint and muscle pain score (measured with: joint and muscle pain subscale score[1,2]; better indicated by lower values)												
2[3]	randomised trials	serious[4]	no serious inconsistency	serious[6]	no serious imprecision	none	55[14]	59	-	SMD 0.40 lower (0.77 to 0.03 lower)	⊕⊕OO LOW	IMPORTANT
Malaise score (measured with: malaise subscale score[1,2]; better indicated by lower values)												
2[3]	randomised trials	serious[4]	no serious inconsistency	serious[6]	no serious imprecision	none	77[14]	82	-	SMD 0.29 lower (0.6 lower to 0.03 higher)	⊕⊕OO LOW	IMPORTANT
Chilliness score (measured with: chilliness subscale score[1,2]; better indicated by lower values)												
2[3]	randomised trials	serious[4]	serious[5]	serious[6]	very serious[15]	none	77[14]	82	-	SMD 0.03 lower (1.12 lower to 1.06 higher)	⊕OOO VERY LOW	IMPORTANT
Nose irritation score (measured with: nose irritation subscale score[1,2]; better indicated by lower values)												
1[3]	randomised trials	serious[4]	not applicable	serious[6]	serious[11]	none	38[16]	42	-	SMD 0.04 lower (0.48 lower to 0.4 higher) NICE analysis MD -0.12 (-1.33 to 1.09)	⊕OOO VERY LOW	IMPORTANT
Pain on swallowing (measured with: pain on slowing subscale score[1,2]; better indicated by lower values)												
1[3]	randomised trials	serious[4]	not applicable	serious[6]	very serious[15]	none	38[16]	42	-	SMD 0.07 lower (0.51 lower to 0.37 higher) NICE analysis MD -0.42	⊕OOO VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NSAID	Placebo	Relative (95% CI)	Absolute		
										(-3.06 to 2.22)		
Eye itching score (measured with: eye itching subscale score[1,2]; better indicated by lower values)												
1[3]	randomised trials	serious[4]	not applicable	serious[6]	serious[11]	none	38[16]	42	-	SMD 0.14 lower (0.58 lower to 0.3 higher) NICE analysis MD -0.28 (-1.16 to 0.60)	⊕OOO VERY LOW	IMPORTANT
Earache score (measured with: earache subscale score[1,2]; better indicated by lower values)												
1[3]	randomised trials	serious[4]	not applicable	serious[6]	serious[11]	none	38[16]	42	-	SMD 0.59 lower (1.04 to 0.14 lower) NICE analysis MD -0.69 (-1.18 to -0.20)	⊕OOO VERY LOW	IMPORTANT
Cough score (measured with: cough subscale score[1,2]; better indicated by lower values)												
2[3]	randomised trials	serious[4]	serious[5]	serious[6]	no serious imprecision	none	77[14]	82	-	SMD 0.05 lower (0.66 lower to 0.56 higher)	⊕OOO VERY LOW	CRITICAL
Sneezing score (measured with: sneezing subscale score[1,2]; better indicated by lower values)												
2[3]	randomised trials	serious[4]	no serious inconsistency	serious[6]	no serious imprecision	none	77[14]	82	-	SMD 0.44 lower (0.75 to 0.12 lower)	⊕⊕OO LOW	IMPORTANT
Sneezing (measured with: total number of sneezes[1,2]; better indicated by lower values)												
1[3]	randomised trials	serious[4]	not applicable	serious[6]	serious[11]	none	38[16]	42	-	SMD 0.51 lower (0.95 to 0.06 lower) NICE analysis MD -8.60 (-15.71 to -1.49)	⊕OOO VERY LOW	IMPORTANT
Rhinorrhoea score (measured with: rhinorrhoea subscale score[1,2]; better indicated by lower values)												
3[3]	randomised trials	serious[4]	no serious inconsistency	serious[6]	no serious imprecision	none	95[17]	104	-	SMD 0.03 higher (0.25 lower to 0.3 higher)	⊕⊕OO LOW	IMPORTANT
Nasal obstruction score (measured with: nasal obstruction subscale score[1,2]; better indicated by lower values)												
3[3]	randomised trials	serious[4]	no serious inconsistency	serious[6]	no serious imprecision	none	95[17]	104	-	SMD 0.15 lower (0.43 lower to 0.13 higher)	⊕⊕OO LOW	IMPORTANT
Nasal obstruction score >5 (assessed with: nasal obstruction subscale score[2])												
1[3]	randomised trials	serious[4]	not applicable	serious[6]	very serious[18]	none	2/13 (15.4%)[20]	0/14 (0%)	RR 5.36 (0.28 to 102.12)	-	⊕OOO VERY LOW	IMPORTANT
Total number of nose blows (measured with: total count[1,2]; better indicated by lower values)												
1[3]	randomised trials	serious[4]	not applicable	serious[6]	very serious[15]	none	38[16]	42	-	SMD 0.17 higher (0.27 lower to 0.61 higher) NICE analysis MD 21.70	⊕OOO VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NSAID	Placebo	Relative (95% CI)	Absolute		
										(-37.67 to 81.07)		
Total mucus weight (measured with: unclear how assessed[1,2]; better indicated by lower values)												
1[3]	randomised trials	serious[4]	not applicable	serious[6]	very serious[15]	none	18[9]	22	-	SMD 0.13 higher (0.49 lower to 0.76 higher) NICE analysis MD 3.00 (-11.56 to 17.56)	⊕OOO VERY LOW	IMPORTANT
Total tissue number count (measured with: total count[1,2]; better indicated by lower values)												
1[3]	randomised trials	serious[4]	not applicable	serious[6]	serious[11]	none	18[9]	22	-	SMD 0.20 lower (0.83 lower to 0.42 higher) NICE analysis MD -10.0 (-40.59 to 20.59)	⊕OOO VERY LOW	IMPORTANT
Dryness in nose score (measured with: nasal dryness subscale score[1,2]; better indicated by lower values)												
1[3]	randomised trials	serious[4]	not applicable	serious[6]	no serious imprecision	none	38[16]	42	-	SMD 0.04 higher (0.4 lower to 0.48 higher) NICE analysis MD 0.09 (-0.91 to 1.09)	⊕⊕OO LOW	IMPORTANT
Reduced sense of smell score (measured with: sense of smell subscale score[1,2]; better indicated by lower values)												
1[3]	randomised trials	serious[4]	not applicable	serious[6]	no serious imprecision	none	38[16]	42	-	SMD 0.08 higher (0.36 lower to 0.51 higher) NICE analysis MD 0.26 (-1.22 to 1.74)	⊕⊕OO LOW	IMPORTANT
Hoarseness score (measured with: hoarseness subscale score[1,2]; better indicated by lower values)												
1[3]	randomised trials	serious[4]	not applicable	serious[6]	serious[11]	none	38[16]	42	-	SMD 0.32 higher (0.12 lower to 0.76 higher) NICE analysis MD 0.94 (-0.35 to 2.23)	⊕OOO VERY LOW	IMPORTANT
Fatigue score (measured with: fatigue subscale score[1,2]; better indicated by lower values)												
1[3]	randomised trials	serious[4]	not applicable	serious[6]	serious[11]	none	38[16]	42	-	SMD 0.18 higher (0.26 lower to 0.62 higher) NICE analysis MD 0.72 (-1.10 to 2.54)	⊕OOO VERY LOW	IMPORTANT
Adverse effects (assessed with: total adverse effects[2])												
2[3]	randomised trials	serious[4]	serious[5]	serious[6]	very serious[18]	none	14/107 (13.1%)[12]	5/113 (4.4%)	RR 2.94 (0.51 to 17.53)	86 more per 1000 (from 22 fewer to 731 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects (assessed with: gastrointestinal adverse effect complaints[2])												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NSAID	Placebo	Relative (95% CI)	Absolute		
3[3]	randomised trials	serious[4]	no serious inconsistency	serious[6]	very serious[8]	none	2/94 (2.1%)[20]	3/95 (3.2%)	RR 0.76 (0.17 to 3.32)	8 fewer per 1000 (from 26 fewer to 73 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects (assessed with: lethargy or drowsiness [2])												
2[3]	randomised trials	serious[4]	no serious inconsistency	serious[6]	very serious[8]	none	1/55 (1.8%)[21]	1/55 (1.8%)	RR 1.00 (0.14 to 6.91)	0 fewer per 1000 (from 16 fewer to 107 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects (assessed with: Feeling hyperactive; unclear how assessed[2])												
1[3]	randomised trials	serious[4]	not applicable	serious[6]	very serious[18]	none	1/23 (4.3%)[9]	0/23 (0%)	RR 3.00 (0.13 to 70.02)	-	⊕OOO VERY LOW	CRITICAL
Adverse effects (assessed with: feeling more awake; unclear how assessed[2])												
1[3]	randomised trials	serious[4]	not applicable	serious[6]	very serious[18]	none	1/23 (4.3%)[9]	0/23 (0%)	RR 3.00 (0.13 to 70.02)	-	⊕OOO VERY LOW	CRITICAL
Adverse effects (assessed with: flushed face[2])												
1[3]	randomised trials	serious[4]	not applicable	serious[6]	very serious[18]	none	1/23 (4.3%)[9]	0/23 (0%)	RR 3.00 (0.13 to 70.02)	-	⊕OOO VERY LOW	CRITICAL
Adverse effects (assessed with: difficulty sleeping[2])												
1[3]	randomised trials	serious[4]	not applicable	serious[6]	very serious[8]	none	0/23 (0%)[9]	1/23 (4.3%)	RR 0.33 (0.01 to 7.78)	29 fewer per 1000 (from 43 fewer to 295 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects (assessed with: light-headedness[2])												
1[3]	randomised trials	serious[4]	not applicable	serious[6]	very serious[8]	none	2/23 (8.7%)[9]	2/23 (8.7%)	RR 1.00 (0.15 to 6.51)	0 fewer per 1000 (from 74 fewer to 479 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects (assessed with: dry mouth[2])												
1[3]	randomised trials	serious[4]	not applicable	serious[6]	very serious[18]	none	1/23 (4.3%)[9]	0/23 (0%)	RR 3.00 (0.13 to 70.02)	-	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI, confidence interval; SMD, standardised mean difference; RR, relative risk; RCT, randomised controlled trial; MD, mean difference; NSAID, non-steroidal anti-inflammatory drug

[1] The analysis uses standardised mean difference as the symptom scores used varied by study
[2] Follow-up point was cumulative in all studies except for 1 RCT which was at 6 days (and cumulative)
[3] Kim et al. 2015
[4] Downgraded 1 level - no RCT was assessed by the Cochrane authors as at low risk of bias
[5] Downgraded 1 level - I^2>50%
[6] Downgraded 1 level - common cold population rather than a direct cough population
[7] NSAIDs varied by study (loxoprofen 60 mg twice daily for 7 days, ibuprofen 200 mg 4 times daily for 5 days, naproxen 3.0 g to 5.0 g for 5 days)

[8] Downgraded 2 levels: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with NSAID, and no meaningful difference or appreciable harm with placebo
[9] Ibuprofen 200 mg 4 times daily for 5 days
[10] The included studies measured duration of illness (days in 1 RCT not reported in the other)
[11] Downgraded 1 level - at a default minimal important difference of 0.5 standard deviation of placebo arm data are consistent with no meaningful difference or appreciable benefit with NSAIDs
[12] NSAIDs varied by study (loxoprofen 60 mg twice daily for 7 days, ibuprofen 200 mg 4 times daily for 5 days)
[13] Loxoprofen 60 mg twice daily for 7 days
[14] NSAIDs varied by study (naproxen 3.0 g to 5.0 g for 5 days, ibuprofen 400 mg 3 times daily for 3 days)
[15] Downgraded 2 levels - at a default minimal important difference of 0.5 SD of placebo arm, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[16] Ibuprofen 400 mg 3 times daily for 3 days

[17] NSAIDs varied by study (loxoprofen 60 mg twice daily for 7 days, ibuprofen 400 mg 3 times daily for 3 days, naproxen 3.0 g to 5.0 g for 5 days)
[18] Downgraded 2 levels: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with NSAID, and no meaningful difference or appreciable benefit with placebo
[19] Ibuprofen 1.2 g daily for 7 days (plus aspirin 4 g daily)
[2] NSAIDs varied by study (naproxen 3.0 g to 5.0 g for 5 days, fenoprofen 200 mg single dose, ibuprofen 200 mg 4 times daily for 5 days)
[2] NSAIDs varied by study (fenoprofen 200 mg single dose, ibuprofen 200 mg 4 times daily for 5 days)

Table 33: **GRADE profile – other non-steroidal anti-inflammatory drugs versus Ibuprofen for adults with common cold**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NSAIDs	Ibuprofen	Relative (95% CI)	Absolute		
Global improvement rating (assessed with: marked improvement[1])												
2[2]	randomised trials	serious[3]	no serious inconsistency	serious[4]	serious[5]	none	40/178 (22.5%)[6]	28/187 (15%)[7]	RR 1.52 (0.99 to 2.34)	78 more per 1000 (from 1 fewer to 201 more)	⊕OOO VERY LOW	CRITICAL
Global improvement rating (assessed with: moderate to marked improvement[1])												
2[2]	randomised trials	serious[3]	no serious inconsistency	serious[4]	serious[5]	none	121/178 (68%)[6]	106/187 (56.7%)[7]	RR 1.20 (1.02 to 1.41)	113 more per 1000 (from 11 more to 232 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: NSAID, non-steroidal anti-inflammatory drug; CI, confidence interval; RCT, randomised controlled trial; RR, relative risk												

[1] Follow-up in studies was cumulative
[2] Kim et al. 2015
[3] Downgraded 1 level - no RCT was assessed by the Cochrane authors as at low risk of bias
[4] Downgraded 1 level - common cold population rather than a direct cough population
[5] Downgraded 1 level: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable benefit with NSAIDs
[6] 1 RCT was loxoprofen 180 mg/day, 2nd RCT fentiazac 300 mg/day
[7] Ibuprofen 600 mg for 3 days

H.4 Expectorants

Table 34: **GRADE profile – guaifenesin versus placebo for adults and young people with acute cough**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Guaifenesin	Placebo	Relative (95% CI)	Absolute		
Cough frequency (not defined) at 36 hours												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	65		There was no significant difference in cough frequency with guaifenesin5 compared with placebo (p=0.5)[4]		⊕⊕OO LOW	CRITICAL
Cough frequency and intensity (not defined) at 3 days												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	239		Guaifenesin[6] reduced cough frequency and intensity (75% of participants taking guaifenesin stated that the medicine was helpful compared with 31% in the control group, p< 0.01)[5]		⊕⊕OO LOW	CRITICAL
Cough severity (not defined) at 36 hours												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	65		There was no significant difference in cough severity with guaifenesin[4] compared with placebo (p=0.2)[5]		⊕⊕OO LOW	CRITICAL
Cough severity (not defined) at 4 and 7 days												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	378		There was no difference in total spontaneous symptom severity scores at 7 days but there was a significant reduction at day 4 in mean score from baseline with extended release guaifenesin[7] (mean score reduction from baseline of 7.1 with guaifenesin compared with 5.7 with placebo, p=0.04p=0.04)[5]		⊕⊕OO LOW	CRITICAL
Sputum thickness (follow-up 36 hours)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	65		Guaifenesin[4] significantly reduced sputum thickness at (96% of participants compared with 54%; p=0.001)[5]		⊕⊕OO LOW	CRITICAL
Adverse events (follow-up 3-7 days)												
2[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[3]	none	617		There was no significant difference between guaifenesin and placebo; p values not reported.		⊕OOO VERY LOW	CRITICAL

Abbreviations: p, p value; RCT, randomised controlled trial

[1] Smith et al. 2014
[2] Downgraded 1 level - unclear risk of bias for random sequence generation, allocation concealment, selective reporting. No power calculation
[3] Downgraded 1 level - not assessable
[4] Guaifenesin 480 mg/30 ml every 6 hours for 30 hours
[5] NICE analysis couldn't be performed as absolute figures were not reported
[6] Guaifenesin 200 mg/10 ml 4 times daily for 3 days
[7] Guaifenesin (extended-release) 1200 mg twice daily for 7 days

