National Institute for Health and Care Excellence

APG Sinusitis (acute)

Sinusitis (acute): antimicrobial prescribing guideline

Evidence review

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Final version

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Contents

1 Context

1.1 Background

Acute sinusitis (also sometimes called rhinosinusitis) is a self-limiting upper respiratory tract infection (Respiratory tract infections (self-limiting): prescribing antibiotics [2008] NICE guideline CG69). In people who are not treated, about half will have complete cure and about three quarters will have clinically improved symptoms at 2 weeks (Rosenfeld et al. 2007). Acute sinusitis usually follows a common cold and is defined as sinonasal inflammation lasting less than 4 weeks associated with sudden onset of symptoms. Diagnosing acute sinusitis is usually done clinically by examination and the presence of multiple symptoms. Anterior rhinoscopy may reveal evidence of inflammation, mucosal oedema and discharge. Measuring erythrocyte sedimentation rate or C-reactive protein, or carrying out endoscopy or imaging is not usually required in uncomplicated cases (International Consensus Statement on Allergy and Rhinology: rhinosinusitis [2016]).

In adults symptoms of acute sinusitis include:

- nasal blockage, obstruction or congestion, or nasal discharge (anterior or posterior nasal drip), and
- facial pain or pressure (which may be localized over the infected sinus or may affect teeth, upper jaw, eye, side of face, or forehead), or reduction or loss of the sense of smell.

In children, who often present with non-specific symptoms in the upper respiratory tract, symptoms of acute sinusitis include:

- nasal blockage, obstruction or congestion, or discoloured nasal discharge (anterior or posterior nasal drip), or
- a cough that may occur during the day or night.

Facial pain or pressure is less prevalent in children, but they may experience ear discomfort from Eustachian tube blockage. Children aged under 5 who present with fever should be assessed and managed as outlined in the NICE guideline on fever in under 5s: assessment and initial management (2017).

In both adults and children symptoms of allergy (sneezing, itching, watery rhinorrhoea and watery eyes) should be considered to rule out allergic rhinitis.

Acute sinusitis is usually triggered by a viral upper respiratory tract infection, and only 0.5 to 2.2% of acute viral sinusitis becomes complicated by a bacterial infection. However, it is difficult to distinguish between acute viral sinusitis and acute bacterial sinusitis clinically, particularly without endoscopy or imaging. Symptoms alone such as purulent nasal discharge, fever or facial pain cannot distinguish between viral or bacterial infection, but bacterial infection is more likely with duration of symptoms greater than 10 days. Clinical factors that have been suggested to be more associated with a bacterial cause are as follows (International Consensus Statement on Allergy and Rhinology: rhinosinusitis), with multiple factors possibly making a bacterial infection more likely:

- persistence of symptoms beyond 10 days
- discoloured or purulent nasal discharge
- severe localised unilateral pain (particularly pain over teeth and jaw)
- fever
- marked deterioration after an initial milder phase ('double-sickening').

However, a systematic review by Young et al. 2008 found common clinical signs and symptoms could not confidently identify sub-groups of people who may benefit from antibiotics, with only purulent nasal discharge in the pharynx (noted by the physician using a rhinoscope) having some prognostic value.

In bacterial infections, the most common causative pathogens are *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* and *Staphylococcus aureus* (European Position Paper [EPOS] on Rhinosinusitis and Nasal Polyps [2012]).

Respiratory tract infections, including acute sinusitis, are a common reason for consultations in primary care, and therefore are a common reason for potential antibiotic prescribing. In 2005 it was estimated that a quarter of the population visited their GP because of a respiratory tract infection each year (NICE guideline on respiratory tract infections (self-limiting): prescribing antibiotics: full guideline [2008]). However, consultation rates for acute respiratory tract infections in primary care have been decreasing (Gulliford et al. 2009), as have prescriptions for antimicrobials generally in primary care (English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) report [2016]).

UK primary care data for adults from 2011 found there was a mean rate of 217 respiratory tract infection consultations per 1000 person years, and a mean rate of 119 antibiotic prescriptions for respiratory tract infections per 1000 person years (Gulliford et al. 2014). Consultations for sinusitis specifically accounted for 9% of all respiratory tract infection consultations, but the median practice issued an antibiotic prescription for 91% of these (varying between 67% in the lowest prescribing practices to 100% in the highest prescribing practices).

1.2 Managing self-limiting infections

Acute sinusitis 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 antibiotic prescribing or immediate prescribing).

The NICE guideline on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) also has recommendations to not issue immediate antimicrobial prescriptions to people who are likely to have a self-limiting condition. Instead other options such as self-care with over the counter preparations, back-up 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 symptoms in acute sinusitis include paracetamol or ibuprofen, nasal or oral decongestants, nasal saline, antihistamines, mucolytics, applying warm face packs and steam inhalation. However, the evidence for these is limited (see Clinical effectiveness).

1.2.2 No antibiotic prescribing strategies

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

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

1.2.3 Antibiotic prescribing strategies

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

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

1.3 Safety netting advice

The NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population (2017) recommends that people with self-limiting infections should be given explicit advice on when to seek medical help, which symptoms should be considered 'red flags' and safety-netting advice, such as how long symptoms are likely to last with and without antimicrobials, what to do if symptoms get worse, what to do if they experience adverse effects from the treatment and when to ask again for medical advice.

The NICE clinical knowledge summary on sinusitis recommends that people with acute sinusitis should be advised to make a follow-up appointment if their symptoms rapidly

deteriorate, or they develop a high temperature or marked local pain that is predominately unilateral.

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

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

- a severe systemic infection (see the NICE guideline on sepsis)
- symptoms and signs suggestive of intraorbital complications, indicated by periorbital oedema or cellulitis, a displaced globe, double vision, ophthalmoplegia, or reduced visual acuity
- symptoms and signs suggestive of intracranial complications, indicated by severe frontal headache, swelling over the frontal bone, symptoms or signs of meningitis, or focal neurological signs.

The International Consensus Statement on Allergy and Rhinology: rhinosinusitis (2016) states that sinus disease is the underlying cause of about 10% of intracranial suppuration and is associated with 10% to 90% of periorbital infections. However complications are rare, with an incidence in large epidemiological studies of 2.5 to 4.3 per million people per year. The most common complications were orbital, then intracranial, with osseous complications being least common. Orbital complications occurred mainly in small children, with intracranial complications occurring at any age.

2 Evidence selection

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

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

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

2.1 Literature search

A literature search was developed to identify evidence for the effectiveness and safety of interventions for managing acute sinusitis (see appendix C: literature search strategy for full details). The literature search identified 6,682 references. These references were screened using their titles and abstracts and 298 full text references were obtained and assessed for relevance. Seventy-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 from the literature search are described in the interim process guide (2017). Fourteen of the 73 references were prioritised by the committee as the best available evidence and were included in this evidence review (see appendix F: included studies).

The 59 references that were not prioritised for inclusion are listed in appendix I: not prioritised studies, with reasons for not prioritising the studies. Studies that assessed oral corticosteroids, therapeutic ultrasound, probiotics and herbal medicines were not prioritised by the committee. The committee agreed that oral corticosteroids are not currently used in routine clinical practice for managing acute sinusitis and there would be safety concerns associated with their use when managing a self-limiting infection. Furthermore the literature search did not identify any RCTs that add to what is currently known. Herbal remedies and probiotics were not prioritised as all the RCTs identified were non-UK studies with preparations unlikely to be available in the UK. Therapeutic ultrasound was not prioritised as it was unlikely to be available in the UK for managing acute sinusitis. Also see appendix E: evidence prioritisation for more information on study selection.

The remaining 225 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 to 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
Nasal saline (adults and children)					
King et al. 2015 Systematic review. Multiple countries. Follow-up up to 28 days	n=749 (5 RCTs)	Adults and children with clinical diagnosis of acute upper respiratory tract infection featuring nasal or sinus symptoms for less than 4 weeks	Nasal saline irrigation (spray, drops or jet flow) with or without standard treatment	No treatment or standard treatment	Change in severity of symptoms or time to resolution of symptoms
Abbreviations: RCT, Randomised controlled trial					

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

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Nasal decongestants (children)					
Smith et al. 2013 Systematic review. Multiple countries. Follow-up up to 14 days	n=100 (2 RCTs)	Children with acute uncomplicated sinusitis	Decongestant nasal spray (with decongestant-antihistamine syrup in 1 RCT)	Placebo or intranasal Ems mineral salts	Improvement in symptoms
Nasal corticosteroids (adults and children)					
Zalmanovici Trestioreanu et al. 2013 Systematic review. Multiple countries. Follow up 15 or 21 days	n=1,943 (4 RCTs)	Adults and children with clinical diagnosis of acute sinusitis confirmed by radiological evidence or nasal endoscopy	Nasal corticosteroid	Placebo or no treatment	Proportion of participants with resolution or improvement of symptoms
Keith et al. 2012	n=737	Adults and children aged ≥12 years with uncomplicated acute	2 intervention arms:	Placebo	Mean change from baseline in daily MSS during treatment period

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
RCT. Multiple countries. Follow up 14 days		sinusitis (excluding pregnant women)	fluticasone nasal spray 110 micrograms daily for 14 days fluticasone nasal spray 110 micrograms twice a day for 14 days		
Meltzer et al. 2005 RCT. Reported in 3 publications. Multiple countries. Follow-up 14 days	n=981	Adults and children aged ≥12 years with signs and symptoms of acute sinusitis	3 intervention arms: mometasone nasal spray 200 micrograms once a day for 15 days mometasone nasal spray 200 micrograms twice a day for 15 days amoxicillin 500 mg three times daily for 10 days	Placebo	Mean am/pm MSS during treatment period
Abbreviations: MSS, Major symptom score; RCT, Randomised controlled trial					

Table 3: Summary of included studies: antimicrobials

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Back-up antibiotics (adults)					
de la Poza Abad et al. 2016 Open label RCT. Spain	n=405	Adults with acute uncomplicated sinusitis (method of diagnosis unclear)	3 interventions: no prescription patient-led back-up prescription delayed prescription collection	Immediate antibiotic prescription	Duration and severity of symptoms
Antibiotics versus placebo (adults and children)					
Ahovuo-Saloranta et al. 2014[1]	n=1,915 (9 RCTs)	Adults with clinically diagnosed acute maxillary sinusitis,	Antibiotic (penicillin or amoxicillin)	Placebo	Clinical failure (lack of full recovery or

[1] Ahovuo-Saloranta et al. 2014 was withdrawn for technical reasons, but the content of the review remains valid.

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Systematic review and meta-analysis. Multiple countries. Follow-up to 60 days		confirmed or not by imaging or bacterial culture			improvement) at 7 to 15 days follow-up
Cronin et al. 2013 Systematic review and meta-analysis. Multiple countries. Follow-up at 14 days	n=392 (4 DB RCTs)	Children with clinically diagnosed or imaged or laboratory confirmed acute sinusitis	Antibiotic (amoxicillin, co-amoxiclav and cefuroxime)	Placebo	Efficacy of antibiotics compared with placebo in the treatment of sinusitis in children
Falagas et al. 2008 Systematic review and meta-analysis. Multiple countries. Follow-up at 14-15 days	n=3,291 (17 DB RCTs)	Adults and children with clinically diagnosed, imaged or laboratory confirmed acute sinusitis	Antibiotic (different antibiotics were used, but 10 RCTs used amoxicillin	Placebo	Proportion of participants cured or improved
Lemiengre et al. 2012 Systematic review and meta-analysis. Multiple countries. Follow-up at 14 days	n=2,450 (10 RCTs)	Adults with clinically diagnosed acute sinusitis	Antibiotic (different antibiotics were used in the RCTs)	Placebo	Proportion of participants cured at a specific time point
Rosenfeld et al. 2007 Systematic review and meta-analysis. Multiple countries. Follow-up at 14-15 days	n=3,159 (13 DB RCTs)	Adults and children with acute sinusitis	Antibiotic (different antibiotics were used in the RCTs)	Placebo	Natural history of acute sinusitis
Smith 2013 Systematic review. Multiple countries. Follow-up at 14 days	n=392 (4 DB RCTs)	Children with clinically diagnosed or imaged or laboratory confirmed acute sinusitis	Antibiotic (amoxicillin, co-amoxiclav and cefuroxime)	Placebo	Efficacy of antibiotics compared with placebo in the treatment of sinusitis in children
Young et al. 2008 Systematic review and meta-analysis. Multiple countries. Follow-up at 14-15 days	n=2782 (10 DB RCTs)	Adults with clinically diagnosed sinusitis	Antibiotic (different antibiotics were used in the RCTs)	Placebo	To assess whether common signs and symptoms can be used to identify a sub-group of patients who benefit from antibiotics.

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Antibiotics versus other antibiotics (adults and children)					
Ahovuo-Saloranta et al. 2014[2] Systematic review. Multiple countries. Follow-up at 7 to 15 and 16 to 60 days	n=not reported (54 RCTs)	Adults with clinically diagnosed acute maxillary sinusitis, confirmed or not by imaging or bacterial culture	Antibiotics of different classes	Other antibiotics	Clinical failure (lack of full recovery or improvement) at 7 to 15 days follow-up
Karageorgopoulos at al. 2008 Systematic review. Multiple countries. Follow-up at 31 days	n=4,640 (11 RCTs: 5 open label studies, 5 DB RCT and 1 investigator blinded study)	Adults with clinically diagnosed acute maxillary sinusitis, confirmed or not by imaging or bacterial culture	Quinolone antibiotics	Beta-lactam antibiotics	Clinical success (clinical cure or substantial improvement in symptoms) at the test of cure time point
Smith 2013 Systematic review. Multiple countries. Follow-up at 3-20 days	n=485 (5 RCTs)	Children with clinically diagnosed, imaged or laboratory confirmed acute sinusitis	Antibiotics of different classes	Other antibiotics	Cure or improvement at follow-up
Duration of antibiotic treatment (adults)					
Falagas et al. 2009 Systematic review. Multiple countries. Follow-up varied according to study	n=4,430 (12 RCTs)	Adults with diagnosis of acute bacterial sinusitis confirmed by radiograph in all studies	Antibiotic (short course for 3-7 days)	Same antibiotic at the same dose (longer course for 6-10 days)	Clinical success defined as cure (complete resolution) or improvement of symptoms and signs
Abbreviations: RCT, Randomised controlled trial; DB, Double blind					

[2] Ahovuo-Saloranta et al. 2014 was withdrawn for technical reasons, but the content of the review remains valid.

3 Clinical effectiveness

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

3.1 Non-pharmacological interventions

3.1.1 Nasal saline in adults and children

The evidence review for nasal saline is based on 1 systematic review and meta-analysis of 5 randomised controlled trials (RCTs) (King et al. 2015) in adults and children with acute upper respiratory tract infection featuring nasal or sinus symptoms.

This systematic review (n=749) compared nasal saline (spray, drops or jet flow) with or without standard treatment to no treatment or standard treatment for up to 28 days. The included trials were generally small and of low quality, and measured various outcomes making pooling of data difficult. When the results from 2 RCTs in adults were compared in a meta-analysis there was no difference between groups in the time to resolution of symptoms: 9.24 days in the control group and 0.74 lower in the nasal saline group (95% confidence interval [CI] 2.58 lower to 1.11 higher; very low quality evidence). Most of the included studies found that nasal saline had no benefit on nasal symptom scores (low quality evidence). In the largest trial in children aged 6 to 10 years, there were statistically significant reductions in nasal symptom score, nasal secretion type score and nasal breathing score, but the clinical importance of these improvements may be minimal. The reduction in nasal secretion score at up to 3 weeks with nasal saline compared with control was about 0.3 points on 4-point scale (moderate quality evidence).

3.1.2 Other non-pharmacological interventions

No systematic reviews or RCTs were identified that compared steam inhalation or applying warm face packs with placebo or another intervention in adults or children with acute sinusitis.

3.2 Non-antimicrobial pharmacological interventions

3.2.1 Nasal decongestants in adults and children

The evidence review for nasal decongestants is based on 1 systematic review (Smith et al. 2013), which included 2 RCTs of nasal decongestants in children with acute uncomplicated sinusitis. No systematic reviews or RCTs were identified that compared nasal decongestants with placebo or another intervention in adults with acute sinusitis.

In 1 RCT (n=34) oxymetazoline nasal spray plus a decongestant-antihistamine syrup was compared with placebo nasal spray and syrup, and there was no difference between groups in mean symptom scores at day 3 or 14 (low quality evidence). In the other RCT (n=66), there was no difference between xylometazoline nasal spray and intranasal Ems mineral salts in mucosal inflammation symptoms at day 14. However, at day 7 there was less nasal discharge in the mineral salts group (p=0.0163; low quality evidence).

3.2.2 Nasal corticosteroids in adults and children

Nasal corticosteroid compared with placebo

The evidence review for nasal corticosteroids is based on 1 systematic review and meta-analysis of 4 placebo-controlled, double-blind RCTs (Zalmanovici Trestioreanu et al. 2013) and 2 double blind RCTs (Keith at al. 2012 and Meltzer at al. 2005) in adults and children with acute sinusitis. Meltzer et al (2005) (reported in 3 publications) was included in the systematic review but the results for all comparisons were not presented separately. Only 1 RCT in the systematic review (Barlan et al. 1997) was conducted specifically in children, and it was not possible for these data to be included in the meta-analysis.

The systematic review (Zalmanovici Trestioreanu et al. 2013; n=1,943) in adults and children compared a nasal corticosteroid with placebo for 15 or 21 days. Diagnosis was confirmed by radiology or nasal endoscopy and many participants were also taking an antimicrobial. When the results from 3 RCTs were included in a meta-analysis, participants receiving a nasal corticosteroid (all doses, with or without an antibiotic) were significantly more likely to experience symptom resolution compared with placebo or no treatment (73.0% versus 66.4%; relative risk [RR] 1.11, 95% CI 1.04 to 1.18; number needed to treat [NNT] 16 [95% CI 9 to 48]; moderate quality evidence). However, a fixed-effects model was used for the analysis when there was considerable heterogeneity between the studies; the result was no longer statistically significant when a random effects model was used (RR 1.14, 95% CI 0.97 to 1.34; low quality evidence).