H.5 Antitussives

Table 35: GRADE profile – codeine versus placebo for adults with acute cough

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Codeine	Placebo	Relative (95% CI)	Absolute		
Reduction of cough symptoms over 5 days												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	81		There was no significant difference in reducing cough symptoms with codeine[4] compared with placebo (p=0.23).		⊕⊕OO LOW	CRITICAL
Reduction of cough symptoms at 90 minutes												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	82		There was no significant difference in reducing cough symptoms with codeine[5] compared with placebo (p=0.8).		⊕⊕OO LOW	CRITICAL

Abbreviations: p, p value; RCT, randomised controlled trial

[1] Smith et al. 2014
[2] Downgraded 1 level - unclear risk of bias unclear risk of bias for random sequence generation, allocation concealment, selective reporting. No power calculation
[3] Downgraded 1 level - not assessable
[4] Codeine linctus 30 mg/10 ml 4 times daily for 4 days
[5] Codeine phosphate 50 mg as a single dose

Table 36: GRADE profile – codeine versus placebo for children with acute cough

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Codeine[1]	Placebo	Relative (95% CI)	Absolute		
Reduction of cough score (4 item symptom score)[2]												
1[3]	randomised trials	serious[4]	not applicable	no serious indirectness	serious[5]	none	17	13	There was no significant difference in cough score at follow-up with codeine (cough score reduction 2.2)[6] compared with placebo (cough score reduction 2.2[6] p=not stated).		⊕⊕OO LOW	CRITICAL
Adverse effects (mainly drowsiness, diarrhoea and hyperactivity)[2]												
1[3]	randomised trials	serious[4]	not applicable	no serious indirectness	very serious[7]	none	5/17 (29%)	7/13 (54%)	There was no significant difference in adverse effects with codeine compared with placebo (p=0.8). NICE analysis RR 0.55 (0.22 to 1.33)	-	⊕OOO VERY LOW	CRITICAL

Abbreviations: p, p value; RR, Relative risk; RCT, randomised controlled trial

[1] Codeine 10 mg in 5 ml as a single dose at bedtime for 3 nights
[2] Follow-up period not defined

[3] Smith et al. 2014
[4] Downgraded 1 level - unclear risk of bias unclear risk of bias for random sequence generation, allocation concealment, selective reporting. No power calculation
[5] Downgraded 1 level - not assessable
[6] Unclear if this is a mean or median cough score reduction (not reported)
[7] Downgraded 2 levels: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with codeine, and no meaningful difference or appreciable harm with placebo

Table 37: GRADE profile – dextromethorphan versus placebo for adults with acute cough

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dextromethorphan	Placebo	Relative (95% CI)	Absolute		
Cough frequency (not defined) at 180 minutes												
2[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[3]	none	495 adults		1 RCT (n=44) found no significant difference in decline in cough frequency with dextromethorphan[4] compared with placebo (p=0.38). 1 RCT (n=451) found that dextromethorphan[4] reduced cough counts (mean changes of cough counts between active treatment and placebo varied from 19% to 36%, p< 0.05)		⊕OOO VERY LOW	CRITICAL
Cough severity (not defined) at 180 minutes												
3[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[3]	none	1205 adults		1 RCT (n=451) found that dextromethorphan[4] reduced cough severity measured by subjective visual analogue scales; p value not reported. 1 RCT (n=44) found no significant difference in improving cough severity with dextromethorphan[4] compared with placebo (mean difference in decline in cough scores 0.5, p=0.08). 1 RCT (n=710) found that dextromethorphan[4] reduced cough severity (average treatment difference 12% to 17% in favour of dextromethorphan), measured by 3-hour continuous cough recording of cough bouts (p=0.004), cough components (p=0.003), cough effort (p=0.001), cough intensity and cough latency (p=0.002)		⊕OOO VERY LOW	CRITICAL
Abbreviations: p, p value; RCT, randomised controlled trial												

[1] Smith et al. 2014
[2] Downgraded 1 level - unclear risk of bias for random sequence generation, allocation concealment, selective reporting. No power calculation
[3] Downgraded 1 level - not assessable
[4] Dextromethorphan 30 mg as a single dose

Table 38: GRADE profile – dextromethorphan versus placebo, no treatment or other treatment for children with acute cough

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dextromethorphan	Placebo or no/other treatment	Relative (95% CI)	Absolute		
Composite symptom score (Daily symptom score recorded by parents including cough frequency and severity on a scale from 0 to 3) at 3 days												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	50		There was no significant difference in composite symptom score with dextromethorphan[4] compared with placebo (mean difference in cough symptom scores on day 3 of 0.04; p value not reported)		⊕⊕OO LOW	CRITICAL
Composite symptom score at 1-3 days												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	57		There was no significant difference in composite symptom score with dextromethorphan[5] compared with placebo or codeine (p=0.41)		⊕⊕OO LOW	CRITICAL
Composite symptom score at 12 hours												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	100		There was no significant difference in composite symptom score with dextromethorphan[6] compared with placebo or antihistamine (mean difference 0.79; p value not reported)		⊕⊕OO LOW	CRITICAL
Composite symptom score at 3 days												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	80		There was no significant difference in composite symptom score with dextromethorphan[7] compared with placebo; p values not reported.		⊕⊕OO LOW	CRITICAL
Cough frequency (not defined) at 1 day												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	100		There was no significant difference in cough frequency with dextromethorphan[6] compared with placebo; p value not reported		⊕⊕OO LOW	CRITICAL
Child and parental sleep disturbance at 1 day												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	100		There was no significant difference in child or parental sleep with dextromethorphan[6] compared with placebo; p value not reported		⊕⊕OO LOW	CRITICAL
Adverse effects at 3 days												
3[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[3]	none	227		There was no difference with dextromethorphan compared with placebo; p=0.8 in 1 RCT; p values not reported in 2 RCTs.		⊕OOO VERY LOW	CRITICAL
Adverse effects (mainly drowsiness, diarrhoea and hyperactivity)[8]												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dextromethorphan	Placebo or no/other treatment	Relative (95% CI)	Absolute		
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[9]	none	6/19 (32%)	7/13 (54%)	There was no significant difference in adverse effects with dextromethorphan[5] compared with placebo (p=0.2). NICE analysis RR 0.88 (0.44 to 1.76)		⊕OOO VERY LOW	CRITICAL
Adverse effects (mainly gastrointestinal and dizziness)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	34%	5%	Difference between dextromethorphan[7] and placebo but no analysis or data reported (p value not reported)		⊕⊕OO LOW	CRITICAL

Abbreviations: p, p value; RCT, randomised controlled trial

[1] Smith et al. 2014
[2] Downgraded 1 level - unclear risk of bias
[3] Downgraded 1 level - not assessable
[4] Dextromethorphan 1.5 mg per ml 5 ml 3 times daily for children under 7 years and 10 ml 3 times daily for older children
[5] Dextromethorphan 15 mg/5 ml and codeine 10 mg/ 5 mg as a single dose at bedtime for 3 nights
[6] Dextromethorphan as single dose based on age (not further defined)
[7] Dextromethorphan 5 mg 6- to 8-hourly
[8] Follow-up period not defined
[9] Downgraded 2 levels: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit/harm with dextromethorphan, and no meaningful difference or appreciable harm with placebo, no or other treatment

Table 39: GRADE profile – dextromethorphan plus salbutamol versus dextromethorphan or placebo for adults with acute cough

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dextromethorphan plus salbutamol	Dextromethorphan alone or placebo	Relative (95% CI)	Absolute		
Cough frequency (not defined) during daytime at 4 days												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	108		There was no significant difference in reducing daytime cough frequency with dextromethorphan plus salbutamol[4] compared with placebo or dextromethorphan alone; p value not reported.		⊕⊕OO LOW	CRITICAL
Cough severity (not defined) during daytime at 4 days												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	108		There was no significant difference in reducing daytime cough severity with dextromethorphan plus salbutamol[4] compared with placebo or		⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Dextromethorphan plus salbutamol	Dextromethorphan alone or placebo	Relative (95% CI)	Absolute		
									dextromethorphan alone; p value not reported.			
Cough severity (not defined) at night at 4 days												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	108		Dextromethorphan plus salbutamol[4] significantly relieved cough at night when compared with placebo or dextromethorphan alone (mean symptom score 0.19 versus 0.67 and 0.44, respectively, p<0.01).		⊕⊕OO LOW	CRITICAL
Adverse effects at 4 days												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	108		Dextromethorphan plus salbutamol[4] led to more tremor than placebo (p<0.05), and no serious adverse effects were reported.		⊕⊕OO LOW	CRITICAL
Abbreviations: p, p value; RCT, randomised controlled trial												

[1] Smith et al. 2014
[2] Downgraded 1 level - unclear risk of bias for random sequence generation, allocation concealment, incomplete outcome data, selective reporting
[3] Downgraded 1 level - not assessable
[4] Dextromethorphan (30 mg) in combination with salbutamol (2 mg) 3 times daily for 4 days

H.6 Antihistamines and decongestants

Table 40: GRADE profile – loratadine plus pseudoephedrine versus placebo for adults with acute cough

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Loratadine plus pseudoephedrine	Placebo	Relative (95% CI)	Absolute		
Composite symptom score at 5 days												
1[1]	randomised trials	serious[2]	not applicable	serious[3]	serious[4]	none	142[5]	141	There was no significant difference in composite symptoms score with loratadine plus pseudoephedrine[6] compared with placebo; p value not reported.		⊕OOO VERY LOW	CRITICAL
Adverse effects at 5 days												
1[1]	randomised trials	serious[2]	not applicable	serious[3]	serious[6]	none	43/142 (30%)	30/141 (21%)	There was no significant difference with loratadine plus pseudoephedrine[6] compared with placebo; p values not reported.			CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Loratadine plus pseudoephedrine	Placebo	Relative (95% CI)	Absolute		
									NICE analysis: RR 1.42 (0.95 to 2.13)		⊕OOO VERY LOW	
Abbreviations: p, p value; RCT, randomised controlled trial												

[1] Smith et al. 2014
[2] Downgraded 1 level - unclear risk of bias
[3] Downgraded 1 level - common cold population not specific to acute cough
[4] Downgraded 1 level - not assessable
[5] loratadine 5 mg and pseudoephedrine 120 mg combination twice daily for 5 days
[6] Downgraded 1 level: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with loratadine plus pseudoephedrine

Table 41: GRADE profile – clemastine or chlorpheniramine versus placebo for children with acute cough

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clemastine or Chlorpheniramine	Placebo	Relative (95% CI)	Absolute		
Composite symptom score at 3 days												
1[1]	randomised trials	serious[2]	not applicable	serious[3]	serious[4]	none	143		There was no significant difference in cough scores with clemastine or chlorpheniramine[5] (improved by 39.6%) and placebo (improved by 27.6%; p=0.2).		⊕OOO VERY LOW	CRITICAL
Adverse effects at 3 days (drowsiness or sleepiness)												
1[1]	randomised trials	serious[2]	not applicable	serious[3]	serious[4]	none	143		There was no significant difference between clemastine or chlorpheniramine[5] and placebo groups; 20% of all children in both groups, p values not reported.		⊕OOO VERY LOW	CRITICAL
Abbreviations: p, p value; RCT, randomised controlled trial												

[1] Smith et al. 2014
[2] Downgraded 1 level - unclear risk of bias
[3] Downgraded 1 level - population with common cold not specific to acute cough
[4] Downgraded 1 level - not assessable
[5] Clemastine fumarate (0.05 mg/kg/d twice daily) and chlorpheniramine maleate syrup (0.35 mg/kg/d 3 times daily) for 3 days

Table 42: GRADE profile – diphenhydramine versus placebo for children acute cough in children

Quality assessment	No of patients	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Diphenhydramine	Placebo	Relative (95% CI)	Absolute		
Cough frequency (not defined) at 1-2 days												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	100		There was no significant difference in reducing cough frequency with diphenhydramine compared with placebo; p values not reported.		⊕⊕OO LOW	CRITICAL
Composite symptom score at 1-2 days												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	100		There was no significant difference in composite symptom scores with diphenhydramine compared with placebo; p values not reported.		⊕⊕OO LOW	CRITICAL
Sleep disturbance in children and their parents at 1-2 days												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	100		There was no significant difference in composite symptom scores with diphenhydramine compared with placebo; p values not reported.		⊕⊕OO LOW	CRITICAL
Adverse effects at 1-2 days												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	100		There was no significant difference with diphenhydramine compared with placebo; p values not reported.		⊕⊕OO LOW	CRITICAL

Abbreviations: p, p value; RCT, randomised controlled trial

[1] Smith et al. 2014
[2] Downgraded 1 level - unclear risk of bias
[3] Downgraded 1 level - not assessable
[4] Diphenhydramine as single dose 1.25 mg/kg

Table 43: GRADE profile – promethazine versus placebo or dextromethorphan for children with acute cough

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Promethazine	Placebo or dextromethorphan	Relative (95% CI)	Absolute	Quality	Importance
Composite symptom score at 3 days												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	120		There was no significant difference in composite symptom score with promethazine compared with placebo or dextromethorphan; p values not reported.		⊕⊕OO LOW	CRITICAL
Adverse effects at 3 days[4]												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	120		There was no significant difference between promethazine compared with dextromethorphan or placebo; p values not reported.		⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Promethazine	Placebo or dextromethorphan	Relative (95% CI)	Absolute		
Abbreviations: p, p value; RCT, randomised controlled trial												

[1] Smith et al. 2014
[2] Downgraded 1 level - unclear risk of bias
[3] Downgraded 1 level - not assessable
[4] Adverse events were reported in 34% of participants taking dextromethorphan, 32% taking promethazine and 5% taking placebo. These included drowsiness, irritability, abdominal pain and nausea
[5] promethazine 0.5 mg/kg 8-hourly for 3 days

H.7 Mucolytics

Table 44: GRADE profile – acetylcysteine or carbocisteine versus placebo for children with upper or lower respiratory infection

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acetylcysteine or carbocysteine	Placebo	Relative (95% CI)	Absolute		
Febrile state after 6 days in children												
3[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	very serious[4]	none	0/74 (0%)[5]	4/65 (6.2%)	RR 0.20 (0.02 to 1.62)[6]	49 fewer per 1000 (from 60 fewer to 38 more)	⊕OOO VERY LOW	CRITICAL
Cough after 6 to 7 days in children												
3[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	serious[7]	none	3/74 (4.1%)[5]	9/65 (13.8%)	RR 0.29 (0.09 to 0.94)[6]	98 fewer per 1000 (from 8 fewer to 126 fewer)	⊕OOO VERY LOW	CRITICAL
Cough at end of treatment in children (assessed at 28 days)												
1[1]	randomised trials	serious[2]	not applicable	serious[3]	very serious[4]	none	3/50 (6%)[8]	4/50 (8%)	RR 0.67 (0.16 to 2.76)[6]	26 fewer per 1000 (from 67 fewer to 141 more)	⊕OOO VERY LOW	CRITICAL
Dyspnoea after 6 to 7 days in children												
4[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	very serious[4]	none	6/123 (4.9%)[5]	9/122 (7.4%)	RR 0.64 (0.26 to 1.57)[6]	27 fewer per 1000 (from 55 fewer to 42 more)	⊕OOO VERY LOW	CRITICAL
Thoracic semeiologic alterations after 5 days in children (assessed with: for example wheezing or rattling)												
2[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	very serious[4]	none	0/55 (0%)[8]	3/54 (5.6%)	RR 0.14 (0.01 to 2.63)[6]	48 fewer per 1000 (from 55 fewer to 91 more)	⊕OOO VERY LOW	CRITICAL
Thoracic semeiologic alterations at the end of treatment in children (assessed with: for example wheezing or rattling at 28 days)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Acetylcysteine or carbocysteine	Placebo	Relative (95% CI)	Absolute		
2[1]	randomised trials	serious[2]	no serious inconsistency	serious[3]	serious[7]	none	1/50 (2%)	8/50 (16%)	RR 0.17 (0.03 to 0.99)	133 fewer per 1000 (from 2 fewer to 155 fewer)	⊕OOO VERY LOW	CRITICAL
Bad general condition after 6 to 7 days in children (assessed with: not defined)												
2[1]	randomised trials	serious[2]	serious[9]	serious[3]	very serious[4]	none	24/93 (25.8%)[10]	32/89 (36%)	RR 0.78 (0.31 to 1.95)	79 fewer per 1000 (from 248 fewer to 342 more)	⊕OOO VERY LOW	CRITICAL
Productive cough at end of treatment in children												
1[1]	randomised trials	serious[2]	not applicable	serious[3]	very serious[4]	none	3/50 (6%)[8]	7/50 (14%)	RR 0.41 (0.11 to 1.56)	83 fewer per 1000 (from 125 fewer to 78 more)	⊕OOO VERY LOW	CRITICAL
Appetite trouble at the end of treatment in children (assessed with: at 5 to 9 days)												
1[1]	randomised trials	serious[2]	not applicable	serious[3]	very serious[7]	none	0/19 (0%)	1/11 (9.1%)	RR 0.20 (0.01 to 4.53)	73 fewer per 1000 (from 90 fewer to 321 more)	⊕OOO VERY LOW	CRITICAL
Expectoration at end of treatment in children (assessed with: at 7 days)												
1[1]	randomised trials	serious[2]	not applicable	serious[3]	serious[7]	none	9/49 (18.4%)	19/57 (33.3%)	RR 0.55 (0.27 to 1.1)	150 fewer per 1000 (from 243 fewer to 33 more)	⊕OOO VERY LOW	CRITICAL
Pulmonary function after day 3 (assessed with: pulmonary function test alteration)												
1[1]	randomised trials	serious[2]	not applicable	serious[3]	very serious[4]	none	25/49 (51%)	26/57 (45.6%)	RR 1.12 (0.75 to 1.66)	55 more per 1000 (from 114 fewer to 301 more)	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI, confidence interval; RR, relative risk; RCT, randomised controlled trial; FEM, fixed effect model; REM, random effect model

[1] Chalumeau and Duijvestjin 2013
[2] Downgraded 1 level - no RCT was assessed by the Cochrane authors as at low risk of bias
[3] Downgraded 1 level - all of the included studies allowed concomitant use of other interventions (mostly antibiotics, but also bronchodilators and antihistamines in 1 RCT), the population was heterogeneous but was in 5 of the 6 included studies acute bronchitis or lower acute respiratory infection, 1 study was bronchial asthma and acute bronchitis population
[4] Downgraded 2 levels: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with acetylcysteine or carbocysteine, and no meaningful difference or appreciable harm with placebo
[5] Intervention varied between studies (oral acetylcysteine, oral carbocisteine)
[6] NICE analysis using FEM (I^2=0.0%)
[7] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit/harm with acetylcysteine or carbocysteine
[8] Oral acetylcysteine
[9] Downgraded 1 level - I^2>50% (REM model used in NICE analysis)
[10] Oral carbocisteine

H.8 Bronchodilators

Table 45: GRADE profile – beta-2 agonists versus placebo or other treatment for adults with acute cough or acute bronchitis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Beta-2 agonists	Placebo or other treatment	Relative (95% CI)	Absolute		
Cough after 7 days												
3[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[4]	none	70/110 (63.6%)[5]	78/110 (70.9%)	RR 0.86 (0.63 to 1.18)	99 fewer per 1000 (from 262 fewer to 128 more)	⊕OOO VERY LOW	CRITICAL
Productive cough after 7 days												
2[1]	randomised trials	serious[2]	serious[3]	serious[6]	very serious[7]	none	23/60 (38.3%)[8]	31/59 (52.5%)	RR 0.76 (0.32 to 1.84)	126 fewer per 1000 (from 357 fewer to 441 more)	⊕OOO VERY LOW	CRITICAL
Night cough after 7 days												
3[1]	randomised trials	serious[2]	no serious inconsistency	serious[6]	very serious[7]	none	25/103 (24.3%)[9]	31/107 (29%)	RR 0.84 (0.54 to 1.33)	46 fewer per 1000 (from 133 fewer to 96 more)	⊕OOO VERY LOW	CRITICAL
Mean cough score after 1 day (better indicated by lower values)												
3[1]	randomised trials	serious[2]	serious[3]	serious[6]	very serious[10]	none	126[11]	124	-	SMD 0.08 lower (0.47 lower to 0.32 higher)	⊕OOO VERY LOW	CRITICAL
Mean cough score after 2 days (better indicated by lower values)												
3[1]	randomised trials	serious[2]	no serious inconsistency	serious[6]	serious[12]	none	126[11]	125	-	SMD 0.10 lower (0.35 lower to 0.15 higher)	⊕OOO VERY LOW	CRITICAL
Mean cough score after 3 day (better indicated by lower values)												
3[1]	randomised trials	serious[2]	no serious inconsistency	serious[6]	serious[12]	none	126[11]	125	-	SMD 0.17 lower (0.42 lower to 0.08 higher)	⊕OOO VERY LOW	CRITICAL
Mean cough score after 4 days (better indicated by lower values)												
3[1]	randomised trials	serious[2]	no serious inconsistency	serious[6]	serious[12]	none	126[11]	125	-	SMD 0.14 lower (0.38 lower to 0.11 higher)	⊕OOO VERY LOW	CRITICAL
Mean cough score after 5 days (better indicated by lower values)												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[12]	none	87[13]	89	-	SMD 0.23 lower (0.52 lower to 0.07 higher)	⊕⊕OO LOW	CRITICAL
Mean cough score after 6 days (better indicated by lower values)												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	87[13]	88	-	SMD 0.20 lower (0.49 lower to 0.1 higher)	⊕⊕⊕O MODERATE	CRITICAL
Mean cough score after 7 days (better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Beta-2 agonists	Placebo or other treatment	Relative (95% CI)	Absolute		
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	no serious imprecision	none	50[14]	51	-	SMD 0.11 higher (0.28 lower to 0.5 higher) NICE analysis MD 0.08 (-0.21 to 0.37)	⊕⊕⊕O MODERATE	CRITICAL
Not working by day 7 (assessed with: adult participants working or not after 7 days)												
2[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	very serious[7]	none	22/76 (28.9%)[14]	23/73 (31.5%)	RR 0.82 (0.28 to 2.34)	57 fewer per 1000 (from 227 fewer to 422 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects (assessed with: shaking, tremor or nervousness)												
3[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[4]	none	58/105 (55.2%)[13]	12/106 (11.3%)	RR 7.94 (1.17 to 53.94)	786 more per 1000 (from 19 more to 1000 more)	⊕OOO VERY LOW	CRITICAL
Other adverse effects (assessed with: other adverse effects not described)												
2[1]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[7]	none	12/74 (16.2%)[14]	15/76 (19.7%)	RR 0.83 (0.42 to 1.63)	34 fewer per 1000 (from 114 fewer to 124 more)	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI, confidence interval; RR, relative risk; SMD, standardised mean difference; RCT, randomised controlled trial

[1] Becker et al. 2015
[2] Downgraded 1 level - no RCT was assessed by the Cochrane authors as being at low risk of bias
[3] Downgraded 1 level - I^2>50%
[4] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with beta-2 agonists
[5] Intervention varied between studies (inhaled albuterol, oral albuterol and inhaled fenoterol)
[6] Downgraded 1 level - 1 RCT used combination including dextromethorphan which is an antitussive
[7] Downgraded 2 levels: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with beta-2 agonists, and no meaningful difference or appreciable harm with placebo or other treatment
[8] Intervention varied by study (inhaled albuterol, salbutamol oral with dextromethorphan)
[9] Intervention varied by study (inhaled albuterol, oral albuterol, oral salbutamol with dextromethorphan)
[10] Downgraded 2 levels - at a default minimal important difference of 0.5 of the standard deviation of the placebo arm, data suggest no meaningful difference, appreciable harm or appreciable benefit
[11] Intervention varied by study (oral albuterol, inhaled fenoterol, oral salbutamol with dextromethorphan)
[12] Downgraded 1 level - at a default minimal important difference of 0.5 of the standard deviation of the placebo arm, data are consistent with no meaningful difference or appreciable harm with beta 2 agonist
[13] Intervention varied between studies (oral albuterol, inhaled fenoterol)
[14] Oral albuterol (salbutamol)

Table 46: GRADE profile – beta-2 agonists versus placebo or other treatment for children with acute cough or acute bronchitis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Beta-2 agonists	Placebo or other treatment	Relative (95% CI)	Absolute		
Cough after 7 days												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[3]	none	11/30 (36.7%)[4]	12/29 (41.4%)	RR 0.89 (0.47 to 1.68)	46 fewer per 1000 (from 219 fewer to 281 more)	⊕OOO VERY LOW	CRITICAL
Mean cough score after 1 day (better indicated by lower values)												
2[1]	randomised trials	serious[2]	no serious inconsistency	serious[5]	no serious imprecision	none	49[6]	47	-	SMD 0.35 higher (0.05 lower to 0.76 higher)	⊕⊕OO LOW	CRITICAL
Mean cough score after 2 days (better indicated by lower values)												
2[1]	randomised trials	serious[2]	no serious inconsistency	serious[5]	no serious imprecision	none	49[6]	47	-	SMD 0.19 higher (0.21 lower to 0.59 higher)	⊕⊕OO LOW	CRITICAL
Mean cough score after 3 days (better indicated by lower values)												
2[1]	randomised trials	serious[2]	no serious inconsistency	serious[5]	no serious imprecision	none	48[6]	47	-	SMD 0.36 higher (0.05 lower to 0.77 higher)	⊕⊕OO LOW	CRITICAL
Mean cough score after 4 days (better indicated by lower values)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[7]	none	23[4]	23	-	SMD 0.22 higher (0.36 lower to 0.8 higher) NICE analysis MD 1.0 (-1.59 to 3.59)	⊕⊕OO LOW	CRITICAL
Mean cough score after 5 days (better indicated by lower values)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[7]	none	23[4]	23	-	SMD 0.42 higher (0.17 lower to 1 higher) NICE analysis MD 1.7 (-0.61 to 4.01)	⊕⊕OO LOW	CRITICAL
Mean cough score after 6 days (better indicated by lower values)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[7]	none	23[4]	23	-	SMD 0.46 higher (0.13 lower to 1.04 higher) NICE analysis MD 2.20 (-0.53 to 4.93)	⊕⊕OO LOW	CRITICAL
Mean cough score after 7 days (better indicated by lower values)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[8]	none	23[4]	23	-	SMD 0.0 higher (0.58 lower to 0.58 higher) NICE analysis MD 0.00 (-1.14 to 1.14)	⊕OOO VERY LOW	CRITICAL
Adverse effects (assessed with: shaking or tremor)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Beta-2 agonists	Placebo or other treatment	Relative (95% CI)	Absolute		
2[1]	randomised trials	serious[2]	no serious inconsistency	serious[5]	very serious[9]	none	6/55 (10.9%)[6]	0/53 (0%)	RR 6.76 (0.86 to 53.18)	-	⊕OOO VERY LOW	CRITICAL
Other adverse effects (assessed with: other adverse effects not described)												
2[1]	randomised trials	serious[2]	serious[10]	no serious indirectness	serious[3]	none	21/55 (38.2%)	20/53 (37.7%)	RR 1.00 (0.41 to 2.41)	0 fewer per 1000 (from 223 fewer to 532 more)	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI, confidence interval; RR, relative risk; SMD, standardised mean difference; RCT, randomised controlled trial

[1] Becker et al. 2015
[2] Downgraded 1 level - no RCT was assessed by the Cochrane authors as being at low risk of bias
[3] Downgraded 2 levels - at a default 25% minimal important difference, data are consistent with no meaningful difference, appreciable harm or appreciable benefit
[4] Oral albuterol (salbutamol)
[5] Downgraded 1 level - 1 RCT used combination including dextromethorphan which is an antitussive
[6] Intervention varied between studies (oral albuterol; dextromethorphan and salbutamol)
[7] Downgraded 1 level - at a default minimal important difference of 0.5 of the standard deviation of the placebo arm, data are consistent with no meaningful difference or appreciable harm with beta-2 agonist
[8] Downgraded 2 levels – at a default minimal important difference of 0.5 of the standard deviation of the placebo arm, data are consistent with no meaningful difference, appreciable harm or appreciable benefit, very wide 95% confidence interval
[9] Downgraded 2 levels: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with beta-2 agonists, and no meaningful difference or appreciable benefit/harm with placebo or other treatment
[10] Downgraded 1 level - I^2>50%

Table 47: GRADE profile – beta-2 agonists versus erythromycin for adults with acute cough or acute bronchitis

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Beta-2 agonists	Erythromycin	Relative (95% CI)	Absolute		
Cough after 7 days in adults												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	7/17 (41.2%)[4]	15/17 (88.2%)	RR 0.47 (0.26 to 0.85)	468 fewer per 1000 (from 132 fewer to 653 fewer)	⊕⊕OO LOW	CRITICAL
Productive cough after 7 days in adults												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	5/14 (35.7%)[4]	13/17 (76.5%)	RR 0.47 (0.22 to 0.99)	405 fewer per 1000 (from 8 fewer to 596 fewer)	⊕⊕OO LOW	CRITICAL
Night cough after 7 days in adults												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[5]	none	5/10 (50%)[4]	7/12 (58.3%)	RR 0.86 (0.39 to 1.88)	82 fewer per 1000 (from 356 fewer to 513 more)	⊕OOO VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Beta-2 agonists	Erythromycin	Relative (95% CI)	Absolute		
Abbreviations: RR, relative risk; CI, confidence interval; RCT, randomised controlled trial												

[1] Becker et al. 2015
[2] Downgraded 1 level - no RCT was assessed by the Cochrane authors as at low risk of bias
[3] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with beta-2 agonists][4] Oral albuterol
[5] Downgraded 2 levels: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with beta-2 agonists, and no meaningful difference or appreciable benefit/harm with erthromycin

H.9 Corticosteroids

Table 48: GRADE profile – inhaled corticosteroids versus placebo for adults with acute and subacute cough