When different doses were analysed, people using a higher dose of nasal corticosteroid (equivalent to mometasone 400 micrograms a day) were significantly more likely to experience symptom resolution compared with placebo (2 RCTs, n=1,130: 72.7% versus 66.7%; RR 1.10, 95% CI 1.02 to 1.18; NNT 17 [95% CI 9 to 161]; high quality evidence). About half of participants were also receiving an antibiotic in this analysis. A lower dose of nasal corticosteroid (equivalent to mometasone 200 micrograms a day) was not significantly more effective than placebo (moderate quality evidence). There were no statistically significant differences in the rates of relapse in symptoms with a nasal corticosteroid compared with placebo (2 RCTs; all doses, with or without an antibiotic; moderate quality evidence).

One double blind RCT (Keith at al. 2012; n=737) compared 2 doses of fluticasone nasal spray (110 micrograms once a day and twice a day) with placebo in adults and children aged 12 years and over with acute sinusitis symptoms for longer than 10 days. People with sudden onset acute sinusitis that was suspected to be bacterial based on symptoms (high temperature and persistent severe facial or tooth pain) were excluded. There was a statistically significant reduction in major symptom score during treatment with fluticasone for 14 days compared with placebo. The mean difference with fluticasone 110 micrograms once a day compared with placebo was −0.386 (95% CI −0.67 to −0.10, p=0.008); and with the twice a day dose it was −0.357 (95% CI −0.64 to −0.07, p=0.014) from a baseline score of about 7 in all groups (moderate quality evidence). It is not clear whether this is a clinically important difference. The differences in median times to symptom improvement were not statistically significant between the 2 doses of fluticasone (7 days) and placebo (8 days; moderate quality evidence). There was also no significant difference in the participant's use of antibiotics during the study period (<3% in all groups; moderate quality evidence) and in quality of life (measured by the SNOT-20 score; high quality evidence).

Nasal corticosteroid compared with antibiotic

One double-blind RCT included in the systematic review (Meltzer at al. 2005; n=981) compared 2 doses of mometasone nasal spray for 15 days (200 micrograms once a day and 200 micrograms twice a day) with amoxicillin 500 mg three times daily for 10 days and placebo in adults and children aged 12 years and over with symptoms for at least 7 days. People with sudden onset acute sinusitis that was suspected to be bacterial based on symptoms (high temperature, persistent severe unilateral facial or tooth pain, facial swelling, dental involvement, or a worsening of symptoms after initial improvement) were excluded.

Meltzer et al. (2005) showed that there was a statistically significant reduction in major symptom score of about −0.6 with mometasone 200 micrograms twice a day compared with amoxicillin 500 mg three times daily (p=0.002) from a baseline of about 8 in both groups (moderate quality evidence). It is not clear whether this is a clinically important difference. There was no significant difference between mometasone 200 micrograms once a day and amoxicillin (p=0.193; moderate quality evidence).

2.3 Other non-antimicrobial pharmacological interventions

No systematic reviews or RCTs were identified that compared paracetamol or ibuprofen with placebo or another intervention in adults or children with acute sinusitis. However, these medicines have a well-established efficacy and safety profile for managing pain and fever (see Safety and tolerability).

No systematic reviews or RCTs were identified that compared oral decongestants, antihistamines, or mucolytics with placebo or another intervention in adults or children with acute sinusitis.

3 Antimicrobials in adults

The evidence review for antimicrobials in adults is based on 7 systematic reviews and 1 RCT. The included studies cover the natural history of acute sinusitis, prognostic factors, back-up antibiotic prescribing, antibiotics versus placebo, antibiotics versus other antibiotics and the duration of antibiotic treatment. Most of the studies included in the systematic reviews allowed the use of other symptomatic relief medicines and many were limited by excluding people with severe or worsening illness.

One systematic review (Rosenfeld et al. 2007) examined the natural history of acute sinusitis in adults from placebo groups in studies where antibiotics were compared with placebo. This found that, when people were untreated 45% of adults will have complete cure (4 RCTs: 95% CI 23% to 70%; moderate quality evidence) and 73% of adults will have clinically improved symptoms (3 RCTs: 95% CI 67% to 78%) at 14 to 15 days.

3.1 Back-up antibiotics

One open label RCT (de la Poza Abad et al. 2015) found that a back-up antibiotic prescription (either patient-led collection or delayed collection [after 3 days]) or no antibiotic prescription was as effective (in symptom severity and duration) as an immediate antibiotic prescription for managing upper respiratory tract infections (including acute uncomplicated sinusitis). There were no significant differences in the duration or severity of symptoms between any groups at follow-up (days 2, 7, 15 and 22; low to moderate quality evidence).

There were significantly lower rates of antibiotic collection in the delayed collection prescription group (26%, p<0.001) and patient-led back-up prescription group (34.7%, p<0.001) compared with the immediate prescription group (89.1%; low quality evidence). Antibiotic use was also significantly lower in the delayed collection prescription group (23%, p<0.001) and patient-led back-up prescription group (32.6%, p<0.001), compared with an immediate prescription (91.1%; low quality evidence).

3.3.2 Antibiotics compared with placebo

Overall treatment effect for antibiotics (cure or improvement)

Three systematic reviews (Ahovuo-Saloranta et al. 2014; Falagas et al. 2008; Rosenfeld et al. 2007) measured overall treatment effect for antibiotics compared with placebo. In summary, antibiotics did not significantly increase the proportion of adults with cure or improvement at 3 to 5 days follow-up compared with placebo. At longer durations of follow up (approximately 7 to 15 days) there was a statistically significant difference in effectiveness for antibiotics compared with placebo. However, the clinical difference in cure or improvement was small, and this benefit was not maintained in the longer term (approximately 16 to 60 days follow up).

In a meta-analysis of 16 RCTs (Falagas et al. 2008) 77.2% of participants had overall cure or improvement with antibiotics compared with 67.8% of participants in the placebo groups. The estimated odds ratio (OR) was 1.64 (n=2,648: 95% CI 1.35 to 2.00; NNT 11 [95% CI 8 to 17]; high quality evidence). This effect was seen at both 7 to 11 days follow up (9 RCTs, n=1,251: OR 1.95, 95% CI 1.35 to 2.81; moderate quality evidence) and 14 to 15 days follow up (7 RCTs, n=1,397: OR 1.51, 95% CI 1.14 to 1.99; high quality evidence).

In a meta-analysis of 5 RCTs (Ahovuo-Saloranta et al. 2014) clinical failure (a lack of cure or improvement) was significantly lower in the antibiotic group compared with the placebo group at 7 to 15 days follow up; 8.7% of the antibiotic group had clinical failure compared with 13.6% of the placebo group (n=1,058, RR 0.66, 95% CI 0.47 to 0.94; NNT 21 [95% CI 12 to 88]; moderate quality evidence). At 16 to 60 days follow up there was no significant difference between the groups (2 RCTs; data not pooled; low to moderate quality evidence).

A meta-analysis by Rosenfeld et al (2007) measured cure or improvement at 3 to 5 days follow up and found no significant effect for antibiotics compared with placebo (2 RCTs, n=258: risk difference 0.103, p=0.124) (very low quality evidence). However, a significant effect at both 7 to 12 days follow up (5 RCTs, n=543: risk difference 0.142, p=0.038; low quality evidence) and 14 to 15 days follow up (3 RCTs, n=800: risk difference 0.073, p=0.013; high quality evidence) was found. At 7 to 12 days follow up, 87.5% of the antibiotic group had cure or improvement compared with 77.4% of the placebo group (NNT 10 [95% CI 6 to 24]).

Cure or clinical failure (a lack of full recovery)

Five systematic reviews estimated ‘cure’ as an outcome, but the definitions used and duration of follow up varied. All studies (Ahovuo-Saloranta et al. 2014, Falagas et al. 2008, Lemiengre et al. 2012, Rosenfeld et al. 2007 and Young et al. 2008) found some evidence of benefit for antibiotics compared with placebo.

The meta-analysis by Falagas et al (2008) found that the proportion of participants cured was significantly higher with antibiotics compared with placebo (12 RCTs,

n=1,813: 57.2% versus 46.0%; OR 1.82, 95% CI 1.34 to 2.46; NNT 9 [95% CI 7 to 15]; low quality evidence).

The meta-analysis by Ahovuo-Saloranta et al (2014) examined clinical failure (a lack of full recovery). Clinical failure rates were significantly lower with antibiotics compared with placebo at 7 to 15 days follow up (5 RCTs, n=680: 47.0% versus 61.4%; RR 0.73, 95% CI 0.63 to 0.85; NNT 7 [95% CI 5 to 15]; moderate quality evidence), but not at 16 to 60 days follow up (1 RCT, n=169: RR 0.63, 95% CI 0.38 to 1.05; moderate quality evidence).

In a meta-analysis of 8 RCTs (Lemiengre et al. 2012; n=1,687) the estimated OR for overall cure was 1.25 (95% CI 1.02 to 1.53) for antibiotics compared with placebo (60.6% versus 55.0% respectively; NNT 18 [95% CI 10 to 116]; high quality evidence). However, no significant difference in cure was shown at 7 days follow up (4 RCTs, n=856), 10 days follow up (4 RCTs, n=1,048) or 14 days follow up (3 RCTs, n=467) (moderate to high quality evidence).

A meta-analysis (Rosenfeld et al. 2007) found that antibiotics had no significant effect on cure compared with placebo at 3 to 5 days follow up (3 RCTs, n=397; low quality evidence) or 14 to 15 days follow up (4 RCTs, n=1,104; moderate quality evidence), but did find a significant effect at 7 to 12 days follow up (9 RCTs, n=1,607: risk difference 0.145, p=0.007; low quality evidence). At 7 to 12 days follow up, 46.0% of the antibiotic group had cure compared with 36.3% of the placebo group (NNT 10 [95% CI 7 to 21]).

A further meta-analysis of 11 RCTs (Young et al. 2008; n=2,682) found that overall cure was significantly improved with antibiotics compared with placebo at 8 to 15 days follow up (OR 1.35, 95% CI 1.15 to 1.59; moderate quality evidence). An analysis of individual patient data estimated the OR as 1.37 (n=2,540, 95% CI 1.13 to 1.66; authors estimated NNT 15; very low quality evidence).

Time to resolution of symptoms

In general, antibiotics make little difference to the duration of illness in acute sinusitis, which can last 2 to 3 weeks. One systematic review (Falagas et al. 2008) noted that 3 RCTs reported time to resolution of specific symptoms (facial pain and purulent rhinorrhoea). The authors stated that most of the relevant RCTs reported faster symptom resolution in participants in the antibiotic groups compared with placebo groups, although this was not always statistically significant (low quality evidence).

In a meta-analysis of 3 RCTs, Lemiengre et al. (2012) found that antibiotics were beneficial for resolution of purulent secretions irrespective of the timing of the endpoint (n=660: OR 1.58, 95% CI 1.13 to 2.22; moderate quality evidence) compared with placebo. However, there was no significant difference between antibiotics and placebo in pain symptoms (4 RCTs: data not pooled; full resolution of pain occurred within 4 to 7 days in most participants; low quality evidence) or in illness duration (3 RCTs: data not pooled; low quality evidence).

Quality of life and impact of illness

One systematic review (Ahovuo-Saloranta et al. 2014) reported that 2 RCTs assessed quality of life (measured by the mean SNOT-16 score; range of scores 0 to 3). In 1 RCT reporting mean scores, there was no significant difference between antibiotic and placebo at day 3 and 10, but there was a significant difference at day 7 in favour of antibiotic (p=0.02; low quality evidence). The other RCT reported SNOT-16 total scores (range of scores 0 to 48), and there was a significantly greater

reduction at day 6 to 8 in the antibiotic group compared with the placebo group (−17.54 versus −12.83 respectively, p=0.032) from baseline values of about 28 in both groups (low quality evidence).

One systematic review (Ahovuo-Saloranta et al. 2014) reported that 1 RCT found that the mean duration of absence from work was the same in both antibiotic and placebo groups (0.55 days; low quality evidence). Two RCTs provided data on activity impairment (moderate quality evidence). One study found no significant differences between groups (1.15 days versus 1.67 days in the antibiotic and placebo groups respectively). The other study reported that from day 3 the antibiotic group experienced a greater improvement in activity impairment compared with placebo. At day 6 to 8, the mean changes in the scores for activity impairment were: −6.1 (SD ± 5.9) in the antibiotic group and −3.7 (SD ± 5.8) in the placebo group.

The systematic review by Lemiengre et al (2012) found no significant difference between antibiotic and placebo groups for activity restriction (5 RCTs: no pooled analysis; low quality evidence).

Patient perception of antibiotic effectiveness

One systematic review (Lemiengre et al. 2012) pooled studies in which the person themselves determined that they were cured and found that antibiotics were significantly better than placebo (5 RCTs: OR 1.40, 95% CI 1.08 to 1.82; high quality evidence). However, pooling studies in which the investigator determined that the person was cured showed no benefit from antibiotics compared with placebo (3 RCTs: OR 1.05, 95% CI 0.76 to 1.46; high quality evidence).

3.3 Identifying people more likely to have a bacterial infection

It is difficult to distinguish between acute viral sinusitis and acute bacterial sinusitis clinically, and various clinical factors have been suggested to be more associated with a bacterial cause. However, a systematic review by Young et al. 2008 found that common clinical signs and symptoms could not confidently identify sub-groups of people who may benefit from antibiotics.

The systematic review did report that people with purulent nasal discharge in the pharynx (sign noted by the physician) (mean effect on odds of cure if untreated 0.65, 95% CI 0.45 to 0.96; authors estimated NNT 8) took longer to cure, but were more likely to benefit from antibiotics than other people.

The authors also suggested that treating people with a temperature above 37.5°C may offer additional benefit.

However, Young et al (2008) also found that the following people took longer to cure, but were no more likely to benefit from antibiotics:

- people reporting longer duration of symptoms (including for 6, 7 and 10 days or more)
- people reporting severe symptoms
- older people.

The authors stated that conclusions could not be drawn on sub groups of people who had a previous common cold (a common cold and then worsening with symptoms of sinusitis), face pain on bending, unilateral face pain, pain in teeth, and purulent nasal discharge due to imprecise results. It is also important to note that although people reporting more severe symptoms were no more likely to benefit from antibiotics, this finding should be interpreted with caution. All the trials included in this systematic

review excluded people with signs and symptoms suggestive of a serious complication (for example high fever, periorbital swelling, erythema or intense facial pain) where immediate antibiotics are required.

A further systematic review (Falagas et al. 2008) included a sub-group analysis and found no differences in cure or improvement for antibiotics compared with placebo in the following sub groups (low quality evidence):

- timing of assessment: 7 to 11 days (9 RCTs) or 14 to 15 days (7 RCTs); p=0.43
- diagnostic criteria for the study: imaging (6 RCTs) or clinical criteria 8 RCTs; p=0.30
- year of publication: before 2000 (6 RCTs) or after 2000 (10 RCTs); p=0.21.

3.4 Choice of antibiotic

Overall treatment effect for different antibiotics

Overall, evidence from 2 systematic reviews (Ahovuo-Saloranta et al. 2014 and Karageorgopoulos et al. 2008) did not suggest major differences in clinical effectiveness between classes of antibiotics, including penicillins, cephalosporins, macrolides, tetracyclines, folate inhibitors and quinolones.

A systematic review (Ahovuo-Saloranta et al. 2014) found that clinical failure (full recovery or improvement) at 7 to 15 days follow up was significantly higher with a cephalosporin (12%) compared with co-amoxiclav (8%) (6 RCTs, n=1,887: RR 1.37, 95% CI 1.04 to 1.80; low quality evidence). However, this result was not significant at 16 to 60 days follow up (7 RCTs, n=1,415; moderate quality evidence). There was no significant difference between macrolides and co-amoxiclav at either 7 to 15 days follow up (7 RCTs, n=1,807; moderate quality evidence) or 16 to 60 days follow up (4 RCTs, n=908; low quality evidence). There were also no significant differences between non penicillins (cephalosporins, macrolides and folate inhibitors) and beta lactamase sensitive penicillins (amoxicillin or phenoxymethylpenicillin) at either 7 to 15 days follow up (7 RCTs, n=1,083; moderate quality evidence) or 16 to 60 days follow up (1 RCT, n=436; moderate quality evidence). Additionally, there was no difference between tetracyclines and mixed classes of antibiotics (cephalosporins, folate inhibitors, macrolides and penicillins) at 7 to 15 days follow up (5 RCTs, n=807; low quality evidence).

One systematic review (Karageorgopoulos et al. 2008) compared the efficacy of quinolone antibiotics and beta-lactam antibiotics and found no significant difference between groups in clinical success (clinical cure or substantial improvement in symptoms) at the test-of-cure time point (5 RCTs, n=2,133; moderate quality evidence). A significant difference was found for clinical success (cure or improvement determined clinically) at the test-of-cure time point of each study favouring quinolones (11 RCTs, n=4,640, OR 1.24, 95% CI 1.03 to 1.49; moderate quality evidence) and 'respiratory quinolones' (moxifloxacin, levofloxacin and gatifloxacin) (8 RCTs, n=2,797: OR 1.29, 95% CI 1.03 to 1.63; moderate quality evidence), compared with beta lactam antibiotics.

Phenoxymethylpenicillin compared with amoxicillin

Three RCTs in adults (Lindbaek et al. 1996, Lindbaek et al. 1998 and Varonen et al. 2003) were identified in the systematic reviews (Ahovuo-Saloranta et al. 2014 and Lemiengre et al. 2012) that compared phenoxymethylpenicillin (1320 mg three times a day for 10 days in 2 RCTs and 1500 mg twice a day for 7 days in 1 RCT) with amoxicillin (500 mg three times a day for 10 days in 2 RCTs and 750 mg twice daily

for 7 days in 1 RCT). None of the 3 RCTs found a significant difference in cure or improvement between phenoxymethylpenicillin and amoxicillin at 10 days (2 RCTs; data not pooled; moderate to high quality evidence) or 14 to 16 days (1 RCT; moderate quality evidence). In 2 RCTs (Lindbaek et al. 1996 and Lindbaek et al. 1998) there was no significant difference in clinical severity of participants at 10 days for phenoxymethylpenicillin compared to amoxicillin (data not pooled; moderate to high quality evidence).