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Inhaled corticosteroids	Placebo	Relative (95% CI)	Absolute		
Mean cough score at end of second week of treatment in adults (measured with: cough score 0=absent, 1=mild, 2=moderate, 3=severe; plus other LRT symptoms[1]; better indicated by lower values)												
1[2]	randomised trials	serious[3]	Not applicable	serious[4]	serious[5]	none	65[6]	68	-	MD 0.50 lower (0.55 to 0.45 lower)[7,8]	⊕OOO VERY LOW	CRITICAL
Mean cough score in second week in non-smoking adults (assessed with: reduced by at least 50% [9])												
1[2]	randomised trials	serious[3]	Not applicable	serious[4]	serious[10]	none	23/43 (53.5%)	33/41 (80.5%)	RR 0.66 (0.48 to 0.91)[11]	274 fewer per 1000 (from 72 fewer to 419 fewer)	⊕OOO VERY LOW	IMPORTANT
Mean symptom score at 2 weeks in adults (measured with: combined scores from subscales[12]; better indicated by lower values)												
1[2]	randomised trials	serious[3]	Not applicable	no serious indirectness	very serious[13]	none	15[14]	15	-	MD 0.34 lower (3.14 lower to 2.46 higher)[15]	⊕OOO VERY LOW	CRITICAL
Little or no overall improvement at 7 to 14 days in adults (assessed with: daily symptom score cards)												
1[2]	randomised trials	serious[3]	Not applicable	no serious indirectness	very serious[16]	none	10/49 (20.4%)[17]	15/49 (30.6%)	RR 0.67 (0.33 to 1.34)[18]	101 fewer per 1000 (from 205 fewer to 104 more)	⊕OOO VERY LOW	CRITICAL
Mean symptom score at 4 weeks in adults (measured with: combined from subscales[12]; better indicated by lower values)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Inhaled corticosteroids	Placebo	Relative (95% CI)	Absolute		
1[2]	randomised trials	serious[3]	Not applicable	no serious indirectness	very serious[13]	none	14[14]	12	-	MD 0.40 lower (2.48 lower to 1.68 higher)[15]	⊕OOO VERY LOW	CRITICAL
Average daily cough score in the second week in smokers versus non-smokers (adults) (measured with: cough score 0=absent, 1=mild, 2=moderate, 3=severe; plus other LRT symptoms[1]; better indicated by lower values)												
1[2]	randomised trials	serious[3]	Not applicable	serious[4]	serious[19]	none	68[6,20]	65[21]	-	MD 0.9 lower (1.3 to 0.4 lower)[22]	⊕OOO VERY LOW	IMPORTANT
Severe symptoms at day 11 in adults (assessed with: not defined)												
1[2]	randomised trials	serious[3]	Not applicable	no serious indirectness	very serious[16]	none	1/32 (3.1%)[23]	2/38 (5.3%)	RR 0.59 (0.06 to 6.25)[24]	22 fewer per 1000 (from 49 fewer to 276 more)	⊕OOO VERY LOW	CRITICAL
Additional treatment sought after 2 weeks of treatment in adults (assessed with: not defined)												
1[2]	randomised trials	serious[3]	Not applicable	serious[4]	serious[25]	none	28/65 (43.1%)	42/67 (62.7%)	RR 0.69 (0.49 to 0.96)[26]	194 fewer per 1000 (from 25 fewer to 320 fewer)	⊕OOO VERY LOW	IMPORTANT
Adverse effects (hoarseness) in adults (assessed with: during treatment period)												
1[2]	randomised trials	serious[3]	Not applicable	serious[4]	very serious[16]	none	9/65 (13.8%)	10/68 (14.7%)	RR 0.93 (0.35 to 2.47)	10 fewer per 1000 (from 96 fewer to 216 more)	⊕OOO VERY LOW	CRITICAL

Abbreviations: LRT, lower respiratory tract; RCT, randomised controlled trial; ITT, intention to treat analysis; ANCOVA, analysis of covariance; ANOVA, analysis of variance; AUC, area under curve; p, p value; CI, confidence interval; RR, relative risk;

[1] Other LRT symptoms included sputum, wheeze, shortness of breath, tightness of chest and hoarseness
[2] El-Gohary et al. 2013
[3] Downgraded 1 level - no RCT assessed by the authors was at low risk of bias
[4] Downgraded 1 level - study included small number of people with chronic cough (>8 weeks duration)
[5] Downgraded 1 level - at a default minimal important difference of 0.5 standard deviation of the control arm, data are consistent with no meaningful difference or appreciable benefit with inhaled corticosteroid
[6] Inhaled fluticasone proprionate, 500 µg twice daily for 14 days via spacer device
[7] ITT analysis
[8] The authors conducted an ANCOVA analysis that showed that when adjusted for bronchial hyper-responsiveness, smoking status and baseline cough score the difference was -0.5 (95% CI -0.9 to-0.1) for those using corticosteroid versus placebo
[9] Data for smokers not reported
[10] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with inhaled corticosteroids.
[11] In non-smokers, the perception of improvement by corticosteroid cohort was greater (p=0.004) than in the smokers (p=0.56)
[12] Comprises frequency of cough, frequency of coughing bouts, symptoms associated with cough, night-time cough, frequency of taking medicines to relieve cough.
[13] Downgraded 2 levels - at a default minimal important difference of 0.5 standard deviation of the control arm, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[14] Inhaled dry powder budesonide 100 µg twice daily for 4 weeks

[15] The study also used ANOVA to assess changes between treatment and placebo symptom scores from baseline at 2 and 4 weeks, these were not significant
[16] Downgraded 2 levels: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with inhaled corticosteroids, and no meaningful difference or appreciable harm with [name of placebo
[17] Beclomethasone 100 µg four time daily for 7 to 14 days
[18] No other clinical differences were reported
[19] Downgraded 1 level - unable to assess due to insufficient data
[20] Of whom 24 (36%) were current smokers
[21] Of whom 24 (37%) were current smokers
[22] Adjusted for baseline cough score, non-significant difference for smokers (0.1 point higher, 95% CI -0.6 to 0.9, p=0.74)
[23] Beclomethasone 100 mcg 2 puffs twice daily7 days followed by 200 µg twice daily for 4 days
[24] Beclomethasone inhaler significantly decreased the cough epoch (one or more single cough separated by less than one second) frequency from 7 am until 11 pm and 0:00 am and 24;00 pm respectively (AUC p=0.035) no additional data provided
[25] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with inhaled corticosteroids
[26] The percentages for non-smokers were 39% and 68%, respectively (p=0.014), compared with 50% and 54% for smokers, respectively.

H.10 Back-up antibiotics

Table 49: **GRADE profile – back-up antibiotic versus immediate or no antibiotics for adults with bronchitis (cough)**

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Back-up antibiotic prescription	Immediate or no antibiotics	Relative (95% CI)	Absolute		
Cough duration in adults (measured with: days (mean and standard deviation); better indicated by lower values)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	32[4]	32[5]	-	MD 2.60 higher (1.30 lower to 6.50 higher)	⊕⊕OO LOW	CRITICAL
Cough duration in adults (measured with: days (mean and standard deviation); better indicated by lower values)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	32[6]	32[5]	-	MD 1.00 lower (4.11 lower to 2.11 higher)	⊕⊕OO LOW	CRITICAL
Cough duration in adults (measured with: days (mean and standard deviation); better indicated by lower values)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	32[4]	32[7]	-	MD 0.50 lower (3.53 lower to 4.53 higher)	⊕⊕OO LOW	CRITICAL
Cough duration in adults (measured with: days (mean and standard deviation); better indicated by lower values)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	32[6]	32[7]	-	MD 3.10 lower (6.37 lower to 0.17 higher)	⊕⊕OO LOW	CRITICAL
Pain duration in adults (measured with: days (mean and standard deviation); better indicated by lower values)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	32[4]	32[5]	-	MD 0.50 higher (0.34 lower to 4.42 higher)	⊕⊕OO LOW	CRITICAL
Pain duration in adults (measured with: days (mean and standard deviation); better indicated by lower values)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	32[6]	32[5]	-	MD 1.60 lower (5.26 lower to 2.06 higher)	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Back-up antibiotic prescription	Immediate or no antibiotics	Relative (95% CI)	Absolute		
Pain duration in adults (measured with: days (mean and standard deviation); better indicated by lower values)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	32[4]	32[7]	-	MD 1.20 lower (5.07 lower to 2.67 higher)	⊕⊕OO LOW	CRITICAL
Pain duration in adults (measured with: days (mean and standard deviation); better indicated by lower values)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	32[6]	32[7]	-	MD 3.30 lower (6.91 lower to 0.31 higher)	⊕⊕OO LOW	CRITICAL
Fever duration in adults (measured with: days (mean and standard deviation); better indicated by lower values)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	32[4]	32[5]	-	MD 1.50 higher (1.34 lower to 4.34 higher)	⊕⊕OO LOW	CRITICAL
Fever duration in adults (measured with: days (mean and standard deviation); better indicated by lower values)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	32[6]	32[5]	-	MD 0.60 higher (1.94 lower to 3.14 higher)	⊕⊕OO LOW	CRITICAL
Fever duration in adults (measured with: days (mean and standard deviation); better indicated by lower values)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	very serious[8]	none	32[4]	32[7]	-	MD 1.60 lower (8.82 lower to 5.62 higher)	⊕OOO VERY LOW	CRITICAL
Fever duration in adults (measured with: days (mean and standard deviation); better indicated by lower values)												
1[1]	randomised trials	serious[2]	not applicable	no serious indirectness	serious[3]	none	32[6]	32[7]	-	MD 2.50 lower (5.67 lower to 0.67 higher)	⊕⊕OO LOW	CRITICAL

Abbreviations: CI, confidence interval; MD, mean difference; RCT, randomised controlled trial

[1] Spurling et al. 2017
[2] Downgraded 1 level - no RCT was assessed by the Cochrane authors as at low risk of bias
[3] Downgraded 1 level - at a default minimal important difference of 0.5 standard deviation of the control arm, data are consistent with no meaningful difference or appreciable benefit with back-up antibiotic prescribing
[4] Delayed antibiotic prescription at the time of visit
[5] Immediate antibiotic prescription
[6] Delayed antibiotic prescription requiring collection
[7] No antibiotic
[8] Downgraded 2 levels - at a default minimal important difference of 0.5 standard deviation of the control arm, data are consistent with no meaningful difference, appreciable harm or appreciable benefit

Table 50: GRADE profile – back-up antibiotic versus immediate or no antibiotic for people with respiratory infections

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Back-up antibiotic prescription	Immediate or no antibiotic prescription	Relative (95% CI)	Absolute		
Pain on days 3 to 6 (assessed with: number of people with pain, delayed versus immediate antibiotics)												
4[1]	randomised trials	serious[2]	very serious[3]	serious[4]	very serious[5]	none	232/422 (55%)	155/403 (38.5%)	RR 1.52 (0.84 to 2.74)	200 more per 1000 (from 62 fewer to 669 more)	⊕OOO VERY LOW	IMPORTANT
Pain severity on day 3 (better indicated by lower values, delayed versus immediate antibiotics)												
2[1]	randomised trials	serious[2]	no serious inconsistency	serious[4]	no serious imprecision	none	166	161	-	SMD 0.35 higher (0.13 to 0.57 higher)	⊕⊕OO LOW	IMPORTANT
Malaise on day 3 (assessed with: number of people with malaise, delayed versus immediate antibiotics)												
2[1]	randomised trials	serious[2]	serious[3]	serious[4]	very serious[5]	none	90/268 (33.6%)	23/246 (9.3%)	RR 4.50 (0.86 to 23.41)	327 more per 1000 (from 13 fewer to 1000 more)	⊕OOO VERY LOW	IMPORTANT
Malaise severity on day 3 (better indicated by lower values, delayed versus immediate antibiotics)												
2[1]	randomised trials	serious[2]	no serious inconsistency	serious[4]	no serious imprecision	none	205	193	-	SMD 0.29 higher (0.09 to 0.48 higher)	⊕⊕OO LOW	IMPORTANT
Fever on days 3 to 6 (assessed with: number of people with fever, delayed versus immediate antibiotics)												
2[1]	randomised trials	serious[2]	no serious inconsistency	serious[4]	serious[6]	none	47/199 (23.6%)	52/195 (26.7%)	RR 0.90 (0.65 to 1.25)	27 fewer per 1000 (from 93 fewer to 67 more)	⊕OOO VERY LOW	IMPORTANT
Fever severity on day 3 (better indicated by lower values, delayed versus immediate antibiotics)												
3[1]	randomised trials	serious[2]	serious[3]	serious[4]	serious[7]	none	234	228	-	MD 0.34 higher (0.33 lower to 1.01 higher)	⊕OOO VERY LOW	IMPORTANT
Antibiotic use (assessed with: delayed prescription at time of visit or delayed collection versus immediate antibiotics)												
7[1]	randomised trials	serious[2]	serious[3]	serious[4]	no serious imprecision	none	310/1015 (30.5%)	882/948 (93%)	RR 0.34 (0.27 to 0.44)	614 fewer per 1000 (from 521 fewer to 679 fewer)	⊕OOO VERY LOW	IMPORTANT
Antibiotic use (assessed with: delayed prescription at time of visit versus immediate antibiotics)												
3[1]	randomised trials	serious[2]	serious[3]	serious[4]	no serious imprecision	none	114/297 (38.4%)	217/250 (86.8%)	RR 0.45 (0.34 to 0.58)	477 fewer per 1000 (from 365 fewer to 573 fewer)	⊕OOO VERY LOW	IMPORTANT
Antibiotic use (assessed with: delayed collection versus immediate antibiotics)												
5[1]	randomised trials	serious[2]	serious[3]	serious[4]	no serious imprecision	none	196/718 (27.3%)	665/698 (95.3%)	RR 0.29 (0.22 to 0.39)	676 fewer per 1000 (from 581 fewer to 743 fewer)	⊕OOO VERY LOW	IMPORTANT
Antibiotic use (assessed with: delayed prescription at the time of visit or delayed collection versus no antibiotics)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Back-up antibiotic prescription	Immediate or no antibiotic prescription	Relative (95% CI)	Absolute		
4[1]	randomised trials	serious[2]	no serious inconsistency	serious[4]	no serious imprecision	none	189/677 (27.9%)	77/564 (13.7%)	RR 2.09 (1.46 to 2.99)	149 more per 1000 (from 63 more to 272 more)	⊕⊕OO LOW	IMPORTANT
Antibiotic use (assessed with: delayed prescription at time of visit versus no antibiotic)												
2[1]	randomised trials	serious[2]	no serious inconsistency	serious[4]	no serious imprecision	none	72/204 (35.3%)	19/149 (12.8%)	RR 2.81 (1.77 to 4.47)	231 more per 1000 (from 98 more to 442 more)	⊕⊕OO LOW	IMPORTANT
Antibiotic use (assessed with: delayed collection versus no antibiotic)												
3[1]	randomised trials	serious[2]	serious[3]	serious[4]	serious[5]	none	117/473 (24.7%)	58/415 (14%)	RR 1.79 (1.10 to 2.90)	110 more per 1000 (from 14 more to 266 more)	⊕OOO VERY LOW	IMPORTANT
Patient satisfaction (assessed with: delayed antibiotic versus immediate antibiotic)												
6[1]	randomised trials	serious[2]	serious[3]	serious[4]	no serious imprecision	none	732/855 (85.6%)	707/778 (90.9%)	RR 0.96 (0.91 to 1.01)	36 fewer per 1000 (from 82 fewer to 9 more)	⊕OOO VERY LOW	IMPORTANT
Patient satisfaction (assessed with: delayed antibiotic prescription versus no antibiotic)												
4[1]	randomised trials	serious[2]	no serious inconsistency	serious[4]	no serious imprecision	none	583/671 (86.9%)	465/564 (82.4%)	RR 1.06 (1.01 to 1.11)	49 more per 1000 (from 8 more to 91 more)	⊕⊕OO LOW	IMPORTANT
Adverse effects (vomiting) (assessed with: delayed versus immediate antibiotics)												
3[1]	randomised trials	serious[2]	serious[3]	serious[4]	very serious[5]	none	87/429 (20.3%)	37/459 (8.1%)	RR 2.29 (0.48 to 10.80)	104 more per 1000 (from 42 fewer to 790 more)	⊕OOO VERY LOW	IMPORTANT
Adverse effects (diarrhoea) (assessed with: delayed versus immediate antibiotics)												
4[1]	randomised trials	serious[2]	serious[3]	serious[4]	serious[6]	none	58/528 (11%)	91/545 (16.7%)	RR 0.65 (0.36 to 1.16)	58 fewer per 1000 (from 107 fewer to 27 more)	⊕OOO VERY LOW	IMPORTANT
Adverse effects (rash) (assessed with: delayed versus immediate antibiotics)												
2[1]	randomised trials	serious[2]	no serious inconsistency	serious[4]	very serious[5]	none	19/330 (5.8%)	20/350 (5.7%)	RR 1.03 (0.56 to 1.89)	2 more per 1000 (from 25 fewer to 51 more)	⊕OOO VERY LOW	IMPORTANT
Re-consultation rate (assessed with: delayed versus immediate antibiotics)												
2[1]	randomised trials	serious[2]	no serious inconsistency	serious[4]	very serious[5]	none	21/187 (11.2%)	21/192 (10.9%)	RR 1.04 (0.59 to 1.83)	4 more per 1000 (from 45 fewer to 91 more)	⊕OOO VERY LOW	IMPORTANT
Abbreviations: CI, confidence interval; RR, relative risk; MD, mean difference; SMD, standardised mean difference; RCT, randomised controlled trial												