Two RCTs assessed the median duration of illness with phenoxymethylpenicillin compared with amoxicillin. In 1 RCT (Lindbaek et al. 1996) the median duration of an acute sinusitis episode was 11 days in the phenoxymethylpenicillin group and 9 days in the amoxicillin group, with both antibiotics being significantly better than placebo ($p=0.008$ for phenoxymethylpenicillin versus placebo and $p<0.001$ for amoxicillin versus placebo; low quality evidence). In the other RCT (Lindbaek et al. 1998) the median duration of illness was 13.5 days in the phenoxymethylpenicillin group and 10 days in the amoxicillin group and (this difference was not statistically significant; moderate quality evidence). The remaining RCT (Varonen et al. 2003) found no significant difference in mean duration of illness (amoxicillin or phenoxymethylpenicillin compared with placebo: 6 days versus 6.4 days, $p=0.66$; low quality evidence).

3.3.5 Frequency of antibiotic dosing

No systematic reviews or RCTs were identified in adults that compared the frequency of antibiotic dosing.

3.3.6 Antibiotic course length

One systematic review (Falagas et al. 2009) of 12 RCTs in adults (n=4,430) found no significant difference in cure or improvement between a short course of antibiotic (3 to 7 days) compared with a long course (6 to 10 days; high quality evidence). There was also no difference in cure or improvement in a subgroup analysis for treatment duration of 5 days compared with 10 days (7 RCTs, n=2,715; high quality evidence) and in a sub group of short course compared with long course of beta-lactam antibiotics (6 RCTs, n=2,649; high quality evidence). There were also no significant differences in microbiological efficacy (high quality evidence) and relapses (in the full population and in sub group analyses; low quality evidence).

3.4 Antimicrobials in children

The evidence review for antimicrobials in children is based on 3 systematic reviews. The included studies cover antibiotics versus placebo and antibiotics versus other antibiotics. Most of the studies included in the systematic reviews allowed the use of other symptomatic relief medicines and many were limited by excluding children (or in one case only including children) with severe or worsening illness.

A systematic review that examined the natural history of acute sinusitis in adults (Rosenfeld et al. 2007) included studies of children aged 12 years and over, so the findings may be generalisable to older children (see antimicrobials in adults).

3.4.1 Back-up antibiotics

No systematic reviews or RCTs were identified that compared back-up antibiotics with another intervention in children.

3.4.2 Antibiotics compared with placebo

Two systematic reviews (Cronin et al. 2013 and Falagas et al. 2008) measured cure or symptom improvement for antibiotics compared with placebo in children and young people.

In a meta-analysis by Cronin et al (2013) (4 RCTs, n=362) in children and young people, there was a significant improvement in symptoms at 10 to 14 days follow up with antibiotics compared with placebo. The pooled OR was 2.00 (95% CI 1.16 to 3.47; NNT 8; low quality evidence).

One systematic review (Falagas et al. 2008) included RCTs in both adults and children. In a sub-group meta-analysis in children (3 RCTs, n=326) antibiotics were not shown to have significant benefit for the outcome of cure or improvement compared with placebo (OR 1.66, 95% CI 0.95 to 2.90; moderate quality evidence).

3.4.3 Choice of antibiotic

One systematic review (Smith 2013) reviewed the efficacy of antibiotics in 5 RCTs in children. Cure rates in 4 RCTs that reported this outcome exceeded 80% and no significant differences were found between the antibiotics that were used in the studies (very low quality evidence).

3.4.4 Frequency of antibiotic dosing

No systematic reviews or RCTs were identified in children that compared the frequency of antibiotic dosing.

3.4.5 Antibiotic course length

No systematic reviews or RCTs were identified in children that compared short and long courses of antibiotics.

4 Safety and tolerability

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

4.1 Non-pharmacological interventions

4.1.1 Nasal saline

In the systematic review by King et al (2015) (5 randomised controlled trials [RCTs], n=749) of nasal saline in adults and children with acute upper respiratory tract infection featuring nasal or sinus symptoms, only 3 RCTs reported adverse events (low to moderate quality evidence). Minor nasal discomfort or irritation was the only side effect reported by a minority of participants. This was particularly reported with the use of products with higher flows or concentrations.

4.2 Non-antimicrobial pharmacological interventions

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

4.2.1 Oral analgesia

Paracetamol is widely used to treat pain and fever in children. It is generally well tolerated. However, liver damage (and less frequently renal damage) can occur following 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] August 2017).

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

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.

4.2.2 Nasal decongestants

Nasal decongestants containing sympathomimetic drugs, which vasoconstrict mucosal blood vessels reducing oedema of the nasal mucosa, should not be used for longer than 7 days. This is because they can cause rebound congestion (rhinitis medicamentosa) on withdrawal, due to secondary vasodilatation. This can lead to a

temporary increase in nasal congestion and further use of the decongestant. The BNF (August 2017) advises that ephedrine nasal drops are the safest sympathomimetic preparation, with the more potent sympathomimetic drugs oxymetazoline and xylometazoline more likely to cause a rebound effect.

The systematic review by Smith (2013) (2 RCTs, n=100) of nasal decongestants (oxymetazoline or xylometazoline nasal spray) in children with acute uncomplicated sinusitis gave no data on adverse events.

4.2.3 Nasal corticosteroids

Systemic absorption of nasal corticosteroids may follow nasal administration particularly if high doses are used or if treatment is prolonged (BNF August 2017). Steroid burden needs to be considered in people already taking oral or inhaled corticosteroids (Ekins-Daukes et al. 2002). The MHRA has advised that a review of data for inhaled and nasal corticosteroids suggests that in addition to the known systemic effects of corticosteroids (mineralocorticoid side effects, for example hypertension, sodium and water retention, and potassium and calcium loss; and glucocorticoid side effects, for example diabetes and osteoporosis), a range of psychological or behavioural effects may also occur (MHRA Drug Safety Update, September 2010). These include:

- psychomotor hyperactivity
- sleep disorders
- anxiety
- depression
- aggression (particularly in children).

In Zalmanovici Trestioreanu et al (2013) (4 RCTs; n=1,943), no significant adverse events were reported and there were no significant differences in any adverse events (low quality evidence) and dropouts before the end of the study with nasal corticosteroids compared with placebo (moderate quality evidence).

In Keith et al (2012) (n=737) adverse events were similar in all groups; 17.1%, 18.3% and 16.7% in the fluticasone daily, fluticasone twice a day and placebo groups respectively (low quality evidence). There were no significant differences between groups (NICE analysis).

In Meltzer et al (2005) (n=981) there were also no significant differences in adverse events between the mometasone, amoxicillin and placebo groups (moderate quality evidence).

4.3 Antimicrobials

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

Common side effects with penicillins (such as phenoxymethylpenicillin) include anaphylaxis, angioedema, diarrhoea, fever, hypersensitivity reactions, joint pains and rashes (BNF August 2017). Allergic reactions to penicillins occur in 1 to 10% of treated people and anaphylactic reactions occur in less than 0.05%. People with a

history of atopic allergy (for example, asthma, eczema, and hayfever) are at a higher risk of anaphylactic reactions to penicillins. People with a history of immediate hypersensitivity to penicillins may also react to cephalosporins and other beta-lactam antibiotics. Co-amoxiclav also has a warning that cholestatic jaundice can occur either during or shortly after its use, more commonly in people over 65 years and men. The risk of acute liver toxicity is about 6 times greater with co-amoxiclav than with amoxicillin and the duration of treatment should be appropriate to the indication, not usually exceeding 14 days (BNF August 2017).

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 August 2017).

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

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

22.1 Back-up antibiotics

One open label RCT (de la Poza Abad et al. 2015) in adults with upper respiratory tract infections (including sinusitis) found no significant differences in adverse effects between the back-up antibiotic prescription groups and no antibiotic prescription group, compared with immediate antibiotic prescribing (low quality evidence). There were also no significant differences in the need for unscheduled healthcare (low quality evidence).

23.2 Antibiotics in adults

In Falagas et al (2008) there were significantly more adverse events with antibiotics (30.3%) compared with placebo (21.7%) (12 RCTs, n=1,963: OR 1.87, 95% CI 1.21 to 2.90; number needed to harm [NNH] 11 [95% CI 8 to 21]; moderate quality evidence), with diarrhoea and gastrointestinal complaints more frequently reported with antibiotics (OR 2.28, 95% CI 1.24 to 4.21; low quality evidence). Dropouts, disease complications and disease recurrence were not significantly different between groups (very low to low quality evidence).

In Lemiengre et al (2012) (7 RCTs, n=1,371) there were significantly more adverse effects with antibiotics compared with placebo (27.3% versus 15.0% respectively, odds ratio [OR] 2.10, 95% confidence interval [CI] 1.60 to 2.77; NNH 8 [95% CI 6 to 12]; high quality evidence). Diarrhoea was reported in 15.9% of the antibiotic group and 10.4% of placebo group (Peto OR 1.81, 95% CI 1.18 to 2.78; NNH 18 [95% CI 9 to 108]; moderate quality evidence). The systematic review also reported similar findings for studies not included in the meta-analysis.

Significantly more participants in the placebo group had to start antibiotic therapy in comparison to the antibiotic group due to an abnormal course of illness (exacerbation, ongoing symptoms, respiratory complications, and treatment failure),

10.7% versus 5.6% respectively (8 RCTs, n=2,175: Peto OR 0.49, 95% CI 0.36 to 0.66; high quality evidence).

A further systematic review (Rosenfeld et al. 2008) (10 RCTs, n=1,853) also found significantly more adverse events with antibiotics compared with placebo (any adverse event: 28.4% versus 19.7%, p=0.000, NNH 11 [95% CI 8 to 20]; diarrhoea: 12.3% versus 7.2%, p=0.027; NNH 18 [95% CI 12 to 39]; low quality evidence).

In Ahovuo-Saloranta et al (2014) (9 RCTs, n=1,818) drop outs due to adverse effects were infrequent and there were no significant differences between antibiotic (1.5%) and placebo (1%) groups in the included RCTs (low quality evidence). In this systematic review there were significantly fewer drop-outs due to adverse effects in studies of cephalosporins (1.3%) or macrolides (2.1%), compared with co-amoxiclav (4.4% or 4.8%). The Peto OR for cephalosporins compared with co-amoxiclav was 0.32 (9 RCTs, n=2,973: 95% CI 0.21 to 0.49; high quality evidence) and for macrolides compared with co-amoxiclav it was 0.47 (8 RCTs, n=2,550: 95% CI 0.30 to 0.72; high quality evidence). Non-penicillins (1.3%) also had a significantly lower proportion of drop-outs due to adverse effects compared with beta-lactam penicillins (2.3%) (7 studies, n=1,208: Peto OR 0.58, 95% CI 0.25 to 1.35; low quality evidence). No significant difference was found between tetracyclines and mixed classes of antibiotics (low quality evidence).

A systematic review of quinolones compared with beta-lactam antibiotics (Karageorgopoulos et al. 2008) found no significant difference in the total number of adverse events (recorded in evaluable participants) either in studies which included 'respiratory quinolones' (moxifloxacin, levofloxacin and gatifloxacin) or all quinolones, compared with beta lactam antibiotics (very low to low quality evidence). No significant differences were found between groups for withdrawals due to adverse effects (very low quality evidence).

In a systematic review (Falagas et al. 2009) of short course versus long course antibiotics, rates of adverse events were found to be similar (10 RCTs, n=4,172: OR 0.88, 95% CI 0.71 to 1.09; high quality evidence). However, in subgroup analyses, there were significantly fewer adverse events with a 5 day course compared with a 10 day course of antibiotics (5 RCTs, n=2,151: OR 0.79, 95% CI 0.63 to 0.98; moderate quality evidence), but there was no significant difference between a short and long course of beta-lactam antibiotics (5 RCTs, n=2,217; very low quality evidence).

Phenoxymethylpenicillin compared with amoxicillin

Three RCTs in adults were identified in the systematic reviews (Ahovuo-Saloranta et al. 2014 and Lemiengre et al. 2012) that compared phenoxymethylpenicillin with amoxicillin. In 1 RCT (Lindbaek et al. 1996) there were no significant differences in adverse events (low quality evidence). Lindbaek et al (1998) did not report adverse effects beyond stating that 3 particpants (2 in the amoxicillin group and 1 in the penicillin group) stopped taking initial treatment after a few days due to marked gastrointestinal side effects (moderate quality evidence). Varonen et al (2003) did not report any differences in adverse events for individual antibiotics (moderate quality evidence).

3.3 Antibiotics in children

One systematic review comparing antibiotics with placebo in children (Cronin et al. 2013) found that adverse effects were mostly gastrointestinal (mainly diarrhoea) and

were 3 times more common in children treated with an antibiotic (4 RCTs, no analysis reported; very low quality evidence).

One systematic review (Smith. 2013) of antibiotics compared with other antibiotics found that 4 out of 5 RCTs reported information about adverse events. 3 RCTs reported no significant differences in adverse events between groups (very low quality evidence). One study reported a higher rate of diarrhoea (18.1%) in children receiving co-amoxiclav compared with cefditoren (4.5%, p=0.02). However, the study reports that diarrhoea was self-limiting and no children stopped treatment or withdrew from the study (very low quality evidence).

5 Antimicrobial resistance

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

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

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

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

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

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

In acute bacterial sinusitis, the most common causative pathogens are *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis* and *Staphylococcus aureus* (EPOS 2012 position paper). Data from the ESPAUR report 2016 on the antibiotic susceptibility of pathogens causing bacteraemia show that for Streptococcus pneumoniae the proportion of bloodstream isolates that are not susceptible to penicillins was about 5% in 2015, with a corresponding 8% not susceptible to macrolides. These figures have stayed relatively stable for the past 5 years. For staphylococcus aureus, the proportion of bloodstream isolates that are not susceptible to methicillin was about 8% in 2015, a decrease over the past 5 years.

6 Other considerations

6.1 Resource impact

6.1.1 Nasal corticosteroids

High-dose nasal corticosteroids equivalent to mometasone 200 micrograms twice a day are recommended. Nasal corticosteroids are available as generic and proprietary products and costs per unit (excluding VAT) range between £1.71 and £12.99 (Drug Tariff, October 2017).

6.1.2 Antibiotics

In a 2011 survey of UK primary care in adults (Gulliford et al. 2014), consultations for sinusitis accounted for 9% of all respiratory tract infection consultations, but the median practice issued an antibiotic prescription for 91% of these. There is potential for resource savings if a no antibiotic or a back-up antibiotic prescription strategy is used. One open label RCT (de la Poza Abad et al. 2015) found there were significantly lower rates of antibiotic collection in the delayed collection prescription group (26%, p<0.001) and patient-led back-up prescription group (34.7%, p<0.001) compared with the immediate prescription group (89.1%; low quality evidence).

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

6.2 Medicines adherence

Medicines adherence may be a problem for some people with medicines that require frequent dosing (for example, some antibiotics) (NICE guideline on medicines adherence [2009]). Longer treatment durations for an acute illness (for example, for nasal corticosteroids) may also cause problems with medicines adherence for some people.

The systematic review by Rosenfeld et al (2007) reported that only 38% of the included studies reported an explicit measure of medicines adherence. When this was reported, the authors state that medicines adherence was usually ‘high’.

6.3 Regulatory status

6.3.1 Nasal corticosteroids

Nasal corticosteroids (for example, budesonide, fluticasone and mometasone) are licensed for use in managing allergic disorders, such as allergic rhinitis. See the summaries of product characteristics for information on licensed indications of individual medicines. None are specifically licensed for treating acute sinusitis, so use for this indication would be off label. The prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council's Good practice in prescribing and managing medicines and devices for further information.

7 Terms used in the guideline

7.1 Major symptom score

The major symptom score (MSS) is the total score of 3 or 5 single symptom assessments. The 3 symptoms are nasal congestion/stuffiness, sinus headache/pressure or facial pain/pressure and postnasal drip (Keith at al. 2012). The 5 symptoms are: rhinorrhoea/anterior discharge, postnasal drip, nasal congestion/stuffiness, sinus headache, and facial pain/pressure/tenderness on palpation over the paranasal sinuses (Meltzer at al. 2005). Each symptom is rated as 0 (no symptoms), 1 (mild symptoms), 2 (moderate symptoms), or 3 (severe symptoms).

7.2 Sino nasal outcome test

The Sino Nasal Outcome Test (SNOT) is a self-administered questionnaire that measures quality of life in people with sinonasal conditions. SNOT-16 is a 16 item questionnaire and SNOT-20 is a 20 item questionnaire. The SNOT-20 questionnaire consists of 20 individual items (need to blow nose, sneezing, runny nose, cough, post-nasal discharge, thick nasal discharge, ear fullness, dizziness, ear pain, facial pain/pressure, difficulty falling asleep, wake up at night, lack of a good night's sleep, wake up tired, fatigue, reduced productivity, reduced concentration, frustrated/restless/irritable, sad, and embarrassed), each rated using a 0–5 scale, where 0=none, 1=very mild, 2=mild, 3=moderate, 4=severe, 5=bad as it can be (Keith at al. 2012).

Appendices

Appendix A: Evidence sources

Key area	Key question(s)	Evidence sources
Background	• What is the natural history of the infection? • What is the expected duration and severity of symptoms with or without antimicrobial treatment? • What are the most likely causative organisms? • What are the usual symptoms and signs of the infection? • What are the known complication rates of the infection, with and without antimicrobial treatment? • Are there any diagnostic or prognostic factors to identify people who may or may not benefit from an antimicrobial?	• NICE guideline CG69: Respiratory tract infections (self-limiting): prescribing antibiotics (2008) • NICE guideline CG160: Fever in under 5s: assessment and initial management (2017) • International consensus statement on allergy and rhinology: rhinosinusitis (2016) • European position paper (EPOS) on rhinosinusitis and nasal polyps (2012) • English surveillance programme for antimicrobial utilisation and resistance (ESPAUR) report (2016) • Gulliford et al. 2009 • Rosenfeld et al. 2007 • Young et al. 2008 • Committee experience
Safety netting	• What safety netting advice is needed for managing the infection?	• NICE guideline NG15: Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) • NICE clinical knowledge summary on sinusitis • Committee experience
Red flags	• What symptoms and signs suggest a more serious illness or condition (red flags)?	• NICE guideline NG51: Sepsis: recognition, diagnosis and early management (2016)

Key area	Key question(s)	Evidence sources
		• International Consensus Statement on Allergy and Rhinology: rhinosinusitis (2016) • Committee experience
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
Non-antimicrobial pharmacological interventions	• What is the clinical effectiveness and safety of non-antimicrobial pharmacological interventions for managing the infection or symptoms?	• Evidence review – see appendix F for included studies • NICE guideline CG160: Fever in under 5s: assessment and initial management (2017) • British National Formulary (BNF) (May 2017) • MHRA Drug Safety Update (September 2010) • Ekins-Daukes et al. 2002
Antimicrobial prescribing strategies	• What is the clinical effectiveness and safety of antimicrobial prescribing strategies (including back-up prescribing) for managing the infection or symptoms?	• Evidence review – see appendix F for included studies
Antimicrobials	• What is the clinical effectiveness and safety of antimicrobials for managing the infection or symptoms?	• Evidence review – see appendix F for included studies • NICE guideline CG160: Fever in under 5s: assessment and initial management (2017) • BNF (May 2017)
	• Which people are most likely to benefit from an antimicrobial?	• Evidence review – see appendix F for included studies
	• Which antimicrobial should be prescribed if one is indicated (first, second and third line treatment, including people with drug allergy)?	• Evidence review – see appendix F for included studies
	• What is the optimal dose, duration and route of administration of antimicrobials?	• Evidence review – see appendix F for included studies • BNF (May 2017)

Key area	Key question(s)	Evidence sources
		• BNF for children (BNF-C) (May 2017) • Summary of product characteristics
Antimicrobial resistance	• What resistance patterns, trends and levels of resistance exist both locally and nationally for the causative organisms of the infection • What is the need for broad or narrow spectrum antimicrobials? • What is the impact of specific antimicrobials on the development of future resistance to that and other antimicrobials?	• NICE guideline NG15: Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) • Chief medical officer (CMO) report (2011) • ESPAUR report (2016) • EPOS position paper (2012) • Butler et al. 2006 • Costelloe et al. 2010
Resource impact	• What is the resource impact of interventions (such as escalation or de-escalation of treatment)?	• Evidence review – see appendix F for included studies • Drug Tariff (May 2017) • Gulliford et al. 2014
Medicines adherence	• What are the problems with medicines adherence (such as when longer courses of treatment are used)?	• Evidence review – see appendix F for included studies • NICE guideline NG76: Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence (2009)
Regulatory status	• What is the regulatory status of interventions for managing the infection or symptoms?	• Summary of product characteristics

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Appendix B: Review protocol

Review protocol for sinusitis (acute)			Notes
I	Review question	What pharmacological (antimicrobial and non-antimicrobial) and non-pharmacological interventions are effective in managing acute rhinosinusitis or sinusitis?	• Antimicrobial includes antibiotics • non-antimicrobial includes analgesia, antiseptics, decongestants and antihistamines • search will include terms for acute sinusitis and acute rhinosinusitis
II	Types of review question	Intervention questions will primarily be addressed through the search.	These will, for example, also identify natural history in placebo groups and causative organisms in studies that use laboratory diagnosis, and relative risks of differing management options.
III	Objective of the review	To determine the effectiveness of prescribing and other management interventions in managing acute rhinosinusitis or sinusitis in line with the major goals of antimicrobial stewardship. This includes interventions that lead prescribers to: • optimise outcomes for individuals • reduce overuse, misuse or abuse of antimicrobials All of the above will be considered in the context of national antimicrobial resistance patterns where available, if not available committee expertise will be used to guide decision-making.	The secondary objectives of the review of studies will include: • indications for prescribing an antimicrobial (for example 'red flags', individual patient factors including adverse events and illness severity) • indications for no or delayed antimicrobial • 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 acute rhinosinusitis or sinusitis of any severity. Signs and symptoms up to 12 weeks	Subgroups of interest, those:

	disease/ condition/ issue/ domain	will be included, but evidence identified for treatment duration up to 4 weeks will be prioritised. 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). • with true allergy.
V	Eligibility criteria – intervention(s)/ exposure(s)/ prognostic factor(s)	The review will include studies which include: • Non-pharmacological interventions[3]. • Non-antimicrobial pharmacological interventions[4]. • Antimicrobial pharmacological interventions[5]. For the treatment of acute rhinosinusitis or sinusitis in primary, secondary or other care settings (for example walk-in-centres, urgent care, and minor ailment schemes) either by prescription or by any other legal means of supply of medicine (for example patient group direction).	Limited to those interventions commonly in use (as agreed by the committee)
VI	Eligibility criteria – comparator(s)/ control or reference (gold) standard	Any other plausible strategy or comparator, including: • Placebo or no treatment • Non-pharmacological interventions • Non-antimicrobial pharmacological interventions • Antimicrobial pharmacological interventions	Placebo or no treatment, previous studies have demonstrated that most cases (up to 98%) of sinusitis are caused by viral infections not susceptible to antibiotic therapy therefore we reasonably anticipate that some studies may have placebo or no treatment arms.
VII	Outcomes and prioritisation	a) Clinical outcomes such as: • mortality • rate of complications with or without treatment including escalation of treatment	The committee have agreed that the following outcomes are critical:

3 Non-pharmacological interventions include: no intervention, watchful waiting, back-up prescribing, steam inhalation, saline nasal irrigation, smoking cessation

4 Non-antimicrobial pharmacological interventions include: analgesics (paracetamol, ibuprofen), antihistamines, antiseptics, decongestants

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

		• reduction in symptoms (duration or severity) • 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) • severity of symptoms (for example mild vs. moderately bad vs worse) • safety, tolerability, and adverse effects. b) Thresholds or indications for antimicrobial treatment (which people are most, or least likely to benefit from antimicrobials) c) Changes in antimicrobial resistance patterns, trends and levels as a result of treatment d) Patient-reported outcomes, such as medicines adherence, patient experience and patient satisfaction, medicalisation? e) Ability to carry out activities of daily living f) Service user experience g) Health and social care related quality of life, including long-term harm or disability h) Health and social care utilisation (including length of stay, ITU stays, planned and unplanned contacts). The committee considered which outcomes should be prioritised when multiple outcomes are reported (critical and important outcomes). Additionally, the committee were asked to consider what clinically important features of study design may be important for this condition (for example length of study follow-up, treatment failure/recurrence, important outcomes of interest such as sequela or progression to more severe illness).	• reduction in symptoms (duration or severity) for example difference in time to substantial improvement • time to clinical cure (mean or median time to resolution of illness) • rate of complications (including mortality) with or without treatment, including escalation of treatment • health and social care utilisation (including length of stay, ITU stays, planned and unplanned contacts). • thresholds or indications for antimicrobial treatment (which people are most, or least likely to benefit from antimicrobials) The committee have agreed that the following outcomes are important: • patient-reported outcomes, such as medicines adherence, patient experience • changes in antimicrobial resistance patterns, trends and levels as a result of treatment
VIII	Eligibility criteria – study design	The search will look for: • Systematic reviews of randomised controlled trials (RCTs) • RCTs If insufficient evidence is available progress to: • Controlled trials • Systematic reviews of non-randomised controlled trials	Committee to advise the NICE project team on the inclusion of information from other condition specific guidance and on whether to progress due to insufficient evidence.

		• Non-randomised controlled trials • Observational and cohort studies • Pre and post intervention studies (before and after) • Time series studies	
IX	Other inclusion exclusion criteria	The scope sets out what the guidelines will and will not include (exclusions). Further exclusions specific to this guideline include: • non-English language papers, studies that are only available as abstracts • for antimicrobial resistance non-UK papers • Fungal rhinosinusitis	
X	Proposed sensitivity/ sub-group analysis, or meta-regression	The search may identify studies in population subgroups (for example adults, older adults, children (those aged under 18 years of age), and people with co-morbidities or characteristics that are protected under the Equality Act 2010 or in the NICE equality impact assessment). These will be analysed within these categories to enable the production of management recommendations.	
XI	Selection process – duplicate screening/ selection/ analysis	All references from the database searches will be downloaded, de-duplicated and screened on title and abstract against the criteria above. A randomly selected initial sample of 10% of records will be screened by two reviewers independently. The rate of agreement for this sample will be recorded, and if it is over 90% then remaining references will screened by one reviewer only. Disagreement will be resolved through discussion. Where abstracts meet all the criteria, or if it is unclear from the study abstract whether it does, the full text will be retrieved. If large numbers of papers are identified at full text, the Committee may consider prioritising the evidence for example, evidence of higher quality in terms of study type or evidence with critical or highly important outcomes.	
XII	Data management (software)	Data management will be undertaken using EPPI-reviewer software. Any pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome.	

XIII	Information sources – databases and dates	Medline; Medline in Process; Embase; PubMed; Cochrane database of systematic reviews (CDSR); Database of abstracts of effectiveness (DARE) (legacy); Cochrane Central Register of Controlled Trials (CENTRAL); Health Technology Assessment (HTA) database; Clinicaltrials.gov • All the above to be searched from 2000 to present day. • Filters for systematic reviews, RCTs and comparative studies to be applied, unless numbers without filters are low • Searches to be limited to studies reported in English. • Animal studies and conference abstracts to be excluded Medicines and Healthcare products Regulatory Agency (MHRA) website; European Medicines Agency (EMA) website; U.S. Food and Drug Administration (FDA) website; Drug Tariff; MIMs • The above to be searched for advice on precautions, warnings, undesirable effects of named antimicrobials.	
XIV	Identify if an update	Not applicable at this time.	
XV	Author contacts	Web: https://www.nice.org.uk/guidance/indevelopment/gid-apg10002 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 introduction to the evidence review in the guideline.	
XXVI	Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by NICE and chaired by Dr Tessa Lewis in line with the interim process guide (2017). Staff from NICE undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where	

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

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Appendix C: Literature search strategy

Database: Ovid MEDLINE(R) <1946 to December Week 1 2016>
Search Strategy: Sinusitis (acute)

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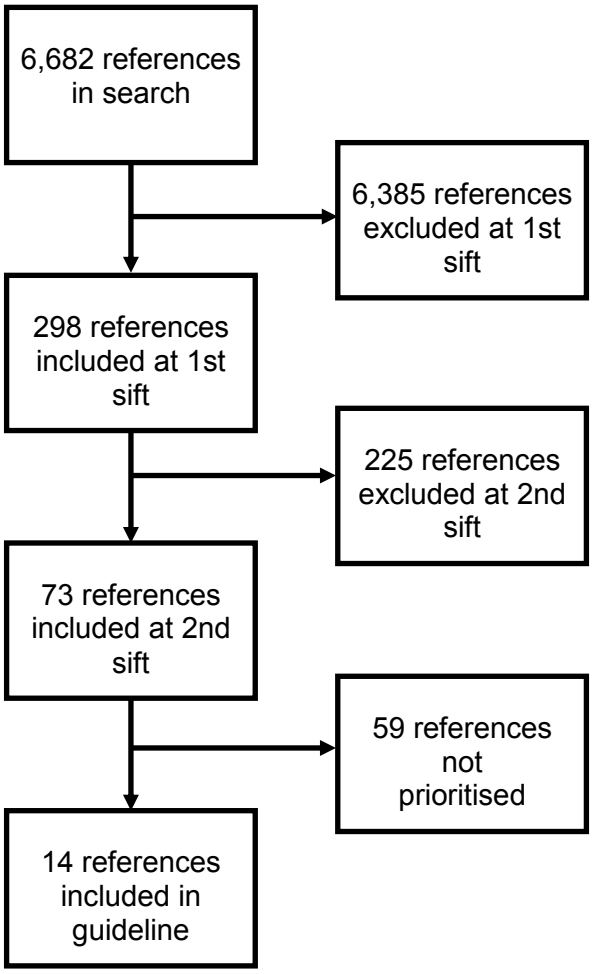
1 exp sinusitis/ (19965)
2 rhinitis/ (11536)
3 sinusit*.tw. (13598)
4 rhinosinusit*.tw. (6099)
5 ((acute* or purulent* or suppurat*) adj3 rhinitis*).tw. (324)
6 (sinus* adj4 headache*).tw. (414)
7 Facial Pain/ (5977)
8 ((pain or tender*) adj4 (face or faces or facial or cheek or cheeks or forehead or foreheads or eye or eyes or sinus*)).tw. (6785)
9 or/1-8 (42618)
10 amoxicillin/ or cefuroxime/ or erythromycin/ or azithromycin/ or Clarithromycin/ or Amoxicillin-Potassium Clavulanate Combination/ or Penicillin V/ or Doxycycline/ (44472)
11 (amoxicillin* or amix* or amoram* or amoxident* or galenamox* or rimoxallin* or amoxil*).tw. (11820)
12 (cefuroxime* or zinacef* or zinnat*).tw. (3882)
13 (erythromycin* or tiloryth* or primacine* or erymax* or erythrocin* or erythroped* or erythroped A).tw. (19363)
14 (azithromycin* or zithromax* or zedbac*).tw. (6278)
15 (clarithromycin* or klaricid* or mycifor XL or coamoxiclav* or "co-amoxiclav*" or augmentin*).tw. (19335)
16 (phenoxymethylpenicillin* or "phenoxymethyl penicillin*" or "penicillin V").tw. (1613)
17 (doxycyclin* or periostat* or vibramycin* or vibrox* or efracea* or adjusan* or doxyhexal*).tw. (11561)
18 Trimethoprim, Sulfamethoxazole Drug Combination/ or (Cotrimoxazole or "Co-trimoxazole" or Septrin).tw. (10102)
19 (moxifloxacin or avelox).tw. (3446)
20 exp Tetracyclines/ (48076)
21 tetracycline*.tw. (32230)
22 exp Macrolides/ (108095)
23 macrolide*.tw. (13693)
24 exp Clindamycin/ (5634)
25 clindamycin*.tw. (8895)
26 exp Metronidazole/ (12350)
27 metronidazole*.tw. (13090)
28 Fusidic Acid/ (1616)
29 fusid*.tw. (1743)
30 exp penicillins/ (81945)
31 penicillin*.tw. (51572)
32 exp cephalosporins/ (43510)

33 cephalosporin*.tw. (19467)
34 or/10-33 (340979)
35 Acetaminophen/ or Ibuprofen/ (24516)
36 (paracetamol* or acetaminophen* or panadol* or perfalgan* or calpol*).tw. (20086)
37 (ibuprofen* or arthrofen* or ebufac* or rimafen* or brufen* or calprofen* or feverfen* or nurofen* or orbifen*).tw. (10745)
38 or/35-37 (34110)
39 analgesics/ or analgesics, non-narcotic/ or analgesics, short-acting/ (56215)
40 (analgesi* or pain relief* or pain reliev*).tw. (115901)
41 39 or 40 (146657)
42 watchful waiting/ (2487)
43 "no intervention*".tw. (6026)
44 (watchful* adj2 wait*).tw. (1910)
45 (wait adj2 see).tw. (1120)
46 (active* adj2 surveillance*).tw. (5307)
47 (expectant* adj2 manage*).tw. (2579)
48 ((prescription* or prescrib*) adj4 ("red flag" or strateg* or appropriat* or inappropriat* or unnecessary or defer* or delay* or no or non or behaviour* or behavior* or optimal or optimi* or reduc* or decreas* or declin* or rate* or improv*)).tw. (20502)
49 ((misuse or "mis-use" or overuse or "over-use" or "over-prescri*" or abuse) adj4 (bacter* or antibacter* or anti-bacter* or "anti bacter*" or antimicrobial or anti-microbial or "anti microbial" or antibiot* or anti-biot* or "anti biot*")).tw. (1422)
50 ((delay* or defer*) adj3 (treat* or therap* or interven*)).tw. (25472)
51 or/42-50 (64781)
52 anti-infective agents/ or exp anti-bacterial agents/ or exp anti-infective agents, local/ (909765)
53 (antibacter* or anti-bacter* or antibiot* or anti-biot* or antimicrobial* or anti-microbial*).tw. (388436)
54 (delay* or defer* or back-up* or backup* or immediate* or rapid* or short* or long* or standby or "stand by" or rescue or escalat* or "de-escalat*" or (prescribing adj strateg*) or "red flag*").tw. (3605250)
55 (52 or 53) and 54 (151848)
56 Nasal sprays/ (364)
57 Nasal Decongestants/ (1685)
58 ((nasal* or intranasal* or nose or noses) adj3 (spray* or anti-inflammat* or antiinflammat* or steroid* or corticosteroid* or adrenal cortex hormone* or decongest*)).tw. (5178)
59 ((inhale* or inhalant* or inhalator*) adj3 (anti-inflammat* or antiinflammat* or steroid* or corticosteroid* or adrenal cortex hormone* or decongest*)).tw. (10409)
60 ((face* or facial* or warm*) adj2 (pack or packs or compress)).tw. (86)
61 Steam/ (2361)
62 steam*.tw. (6501)
63 Therapeutic Irrigation/ (17385)
64 irrigat*.tw. (24222)
65 or/56-64 (59245)
66 Smoking Cessation/ (28156)