[1] Spurling et al. 2017
[2] Downgraded 1 level - only 1 RCT was assessed by the Cochrane authors as at low risk of bias
[3] Downgraded 1 level - I^2>50%
[4] Downgraded 1 level - these outcomes relate to all respiratory infections (sore throat, common cold and acute otitis media) rather than bronchitis (cough) alone
[5] Downgraded 2 levels: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with back-up antibiotic prescribing, and no meaningful difference or appreciable benefit with immediate or no antibiotic prescribing
[6] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with back-up antibiotic prescribing
[7] Downgraded 1 level - at a default minimal important difference of 0.5 standard deviation of the control arm, data are consistent with no meaningful difference or appreciable benefit with back-up antibiotic prescribing

H.11 Antibiotics

Table 51: GRADE profile – antibiotics versus placebo, no treatment or other treatment in people with acute bronchitis (clinical improvement)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotics	Placebo or no/other treatment	Relative (95% CI)	Absolute		
Clinically improved with antibiotics versus placebo or other comparator (assessed with: number of participants with no activity limitation or cured/globally improved[1])												
11[2]	randomised trials	serious[3]	serious[4]	no serious indirectness	no serious imprecision	none	1407/1922 (73.2%)[5]	1277/1919 (66.5%)	RR 1.07 (0.99 to 1.15)	47 more per 1000 (from 7 fewer to 100 more)	⊕⊕OO LOW	CRITICAL
Clinically improved with antibiotics versus placebo (assessed with: number of participants with no activity limitation or cured/globally improved[1])												
10[2]	randomised trials	serious[6]	serious[4]	no serious indirectness	no serious imprecision	none	1321/1825 (72.3%)[7]	1195/1827 (65.4%)	RR 1.08 (1.00 to 1.17)	64 more per 1000 (from 13 more to 127 more)	⊕⊕OO LOW	CRITICAL
Subgroup analysis: clinically improved with doxycycline versus placebo (assessed with: number of participants with no activity limitation or cured/globally improved[8])												
3[2]	randomised trials	no serious risk of bias	serious[4]	no serious indirectness	no serious imprecision	none	193/214 (90.2%)	172/207 (83.1%)	RR 1.06 (0.95 to 1.17)	50 more per 1000 (from 42 fewer to 141 more)	⊕⊕⊕O MODERATE	CRITICAL
Subgroup analysis: clinically improved with erythromycin versus placebo (assessed with: number of participants with no activity limitation or cured/globally improved[9])												
2[2]	randomised trials	serious[10]	no serious inconsistency	no serious indirectness	serious[11]	none	40/46 (87%)	34/47 (72.3%)	RR 1.22 (0.99 to 1.5)	159 more per 1000 (from 7 fewer to 362 more)	⊕⊕OO LOW	CRITICAL
Subgroup analysis: clinically improved with amoxicillin versus placebo (assessed with: number of participants with no activity limitation or cured/globally improved)												
2[2]	randomised trials	no serious risk of bias	serious[4,12]	no serious indirectness	serious[11]	none	809/1238 (65.3%)	713/1229 (58%)	RR 1.09 (0.85 to 1.4)	52 more per 1000 (from 87 fewer to 232 more)	⊕⊕OO LOW	CRITICAL
Subgroup analysis: clinically improved with cefuroxime versus placebo (assessed with: number of participants with no activity limitation or cured/globally improved)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotics	Placebo or no/other treatment	Relative (95% CI)	Absolute		
1[2]	randomised trials	serious[13]	not applicable	no serious indirectness	serious[11]	none	158/171 (92.4%)	136/172 (79.1%)	RR 1.17 (1.07 to 1.28)	134 more per 1000 (from 55 more to 221 more)	⊕⊕OO LOW	CRITICAL
Limitation in work or activity (antibiotics versus placebo or other treatment) (assessed at follow-up[14])												
5[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[15]	none	23/239 (9.6%)[16]	34/239 (14.2%)	RR 0.75 (0.46 to 1.22)	36 fewer per 1000 (from 77 fewer to 31 more)	⊕⊕⊕O MODERATE	IMPORTANT
Mean days of feeling ill (measured with: antibiotics (erythromycin, doxycycline or amoxicillin) versus placebo or no treatment[17]; better indicated by lower values)												
5[2]	randomised trials	serious[18]	no serious inconsistency	no serious indirectness	no serious imprecision	none	411	398	-	MD 0.64 lower (1.16 to 0.13 lower)	⊕⊕⊕O MODERATE	CRITICAL
Mean days of feeling ill (measured with: erythromycin or doxycycline versus placebo[17,19]; better indicated by lower values)												
4[2]	randomised trials	serious[20]	no serious inconsistency	no serious indirectness	no serious imprecision	none	217	218	-	MD 0.58 lower (1.16 lower to 0 higher)	⊕⊕⊕O MODERATE	CRITICAL
Mean days of feeling ill (measured with: subgroup of doxycycline versus placebo[8]; better indicated by lower values)												
3[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	192	191	-	MD 0.64 lower (1.24 to 0.04 lower)	⊕⊕⊕⊕ HIGH	CRITICAL
Mean days of impaired activity (measured with: erythromycin, doxycycline and amoxicillin versus placebo or no treatment[17]; better indicated by lower values)												
6[2]	randomised trials	serious[21]	no serious inconsistency	no serious indirectness	no serious imprecision	none	397	370	-	MD 0.49 lower (0.94 to 0.04 lower)	⊕⊕⊕O MODERATE	IMPORTANT
Mean days of impaired activity (measured with: erythromycin or doxycycline) versus placebo[14,19]; better indicated by lower values)												
5[2]	randomised trials	serious[22]	no serious inconsistency	no serious indirectness	no serious imprecision	none	203	190	-	MD 0.48 lower (0.96 lower to 0.01 higher)	⊕⊕⊕O MODERATE	IMPORTANT

Abbreviations: RR, relative risk; MD, mean difference; CI, confidence interval; RCT, randomised controlled trial

[1] Length of follow-up varied between studies (7 - 14 days)
[2] Smith et al. 2017
[3] Downgraded 1 level - only 7 of 11 RCTs were assessed by the Cochrane authors as at low risk of bias
[4] Downgraded 1 level - I^2>50% (random effects model used)
[5] Antibiotics included doxycycline, co-trimoxazole, erythromycin, cefuroxime, azithromycin, amoxicillin and co-amoxiclav. Comparators were placebo or other treatment (2 RCTs vitamin C and ibuprofen)
[6] Downgraded 1 level - only 5 of 9 RCTs were assessed by the Cochrane authors as at low risk of bias
[7] Antibiotics included doxycycline, co-trimoxazole, erythromycin, cefuroxime and amoxicillin
[8] Length of follow-up varied between studies (7 - 11 days)
[9] Length of follow-up varied between studies (8 - 14 days)
[10] Downgraded 1 level - only 1 of 2 RCTs was assessed by the Cochrane authors as at low risk of bias
[11] Downgraded 1 level: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable benefit with antibiotics
[12] Two RCTs showed different results for amoxicillin versus placebo (1 RCT showed significant but imprecise effect, Little 2013, n=1807, RR 1.22 (95% CI 1.12 to 1.33); the 2nd RCT showed no statistically significant effect, Nduba 2008, n=660, RR 0.97 (95% CI 0.91 to 1.04); both trials were at low risk of bias)

[13] Downgraded 1 level - this RCT was assessed by Cochrane authors at unclear risk of bias
[14] Length of follow-up varied between studies (7 -14 days)
[15] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with antibiotics
[16] Antibiotics included erythromycin, azithromycin, co-trimoxazole and doxycycline
[17] Length of follow-up varied between studies (7 - 18 days)
[18] Downgraded 1 level - only 2 of 5 RCTs were assessed by the Cochrane authors as at low risk of bias
[19] Omits 1 study (Little 2005) which had a no treatment rather than placebo arm
[20] Downgraded 1 level - only 2 of 4 RCTs were assessed by the Cochrane authors as at low risk of bias
[21] Downgraded 1 level - only 2 of 6 RCTs were assessed by the Cochrane authors as at low risk of bias
[22] Downgraded 1 level - only 2 of 5 RCTs were assessed by the Cochrane authors as at low risk of bias

Table 52: GRADE profile – antibiotics versus placebo for people with acute bronchitis (no improvement outcomes)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotics	Placebo	Relative (95% CI)	Absolute		
Not improved at physician follow-up (assessed with: erythromycin, cefuroxime, doxycycline or co-amoxiclav versus placebo[1])												
6[2]	randomised trials	serious[3]	serious[4]	no serious indirectness	serious[5]	none	62/450 (13.8%)	101/441 (22.9%)	RR 0.58 (0.3 to 1.14)	96 fewer per 1000 (from 160 fewer to 32 more)	⊕OOO VERY LOW	CRITICAL
Not improved at physician follow-up (assessed with: erythromycin, cefuroxime or doxycycline versus placebo[6,7])												
5[2]	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	no serious imprecision	none	32/413 (7.7%)	71/403 (17.6%)	RR 0.44 (0.3 to 0.65)[9]	99 fewer per 1000 (from 62 fewer to 123 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Not improved at physician follow-up (assessed with: subgroup doxycycline versus placebo [10])												
3[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	14/216 (6.5%)	25/207 (12.1%)	RR 0.54 (0.29 to 1.01)	56 fewer per 1000 (from 86 fewer to 1 more)	⊕⊕⊕O MODERATE	CRITICAL
Abnormal lung exam at physician follow-up (assessed with: erythromycin, cefuroxime or doxycycline) versus placebo[7])												
5[2]	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	no serious imprecision	none	58/314 (18.5%)	104/299 (34.8%)	RR 0.54 (0.41 to 0.7)	160 fewer per 1000 (from 104 fewer to 205 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Abnormal lung exam at physician follow-up (assessed with: subgroup of erythromycin versus placebo[7])												
2[2]	randomised trials	serious[12]	serious[13]	no serious indirectness	very serious[14]	none	7/37 (18.9%)	11/31 (35.5%)	RR 0.33 (0.02 to 6.47)	238 fewer per 1000 (from 348 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Abnormal lung exam at physician follow-up (assessed with: subgroup of doxycycline versus placebo[10])												
2[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[14]	none	5/106 (4.7%)	10/96 (10.4%)	RR 0.49 (0.18 to 1.31)	53 fewer per 1000 (from 85 fewer to 32 more)	⊕⊕OO LOW	CRITICAL
Abnormal lung exam at physician follow-up (assessed with: subgroup cefuroxime versus placebo[15])												
1[2]	randomised trials	serious[16]	not applicable	no serious indirectness	no serious imprecision	none	46/171 (26.9%)	83/172 (48.3%)	RR 0.56 (0.42 to 0.75)	212 fewer per 1000 (from 121 fewer to 280 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Abbreviations: RCT, randomised controlled trial; CI, confidence interval; RR, relative risk												

[1] Length of follow-up varied between studies (5 - 14 days)
[2] Smith et al. 2017
[3] Downgraded 1 level - only 2 of 6 RCTs were assessed by the Cochrane reviewers as at low risk of bias
[4] Downgraded 1 level - I^2>50%, random effects model used in NICE analysis, when repeated with authors fixed effects model (RR 0.61, 95% CI 0.48 to 0.79)
[5] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with antibiotics
[6] Omits 1 RCT of (Kaiser 1996) which was a subgroup of an RCT with non-purulent tracheobronchitis in an upper respiratory tract infection cohort
[7] Length of follow-up varied between studies (7 - 14 days)
[8] Downgraded 1 level - only 2 of 5 RCTs were assessed by the Cochrane authors as at low risk of bias
[9] One study of cefuroxime versus placebo (Matthys 2000) accounted for 50.1% of the weight in the analysis had an individual RR 0.36 (95% CI 0.30 to 0.65)
[10] Length of follow-up varied between studies (7 to 11 days)
[11] Downgraded 1 level - only 3 of 5 RCTs were assessed by the Cochrane authors as at low risk of bias
[12] Downgraded 1 level - only 1 of 2 RCTs assessed by the Cochrane authors was at low risk of bias
[13] Downgraded 1 level I^2>50%, NICE analysis used random effects model
[14] Downgraded 2 levels: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with antibiotics, and no meaningful difference or appreciable harm with placebo
[15] Follow-up was at day 7 to 14
[16] Downgraded 1 level – this RCT was at unclear risk of bias (assessed by Cochrane authors)

Table 53: GRADE profile – antibiotics versus placebo or no treatment for people with acute bronchitis (reduction of cough)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotics	Placebo or no treatment	Relative (95% CI)	Absolute		
Cough at follow-up visit in adults (assessed with: erythromycin or doxycycline versus placebo[1])												
4[2]	randomised trials	no serious risk of bias	no serious inconsistency[3]	no serious indirectness	serious[4]	none	47/143 (32.9%)	67/132 (50.8%)	RR 0.64 (0.49 to 0.85)	183 fewer per 1000 (from 76 fewer to 259 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Subgroup analysis: cough at follow-up visit in adults (assessed with: erythromycin versus placebo[1])												
2[2]	randomised trials	serious[5]	no serious inconsistency[3]	no serious indirectness	serious[4]	none	22/34 (64.7%)	24/31 (77.4%)	RR 0.84 (0.61 to 1.15)	124 fewer per 1000 (from 302 fewer to 116 more)	⊕⊕OO LOW	CRITICAL
Subgroup analysis: cough at follow-up visit in adults (assessed with: doxycycline versus placebo[6])												
2[2]	randomised trials	no serious risk of bias	no serious inconsistency[3]	no serious indirectness	serious[4]	none	25/109 (22.9%)	43/101 (42.6%)	RR 0.54 (0.36 to 0.81)	196 fewer per 1000 (from 81 fewer to 272 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Night cough at follow-up visit in adults (assessed with: erythromycin, cefuroxime or doxycycline versus placebo[1])												
4[2]	randomised trials	serious[7]	no serious inconsistency[3]	no serious indirectness	serious[4]	none	80/271 (29.5%)	119/267 (44.6%)	RR 0.67 (0.54 to 0.83)	147 fewer per 1000 (from 76 fewer to 205 fewer)	⊕⊕OO LOW	CRITICAL
Subgroup analysis: night cough at follow-up visit in adults (assessed with: erythromycin versus placebo[1])												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotics	Placebo or no treatment	Relative (95% CI)	Absolute		
2[2]	randomised trials	serious[5]	no serious inconsistency[3]	no serious indirectness	serious[4]	none	9/31 (29%)	16/32 (50%)	RR 0.60 (0.32 to 1.15)	200 fewer per 1000 (from 340 fewer to 75 more)	⊕⊕OO LOW	CRITICAL
Subgroup analysis: night cough at follow-up visit in adults (assessed with: cefuroxime versus placebo[1])												
1[2]	randomised trials	serious[8]	not applicable	no serious indirectness	serious[4]	none	63/171 (36.8%)	96/169 (56.8%)	RR 0.65 (0.51 to 0.82)	199 fewer per 1000 (from 102 fewer to 278 fewer)	⊕⊕OO LOW	CRITICAL
Subgroup analysis: night cough at follow-up visit in adults (assessed with: doxycycline versus placebo[9])												
1[2]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	very serious[10]	none	8/69 (11.6%)	7/66 (10.6%)	RR 1.09 (0.42 to 2.85)	10 more per 1000 (from 62 fewer to 196 more)	⊕⊕OO LOW	CRITICAL
Productive cough at follow-up visit (assessed with: antibiotics (erythromycin, doxycycline or demethyl chlortetracycline) versus placebo[11])												
7[2]	randomised trials	serious[12]	no serious inconsistency[3]	no serious indirectness	no serious imprecision	none	135/366 (36.9%)	129/347 (37.2%)	RR 0.97 (0.82 to 1.16)	11 fewer per 1000 (from 67 fewer to 59 more)	⊕⊕⊕O MODERATE	CRITICAL
Subgroup analysis: productive cough at follow-up visit (assessed with: erythromycin versus placebo[13])												
3[2]	randomised trials	very serious[14]	no serious inconsistency[3]	no serious indirectness	serious[4]	none	50/75 (66.7%)	47/62 (75.8%)	RR 0.87 (0.7 to 1.07)	99 fewer per 1000 (from 227 fewer to 53 more)	⊕OOO VERY LOW	CRITICAL
Subgroup analysis: productive cough at follow-up visit (assessed with: doxycycline versus placebo[6,15])												
3[2]	randomised trials	no serious risk of bias	no serious inconsistency[3]	no serious indirectness	very serious[16]	none	42/210 (20%)	49/202 (24.3%)	RR 0.90 (0.63 to 1.27)	24 fewer per 1000 (from 90 fewer to 65 more)	⊕⊕OO LOW	CRITICAL