67 "tobacco use cessation"/ (1084)
68 Smoking/pc (18945)
69 "Tobacco Use Disorder"/pc (1997)
70 ((quit or quits or quitting or stop or stops or stopping or stopped or stoppage or cease or ceases or ceasing or cessation or cut or cuts or cutting or abstain* or abstinen* or rate* or reduc* or give* up or giving up) adj3 (smoking or cigar* or cigs or tobacco* or smoker* or bidi or bidis or kretek or hand roll* or handroll* or rollup* or roll up*)).ti,ab. (42388)
71 (antismok* or anti smok* or anti-smok*).ti,ab. (1899)
72 or/66-71 (60989)
73 Adrenal Cortex Hormones/ (62948)
74 exp Anti-Inflammatory Agents/ (490626)
75 exp steroids/ (863952)
76 (anti-inflammat* or antiinflammat* or steroid* or corticosteroid* or adrenal cortex hormone* or decongest*).tw. (388670)
77 or/73-76 (1299145)
78 Administration, Intranasal/ (13809)
79 77 and 78 (2490)
80 Self Care/ (30993)
81 ((self or selves or themsel*) adj4 (care or manag*)).tw. (30483)
82 80 or 81 (48453)
83 34 or 38 or 41 or 51 or 55 or 65 or 72 or 79 or 82 (841901)
84 9 and 83 (6882)
85 Animals/ not (Animals/ and Humans/) (4782110)
86 84 not 85 (6645)
87 limit 86 to (letter or historical article or comment or editorial or news) (198)
88 86 not 87 (6447)
89 limit 88 to english language (5090)
90 limit 89 to yr="2000 -Current" (3440)
91 remove duplicates from 90 (3114)
92 exp Drug Resistance, Bacterial/ (77692)
93 exp Drug Resistance, Multiple/ (30993)
94 ((bacter* or antibacter* or anti-bacter* or "anti bacter*") adj4 (resist* or tolera*)).tw. (32082)
95 ((antibiot* or anti-biot* or "anti biot*") adj4 (resist* or tolera*)).tw. (39843)
96 (multi* adj4 drug* adj4 (resist* or tolera*)).tw. (11535)
97 (multidrug* adj4 (resist* or tolera*)).tw. (36858)
98 (multiresist* or multi-resist* or "multi resist*").tw. (5782)
99 ((microb* or antimicrob* or anti-microb* or "anti microb*") adj4 (resist* or tolera*)).tw. (20343)
100 (superbug* or super-bug* or "super bug*").tw. (405)
101 Superinfection/ (1829)
102 (superinvasion* or super-invasion* or "super invasion*" or superinfection* or super-infection* or "super infection*").tw. (5484)
103 R Factors/ (4481)
104 "r factor*".tw. (3726)
105 (resist* factor* or "r plasmid*" or resist* plasmid*).tw. (5234)

106 "red flag*".tw. (1005)
107 or/92-106 (179794)
108 or/10-19 (89635)
109 107 and 108 (16813)
110 Animals/ not (Animals/ and Humans/) (4782110)
111 109 not 110 (15193)
112 limit 111 to (letter or historical article or comment or editorial or news) (439)
113 111 not 112 (14754)
114 limit 113 to english language (12296)
115 limit 114 to yr="2000 -Current" (9085)
116 115 not 90 (8949)
117 90 (3440)
118 limit 117 to yr="2000 - 2004" (887)
119 limit 117 to yr="2005 - 2009" (981)
120 limit 117 to yr="2010 - 2016" (1572)
121 limit 116 to yr="2000 - 2004" (2135)
122 limit 116 to yr="2005 - 2009" (2758)
123 limit 116 to yr="2010 - 2016" (4056)

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?				
Nasal saline	King et al. 2015	–	Ah-See et al. 2011 Inanli et al. 2002	Gelardi et al. 2009 Hauptman et al. 2007 Tugrul et al. 2014 Wang et al. 2009
Therapeutic ultrasound	–	–	–	Hosoien E et al. 2010
Probiotics	–	–	–	Kitz R et al. 2012
Herbal medicines	–	–	–	Guo et al. 2006 Jund et al. 2012 Passali et al. 2015 Pfaar et al. 2012 Ponikau et al. 2012 Tesche et al. 2008
Which non-antimicrobial pharmacological interventions are effective?				
Nasal decongestants	Smith 2013	–	Ah-See et al. 2011 Inanli et al. 2002	–
Nasal corticosteroids	Zalmanovici Trestioreanu et al. 2013	Keith at al. 2012 Meltzer at al. 2005	Ah-See et al. 2011 Hayward et al. 2012 Inanli et al. 2002 Venekamp et al. 2010	Bachert C et al. 2007 Dolor et al. 2001 El-Hennawi et al. 2015 Meltzer et al. 2000 Meltzer et al. 2012 Nayak et al. 2002 Rahmati et al. 2013

Key questions	Included studies[1]		Studies not prioritised[2]	
	Systematic reviews	RCTs	Systematic reviews	RCTs
				Wan et al. 2015 Williamson et al. 2007 Yilmaz et al. 2000
Oral corticosteroids	–	–	Venekamp et al. 2014	Ratau et al. 2004
Which antibiotic prescribing strategies are effective (including back-up antibiotics)?				
Back-up antibiotics	–	de la Poza Abad et al. 2015	–	–
Is an antibiotic effective?				
Antibiotics versus placebo	Ahovuo-Saloranta et al. 2014 Falagas et al. 2008 Lemiengre et al. 2012 Rosenfeld et al. 2007 Young et al. 2008 Cronin et al. 2013	–	Ah-See et al. 2011 Benninger et al. 2000 Burgstaller et al. 2016	Bucher et al. 2003 Garbutt et al. 2001 Garbutt et al. 2012 Hadley et al. 2010 Hansen et al. 2000[a] Hansen et al. 2000[b] Kaiser et al. 2001 Kristo et al. 2005 Merenstein et al. 2005 Wald et al. 2009
Which people are most likely to benefit from an antibiotic?				
Sub-group analyses of antibiotics versus placebo	Young et al. 2008	–	–	–
Which antibiotic is most effective?				
Antibiotics versus different antibiotics	Ahovuo-Saloranta et al. 2014 Karageorgopoulos et al. 2008 Smith 2013	–	Ah-See et al. 2011 Benninger et al. 2000 Mittmann et al. 2002 Sng et al. 2015	Arrieta et al. 2007 Lari et al. 2010 Lari et al. 2012 Marple et al. 2007 Marple et al. 2010 Muhammad et al. 2015

Key questions	Included studies[1]		Studies not prioritised[2]	
	Systematic reviews	RCTs	Systematic reviews	RCTs
				Murray et al. 2005 Ng et al. 2000 Rakkar et al. 2001 Rechtweg et al. 2004 Riffer et al. 2005 Siegert et al. 2000 Varonen et al. 2003
What is the optimal dosage, duration and route of administration of antibiotic?				
Dosage	–	–	–	–
Course length	Falagas et al. 2009	–	Ah-See et al. 2011	Gehanno et al. 2000 Henry et al. 2003 Kutluhan et al. 2002 Poole et al. 2006
Route of administration	–	–	–	–

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

Appendix F: Included studies

Ahovuo-Saloranta A, Rautakorpi UM, Borisenko O et al (2014) Antibiotics for acute maxillary sinusitis in adults. The Cochrane database of systematic reviews 2, CD000243

Cronin MJ, Khan S, Saeed S. The role of antibiotics in the treatment of acute rhinosinusitis in children: a systematic review. Archives of Disease in Childhood 2013; 98: 299-303.

de la Poza Abad M, Mas Dalmau G, Moreno B et al (2016) Prescription Strategies in Acute Uncomplicated Respiratory Infections: A Randomized Clinical Trial. JAMA internal medicine 176(1), 21-9

Falagas ME, Giannopoulou KP, Vardakas KZ et al (2008) Comparison of antibiotics with placebo for treatment of acute sinusitis: a meta-analysis of randomised controlled trials. The Lancet. Infectious diseases 8(9), 543-52

Falagas ME, Karageorgopoulos DE, Grammatikos AP et al (2009) Effectiveness and safety of short vs. long duration of antibiotic therapy for acute bacterial sinusitis: a meta-analysis of randomized trials. British journal of clinical pharmacology 67(2), 161-71

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Appendix G: Quality assessment of included studies

G.1 Nasal saline

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

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

G.2 Nasal decongestants

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

Study reference	Smith 2013
Did the review address a clearly focused question?	Yes
Did the authors look for the right type of papers?	Yes
Do you think all the important, relevant studies were included?	Yes
Did the review's authors do enough to assess the quality of the included studies?	Yes
If the results of the review have been combined, was it reasonable to do so?	Not undertaken
What are the overall results of the review?	See GRADE profiles

Study reference	Smith 2013
How precise are the results?	See GRADE profiles
Can the results be applied to the local population?	Yes
Were all important outcomes considered?	Yes
Are the benefits worth the harms and costs?	See GRADE profiles

G.3 Nasal corticosteroids

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

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

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

Study reference	Keith at al. 2012	Meltzer at al. 2005
Did the trial address a clearly focused issue?	Yes	Yes
Was the assignment of patients to treatments randomised?	Yes	Yes
Were patients, health workers and study personnel blinded?	Yes	Yes
Were the groups similar at the start of the trial?	Yes	Yes
Aside from the experimental intervention, were the groups treated equally?	Yes	Yes
Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes	Yes
How large was the treatment effect?	See GRADE profiles	See GRADE profiles

Study reference	Keith at al. 2012	Meltzer at al. 2005
How precise was the estimate of the treatment effect?	See GRADE profiles	See GRADE profiles
Can the results be applied in your context? (or to the local population)	Yes	Yes
Were all clinically important outcomes considered?	Yes	Yes
Are the benefits worth the harms and costs?	See GRADE profiles	See GRADE profiles

G.4 Antimicrobials

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

Study reference	Ahovuo-Saloranta et al. 2014	Cronin et al. 2013	Falagas et al. 2008	Falagas et al. 2009	Karageorgopoulos et al. 2008	Lemiengre et al. 2012	Rosenfeld et al. 2007	Smith 2013	Young et al. 2008
Did the review address a clearly focused question?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Did the authors look for the right type of papers?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Do you think all the important, relevant studies were included?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No[a]
Did the review's authors do enough to assess the quality of the included studies?	Yes	Yes	Yes	Yes	Unclear[b]	Yes	Yes	Yes	Unclear[c]
If the results of the review have been combined, was it reasonable to do so?	Yes	Unclear[d]	Unclear[e]	Yes	Yes	Yes	Unclear[f]	N/A	Yes
What are the overall results of the review?	See GRADE profiles								
How precise are the results?	See GRADE profiles								
Can the results be applied to the local population?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Were all important outcomes considered?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Study reference	Ahovuo-Saloranta et al. 2014	Cronin et al. 2013	Falagas et al. 2008	Falagas et al. 2009	Karageorgopoulos et al. 2008	Lemiengre et al. 2012	Rosenfeld et al. 2007	Smith 2013	Young et al. 2008
Are the benefits worth the harms and costs?	See GRADE profiles								

[a] Limitations in the search strategy
[b] Quality assessment was reported but it was unclear if the tool used was validated
[c] No reporting of study quality or method of assessment
[d] The results of the meta-analysis suggest moderate heterogeneity in outcome, there is also a large amount of imprecision in the estimates
[e] In some of the analyses the I2 statistic was raised despite use of a random effects model
[f] In some of the analyses the I2 statistic was raised despite use of a random effects model, although some effort was made to address this

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

Study reference	de la Poza Abad et al. 2012	Lindbaek et al. 1996	Lindbaek et al. 1998	Varonen et al. 2003
Did the trial address a clearly focused issue?	Yes	Yes	Yes	Yes
Was the assignment of patients to treatments randomised?	Yes	Yes	Yes	Yes
Were patients, health workers and study personnel blinded?	No[a]	Yes	Yes	Yes
Were the groups similar at the start of the trial?	Yes	Yes	Yes	Yes
Aside from the experimental intervention, were the groups treated equally?	Yes	Yes	Yes	Yes
Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes	Yes	Yes	Yes
How large was the treatment effect?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles
How precise was the estimate of the treatment effect?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles
Can the results be applied in your context? (or to the local population)	Unclear[b]	Yes	Yes	Yes
Were all clinically important outcomes considered?	Yes	Yes	No[c]	Yes

Study reference	de la Poza Abad et al. 2012	Lindbaek et al. 1996	Lindbaek et al. 1998	Varonen et al. 2003
Are the benefits worth the harms and costs?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles

[a] Open label study
[b] Unclear if this study can be generalised to a UK setting
[c] Harms not well described

Appendix H: GRADE profiles

H.1 Nasal saline

Table 10: GRADE profile – nasal saline versus control in adults and children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nasal saline[1]	Control[2]	Relative	Absolute		
Time to resolution of symptoms												
2[3]	randomised trials	serious[4]	serious[5]	no serious indirectness	serious[6]	none	n=111 adults		No difference between groups in mean days to wellness: 9.24 days in the control group and 0.74 days lower (95% CI 2.58 lower to 1.11 higher) in the nasal saline group[7]		⊕OOO VERY LOW	CRITICAL
Nasal symptom score[7] (Better indicated by lower values)												
5[3]	randomised trials	serious[4]	serious[8]	no serious indirectness	serious[8]	none	n=165 adults; 505 children		No difference between groups in nasal symptom scores at day 3 (2 RCTs in adults [n=119 and n=46] and 1 RCT in children up to 24 months [n=46]) or day 7 (2 RCTs in adults [n=119 and n=46]) 1 RCT in children aged 3 to 12 years (n=69) found no difference in scores from week 1 to weeks 2 and 3 for all symptoms apart from daytime rhinorrhoea and nocturnal nasal congestion (p<0.05) 1 RCT in children aged 6 to 10 years (n=390) found a reduction in nasal secretion score at up to 3 weeks with nasal saline compared with control (mean difference −0.31; 95% CI −0.48 to –0.14 on a 4-point scale)		⊕⊕OO LOW	CRITICAL
Nasal secretion type score[8] (Better indicated by lower values)												
1[3]	randomised trials	serious[4]	N/A	no serious indirectness	no serious imprecision	none	n=390 children		1 RCT in children aged 6 to 10 years found a reduction in nasal secretion type score at up to 3 weeks with nasal saline irrigation compared with control (mean difference −0.34; 95% CI −0.50 to –0.18 on a 4-point scale)		⊕⊕⊕O MODERATE	CRITICAL
Nasal patency (Better indicated by lower values)												
2[3]	randomised trials	serious[4]	serious[5]	no serious indirectness	serious[5]	none	n=459 children		1 RCT in children aged 6 to 10 years (n=390) found a reduction in 'breathing score' at up to 3 weeks with nasal saline irrigation compared with		⊕OOO VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nasal saline[1]	Control[2]	Relative	Absolute		
									control (mean difference −0.33; 95% CI −0.47 to –0.19 on a 4-point scale) 1 RCT in children aged 3 to 12 years (n=69) found an improvement in nasal peak expiratory flow rate with nasal saline irrigation compared with control (no data available on size of effect)			
Antibiotic and other medicines use												
2[3]	randomised trials	serious[9]	no serious inconsistency[10]	no serious indirectness	very serious[11]	none	17/298 (5.7%)	11/124 (8.87%)	OR 0.65 (0.29 to 1.46) [11] NICE analysis RR 0.67(0.32 to 1.40)	29 fewer per 1000 (from 61 fewer to 36 more)	⊕OOO VERY LOW	CRITICAL
Adverse events: not tolerated[12]												
1[3]	randomised trials	serious[4]	N/A	no serious indirectness	no serious imprecision	none	6/15 (40%)[13]	7/16 (43.8%)[14]	RR 0.91 (0.40 to 2.10)	39 fewer per 1000 (from 262 fewer to 481 more)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events: dry nose[12]												
1[3]	randomised trials	serious[4]	N/A	no serious indirectness	no serious imprecision	none	7/33 (21.2%)[15]	11/36 (30.6%)[16]	RR 0.69 (0.31 to 1.58)	95 fewer per 1000 (from 211 fewer to 177 more)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events: pain or irritation[12]												
1[3]	randomised trials	serious[4]	N/A	no serious indirectness	no serious imprecision	none	11/33 (33.3%)[15]	4/31 (12.9%)[16]	RR 2.58 (0.92 to 7.27)	204 more per 1000 (from 10 fewer to 809 more)	⊕⊕⊕O MODERATE	CRITICAL
Other adverse events												
1[3]	randomised trials	serious[4]	N/A	no serious indirectness	serious[5]	none	-		1 RCT in children aged 6 to 10 years (n=390) found 8.7% of participants had adverse events in the nasal saline groups, mostly reported by the medium jet group and associated with the higher flow rate		⊕⊕OO LOW	CRITICAL

Abbreviations: CI, Confidence interval; N/A, Not applicable; OR, Odds ratio; RCT, Randomised controlled trial; SD, Standard deviation

[1] Included treatment with hypertonic nasal saline irrigation, normal saline irrigation, isotonic saline irrigation or normal saline drops (with or without standard treatment)
[2] Included no treatment, phenylephrine drops or standard treatment (included antibiotics, mucolytics, nasal decongestants, analgesia, lozenges and cold and flu medicines)
[3] King et al. 2015
[4] Downgraded 1 level - most RCTs were small and at high risk of bias (as assessed by Cochrane authors)
[5] Downgraded 1 level - significant heterogeneity (I^2=78%) with random effects model
[6] Downgraded 1 level - at a default minimal important difference (MID) of 25% or 0.5 SD for continuous data, (approximately 2 days) data are consistent with no meaningful difference or appreciable benefit with nasal saline
[7] This analysis is not reported in in full in the paper, analysis 1.1 by the authors states that the reduction is 0.79 days (95% CI -4.72 to 3.14)
[8] Downgraded 1 level - not assessable
[7] Outcome was measured on a 4-point scale
[8] Nasal secretion type was: absent, serious, seropurulent and purulent
[9] Downgraded 1 level - assessed by Cochrane authors as having a high risk of bias in both randomisation and blinding, with other domains unclear
[10] This analysis is not reported in in full in the paper, analysis by the authors reports OR 0.64 (95% CI 0.29 to 1.44; I^2=0%)

[11] Downgraded 2 levels - at a default MID of 25% data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[12] NICE analysis based upon figures presented in authors review
[13] Saline nasal drops
[14] Phenylephrine nasal drops
[15] Hypertonic saline nasal drops
[16] Normal saline nasal drops

H.2 Nasal decongestants

Table 11: GRADE profile – nasal decongestant versus control in children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nasal decongestant[1]	Control[2]	Relative	Absolute		
Improvement in symptoms - mean symptom score (follow-up 3 or 14 days; Better indicated by lower values)												
1[3]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[4]	none	n=34 children		1 RCT in children aged 1 to 18 years found no difference between the combination of oxymetazoline nasal spray and a decongestant-antihistamine syrup, and placebo in mean symptom score at day 3 or day 14		⊕⊕⊕O MODERATE	CRITICAL
Improvement in symptoms - mucosal inflammation symptoms (follow-up 7 to 14 days; Better indicated by lower values)												
1[3]	randomised trials	serious[5]	N/A	no serious indirectness	serious[4]	none	n=66 children		1 RCT in children aged 2 to 6 years found no difference between xylometazoline nasal spray and intranasal Ems mineral salts in mucosal inflammation symptoms at day 14, but at day 7 there was less nasal discharge with mineral salts (p=0.0163)		⊕⊕OO LOW	CRITICAL
Adverse events												
No data on adverse events were reported												CRITICAL
Abbreviations: RCT, Randomised controlled trial												

[1] Oxymetazoline nasal spray (0.05%) plus decongestant-antihistamine syrup in 1 RCT; xylometazoline nasal spray (0.05%) in 1 RCT. All participants also received amoxicillin for 14 days
[2] Placebo nasal spray and syrup in 1 RCT; intranasal mineral salts in 1 RCT. All participants also received amoxicillin for 14 days
[3] Smith 2013
[4] Downgraded 1 level – not assessable
[5] Downgraded 1 level - RCT was low quality (Jadad score = 2 as assessed by study authors)

H.3 Nasal corticosteroids

Table 12: GRADE profile – nasal corticosteroid versus placebo in adults and children aged 12 years and over

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nasal corticosteroid	Placebo	Relative (95% CI)	Absolute		
Change in symptoms												
Resolution of symptoms (all doses)[1] (follow-up 14 to 21 days)												
3[2]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	no serious imprecision	none	852/1167 (73%)[4]	415/625 (66.4%)	Fixed effects model: RR 1.11 (1.04 to 1.18)	73 more per 1000 (from 27 more to 120 more)	⊕⊕⊕O MODERATE	CRITICAL
3[2]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	serious[5]	none	852/1167 (73%)[4]	415/625 (66.4%)	NICE analysis (random effects model): RR 1.14 (0.97 to 1.34)	-	⊕⊕OO LOW	CRITICAL
Resolution of symptoms (200 micrograms daily dose) (follow-up 14 to 21 days)												
2[2]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	no serious imprecision	none	257/290 (88.6%)[4]	255/300 (85%)	RR 1.04 (0.98 to 1.11)	34 more per 1000 (from 17 fewer to 94 more)	⊕⊕⊕O MODERATE	CRITICAL
Resolution of symptoms (400 micrograms daily dose) (follow-up 14 to 21 days)												
2[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	402/553 (72.7%)[6]	385/577 (66.7%)	RR 1.10 (1.02 to 1.18)	67 more per 1000 (from 13 more to 120 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Mean change from baseline in daily major symptom score[7] (fluticasone 110 micrograms once a day) (follow-up 14 days; Better indicated by lower values)												
1[8]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[5]	none	240	245	-	MD 0.386 lower (0.67 to 0.1 lower)	⊕⊕⊕O MODERATE	CRITICAL
Mean change from baseline in daily major symptom score[7] (fluticasone 110 micrograms twice a day) (follow-up 14 days; Better indicated by lower values)												
1[8]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[5]	none	252	245	-	MD 0.357 lower (0.64 to 0.07 lower)	⊕⊕⊕O MODERATE	CRITICAL
Median time to symptom improvement (fluticasone 110 micrograms once a day) (follow-up 14 days; Better indicated by lower values)												
1[8]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[9]	none	-		7 days vs. 8 days in nasal corticosteroid and placebo groups respectively; authors report no significant difference between groups		⊕⊕⊕O MODERATE	CRITICAL
Median time to symptom improvement (fluticasone 110 micrograms twice a day) (follow-up 14 days; Better indicated by lower values)												
1[8]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[9]	none	-		7 days vs. 8 days in nasal corticosteroid and placebo groups respectively; authors report no		⊕⊕⊕O MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nasal corticosteroid	Placebo	Relative (95% CI)	Absolute		
									significant difference between groups			
Quality of life												
Mean change from baseline in SNOT-20 score (fluticasone 110 micrograms once a day) (follow-up 14 days; Better indicated by lower values)												
1[8]	randomised trials	no serious risk of bias	N/A	no serious indirectness	no serious imprecision	none	240	245	-	MD 0.110 lower (0.26 lower to 0.04 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Mean change from baseline in SNOT-20 score (fluticasone 110 micrograms twice a day) (follow-up 14 days; Better indicated by lower values)												
1[8]	randomised trials	no serious risk of bias	N/A	no serious indirectness	no serious imprecision	none	252	245	-	MD 0.142 lower (0.29 lower to 0 higher)	⊕⊕⊕⊕ HIGH	CRITICAL
Health and social care utilisation												
Use of antibiotics during study period (fluticasone 110 micrograms once a day) (follow-up 14 days)												
1[8]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[9]	none	7/240 (2.9%)	7/245 (2.9%)	No significant differences between nasal corticosteroid and placebo groups (p=0.969)		⊕⊕⊕O MODERATE	CRITICAL
Use of antibiotics during study period (fluticasone 110 micrograms twice a day) (follow-up 14 days)												
1[8]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[9]	none	7/240 (2.9%)	7/245 (2.9%)	No significant differences between nasal corticosteroid and placebo groups (p=0.957)		⊕⊕⊕O MODERATE	CRITICAL
Adverse events												
Adverse events requiring discontinuation (all doses) (follow-up 14 to 21 days)												
4[2]	randomised trials	no serious risk of bias	serious[9]	no serious indirectness	serious[9]	none	-		Authors report no significant difference between nasal corticosteroid and placebo groups; data not reported		⊕⊕OO LOW	CRITICAL
Any adverse events (fluticasone 110 micrograms once a day) (follow-up 14 days)												
1[8]	randomised trials	no serious risk of bias	N/A	no serious indirectness	very serious[10]	none	41/240 (17.1%)	41/245 (16.7%)	RR 1.02 (0.69 to 1.51)[11]	3 more per 1000 (from 52 fewer to 85 more)	⊕⊕OO LOW	CRITICAL
Any adverse events (fluticasone 110 micrograms twice a day) (follow-up 14 days)												
1[8]	randomised trials	no serious risk of bias	N/A	no serious indirectness	very serious[10]	none	46/252 (18.3%)	41/245 (16.7%)	RR 1.09 (0.74 to 1.60)[11]	15 more per 1000 (from 44 fewer to 100 more)	⊕⊕OO LOW	CRITICAL
Drop-outs before end of study (all doses)[1] (follow-up 15 or 21 days)												
3[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	114/1167 (9.8%)[4]	71/625 (11.4%)	RR 0.85 (0.64 to 1.12)	17 fewer per 1000 (from 41 fewer to 14 more)	⊕⊕⊕O MODERATE	CRITICAL
Drop-outs before end of study (200 micrograms daily dose) (follow-up 14 to 21 days)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nasal corticosteroid	Placebo	Relative (95% CI)	Absolute		
2[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	26/290 (9%)[4]	36/300 (12%)	RR 0.75 (0.46 to 1.21)	30 fewer per 1000 (from 65 fewer to 25 more)	⊕⊕⊕O MODERATE	CRITICAL
Drop-outs before end of study (400 micrograms daily dose) (follow-up 14 to 21 days)												
2[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	56/553 (10.1%)[6]	68/577 (11.8%)	RR 0.86 (0.61 to 1.2)	16 fewer per 1000 (from 46 fewer to 24 more)	⊕⊕⊕O MODERATE	CRITICAL
Relapse in symptoms (200 and 400 micrograms daily doses) (follow-up 14 to 21 days)												
2[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	33/525 (6.3%)[4]	30/300 (10%)	RR 0.71 (0.44 to 1.15)	29 fewer per 1000 (from 56 fewer to 15 more)	⊕⊕⊕O MODERATE	CRITICAL
Complications												
No data on complications were reported												CRITICAL

Abbreviations: CI, Confidence interval; MD, Mean difference; N/A, Not applicable; OR, Odds ratio; RCT, Randomised controlled trial; RR, Relative risk; SNOT, Sino nasal outcomes score (see Terms used in the guideline); SD, Standard deviation

[1] Data from 1 RCT in children could not be included in the meta-analysis
[2] Zalmanovici Trestioreanu et al (2013)
[3] Downgraded 1 level - heterogeneity >50%
[4] Mometasone or fluticasone
[5] Downgraded 1 level - at a default minimal important difference (MID) of 25% or 0.5 SD for continuous data, data are consistent with no meaningful difference or appreciable benefit with nasal corticosteroids
[6] Mometasone
[7] Total score of 3 single symptom assessments: nasal congestion/stuffiness, sinus headache/pressure and post-nasal drip (see Terms used in the guideline).
[8] Keith et al (2012)
[9] Downgraded 1 level - not assessable
[10] Downgraded 2 levels - at a default MID of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[11] NICE analysis based upon figures presented in authors review

Table 13: GRADE profile – nasal corticosteroid versus antibiotic in adults and children aged 12 years and over

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mometasone	Amoxicillin[1]	Relative (95% CI)	Absolute		
Mean am/pm major symptom score[2] (mometasone 200 micrograms once a day; follow-up 14 days)												
1[3]	randomised trials[4]	no serious risk of bias	N/A	no serious indirectness	serious[5]	none	243	251	4.16 (from baseline of 8.17) vs. 4.40 (from baseline of 8.53) for mometasone 200 micrograms once a		⊕⊕⊕O MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mometasone	Amoxicillin[1]	Relative (95% CI)	Absolute		
									day and amoxicillin respectively (p=0.193)			
Mean am/pm major symptom score[2] (mometasone 200 micrograms twice a day; follow-up 14 days)												
1[3]	randomised trials[4]	no serious risk of bias	N/A	no serious indirectness	serious[5]	none	235	251	3.80 (from baseline of 8.28) vs. 4.40 (from baseline of 8.53) for mometasone 200 micrograms twice a day and amoxicillin respectively (p=0.002)		⊕⊕⊕O MODERATE	CRITICAL
Worsening or no improvement in symptoms during the treatment phase (treatment failure) (mometasone 200 micrograms once a day; follow-up 14 days)												
1[3]	randomised trials[4]	no serious risk of bias	N/A	no serious indirectness	serious[6]	none	25/243 (10.3%)	18/251 (7.2%)	RR 1.43 (0.80 to 2.56)	31 more per 1000 (from 14 fewer to 112 more)	⊕⊕⊕O MODERATE	IMPORTANT
Worsening or no improvement in symptoms during the treatment phase (treatment failure) (mometasone 200 micrograms twice a day; follow-up 14 days)												
1[3]	randomised trials[4]	no serious risk of bias	N/A	no serious indirectness	serious[5]	none	11 (4.7%)	18 (7.2%)	No significant difference between mometasone 200 micrograms twice a day and amoxicillin (p=0.258)		⊕⊕⊕O MODERATE	IMPORTANT
Patient-reported global response to treatment (mometasone 200 micrograms once a day; follow-up 14 days)												
1[3]	randomised trials[4]	no serious risk of bias	N/A	no serious indirectness	serious[5]	none	243	251	No significant difference between mometasone 200 micrograms once a day and amoxicillin (p value not reported)		⊕⊕⊕O MODERATE	IMPORTANT
Patient-reported global response to treatment (mometasone 200 micrograms twice a day; follow-up 14 days)												
1[3]	randomised trials[4]	no serious risk of bias	N/A	no serious indirectness	serious[5]	none	235	251	Mometasone 200 micrograms twice a day was statistically significantly more effective than amoxicillin (p=0.013)		⊕⊕⊕O MODERATE	IMPORTANT
Adverse events (mometasone 200 micrograms once a day; follow-up 14 days)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Mometasone	Amoxicillin[1]	Relative (95% CI)	Absolute		
1[3]	randomised trials[4]	no serious risk of bias	N/A	no serious indirectness	serious[5]	none	35.4%	33.5%	No significant difference between mometasone 200 micrograms once a day and amoxicillin (p value not reported)		⊕⊕⊕O MODERATE	IMPORTANT
Adverse events (mometasone 200 micrograms twice a day; follow-up 14 days)												
1[3]	randomised trials[4]	no serious risk of bias	N/A	no serious indirectness	serious[5]	none	36.2%	33.5%	No significant difference between mometasone 200 micrograms twice a day and amoxicillin (p value not reported)		⊕⊕⊕O MODERATE	IMPORTANT
Abbreviations: CI, Confidence interval; N/A, Not applicable; RR, Relative risk												

[1] 500mg three times a day for 10 days
[2] Total score of 5 single symptom assessments: rhinorrhoea/anterior discharge, postnasal drip, nasal congestion/stuffiness, sinus headache, and facial pain/pressure/tenderness on palpation over the paranasal sinuses (see Terms used in the guideline).
[3] Meltzer et al (2005)
[4] Study included in Zalmanovici Trestioreanu et al (2013). Only nasal corticosteroids vs. antibiotic outcomes that are not reported separately in the systematic review are included in this GRADE profile
[5] Downgraded 1 level - not assessable
[6] Downgraded 1 level - at a default minimal important difference (MID) of 25%, NICE data analysis are consistent with no meaningful difference or appreciable benefit with nasal corticosteroids, however note that the table data and narrative data in the published study are not consistent. Table II reports the treatment failure for mometasone as 23 (9%) and amoxicillin as 20 (8%) although using these figures the result remains non-significant (RR 1.19, 95% CI 0.67 to 2.11)

H.4 Back-up antibiotics

Table 14: GRADE profile – back-up antibiotic versus immediate antibiotic or no antibiotic in adults

Quality assessment							Effect					Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate antibiotic prescription	Patient-led delayed prescription[1]	Delayed collection prescription[2]	No prescription	Overall p value		
Rhinosinusitis													
Duration of symptoms after 1st visit - spontaneous facial pain (days, mean (SD))													
1[3]	randomised trials	no serious risk of bias[4]	N/A	no serious indirectness	serious[5]	none	7.1 (6.5)	6.1 (5.5)	5.4 (3.6)	8.6 (7.7)	0.48	⊕⊕⊕O MODERATE	CRITICAL
Duration of symptoms after 1st visit - facial pain on touch (days, mean (SD))													

Quality assessment							Effect					Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate antibiotic prescription	Patient-led delayed prescription[1]	Delayed collection prescription[2]	No prescription	Overall p value		
1[3]	randomised trials	no serious risk of bias[4]	N/A	no serious indirectness	serious[5]	none	7.6 (5.2)	9.0 (9.7)	11.6 (9.7)	9.2 (8.4)	0.15	⊕⊕⊕O MODERATE	CRITICAL
Severity of symptoms after 1st visit - spontaneous facial pain (median (interquartile range))													
1[3]	randomised trials	no serious risk of bias[4]	N/A	no serious indirectness	serious[5]	none	2 (1 to 3)	3 (2 to 4)	3 (3 to 4)	2 (1 to 4)	0.33	⊕⊕⊕O MODERATE	CRITICAL
Severity of symptoms after 1st visit - facial pain on touch (median (interquartile range))													
1[3]	randomised trials	no serious risk of bias[4]	N/A	no serious indirectness	serious[5]	none	1 (1 to 2)	3 (2 to 4)	3 (3 to 4)	3 (1 to 5)	0.08	⊕⊕⊕O MODERATE	CRITICAL
Rhinosinusitis and pharyngitis													
Duration of symptoms after 1st visit - headache (days, mean (SD))													
1[3]	randomised trials	no serious risk of bias[4]	N/A	serious[6]	serious[5]	none	4.1 (3.8)	6.3 (6.1)	7.0 (5.9)[7]	9.0 (8.0)[7]	0.03	⊕⊕OO LOW	CRITICAL
Duration of symptoms after 1st visit - nasal mucosity (days, mean (SD))													
1[3]	randomised trials	no serious risk of bias[4]	N/A	serious[6]	serious[5]	none	8.3 (7.2)	9.8 (7.5)	10.1 (7.8)	11.0 (7.4)	0.47	⊕⊕OO LOW	CRITICAL
Duration of symptoms after 1st visit - sore throat (days, mean (SD))													
1[3]	randomised trials	no serious risk of bias[4]	N/A	serious[6]	serious[5]	none	5.9 (4.7)	6.7 (4.6)	7.0 (4.7)	8.1 (6.3)	0.22	⊕⊕OO LOW	CRITICAL
Severity of symptoms after 1st visit - headache (median (interquartile range))													
1[3]	randomised trials	no serious risk of bias[4]	N/A	serious[6]	serious[5]	none	2 (1 to 3)	2 (2 to 3)	2 (2 to 4)	2 (1 to 4)	0.75	⊕⊕OO LOW	CRITICAL
Severity of symptoms after 1st visit - nasal mucosity (median (interquartile range))													
1[3]	randomised trials	no serious risk of bias[4]	N/A	serious[6]	serious[5]	none	2 (1 to 4)	3 (1 to 3)	2 (1 to 4)	3 (1 to 4)	0.30	⊕⊕OO LOW	CRITICAL
Severity of symptoms after 1st visit - sore throat (median (interquartile range))													
1[3]	randomised trials	no serious risk of bias[4]	N/A	serious[6]	serious[5]	none	2 (2 to 4)	3 (2 to 4)	2 (1 to 4)	3 (2 to 4)	0.49	⊕⊕OO LOW	CRITICAL
Uncomplicated upper respiratory tract infections													
Antibiotic collected													
1[3]	randomised trials	no serious risk of bias[4]	N/A	serious[8]	serious[5]	none	90/101 (89.1%)	34/98 (34.7%)	26/100 (26.0%)	N/A	<0.001	⊕⊕OO LOW	IMPORTANT
Antibiotic used													
1[3]	randomised trials	no serious risk of bias[4]	N/A	serious[8]	serious[5]	none	92/101 (91.1%)	32/98 (32.6%)	23/100 (23.0%)	12/98 (12.1%)	<0.001	⊕⊕OO LOW	IMPORTANT
Need for unscheduled healthcare													
1[3]	randomised trials	no serious risk of bias[4]	N/A	serious[8]	serious[5]	none	4/101 (4.0%)	6/98 (6.1%)	4/100 (4.0%)	6/98 (6.1%)	0.84	⊕⊕OO LOW	CRITICAL