Abbreviations: RCT, randomised controlled trial; CI, confidence interval; RR, relative risk;

[1] Length of follow-up varied from 7 to 14 days
[2] Smith et al. 2017
[3] Low heterogeneity I^2<50%
[4] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with antibiotics
[5] Downgraded 1 level - only 1 of 2 RCTs was assessed by the Cochrane authors as at low risk of bias
[6] Length of follow-up varied from 7 to 11 days
[7] Downgraded 1 level - only 2 of 4 RCTs were assessed by the Cochrane authors as at low risk of bias
[8] Downgraded 1 level - the included RCT was assessed by the Cochrane authors as at an unclear risk of bias
[9] Follow-up was at day 11
[10] Downgraded 2 levels: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with antibiotics, and no meaningful difference or appreciable benefit with placebo or no treatment
[11] Follow-up was at 5 to 18 days
[12] Downgraded 1 level - only 4 of 7 RCTs were assessed by the Cochrane authors as at low risk of bias
[13] Follow-up was at 7 to 18 days

[14] Downgraded 2 levels - only 1 of 3 RCTs were assessed by the Cochrane authors as at low risk of bias
[15] Additional study (demethyl chlortetracycline was omitted from the analysis as it is not available in the UK)
[16] Downgraded 2 levels: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with antibiotics, and no meaningful difference or appreciable harm with placebo or no treatment

Table 54: GRADE profile – antibiotics versus placebo or no treatment for people with acute bronchitis (duration of cough)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotics	Placebo or no treatment	Relative (95% CI)	Absolute		
Mean duration of cough in days (measured with: erythromycin, amoxicillin or doxycycline versus placebo or no treatment[1]; better indicated by lower values)												
7[2]	randomised trials	serious[3]	no serious inconsistency[4]	no serious indirectness	no serious imprecision	none	1402	1374	-	MD 0.46 lower (0.87 to 0.04 lower)	⊕⊕⊕O MODERATE	CRITICAL
Mean duration of cough in days (measured with: erythromycin, doxycycline or amoxicillin versus placebo only[5]; better indicated by lower values)												
6[2]	randomised trials	serious[6]	no serious inconsistency[4]	no serious indirectness	no serious imprecision	none	1188	1162	-	MD 0.55 lower (1 to 0.1 lower)	⊕⊕⊕O MODERATE	CRITICAL
Mean duration of cough in days (measured with: subgroup of erythromycin versus placebo[7]; better indicated by lower values)												
1[2]	randomised trials	serious[8]	not applicable	no serious indirectness	no serious imprecision	none	50	42	-	MD 0.18 lower (3.95 lower to 3.59 higher)	⊕⊕⊕O MODERATE	CRITICAL
Mean duration of cough in days (measured with: subgroup of doxycycline versus placebo[9]; better indicated by lower values)												
4[2]	randomised trials	serious[10]	serious[11]	no serious indirectness	serious[12]	none	230	221	-	MD 0.94 lower (2.08 lower to 0.21 higher)	⊕OOO VERY LOW	CRITICAL
Mean duration of cough in days (measured with: subgroup of amoxicillin or erythromycin versus placebo or no treatment[13]; better indicated by lower values)												
2[2]	randomised trials	serious[14]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1122	1111	-	MD 0.31 lower (0.92 lower to 0.3 higher)	⊕⊕⊕O MODERATE	CRITICAL
Mean duration of productive cough in days (measured with: erythromycin, doxycycline or amoxicillin versus placebo or no treatment[15]; better indicated by lower values)												
6[2]	randomised trials	serious[16]	no serious inconsistency[4]	no serious indirectness	no serious imprecision	none	357	342	-	MD 0.43 lower (0.93 lower to 0.07 higher)	⊕⊕⊕O MODERATE	CRITICAL
Mean duration of productive cough in days (measured with: erythromycin or doxycycline) versus placebo[17]; better indicated by lower values)												
5[2]	randomised trials	serious[18]	no serious inconsistency[4]	no serious indirectness	no serious imprecision	none	276	259	-	MD 0.52 lower (1.03 to 0.01 lower)	⊕⊕⊕O MODERATE	CRITICAL
Mean duration of productive cough in days (measured with: subgroup of doxycycline versus placebo[19]; better indicated by lower values)												
4[2]	randomised trials	serious[20]	no serious inconsistency[4]	no serious indirectness	no serious imprecision	none	226	218	-	MD 0.56 lower (1.09 to 0.04 lower)	⊕⊕⊕O MODERATE	CRITICAL
Mean duration of productive cough in days (measured with: subgroup of amoxicillin or erythromycin versus placebo or no treatment[21]; better indicated by lower values)												
2[2]	randomised trials	serious[22]	no serious inconsistency[4]	no serious indirectness	no serious imprecision	none	131	124	-	MD 0.86 higher (0.77 lower to 2.49 higher)	⊕⊕⊕O MODERATE	CRITICAL
Abbreviations: RCT, randomised controlled trial; MD, Mean difference; CI, confidence interval												

[1] Length of follow-up varied from 7 to 21 days
[2] Smith et al. 2017

[3] Downgraded 1 level - only 3 of 7 RCTs were assessed by the Cochrane authors as at low risk of bias
[4] I^2<50%
[5] Omits study by Little et al. 2005 (amoxicillin versus no treatment), length of follow-up varied from 7 to 18 days
[6] Downgraded 1 level - 1 RCT was assessed as at moderate risk of bias by Cochrane reviewers, 2 RCTs were at unclear risk of bias and 3 at low risk of bias
[7] Follow-up was at 14 to 18 days
[8] Downgraded 1 level - 1 included RCT assessed by the Cochrane authors was not found to be at low risk of bias
[9] Length of follow-up varied from 7 to 14 days
[10] Downgraded 1 level - 2 of 4 studies were assessed by the Cochrane authors as at unclear risk of bias
[11] Downgraded 1 level - I^2>50% Random effects model used
[12] Downgraded 1 level - at a default minimal important difference of 0.5 standard deviation of control arm, data are consistent with no meaningful difference or appreciable benefit with antibiotics
[13] Length of follow-up varied from 14 to 21 days
[14] Downgraded 1 level - only 1 of 2 RCTs was assessed by the Cochrane authors as at low risk of bias
[15] Length of follow-up varied from 5 to 18 days
[16] Downgraded 1 level - only 3 of 6 RCTs were assessed by the Cochrane authors as at low risk of bias
[17] Omits study by Howie et al. 1970 (amoxicillin or erythromycin versus no treatment), RCTs varied in follow-up from 7 to 18 days
[18] Downgraded 1 level - only 2 of 5 RCTs were assessed by the Cochrane authors as at low risk of bias
[19] Length of follow-up varied from 7 to 14 days
[20] Downgraded 1 level - only 2 of 4 RCTs were assessed by the Cochrane authors as at low risk of bias
[21] Length of follow-up varied from 5 to 18 days
[22] Downgraded 1 level - only 1 of 2 RCTs were assessed by the Cochrane authors as at low risk of bias

Table 55: GRADE profile – antibiotics versus placebo or no treatment for people with acute bronchitis (adverse effects)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotics	Placebo or no treatment	Relative (95% CI)	Absolute		
Adverse effects (assessed with: antibiotics versus placebo, other comparator or no treatment[1,2])												
12[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	401/1773 (22.6%)	323/1723 (18.7%)	RR 1.20 (1.05 to 1.36)	37 more per 1000 (from 9 more to 67 more)	⊕⊕OO LOW	CRITICAL
Adverse effects (assessed with: subgroup erythromycin versus placebo[2])												
4[3]	randomised trials	serious[6]	serious[7]	no serious indirectness	very serious[8]	none	30/120 (25%)	17/101 (16.8%)	RR 1.37 (0.47 to 3.98)	62 more per 1000 (from 89 fewer to 502 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects (assessed with: subgroup of amoxicillin versus placebo or amoxicillin-clavulanate versus ibuprofen[2])												
2[3]	randomised trials	serious[9]	serious[7]	no serious indirectness	very serious[8]	none	259/991 (26.1%)	210/996 (21.1%)	RR 1.49 (0.73 to 3.04)[10]	103 more per 1000 (from 57 fewer to 430 more)	⊕OOO VERY LOW	CRITICAL
Adverse effects (assessed with: subgroup of doxycycline versus placebo[2])												
2[3]	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	serious[5]	none	27/182 (14.8%)	20/186 (10.8%)	RR 1.38 (0.8 to 2.37)	41 more per 1000 (from 22 fewer to 147 more)	⊕⊕OO LOW	CRITICAL

Abbreviations: RR, relative risk; RCT, randomised controlled trial; FEM, fixed effect model; CI, confidence interval

[1] Antibiotics were erythromycin, azithromycin, co-trimoxazole, amoxicillin, co-amoxiclav, cefuroxime and doxycycline
[2] Length of follow-up varied between studies

[3] Smith et al. 2017
[4] Downgraded 1 level - only 5 of 12 RCTs were assessed by the Cochrane authors as at low risk of bias
[5] Downgraded 1 level: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with antibiotics
[6] Downgraded 1 level - only 1 of 4 RCTs was assessed by the Cochrane authors as at low risk of bias
[7] Downgraded 1 level - I^2>50%, NICE analysis used random effects model
[8] Downgraded 2 levels: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with antibiotics, and no meaningful difference or appreciable benefit with placebo or no treatment
[9] Downgraded 1 level - no RCT was assessed by the Cochrane authors as at low risk of bias
[10] When as additional study of amoxicillin or erythromycin (dependent on age) versus no treatment is added in the RR becomes 1.19 (95% CI 1.03 to 1.38; I2=34% FEM used)
[11] Downgraded 1 level - only 1 of 2 RCTs was assessed by the Cochrane authors as at low risk of bias

Table 56: GRADE profile – antibiotics versus placebo or no treatment for children with prolonged moist/wet cough

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotics	Placebo or no treatment	Relative (95% CI)	Absolute		
Clinical failure; not cured or substantially improved (assessed with: children (aged <7 years) with prolonged moist / wet cough[1])												
2[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	23/67 (34.3%)[4]	53/73 (72.6%)[5]	RR 0.46 (0.32 to 0.65)	392 fewer per 1000 (from 254 fewer to 494 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Clinical failure; not cured or substantially improved (assessed with: children (aged <7 years) with prolonged moist / wet cough excluding children with known *B. Pertussis*[1])												
2[2]	randomised trials	serious[3]	serious[6]	no serious indirectness	very serious[7]	none	17/61 (27.8%)[4]	47/67 (70.1%)[5]	RR 0.40 (0.12 to 1.29)	421 fewer per 1000 (from 617 fewer to 203 more)	⊕OOO VERY LOW	CRITICAL
Clinical failure; not cured or substantially improved (assessed with: children (aged <7 years) with prolonged moist / wet cough (ITT but using those not lost to follow-up only)[1])												
2[2]	randomised trials	serious[3]	serious[8]	no serious indirectness	very serious[7]	none	14/58 (24.1%)[4]	45/66 (68.2%)[5]	RR 0.37 (0.1 to 1.35)	430 fewer per 1000 (from 614 fewer to 239 more)	⊕OOO VERY LOW	CRITICAL
Additional treatment required due to illness (assessed with: children (aged <7 years) with prolonged moist / wet cough [1])												
2[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	3/59 (5.1%)[4]	24/66 (36.4%)[5]	RR 0.14 (0.04 to 0.45)	313 fewer per 1000 (from 200 fewer to 349 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Adverse effects (vomiting, diarrhoea or rash) (assessed with: children (aged <7 years) with prolonged moist / wet cough[1])												
2[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[9]	none	4/61 (6.6%)[4]	3/67 (4.5%)[5]	RR 1.33 (0.36 to 4.89)	15 more per 1000 (from 29 fewer to 174 more)	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI, confidence interval; RR, relative risk; ITT, intention to treat analysis; RCT, randomised controlled trial; OR, odds ratio

[1] Duration of cough >10 days, follow-up at day 8
[2] Marchant et al. 2005
[3] Downgraded 1 level - neither RCT was assessed by the Cochrane authors as at low risk of bias
[4] Antibiotics were erythromycin (all children had oxymetalozone chloride nose drops, additionally salbutamol use was allowed in both groups) in 1 RCT and amoxicillin/clavulanic acid in the other (no antitussives given)

[5] Placebo or no treatment
[6] Downgraded 1 level - I^2=86% NICE analysis (RR) uses random effects model, the study authors used a fixed effect model and OR 0.13 (95% CI 0.05 to 0.30; I^2=0%)
[7] Downgraded 2 levels: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with antibiotics, and no meaningful difference or appreciable harm with placebo or no treatment
[8] Downgraded 1 level - I^2=86% NICE analysis (RR) uses random effects model, the study authors used a fixed effect model and OR 0.12 (95% CI 0.05 to 0.29; I^2=0%)
[9] Downgraded 2 levels: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with antibiotics, and no meaningful difference or appreciable benefit with placebo or no treatment.

Table 57: GRADE profile – antibiotics versus placebo or no treatment for preventing more serious illness in children with undifferentiated acute respiratory infection

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotics	Placebo or no treatment	Relative (95% CI)	Absolute		
Development of AOM (assessed with: children with undifferentiated acute respiratory infection with previous AOM[1])												
3[2]	randomised trials	serious[3]	no serious inconsistency	serious[4]	serious[5]	none	27/211 (12.8%)[6]	37/203 (18.2%)	RR 0.70 (0.45 to 1.11)	55 fewer per 1000 (from 100 fewer to 20 more)	⊕OOO VERY LOW	CRITICAL
Development of AOM (high income countries) (assessed with: children with undifferentiated acute respiratory infection with previous AOM[1])												
2[2]	randomised trials	serious[3]	no serious inconsistency	serious[4]	serious[5]	none[6]	19/161 (11.8%)	28/157 (17.8%)	RR 0.67 (0.39 to 1.14)	59 fewer per 1000 (from 109 fewer to 25 more)	⊕OOO VERY LOW	CRITICAL
Development of pneumonia (assessed with: children with undifferentiated acute respiratory infection)												
1[2]	randomised trials	serious[3]	not applicable	serious[4]	very serious[7]	none	56/447 (12.5%)[8]	53/442 (12%)	RR 1.05 (0.74 to 1.49)	6 more per 1000 (from 31 fewer to 59 more)	⊕OOO VERY LOW	CRITICAL
Development of pneumonia (assessed with: children aged <11 months with undifferentiated acute respiratory infection)												
1[2]	randomised trials	serious[3]	not applicable	serious[4]	very serious[9]	none	19/171 (11.1%)[8]	18/155 (11.6%)	RR 0.96 (0.52 to 1.76)	5 fewer per 1000 (from 56 fewer to 88 more)	⊕OOO VERY LOW	CRITICAL
Development of pneumonia (assessed with: children aged 12 to 58 months with undifferentiated acute respiratory infection)												
1[2]	randomised trials	serious[3]	not applicable	serious[4]	very serious[7]	none	37/276 (13.4%)[8]	35/287 (12.2%)	RR 1.10 (0.71 to 1.69)	12 more per 1000 (from 35 fewer to 84 more)	⊕OOO VERY LOW	CRITICAL

Abbreviations: AOM, acute otitis media; CI, confidence interval; RR, relative risk; RCT, randomised controlled trial

[1] Diagnosis of AOM was based on an assessment of signs and symptoms as well as an otoscopic examination (bulging, opacity or lack of mobility of the tympanic membrane).
[2] Alves et al. 2016
[3] Downgraded 1 level - no RCT was assessed by the Cochrane authors as at low risk of bias
[4] Downgraded 1 level - the authors estimate that only around 75% of their included population (children with undifferentiated acute respiratory tract infection) may have had a cough presentation
[5] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with antibiotics
[6] Amoxicillin-clavulanate