Quality assessment							Effect					Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Immediate antibiotic prescription	Patient-led delayed prescription[1]	Delayed collection prescription[2]	No prescription	Overall p value		
Adverse effects													
1[3]	randomised trials	no serious risk of bias[4]	N/A	serious[8]	serious[5]	none	1/101 (1.0%)	1/98 (1.0%)	0/100 (0%)	3/98 (3.0%)	0.27	⊕⊕OO LOW	CRITICAL
Abbreviations: N/A, Not applicable; SD, Standard deviation													

[1] Patients were given an antibiotic prescription at first consultation
[2] Patients were able to collect an antibiotic prescription 3 days after the first consultation
[3] De la Poza Abad et al (2015)
[4] Study was open label but could not be blinded due to the nature of the interventions
[5] Downgraded 1 level - not assessable
[6] Downgraded 1 level - population includes people with rhinosinusitis and pharyngitis
[7] p<0.05 compared with an immediate antibiotic prescription
[8] Downgraded 1 level - population is people with uncomplicated upper respiratory tract infections, including sinusitis

Table 15: GRADE profile – back-up antibiotic versus immediate antibiotic or no antibiotic in adults (NICE analysis)

Quality assessment							Effect				Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Mean effect (95% CI)	Overall p value		
Rhinosinusitis												
Duration of symptoms after 1st visit – spontaneous facial pain (NICE pairwise analysis of immediate prescription versus delayed collection[1])												
1[2]	randomised trials	no serious risk of bias[3]	N/A	no serious indirectness	serious[4]	none	n=20	n=20	MD 1.70 (-1.59 to 4.99)	-	⊕⊕⊕O MODERATE	CRITICAL
Duration of symptoms after 1st visit – spontaneous facial pain (NICE pairwise analysis of immediate prescription versus patient led delayed collection[2])												
1[2]	randomised trials	no serious risk of bias[3]	N/A	no serious indirectness	very serious[5]	none	n=20	n=19	MD 1.00 (-2.81 to 4.81)	-	⊕⊕OO LOW	CRITICAL
Duration of symptoms after 1st visit – spontaneous facial pain (NICE pairwise analysis of immediate prescription versus no prescription)												
1[2]	randomised trials	no serious risk of bias[3]	N/A	no serious indirectness	serious[6]	none	n=20	n=19	MD -1.50 (-6.01 to 3.01)	-	⊕⊕⊕O MODERATE	CRITICAL
Duration of symptoms after 1st visit – spontaneous facial pain (NICE pairwise analysis of delayed collection[1] versus patient led delayed collection[2])												
1[2]	randomised trials	no serious risk of bias[3]	N/A	no serious indirectness	serious[6]	none	n=20	n=19	MD -0.70 (-3.63 to 2.23)	-	⊕⊕⊕O MODERATE	CRITICAL
Duration of symptoms after 1st visit – spontaneous facial pain (NICE pairwise analysis of delayed collection[1] versus no prescription)												
1[2]	randomised trials	no serious risk of bias[3]	N/A	no serious indirectness	serious[6]	none	n=20	n=19	MD -3.20 (-7.00 to 0.60)	-	⊕⊕⊕O MODERATE	CRITICAL
Duration of symptoms after 1st visit – spontaneous facial pain (NICE pairwise analysis of patient led delayed collection[2] versus no prescription)												
1[2]	randomised trials	no serious risk of bias[3]	N/A	no serious indirectness	serious[6]	none	n=19	n=19	MD -2.50 (-6.75 to 1.75)	-	⊕⊕⊕O MODERATE	CRITICAL

Quality assessment							Effect				Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intervention	Comparator	Mean effect (95% CI)	Overall p value		
Duration of symptoms after 1st visit – facial pain on touch (NICE pairwise analysis of immediate prescription versus delayed collection[1])												
1[2]	randomised trials	no serious risk of bias[3]	N/A	no serious indirectness	serious[6]	none	n=20	n=20	MD -4.00 (-8.82 to 0.82)	-	⊕⊕⊕O MODERATE	CRITICAL
Duration of symptoms after 1st visit – facial pain on touch (NICE pairwise analysis of immediate prescription versus patient led delayed collection[2])												
1[2]	randomised trials	no serious risk of bias[3]	N/A	no serious indirectness	serious[6]	none	n=20	n=19	MD -1.40 (-6.32 to 3.52)	-	⊕⊕⊕O MODERATE	CRITICAL
Duration of symptoms after 1st visit – facial pain on touch (NICE pairwise analysis of immediate prescription versus no prescription)												
1[2]	randomised trials	no serious risk of bias[3]	N/A	no serious indirectness	serious[6]	none	n=20	n=19	MD -1.60 (-6.01 to 2.81)	-	⊕⊕⊕O MODERATE	CRITICAL
Duration of symptoms after 1st visit – facial pain on touch (NICE pairwise analysis of delayed collection[1] versus patient led delayed collection[2])												
1[2]	randomised trials	no serious risk of bias[3]	N/A	no serious indirectness	serious[4]	none	n=20	n=19	MD 2.60 (-3.49 to 8.69)	-	⊕⊕⊕O MODERATE	CRITICAL
Duration of symptoms after 1st visit – facial pain on touch (NICE pairwise analysis of delayed collection[1] versus no prescription)												
1[2]	randomised trials	no serious risk of bias[3]	N/A	no serious indirectness	serious[4]	none	n=20	n=19	MD 2.40 (-3.69 to 8.49)	-	⊕⊕⊕O MODERATE	CRITICAL
Duration of symptoms after 1st visit – facial pain on touch (NICE pairwise analysis of patient led delayed collection[2] versus no prescription)												
1[2]	randomised trials	no serious risk of bias[3]	N/A	no serious indirectness	very serious[5]	none	n=19	n=19	MD -0.20 (-5.97 to 5.57)	-	⊕⊕OO LOW	CRITICAL

Abbreviations: CI, Confidence interval; MD, Mean difference; N/A, Not applicable; SD, Standard deviation

[1] Patients were able to collect an antibiotic prescription 3 days after the first consultation
[2] De la Poza Abad et al (2015)
[3] Study was open label but could not be blinded due to the nature of the interventions
[4] Downgraded 1 level – at a minimal important difference (MID) of 0.5 SD data are consistent with no meaningful difference or appreciable benefit with comparator
[5] Downgraded 2 levels – at a MID of 0.5 SD data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[6] Downgraded 1 level – at a MID of 0.5 SD data are consistent with no meaningful difference or appreciable benefit with intervention

H.5 Antibiotics (adults)

Table 16: GRADE profile – antibiotic versus placebo in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic[1]	Placebo	Relative (95% CI)	Absolute		
Cure or improvement												
Cure or improvement (follow-up 7 to 15 days)												
16[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1094/1417 (77.2%)	835/1231 (67.8%)	OR 1.64 (1.35 to 2.00) NICE analysis RR 1.10 (1.05 to 1.15)	97 more per 1000 (from 62 more to 130 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Cure or improvement (follow-up 7 to 11 days)												
9[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	480/675 (71.1%)	334/576 (58%)	OR 1.95 (1.35 to 2.81) NICE analysis RR 1.16 (1.05 to 1.27)	149 more per 1000 (from 71 more to 215 more)	⊕⊕⊕O MODERATE	CRITICAL
Cure or improvement (follow-up 14 to 15 days)												
9[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	614/742 (82.7%)	501/655 (76.5%)	OR 1.51 (1.14 to 1.99) NICE analysis RR 1.07 (1.02 to 1.12)	66 more per 1000 (from 23 more to 101 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Cure or improvement (sub-group analyses)												
14-16[2]	randomised trials	no serious risk of bias	serious[4]	no serious indirectness	serious[4]	none	-		No significant differences were found for age-group (p=0.95), diagnostic criteria (p=0.30), timing of assessment (p=0.43) or year of study publication (p=0.21)		⊕⊕OO LOW	CRITICAL
Cure or improvement (follow-up 3 to 5 days)												
2[5]	randomised trials	no serious risk of bias	serious[6]	no serious indirectness	very serious[7]	none	88/132 (66.7%)	72/126 (57.1%)	RD 0.103 NICE analysis RR	p=0.124 NICE analysis p=0.12	⊕OOO VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic[1]	Placebo	Relative (95% CI)	Absolute		
									2.61 (0.19 to 36.25)			
Cure or improvement (follow-up 7 to 12 days)												
5[5]	randomised trials	no serious risk of bias	serious[6]	no serious indirectness	serious[3]	none	247/282 (87.5%)	202/261 (77.4%)	RD 0.142 NICE analysis RR 1.18 (0.99 to 1.41)	p=0.038 NICE analysis (p=0.06)	⊕⊕OO LOW	CRITICAL
Cure or improvement (follow-up 14 to 15 days)												
3[5]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	312/382 (81.6%)	308/418 (73.7%)	RD 0.073 (95% CI 0.02 to 0.13) NICE analysis RR 1.10 (1.02 to 1.18)	p=0.013 NICE analysis p=0.01	⊕⊕⊕⊕ HIGH	CRITICAL
Lack of full recovery or improvement (follow-up 7 to 15 days)												
5[8]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	49/566 (8.7%)	67/492 (13.6%)	RR 0.66 (0.47 to 0.94)	46 fewer per 1000 (from 8 fewer to 72 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Lack of full recovery or improvement (follow-up 16 to 60 days; 2 RCTs, data not pooled)												
1[8]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[3]	none	19/73 (26%)	19/45 (42.2%)	RR 0.62 (0.37 to 1.03)	160 fewer per 1000 (from 266 fewer to 13 more)	⊕⊕⊕O MODERATE	CRITICAL
1[8]	randomised trials	no serious risk of bias	N/A	no serious indirectness	very serious[7]	none	9/87 (10.3%)	10/82 (12.2%)	RR 0.85 (0.36 to 1.98)	18 fewer per 1000 (from 78 fewer to 120 more)	⊕⊕OO LOW	CRITICAL
Cure												
Cure at 7 to 15 days (follow-up 7 to 15 days)												
12[2]	randomised trials	no serious risk of bias	serious[6]	no serious indirectness	serious[3]	none	548/957 (57.3%)	394/856 (46%)	OR 1.82 (1.34 to 2.46) NICE analysis RR 1.29 (1.10 to 1.51)	148 more per 1000 (from 73 more to 217 more)	⊕⊕OO LOW	CRITICAL
Clinical cure (follow-up 3 to 5 days)												
3[5]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[7]	none	23/207 (11.1%)	13/190 (6.8%)	RD 0.014 (-0.02 to 0.05)	p=0.451	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic[1]	Placebo	Relative (95% CI)	Absolute		
									NICE analysis RR 1.59 (0.84 to 3.03)	NICE analysis p=0.16		
Clinical cure (follow-up 7 to 12 days)												
9[5]	randomised trials	no serious risk of bias	serious[6]	no serious indirectness	serious[3]	none	376/817 (46%)	287/790 (36.3%)	RD 0.145 (0.04 to 0.25)	p=0.007	⊕⊕OO LOW	CRITICAL
									NICE analysis RR 1.28 (1.02 to 1.61)	NICE analysis p=0.03		
Clinical cure (follow-up 14 to 15 days)												
4[5]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	249/551 (45.2%)	228/553 (41.2%)	RD 0.041 (-0.02 to 0.11)	p=0.214	⊕⊕⊕O MODERATE	CRITICAL
									NICE analysis RR 1.09 (0.97 to 1.23)	NICE analysis p=0.16		
Cure at a specific time point												
8[9]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	517/853 (60.6%)	459/834 (55%)	OR 1.25 (1.02 to 1.53)	54 more per 1000 (from 5 more to 102 more)	⊕⊕⊕⊕ HIGH	CRITICAL
									NICE analysis RR 1.09 (1.01 to 1.18)			
Cure (follow-up 7 days)												
4[9]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	205/427 (48%)	198/429 (46.2%)	OR 1.07 (0.81 to 1.41)	17 more per 1000 (from 52 fewer to 86 more)	⊕⊕⊕⊕ HIGH	CRITICAL
									NICE analysis RR 1.04 (0.90 to 1.19)			
Cure (follow-up 10 days)												
4[9]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	277/519 (53.4%)	262/529 (49.5%)	OR 1.18 (0.92 to 1.52)	41 more per 1000 (from 21 fewer to 103 more)	⊕⊕⊕⊕ HIGH	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic[1]	Placebo	Relative (95% CI)	Absolute		
									NICE analysis RR 1.08 (0.96 to 1.21)			
Cure (follow-up 14 days)												
3[9]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	177/242 (73.1%)	144/225 (64%)	OR 1.48 (0.99 to 2.23) NICE analysis RR 1.13 (1.00 to 1.27)	85 more per 1000 (from 2 fewer to 159 more)	⊕⊕⊕O MODERATE	CRITICAL
Cure at follow-up assessment (follow-up 8 to 15 days)												
11[10]	randomised trials	serious[11]	no serious inconsistency	no serious indirectness	no serious imprecision	none	862/1349 (63.9%)	757/1333 (56.8%)	OR 1.35 (1.15 to 1.59) NICE analysis RR 1.12 (1.05 to 1.19)	72 more per 1000 (from 34 more to 108 more)	⊕⊕⊕O MODERATE	CRITICAL
Cure at follow-up assessment (individual patient data; follow-up 8 to 15 days)												
10[10]	randomised trials	serious[11]	serious[4]	no serious indirectness	serious[4]	none	822/1278 (64.3%)	724/1262 (57.4%)	OR 1.37 (1.13 to 1.66) NICE analysis RR not estimable (IPD)	75 more per 1000 (from 30 more to 117 more)	⊕OOO VERY LOW	CRITICAL
Effect of baseline symptoms on the odds of cure (follow-up 8 to 15 days)												
11[10]	randomised trials	serious[11]	serious[4]	no serious indirectness	serious[4]	none	-		Purulent discharge in the pharynx (clinician noted sign) took longer to cure but people were more likely to benefit from antibiotic than other patients (mean effect on odds of cure if untreated 0.65 (95% CI 0.45 to 0.96). The study also found that temperature >37.5°C may also suggest that antibiotic may offer additional benefit		⊕OOO VERY LOW	CRITICAL
Lack of full recovery (follow-up 7 to 15 days)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic[1]	Placebo	Relative (95% CI)	Absolute		
5[8]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	175/372 (47%)	189/308 (61.4%)	RR 0.73 (0.63 to 0.85)	166 fewer per 1000 (from 92 fewer to 227 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Lack of full recovery (follow-up 16 to 60 days)												
1[8]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[3]	none	18/87 (20.7%)	27/82 (32.9%)	RR 0.63 (0.38 to 1.05)	122 fewer per 1000 (from 204 fewer to 16 more)	⊕⊕⊕O MODERATE	CRITICAL
Lack of cure (clinical failure)												
8[9]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	61/1098 (5.6%)	115/1077 (10.7%)	OR 0.49 (0.36 to 0.66)[10] NICE analysis RR 0.51 (0.38 to 0.69)	51 fewer per 1000 (from 34 fewer to 66 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Duration of symptoms												
Time to resolution of symptoms (follow-up 7 to 15 days; data not pooled)												
8[2]	randomised trials	no serious risk of bias	serious[4]	no serious indirectness	serious[4]	none	-		8 RCTs reported time to resolution of symptoms (3 RCTs reported time to resolution of specific symptoms). The authors report that although not comprehensive, most of the RCTs reported faster symptom resolution in people receiving antibiotics, although this was not always statistically significant		⊕⊕OO LOW	CRITICAL
Illness duration												
2[9]	randomised trials	no serious risk of bias	serious[4]	no serious indirectness	serious[4]	none	-		No significant differences between antibiotics and placebo were reported		⊕⊕OO LOW	CRITICAL
Quality of life												
SNOT-16 score (follow-up 6 to 10 days)												
2[8]	randomised trials	no serious risk of bias	serious[4]	no serious indirectness	serious[4]	none	-		1 RCT reported similar quality of life in antibiotic and placebo groups at day 3 and day 10, but a significant difference at day 7 favoured antibiotic (p=0.02) 1 RCT found that people taking antibiotics had a significantly		⊕⊕OO LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic[1]	Placebo	Relative (95% CI)	Absolute		
									greater mean reduction in SNOT-16 total score compared with placebo at day 6 to 8 (–17.54 vs. –12.83 (p=0.032), from baseline values of about 28 in both groups			
Mean duration of absence from work												
1[8]	randomised trials	no serious risk of bias	serious[4]	no serious indirectness	serious[4]	none	-		1 RCT found that the mean period missed from work was the same with antibiotic compared with placebo (0.55 days in both groups)		⊕⊕OO LOW	IMPORTANT
Activity impairment at days 6 to 8												
1[8]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[3]	none	251 (mean change in score -6.1 [SD± 5.9])	123 (mean change in score -3.7 [SD± 5.8])	NICE analysis MD -2.40 (95% CI -3.66 to -1.14)		⊕⊕⊕O MODERATE	IMPORTANT
1[8]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[4]	none	-		1 RCT found no significant difference between the antibiotic and placebo groups in the period of being unable to do usual non-work activities		⊕⊕⊕O MODERATE	IMPORTANT
Restriction of daily activities												
5[9]	randomised trials	no serious risk of bias	serious[4]	no serious indirectness	serious[4]	none	-		No RCTs found a significant difference in activity restriction between the antibiotic and placebo groups		⊕⊕OO LOW	IMPORTANT
Other efficacy outcomes												
Resolution of purulent secretions[12] (follow-up at any timing of endpoint)												
3[9]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	236/342 (69%)	190/318 (59.7%)	OR 1.58 (1.13 to 2.22) NICE analysis RR 1.16 (1.04 to 1.29)	104 more per 1000 (from 29 more to 170 more)	⊕⊕⊕O MODERATE	CRITICAL
Pain												
4[9]	randomised trials	no serious risk of bias	serious[13]	no serious indirectness	serious[4]	none	-		No significant differences between antibiotics and placebo were reported		⊕⊕OO LOW	CRITICAL
Perception of cure (patient assessment)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic[1]	Placebo	Relative (95% CI)	Absolute		
5[9]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	345/555 (62.1%)	296/546 (54.2%)	OR 1.40 (1.08 to 1.82) NICE analysis RR 1.13 (1.03 to 1.24)	-	⊕⊕⊕⊕ HIGH	IMPORTANT
Perception of cure (investigator assessment)												
3[9]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	172/298 (57.7%)	163/288 (54.7%)	OR 1.05 (0.76 to 1.46) NICE analysis RR 1.02 (0.89 to 1.17)	-	⊕⊕⊕⊕ HIGH	IMPORTANT
Adverse events												
Adverse events (follow-up 7 to 15 days)												
12[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[14]	none	324/1069 (30.3%)	194/894 (21.7%)	OR 1.87 (1.21 to 2.90) NICE analysis RR 1.56 (1.13 to 2.17)	124 more per 1000 (from 34 more to 229 more)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events (follow-up 14 to 15 days)												
10[5]	randomised trials	no serious risk of bias	serious[6]	no serious indirectness	serious[3]	none	272/959 (28.4%)	176/894 (19.7%)	RD 0.11 (0.05 to 0.16) NICE analysis RR 1.84 (1.24 to 2.72)	p=0.0001 NICE analysis p=0.002	⊕⊕OO LOW	CRITICAL
Adverse effects												
7[9]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	193/706 (27.3%)	100/665 (15%)	OR 2.10 (1.6 to 2.77) NICE analysis RR 1.76 (1.43 to 2.18)	121 more per 1000 (from 70 more to 179 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Withdrawal due to adverse events (follow-up 7 to 15 days)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic[1]	Placebo	Relative (95% CI)	Absolute		
17[2]	randomised trials	no serious risk of bias	serious[4]	no serious indirectness	very serious[8]	none	n=3,013		OR 1.42 (95% CI 0.74 to 2.72) NICE analysis RR not estimable	-	⊕OOO VERY LOW	CRITICAL
Withdrawal due to adverse effects (follow-up 7 to 15 days)												
9[7]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[8]	none	15/1013 (1.5%)	8/805 (0.99%)	OR 1.40 (0.6 to 3.25) NICE analysis RR 1.28 (0.57 to 2.89)	4 more per 1000 (from 4 fewer to 22 more)	⊕⊕OO LOW	CRITICAL
Serious adverse events												
1[9]	randomised trials	no serious risk of bias	serious[4]	no serious indirectness	serious[4]	none	-		The systematic review reports 1 serious adverse event related to sinusitis (placebo group) from 1 RCT (brain abscess). 2 further serious adverse events (myocardial infarction and a depressive episode) were not thought to be related to treatment		⊕⊕OO LOW	CRITICAL
Disease complications (follow-up 7 to 15 days)												
9[2]	randomised trials	no serious risk of bias	serious[4]	no serious indirectness	serious[4]	none	n=1,815		OR 0.68 (95% CI 0.22 to 2.09) NICE analysis RR not estimable	-	⊕⊕OO LOW	CRITICAL
Disease recurrence (follow-up 7 to 15 days)												
6[2]	randomised trials	no serious risk of bias	serious[4]	no serious indirectness	serious[4]	none	n=1,421		OR 1.12 (95% CI 0.79 to 1.59) NICE analysis RR not estimable	-	⊕⊕OO LOW	CRITICAL
Relapse (follow-up 60 days)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic[1]	Placebo	Relative (95% CI)	Absolute		
1[7]	randomised trials	no serious risk of bias	N/A	no serious indirectness	very serious[8]	none	23/108 (21.3%)	18/106 (17%)	RR 1.25 (0.72 to 2.19)	42 more per 1000 (from 48 fewer to 202 more)	⊕⊕OO LOW	CRITICAL
Need for antibiotic treatment (treatment failure)												
8[9]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	61/1098 (5.6%)	115/1077 (10.7%)	OR 0.49 (0.36 to 0.66)[16] NICE analysis RR 0.51 (0.38 to 0.69)	51 fewer per 1000 (from 34 fewer to 66 fewer)	⊕⊕⊕⊕ HIGH	IMPORTANT
Diarrhoea and gastrointestinal complaints (follow-up 7 to 15 days)												
14[2]	randomised trials	no serious risk of bias	serious[4]	no serious indirectness	serious[4]	none	n=2,403		OR 2.28 (95% CI 1.24 to 4.21) NICE analysis RR not estimable	-	⊕⊕OO LOW	CRITICAL
Diarrhoea (follow-up 14 to 15 days)												
8[5]	randomised trials	no serious risk of bias	serious[6]	no serious indirectness	serious[3]	none	101/820 (12.3%)	55/763 (6.9%)	RD 0.049 (0.01 to 0.09) NICE analysis RR 1.74 (1.14 to 2.66)	p=0.027 NICE analysis p=0.01	⊕⊕OO LOW	CRITICAL
Diarrhoea[12]												
4[9]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[15]	none	67/421 (15.9%)	41/395 (10.4%)	OR 1.81 (1.18 to 2.78)[15] NICE analysis RR 1.61 (1.14 to 2.27)	70 more per 1000 (from 16 more to 140 more)	⊕⊕⊕O MODERATE	CRITICAL