[7] Downgraded 2 levels: at a default minimal important difference of 25% relative risk increase (RRI), the effect estimate is consistent with no meaningful difference or appreciable harm with antibiotics, and no meaningful difference or appreciable benefit/harm with placebo or no treatment
[8] Ampicillin
[9] Downgraded 2 levels: at a default minimal important difference of 25% relative risk reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with antibiotics, and no meaningful difference or appreciable harm with placebo or no treatment

Appendix I: Studies not-prioritised

Study reference	Reason
Agbabiaka Taofikat B, Guo Ruoling, and Ernst Edzard (2008) Pelargonium sidoides for acute bronchitis: a systematic review and meta-analysis. Phytomedicine: international journal of phytotherapy and phytopharmacology 15(5), 378-85	Higher quality / more recent systematic review included
Anheyer Dennis, Cramer Holger, Lauche Romy, Saha Felix Joyonto, and Dobos Gustav (2017) Herbal Medicine in Children With Respiratory Tract Infection: Systematic Review and Meta-Analysis. Academic pediatrics	Higher quality / more recent systematic review included
Arroll Bruce (2011) Common cold. BMJ clinical evidence 2011	Higher quality / more recent systematic review included
Bjornsdottir Ingunn, Einarson Thomas Ray, Gudmundsson Larus Steinpor, and Einarsdottir Rannveig Alma (2007) Efficacy of diphenhydramine against cough in humans: a review. Pharmacy world & science : PWS 29(6), 577-83	Higher quality / more recent systematic review included
Cheng N, Zhu J, and Ding P (2017) Clinical Effects and Safety of Zhi Sou San for Cough: A Meta-Analysis of Randomized Trials. Evidence-based Complementary and Alternative Medicine 2017, 9436352	Intervention not relevant to UK practice
Chenot J F, and Holzinger F (2011) Systematic review of clinical trials assessing the effectiveness of ivy leaf (Hedera Helix) for acute upper respiratory tract infections. Evidence-based Complementary and Alternative Medicine 2011, 382789	Higher quality / more recent systematic review included
De Blasio , F , Lanata L, Dicpingaitis P V, Saibene F, Balsamo R, and Zanasi A (2013) Efficacy of levodropropizine in the pediatric setting: A meta-analysis of published studies. Trends in Medicine 13(1), 9-14	Intervention not relevant to UK practice
De Blasio , Francesco , Dicpinigaitis Peter V, De Danieli , Gianluca , Lanata Luigi, and Zanasi Alessando (2012) Efficacy of levodropropizine in pediatric cough. Pulmonary pharmacology & therapeutics 25(5), 337-42	Intervention not relevant to UK practice
De Sutter , An I M, van Driel , Mieke L, Kumar Anna A, Lesslar Olivia, and Skrt Alja (2012) Oral antihistamine-decongestant-analgesic combinations for the common cold. The Cochrane database of systematic reviews (2), CD004976	Higher quality / more recent systematic review included
Ding Pinpin, Wang Qian, Yao Jing, Zhou Xian-Mei, and Zhu Jia (2016) Curative Effects of Suhuang Zhike Capsule on Postinfectious Cough: A Meta-Analysis of Randomized Trials. Evidence-based complementary and alternative medicine : eCAM 2016, 8325162	Intervention not relevant to UK practice
Heppermann B, and Jones J S (2009) Honey for the symptomatic relief of cough in children with upper respiratory tract infections. Emergency Medicine Journal 26(7), 522-523	Higher quality / more recent systematic review included
Isbister Geoffrey K, Prior Felicity, and Kilham Henry A (2012) Restricting cough and cold medicines in children. Journal of paediatrics and child health 48(2), 91-8	Higher quality / more recent systematic review included
Jiang Lanhui, Li Ka, and Wu Taixiang (2012) Chinese medicinal herbs for acute bronchitis. The Cochrane database of systematic reviews (2), CD004560	Intervention not relevant to UK practice

Study reference	Reason
Kim Kwan-Il, Shin Seungwon, Lee Nara, Lee Beom-Joon, Lee Junhee, and Lee Hyangsook (2016) A traditional herbal medication, Maekmoondong-tang, for cough: A systematic review and meta-analysis. Journal of ethnopharmacology 178, 144-54	Intervention not relevant to UK practice
Kligler Benjamin, Ulbricht Catherine, Basch Ethan, Kirkwood Catherine Defranco, Abrams Tracee Rae, Miranda Michelle, Singh Khalsa, Karta Purkh, Giles Mary, Boon Heather, and Woods Jen (2006) Andrographis paniculata for the treatment of upper respiratory infection: a systematic review by the natural standard research collaboration. Explore (New York, and N.Y.) 2(1), 25-9	Higher quality / more recent systematic review included
Liu Wei, Jiang Hong-Li, and Mao Bing (2013) Chinese herbal medicine for postinfectious cough: a systematic review of randomized controlled trials. Evidence-based complementary and alternative medicine : eCAM 2013, 906765	Intervention not relevant to UK practice
McDonagh Marian, Peterson Kim, Winthrop Kevin, Cantor Amy, Holzhammer Brittany, and Buckley David I (2016) Improving Antibiotic Prescribing for Uncomplicated Acute Respiratory Tract Infections.	Higher quality / more recent systematic review included
Nitsche Maria Pia, and Carreno Monica (2016) Is honey an effective treatment for acute cough in children?. ?Es la miel un tratamiento efectivo para la tos en poblacion pediatrica? 16 Suppl 2, e6454	Higher quality / more recent systematic review included
Ryan Teresa, Brewer Melanie, and Small Leigh (2008) Over-the-counter cough and cold medication use in young children. Pediatric nursing 34(2), 174-184	Higher quality / more recent systematic review included
Wei Jiafu, Ni Juan, Wu Taixiang, Chen Xiaoyan, Duan Xin, Liu Guanjian, Yiao Jieqi, Wang Qin, Zhen Jie, and Zhou Likun (2006) A systematic review of Chinese medicinal herbs for acute bronchitis. Journal of alternative and complementary medicine (New York, and N.Y.) 12(2), 159-69	Intervention not relevant to UK practice
Zanasi Alessandro, Lanata Luigi, Fontana Giovanni, Saibene Federico, Dicpinigaitis Peter and De Blasio Francesco (2015) Levodropropizine for treating cough in adult and children: a meta-analysis of published studies. Multidisciplinary Respiratory Medicine (2015) 10:19	Higher quality / more recent systematic review included

Appendix J: Excluded studies

Study reference	Reason for exclusion
Aabenhus R, Jensen J-UIS, Jorgensen KJ et al. (2014) Biomarkers as point-of-care tests to guide prescription of antibiotics in patients with acute respiratory infections in primary care. The Cochrane database of systematic reviews (11), CD010130	Excluded on study intervention – biomarkers
Aberdein J, Singer M (2006) Clinical review: A systematic review of corticosteroid use in infections. Critical Care 10(1), 203	Excluded on relevance to the review question – not cough infection
Abou-Shaaban M, Ali AA, Rao PGM et al. (2016) Drug utilization review of cephalosporins in a secondary care hospital in United Arab Emirates. International journal of clinical pharmacy 38(6), 1367-1371	Excluded on study type – not a systematic review or RCT
Abouzgheib W, Pratter MR, Bartter T (2007) Cough and asthma. Current opinion in pulmonary medicine 13(1), 44-8	Excluded on study population – chronic cough and asthma
Anderson-James S, Marchant JM, Acworth JP et al. (2013) Inhaled corticosteroids for subacute cough in children. The Cochrane database of systematic reviews (2), CD008888	Excluded on study population – bronchiolitis
Anonymous (2013) Does amoxicillin help patients with acute LRTI? Drug and Therapeutics Bulletin 51(3), 29	Excluded on study type – not a systematic review or RCT
Antoniu SA, Mihaescu T, Donner CF (2007) Pharmacotherapy of cough-variant asthma. Expert opinion on pharmacotherapy 8(17), 3021-8	Excluded on relevance to the review question – cough variant asthma out-of-scope
Arroll B, Kenealy T, Falloon K (2008) Are antibiotics indicated as an initial treatment for patients with acute upper respiratory tract infections? A review. The New Zealand medical journal 121(1284), 64-70	Excluded on study population – general upper respiratory infection
Bailey EJ, Chang AB, Thomas D (2008) In children with prolonged cough, does treatment with antibiotics have a better effect on cough resolution than no treatment? Part A: Evidence-based answer and summary. Paediatrics and Child Health 13(6), 512-513	Excluded on study type – not a systematic review or RCT
Balaji V, Sivaraj R, Nirmala P (2015) Comparative study of safety and efficacy of azithromycin and amoxicillin in treating children with lower respiratory tract infection. International journal of current pharmaceutical research 7(3), 56-57	Excluded on study population – general lower respiratory infection
Bartley J (2010) Vitamin D, innate immunity and upper respiratory tract infection. The Journal of laryngology and otology 124(5), 465-9	Excluded on study type – not a systematic review or RCT
Basri RS, Weiland DA, Ledgerwood GL (2008) Treatment recommendations for patients with common respiratory tract infections with variables indicative of treatment failure. The Journal of family practice 57(2 Suppl Managing), S19-23	Excluded on study type – not a systematic review or RCT
Bastian P, Fal AM, Jambor J et al. (2013) Candelabra aloe (Aloe arborescens) in the therapy and prophylaxis of upper respiratory tract infections: traditional use and recent research results. Wiener medizinische Wochenschrift (1946) 163(3-4), 73-9	Excluded on study type – not a systematic review or RCT
Becker LA, Hom J, Villasis-Keever M et al. (2011) Beta2-agonists for acute bronchitis. The Cochrane database of systematic reviews (7), CD001726	Excluded on evidence - updated study available

Study reference	Reason for exclusion
Beeh KM, Beier J, Esperester A et al. (2008) Antiinflammatory properties of ambroxol. European journal of medical research 13(12), 557-62	Excluded on study population – COPD
Belvisi MG (2015) Therapeutic advances for treatment-resistant cough. The Lancet 385(9974), 1160-1162	Excluded on relevance to the review question – refractory chronic cough out-of-scope
Blasi F, Page C, Rossolini G et al. (2016) The effect of N-acetylcysteine on biofilms: Implications for the treatment of respiratory tract infections. Respiratory medicine 117, 190-7	Excluded on study population – includes COPD, cystic fibrosis, bronchiectasis, otitis and bronchitis
Blasi F, Stolz D, Piffer F (2010) Biomarkers in lower respiratory tract infections. Pulmonary pharmacology & therapeutics 23(6), 501-7	Excluded on relevance to the review question – biomarkers out-of-scope
Blondeau JM, Tillotson G (2008) Role of gemifloxacin in the management of community-acquired lower respiratory tract infections. International journal of antimicrobial agents 31(4), 299-306	Excluded on study type – not a systematic review or RCT
Bolser DC (2006) Cough suppressant and pharmacologic protussive therapy: ACCP evidence-based clinical practice guidelines. Chest 129(1 Suppl), 238S-249S	Excluded on evidence – higher quality evidence available
Bruyndonckx R, Stuart B, Little P et al. (2017) Amoxicillin for acute lower respiratory tract infection in primary care: subgroup analysis by bacterial and viral aetiology. Clinical microbiology and infection	Excluded on evidence – this article reports findings included within an included systematic review
Cals JWL, Hopstaken RM, Le Doux PHA et al. (2008) Dose timing and patient compliance with two antibiotic treatment regimens for lower respiratory tract infections in primary care. International Journal of Antimicrobial Agents 31(6), 531-536	Excluded on population – COPD and asthma
Chang A B, Winter D, and Acworth J P (2006) Leukotriene receptor antagonist for prolonged non-specific cough in children. The Cochrane database of systematic reviews (2), CD005602	Excluded on study population – probable asthma population
Chaudhary M, Shrivastava S, Sehgal R (2009) Evaluation of efficacy and safety of fixed dose combination of ceftazidime-tobramycin in comparison with ceftazidime in lower respiratory tract infections. Current clinical pharmacology 4(1), 62-66	Excluded on study population – mixed pneumonia and bronchitis
Chung KF, Widdicombe JG (2009) Cough: setting the scene. Handbook of experimental pharmacology (187), 1-21	Excluded on relevance to the review question – book chapter no relevant outcomes
De La Poza Abad, M , Dalmau GM, Bakedano MM et al. (2016) Prescription strategies in acute uncomplicated respiratory infections a randomized clinical trial. JAMA Internal Medicine 176(1), 21-29	Excluded on evidence – this article reports findings included within an included systematic review
de Sa Del Fiol, F, Barberato-Filho S, Lopes LC et al. (2015) Vitamin D and respiratory infections. Journal of infection in developing countries 9(4), 355-61	Excluded on study type – not a systematic review or RCT
De Sutter, A (2015) Systematic review: There is no good evidence for the effectiveness of commonly used over-the-counter medicine to alleviate acute cough. Evidence-Based Medicine 20(3), 98	Excluded on study type – not a systematic review or RCT
Dicpinigaitis PV (2006) Potential future therapies for the management of cough: ACCP evidence-based clinical practice guidelines. Chest 129(1 Suppl), 284S-286S	Excluded on relevance to the review question – review article

Study reference	Reason for exclusion
Dong S, Zhong Y, Lu W et al. (2015) Montelukast for Postinfectious Cough: A Systematic Review of Randomized Controlled Trials. The West Indian medical journal ,	Excluded on outcomes – no effect sizes reported
Ebell MH, Lundgren J, Youngpairoj S (2013) How long does a cough last? Comparing patients' expectations with data from a systematic review of the literature. Annals of family medicine 11(1), 5-13	Excluded on outcomes – prognostic study
Eccles R (2006) Mechanisms of the placebo effect of sweet cough syrups. Respiratory physiology & neurobiology 152(3), 340-8	Excluded on study type – not a systematic review or RCT
Eccles R, Mallefet P (2017) Soothing Properties of Glycerol in Cough Syrups for Acute Cough Due to Common Cold. Pharmacy (Basel, and Switzerland) 5(1),	Excluded on study type – not a systematic review or RCT
Eccles R, Turner RB, Dicpinigaitis PV (2016) Treatment of Acute Cough Due to the Common Cold: Multi-component, Multi-symptom Therapy is Preferable to Single-Component, Single-Symptom Therapy--A Pro/Con Debate. Lung 194(1), 15-20	Excluded on study type – not a systematic review or RCT
Fan Y, Ji P, Leonard-Segal A et al. (2013) An overview of the pediatric medications for the symptomatic treatment of allergic rhinitis, cough, and cold. Journal of pharmaceutical sciences 102(12), 4213-29	Excluded on study type – not a systematic review or RCT
Fiocchi A, Calcinai E, Beghi G et al. (2010) Paediatric upper respiratory infections: the role of antibiotics. International journal of immunopathology and pharmacology 23(1 Suppl), 56-60	Excluded on evidence – unable to obtain article
Flamaing J, Knockaert D, Meijers B et al. (2008) Sequential therapy with cefuroxime and cefuroxime-axetil for community-acquired lower respiratory tract infection in the oldest old. Aging clinical and experimental research 20(1), 81-6	Excluded on population – high % of pneumonia
Gardiner SJ, Gavranich JB, Chang AB (2015) Antibiotics for community-acquired lower respiratory tract infections secondary to Mycoplasma pneumoniae in children. The Cochrane database of systematic reviews 1, CD004875	Excluded on population – mixed lower respiratory tract infection
Gillespie D, Hood K, Farewell D et al. (2015) Adherence-adjusted estimates of benefits and harms from treatment with amoxicillin for LRTI: secondary analysis of a 12-country randomised placebo-controlled trial using randomisation-based efficacy estimators. BMJ open 5(3), e006160	Excluded on evidence – this article reports findings included within an included systematic review
Goldman RD (2014) Honey for treatment of cough in children. Canadian family physician Medecin de famille canadien 60(12), 1107-1110	Excluded on study type – not a systematic review or RCT
Gowan J, Roller L (2007) Cough and colds, products and HMRs. Australian Journal of Pharmacy 88(1047), 67-73	Excluded on study type – not a systematic review or RCT
Guirguis-Blake J (2008) Over-the-counter medications for acute cough symptoms. American family physician 78(1), 52-3	Excluded on study type – not a systematic review or RCT
Gutierrez-Castrellon P, Mayorga-Buitron JL, Bosch-Canto V et al. (2012) Efficacy and safety of clarithromycin in pediatric patients with upper respiratory infections: a systematic review with meta-analysis. Revista de investigacion clinica, and organo del Hospital de Enfermedades de la Nutricion 64(2), 126-35	Excluded on study population – sinusitis and tonsillitis
Hayward G, Thompson MJ, Perera R et al. (2015) Corticosteroids for the common cold. The Cochrane database of systematic reviews (10), CD008116	Excluded on outcomes – no outcomes for cough

Study reference	Reason for exclusion
Hayward G, Thompson M, Hay AD (2012) What factors influence prognosis in children with acute cough and respiratory tract infection in primary care? BMJ (Clinical research ed.) 345, e6212	Excluded on study population – mixed pneumonia population
He B-B, Chen F (2006) Clinical efficacy of cefixime in the treatment of children with respiratory tract infection. Chinese journal of antibiotics 31(9), 571-572+575	Exclude on language – non English language paper
Heppermann B (2009) Towards evidence based emergency medicine: Best BETs from the Manchester Royal Infirmary. Bet 3. Honey for the symptomatic relief of cough in children with upper respiratory tract infections. Emergency medicine journal : EMJ 26(7), 522-3	Excluded on study type – not a systematic review or RCT
Holzinger F, Beck S, Dini L et al. (2014) The diagnosis and treatment of acute cough in adults. Deutsches Arzteblatt international 111(20), 356-63	Excluded on study type – not a systematic review or RCT
Holzinger Felix, and Chenot Jean-Francois (2011) Systematic review of clinical trials assessing the effectiveness of ivy leaf (hedera helix) for acute upper respiratory tract infections. Evidence-based complementary and alternative medicine : eCAM 2011, 382789	Duplicate search result
Hurst Jr, Saleh Ad (2014) Randomised controlled trial: neither anti-inflammatory nor antibiotic treatment significantly shortens duration of cough in acute bronchitis compared with placebo. Evidence-based medicine 19(3), 98	Excluded on study type – not a systematic review or RCT
Kelley LK, Allen PJ (2007) Managing acute cough in children: evidence-based guidelines. Pediatric nursing 33(6), 515-24	Excluded on study type – not a systematic review or RCT
King S, Glanville J, Sanders ME et al. (2014) Effectiveness of probiotics on the duration of illness in healthy children and adults who develop common acute respiratory infectious conditions: a systematic review and meta-analysis. The British journal of nutrition 112(1), 41-54	Excluded on study population – mixed upper respiratory infections
Kinkade S, Long NA (2016) Acute Bronchitis. American family physician 94(7), 560-565	Excluded on study type – not a systematic review or RCT
Lamas A, Ruiz de Valbuena, M, Maiz L (2014) Cough in children. Archivos de bronconeumologia 50(7), 294-300	Excluded on study type – not a systematic review or RCT
Laopaiboon M, Panpanich R, Swa M et al. (2015) Azithromycin for acute lower respiratory tract infections. The Cochrane database of systematic reviews (3), CD001954	Excluded on study population – mixed lower respiratory infections
Li S, Yue J, Dong BR et al. (2013) Acetaminophen (paracetamol) for the common cold in adults. The Cochrane database of systematic reviews (7), CD008800	Excluded on outcomes – no outcomes for cough
Li X-J, Yang H-P, Hu J-L et al. (2007) Sequential moxifloxacin therapy in the treatment of community-acquired lower respiratory tract infections. Chinese journal of infection and chemotherapy 7(3), 180-183	Exclude on language – non English language paper
Lindbaek M (2014) Randomised controlled trial: delayed prescribing for respiratory tract infections in primary care results in lower antibiotic use. Evidence-based medicine 19(5), 197	Excluded on study type – not a systematic review or RCT
Lindell A, Kelsberg G, Safranek S (2011) Antibiotics for viral upper respiratory tract infections in children. American Family Physician 83(6), 747-752	Excluded on study population – sore throat
Linder JA (2008) Antibiotics for treatment of acute respiratory tract infections: Decreasing benefit, increasing risk, and the irrelevance	Excluded on study type – not a systematic review or RCT

Study reference	Reason for exclusion
of antimicrobial resistance. Clinical Infectious Diseases 47(6), 744-746	
Little P, Stuart B, Verheij T et al. (2011) The effect of amoxicillin in lower respiratory tract infection (LRTI): a placebo controlled RCT in 16 primary care GRACE networks from 12 countries in Europe. European respiratory society annual congress, amsterdam, the netherlands, and september 24-28 38(55), 822s [4509]	Excluded on study type – not a systematic review or RCT
Little P, Stuart B, Moore M et al. (2013) Amoxicillin for acute lower-respiratory-tract infection in primary care when pneumonia is not suspected: a 12-country, randomised, placebo-controlled trial. The lancet. Infectious diseases 13(2), 123-129	Excluded on evidence – this article reports findings included within an included systematic review
Little P, Moore M, Kelly J et al. (2014) Delayed antibiotic prescribing strategies for respiratory tract infections in primary care: pragmatic, factorial, randomised controlled trial. BMJ (Clinical research ed.) 348, g1606	Excluded on evidence - not a systematic review or RCT
Lowry JA, Leeder JS (2015) Over-the-Counter Medications: Update on Cough and Cold Preparations. Pediatrics in review 36(7), 286-298	Excluded on study type – not a systematic review or RCT
Lu Q, Chen H-Z, Zhang L-E et al. (2006) A prospective multi-center randomized parallel study on efficacy and safety of cefaclor vs. amoxicillin-clavulanate in children with acute bacterial infection of lower respiratory tract. Chinese journal of infection and chemotherapy 6(2), 77-81	Exclude on language – non English language paper
Mathew JL (2009) Cough syrups - Do they work in acute cough? Indian Pediatrics 46(8), 703-706	Excluded on evidence – higher quality evidence available
Marchant J, Masters Ib, Champion A et al. (2012) Randomised controlled trial of amoxycillin clavulanate in children with chronic wet cough. Thorax 67(8), 689-693	Excluded on population – median duration of illness at entry >15 weeks
Mazzone SB, McGovern AE (2007) Sensory neural targets for the treatment of cough. Clinical and experimental pharmacology & physiology 34(10), 955-62	Excluded on study type – not a systematic review or RCT
McKay R, Mah A, Law MR et al. (2016) Systematic Review of Factors Associated with Antibiotic Prescribing for Respiratory Tract Infections. Antimicrobial agents and chemotherapy 60(7), 4106-18	Excluded on outcomes – no outcomes for cough
Miceli SS, Greco M, Monaco S et al. (2015) Effect of multiple honey doses on non-specific acute cough in children. An open randomised study and literature review. Allergologia et immunopathologia 43(5), 449-55	Excluded on comparator – levodropropizine
Min J-Y, Jang YJ (2012) Macrolide therapy in respiratory viral infections. Mediators of inflammation 2012, 649570	Excluded on outcomes – lacks clinical outcomes
Molassiotis A, Bryan G, Caress A et al. (2010) Pharmacological and non-pharmacological interventions for cough in adults with respiratory and non-respiratory diseases: A systematic review of the literature. Respiratory medicine 104(7), 934-44	Excluded on study type – not a systematic review or RCT
Moore Michael, Stuart Beth, Coenen Samuel, Butler Chris C, Goossens Herman, Verheij Theo JM, Little Paul (2014) Amoxicillin for acute lower respiratory tract infection in primary care: subgroup analysis of potential high-risk groups	Excluded on outcomes – prognostic study
Morice AH (2015) Over-the-counter cough medicines: New approaches. Pulmonary pharmacology & therapeutics 35, 149-51	Excluded on study type – not a systematic review or RCT

Study reference	Reason for exclusion
Morice A, Kardos P (2016) Comprehensive evidence-based review on European antitussives. BMJ open respiratory research 3(1), e000137	Excluded on outcomes – no effect sizes reported
Mulholland S, Chang AB (2009) Honey and lozenges for children with non-specific cough. The Cochrane database of systematic reviews (2), CD007523	Excluded on study population – chronic cough
Nct (2013) Non-antibiotic Prescribing for Acute Upper Respiratory Tract Infection: a Randomized-control Trial. Clinicaltrials.gov	Excluded – study in recruitment
Oduwole O, Meremikwu MM, Oyo-Ita A et al. (2014) Cochrane in context: Honey for acute cough in children. Evidence-Based Child Health 9(2), 445-446	Excluded on study type – not a systematic review or RCT
O'Sullivan JW, Harvey RT, Glasziou PP et al. (2016) Written information for patients (or parents of child patients) to reduce the use of antibiotics for acute upper respiratory tract infections in primary care. The Cochrane database of systematic reviews 11, CD011360	Excluded on study intervention – written information
Park CI (2013) Children with "chronic wet cough" (presumed protracted bacterial bronchitis) respond to 14 days of amoxicillin clavulanate. Journal of pediatrics 162(3), 653-654	Excluded on study type – not a systematic review or RCT
Peng F-Y, Deng H, Duan M-G, and Chen H (2006) Evaluation of intravenous moxifloxacin in the treatment of lower respiratory tract infection. Chinese journal of infection and chemotherapy 6(2), 105-109	Exclude on language – non English language paper
Paul IM (2012) Therapeutic options for acute cough due to upper respiratory infections in children. Lung 190(1), 41-4	Excluded on study type – not a systematic review or RCT
Poole PJ, Black PN (2006) Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease. The Cochrane database of systematic reviews (3), CD001287	Excluded on study population – chronic bronchitis and COPD
Ramanuja S, Kelkar PS (2010) The approach to pediatric cough. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, and & Immunology 105(1), 3-42	Excluded on study population – not acute cough population
Ramirez N, Jared M, Hodgden J et al. (2012) Question: does guaifenesin improve outcomes in patients with cough associated with upper respiratory infection compared with no intervention? The Journal of the Oklahoma State Medical Association 105(10), 397-8	Excluded on study type – not a systematic review or RCT
Sarkhail P, Shafiee A, Sarkheil P (2013) Biological activities and pharmacokinetics of praeruptorins from Peucedanum species: a systematic review. BioMed research international 2013, 343808	Excluded on study type – not a systematic review or RCT
Schuetz P, Albrich W, Christ-Crain M et al. (2010) Procalcitonin for guidance of antibiotic therapy. Expert review of anti-infective therapy 8(5), 575-87	Excluded on relevance to the review question – biomarkers out-of-scope
Schuetz P, Amin DN, Greenwald JL (2012) Role of procalcitonin in managing adult patients with respiratory tract infections. Chest 141(4), 1063-1073	Excluded on relevance to the review question – biomarkers out-of-scope
Schuetz P, Chiappa V, Briel M et al. (2011) Procalcitonin algorithms for antibiotic therapy decisions: a systematic review of randomized controlled trials and recommendations for clinical algorithms. Archives of internal medicine 171(15), 1322-31	Excluded on relevance to the review question – biomarkers out-of-scope

Study reference	Reason for exclusion
Schuetz P, Wirz Y, Sager R et al. (2017) Procalcitonin to initiate or discontinue antibiotics in acute respiratory tract infections. The Cochrane database of systematic reviews 10, CD007498	Excluded on relevance to the review question – biomarkers out-of-scope
Shaughnessy AF (2014) Amoxicillin/clavulanate or ibuprofen no better than placebo for acute bronchitis. American Family Physician 89(3), 225-226	Excluded on study type – not a systematic review or RCT
Suchitra N T, Emmanuel S, and Sheeba R M (2013) A Phytopharmacological review on Ichnocarpus frutescens L. Research Journal of Pharmacy and Technology 6(6), 607-609	Excluded on relevance to the review question – no relevant outcomes
Tackett KL, Atkins A (2012) Evidence-based acute bronchitis therapy. Journal of pharmacy practice 25(6), 586-90	Excluded on study type – not a systematic review or RCT
Tandan M, Vellinga A, Bruyndonckx R et al. (2017) Adverse Effects of Amoxicillin for Acute Lower Respiratory Tract Infection in Primary Care: Secondary and Subgroup Analysis of a Randomised Clinical Trial. Antibiotics (Basel, and Switzerland) 6(4)	Excluded on evidence – this article reports findings included within an included systematic review
Teepe J, Broekhuizen Bd, Loens K et al. (2016) Disease Course of Lower Respiratory Tract Infection With a Bacterial Cause. Annals of family medicine 14(6), 534-539	Excluded on evidence – this article reports findings included within an included systematic review
Timmer A, Gunther J, Rucker G et al. (2008) Pelargonium sidoides extract for acute respiratory tract infections. The Cochrane database of systematic reviews (3), CD006323	Excluded on duplication – an updated version has been included
Torjesen I (2017) Immediate antibiotics for uncomplicated RTIs do not reduce risk of admission and death, study finds. BMJ (Online) 357, 2496	Excluded on study type – not a systematic review or RCT
Vassilev ZP, Kabadi S, Villa R (2010) Safety and efficacy of over-the-counter cough and cold medicines for use in children. Expert opinion on drug safety 9(2), 233-42	Excluded on evidence – higher quality evidence available
Wang J, Xu H, Liu P et al. (2017) Network meta-analysis of success rate and safety in antibiotic treatments of bronchitis. International journal of chronic obstructive pulmonary disease 12, 2391-2405	Excluded on study population – acute, chronic and acute exacerbation of chronic bronchitis
Wang J, Xu H, Wang D et al. (2017) Comparison of Pathogen Eradication Rate and Safety of Anti-Bacterial Agents for Bronchitis: A Network Meta-Analysis. Journal of cellular biochemistry 118(10), 3171-3183	Excluded on study population – includes chronic bronchitis population
Wang PX, Yin YS, Chen Y et al (2016) Clinical efficacy and safety of azithromycin versus amoxicillin-clavulanic acid in the treatment of some acute respiratory infections in children: systematic evaluation. Journal of international pharmaceutical research 43(4), 646-651	Excluded on language – non English language paper
Widdicombe J G, and Ernst E (2009) Clinical cough V: complementary and alternative medicine: therapy of cough. Handbook of experimental pharmacology (187), 321-42	Excluded on relevance to the review question – book chapter no relevant outcomes
Wilcox MH, Finch R, Wyncoll D et al. (2011) Fluoroquinolones in the treatment of severe community-acquired. British journal of hospital medicine (London, and England : 2005) Suppl, S1-7	Excluded on study population – pneumonia
Wu T, Zhang J, Qiu Y et al. (2007) Chinese medicinal herbs for the common cold. The Cochrane database of systematic reviews (1), CD004782	Excluded on outcomes – no effect sizes reported

Study reference	Reason for exclusion
Yang M, So T-Y (2014) Revisiting the safety of over-the-counter cough and cold medications in the pediatric population. Clinical pediatrics 53(4), 326-30	Excluded on study type – not a systematic review or RCT
Yuan Z, Yang C, Huang W-X et al. (2007) A multi-center randomized controlled clinical trial of doxycycline versus azithromycin for injection in the treatment of acute bacterial infections. Chinese journal of antibiotics 32(1), 37-42	Excluded on language – non English language paper
Zhang L, Wang Y, Yang D et al. (2015) Platycodon grandiflorus - an ethnopharmacological, phytochemical and pharmacological review. Journal of ethnopharmacology 164, 147-61	Excluded on relevance to the review question – no relevant outcomes
Zhang L, Hu P (2017) Cost-effectiveness analysis of oral versus intravenous drip infusion of levofloxacin in the treatment of acute lower respiratory tract infection in Chinese elderly patients. Clinical interventions in aging 12, 673-678	Excluded on population – COPD and pneumonia