Abbreviations: CI, Confidence interval; IPD, Individual patient data meta-analysis; MD, Mean difference; N/A, Not applicable; OR, Odds ratio; RD, Risk difference; RR, Relative risk; p, P-value; RCT, Randomised controlled trial; SNOT, Sino-nasal outcome test (see Terms used in the guideline); SD, Standard deviation

[1] Antibiotics included penicillins, macrolides and quinolones
[2] Falagas et al (2008)
[3] Downgraded 1 level - at a default minimal important difference (MID) of 25% (or 0.5 SD for continuous data), data are consistent with no meaningful difference or appreciable benefit with antibiotics
[4] Downgraded 1 level - not assessable

[5] Rosenfeld et al (2007)
[6] Downgraded 1 level - heterogeneity >50%
[7] Downgraded 2 levels - at a default MID of 25% data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[8] Ahovuo-Saloranta et al (2014)
[9] Lemiengre et al (2012)
[10] Young et al (2008)
[11] Authors did not report study quality or methods used to assess study quality
[12] Some data could not be pooled, but these data are consistent with the pooled data
[13] Downgraded 1 level - authors state data were too heterogeneous to pool
[14] Downgraded 1 level - at a default MID of 25% data are consistent with no meaningful difference or appreciable benefit with placebo
[15] Peto odds ratio

Table 17: GRADE profile – cephalosporin versus co-amoxiclav in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cephalosporin	Co-amoxiclav	Relative (95% CI)	Absolute		
Lack of full recovery or improvement (clinical failure) (follow-up 7 to 15 days)[1]												
6[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	none	110/944 (11.7%)	80/943 (8.5%)	RR 1.37 (1.04 to 1.80)	31 more per 1000 (from 3 more to 68 more)	⊕⊕OO LOW	CRITICAL
Lack of full recovery or improvement (clinical failure) (follow-up 16 to 60 days)[1]												
7[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	124/724 (17.1%)	109/691 (15.8%)	RR 1.08 (0.85 to 1.37)	13 more per 1000 (from 24 fewer to 58 more)	⊕⊕⊕O MODERATE	CRITICAL
Drop-outs due to adverse effects												
9[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1.3%	4.4%	OR 0.32 (0.21 to 0.49)[5] NICE analysis RR 0.29 (0.18 to 0.48)	-	⊕⊕⊕⊕ HIGH	CRITICAL

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

[1] The systematic review also reported 21 miscellaneous comparisons. None of these studies reported any statistically significant differences in outcomes
[2] Ahuovo-Saloranta et al (2014)
[3] Downgraded 1 level - No RCTs were assessed by Cochrane reviewers as having low risk of bias, and 2 RCTs which represented 70% weight in the meta-analysis were at high risk of bias
[4] Downgraded 1 level - at a default minimal important difference (MID) of 25% data are consistent with no meaningful difference or appreciable benefit with co-amoxiclav
[5] Peto odds ratio

Table 18: GRADE profile – macrolide versus co-amoxiclav in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Macrolide	Co-amoxiclav	Relative (95% CI)	Absolute		
Lack of full recovery or improvement (clinical failure) (follow-up 7 to 15 days)[1]												
7[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	78/950 (8.2%)	82/857 (9.6%)	RR 0.83 (0.62 to 1.13)	16 fewer per 1000 (from 36 fewer to 12 more)	⊕⊕⊕O MODERATE	CRITICAL
Lack of full recovery or improvement (clinical failure) (follow-up 16 to 60 days)[1]												
4[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	44/486 (9.1%)	43/422 (10.2%)	RR 0.85 (0.57 to 1.27)	15 fewer per 1000 (from 44 fewer to 28 more)	⊕⊕OO LOW	CRITICAL
Drop-outs due to adverse effects												
8[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	2.1%	4.8%	OR 0.47 (0.3 to 0.72)[5] NICE analysis RR 0.47 (0.31 to 0.73)	-	⊕⊕⊕⊕ HIGH	CRITICAL

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

[1] The systematic review also reported 21 miscellaneous comparisons. None of these studies reported any statistically significant differences in outcomes
[2] Ahovuo-Saloranta et al (2014)
[3] Downgraded 1 level - at a default minimal important difference (MID) of 25% data are consistent with no meaningful difference or appreciable benefit with co-amoxiclav
[4] Downgraded 2 levels - at a default MID of 25% data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[5] Peto odds ratio

Table 19: GRADE profile – non-penicillin versus beta-lactamase sensitive penicillin in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Non-penicillin	Beta-lactamase sensitive penicillin	Relative (95% CI)	Absolute		
Lack of full recovery or improvement (clinical failure) (follow-up 7 to 15 days)[1]												
7[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[3]	none	36/546 (6.6%)	52/537 (9.7%)	RR 0.70 (0.47 to 1.06)	29 fewer per 1000 (from 51 fewer to 6 more)	⊕⊕⊕O MODERATE	CRITICAL
Lack of full recovery or improvement (clinical failure) (follow-up 16 to 60 days)[1]												
1[2]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[3]	none	17/220 (7.7%)	25/216 (11.6%)	RR 0.67 (0.37 to 1.20)	38 fewer per 1000 (from 73 fewer to 23 more)	⊕⊕⊕O MODERATE	CRITICAL
Drop-outs due to adverse effects												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Non-penicillin	Beta-lactamase sensitive penicillin	Relative (95% CI)	Absolute		
7[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	1.3%	2.3%	OR 0.58 (0.25 to 1.35)[5] NICE analysis RR 0.61 (0.27 to 1.37)	-	⊕⊕OO LOW	CRITICAL
Abbreviations: CI, Confidence interval; OR, Odds ratio; RR, Relative risk												

[1] The systematic review also reported 21 miscellaneous comparisons. None of these studies reported any statistically significant differences in outcomes
[2] Ahovuo-Saloranta et al (2014)
[3] Downgraded 1 level - at a default minimal important difference (MID) of 25% data are consistent with no meaningful difference or appreciable benefit with beta-lactamase sensitive penicillins
[4] Downgraded 2 levels - at a default MID of 25% data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[5] Peto odds ratio

Table 20: GRADE profile – tetracycline versus other antibiotic (mixed classes) in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Tetracycline	Other antibiotic (mixed)	Relative (95% CI)	Absolute		
Lack of full recovery or improvement (clinical failure) (follow-up 7 to 15 days)[1]												
5[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	35/406 (8.6%)	31/401 (7.7%)	RR 1.09 (0.70 to 1.71)	7 more per 1000 (from 23 fewer to 55 more)	⊕⊕OO LOW	CRITICAL[3]
Lack of full recovery or improvement (clinical failure) (follow-up 16 to 60 days)												
No data were reported												CRITICAL[3]
Drop-outs due to adverse effects												
5[1]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[3]	none	2.6%	3.5%	OR 0.73 (0.33 to 1.60)[4] NICE analysis RR 0.75 (0.35 to 1.58)	-	⊕⊕OO LOW	CRITICAL
Abbreviations: CI, Confidence interval; OR, Odds ratio; RR, Relative risk												

[1] The systematic review also reported 21 miscellaneous comparisons. None of these studies reported any statistically significant differences in outcomes
[2] Ahovuo-Saloranta et al (2014)
[3] Downgraded 2 levels - at a default minimal important difference (MID) of 25% data are consistent with no meaningful difference, appreciable benefit or appreciable harm
[4] Peto odds ratio

Table 21: GRADE profile – quinolone versus beta-lactam antibiotic in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quinolone	Beta-lactam antibiotic	Relative (95% CI)	Absolute		
Cure or substantial improvement (ITT population; at the test of cure time point; follow-up 10 to 31 days[1])												
5[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	924/1062 (87%)[4]	922/1071 (86.1%)	OR 1.09 (0.85 to 1.39) NICE analysis RR 1.01 (0.98 to 1.04)	10 more per 1000 (from 21 fewer to 35 more)	⊕⊕⊕O MODERATE	CRITICAL
Cure or substantial improvement - all quinolones (clinically evaluable population; at the test of cure time point and within 21 days from the start of treatment)												
11[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2067/2306 (89.6%)	2041/2334 (87.4%)	OR 1.24 (1.03 to 1.49) NICE analysis RR 1.02 (1.00 to 1.05)	22 more per 1000 (from 3 more to 38 more)	⊕⊕⊕O MODERATE	CRITICAL
Cure or substantial improvement - 'respiratory quinolones' (clinically evaluable population; at the test of cure time point and within 21 days from the start of treatment)												
8[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1230/1376 (89.4%)[4]	1232/1421 (86.7%)	OR 1.29 (1.03 to 1.63) NICE analysis RR 1.03 (1.00 to 1.06)	27 more per 1000 (from 3 more to 47 more)	⊕⊕⊕O MODERATE	CRITICAL
Cure or improvement - all quinolones (within 21 days from the start of treatment)												
7[2]	randomised trials	serious[3]	serious[5]	no serious indirectness	serious[5]	none	n=2,382		OR 1.32 (1.03 to 1.71) NICE analysis not estimable	-	⊕OOO VERY LOW	CRITICAL
Cure or improvement - 'respiratory quinolones' (within 21 days from the start of treatment)												
5[2]	randomised trials	serious[3]	serious[5]	no serious indirectness	serious[5]	none	n=1,758[4]		OR 1.39 (1.02 to 1.88) NICE analysis not estimable	-	⊕OOO VERY LOW	CRITICAL
Eradication of the pathogen (bacteriological success) - all quinolones												
5[2]	randomised trials	serious[3]	serious[5]	no serious indirectness	serious[5]	none	n=868		OR 1.99 (1.24 to 3.19) NICE analysis not estimable	-	⊕OOO VERY LOW	CRITICAL
Eradication of the pathogen (bacteriological success) - 'respiratory quinolones'												
3[2]	randomised trials	serious[3]	serious[5]	no serious indirectness	serious[5]	none	n=506[4]		OR 2.11 (1.09 to 4.08) NICE analysis not estimable	-	⊕OOO VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Quinolone	Beta-lactam antibiotic	Relative (95% CI)	Absolute		
Adverse events (clinically evaluable population) - all quinolones												
9[2]	randomised trials	serious[3]	serious[6]	no serious indirectness	no serious imprecision	none	817/2510 (32.5%)	757/2508 (30.2%)	OR 1.16 (0.95 to 1.4) NICE analysis RR 1.10 (0.97 to 1.24)	32 more per 1000 (from 11 fewer to 75 more)	⊕⊕OO LOW	CRITICAL
Adverse events (clinically evaluable population) - 'respiratory fluoroquinolones'												
6[2]	randomised trials	serious[3]	serious[6]	no serious indirectness	serious[7]	none	547/1359 (40.3%)[4]	514/1373 (37.4%)	OR 1.17 (0.86 to 1.59) NICE analysis RR 1.10 (0.91 to 1.32)	37 more per 1000 (from 35 fewer to 113 more)	⊕OOO VERY LOW	CRITICAL
Serious adverse events - all quinolones												
7[2]	randomised trials	serious[3]	serious[5]	no serious indirectness	serious[5]	none	n=3,004		OR 0.53 (0.3 to 0.93) NICE analysis RR not estimable	-	⊕OOO VERY LOW	CRITICAL
Serious adverse events - 'respiratory quinolones'												
6[2]	randomised trials	serious[3]	serious[5]	no serious indirectness	serious[5]	none	n=2,503[4]		OR 0.53 (0.3 to 0.95) NICE analysis RR not estimable	-	⊕OOO VERY LOW	CRITICAL
Withdrawals due to adverse events - all quinolones												
11[2]	randomised trials	serious[4]	serious[5]	no serious indirectness	serious[5]	none	n=5,584		OR 1.17 (0.88 to 1.56) NICE analysis RR not estimable	-	⊕OOO VERY LOW	CRITICAL
Withdrawals due to adverse events - 'respiratory quinolones'												
8[2]	randomised trials	serious[3]	serious[5]	no serious indirectness	serious[5]	none	n=3,298[4]		OR 1.35 (0.94 to 1.95) NICE analysis RR not estimable	-	⊕OOO VERY LOW	CRITICAL

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

[1] The test of cure time point varied from 10 to 31 days after the start of study treatment
[2] Karageorgopoulos et al (2008)
[3] Moxifloxacin, levofloxacin or gatifloxacin

[4] Downgraded 1 level - RCTs were assessed for methodological quality, but it is not clear whether a validated tool was used. Of the 11 RCTs included in the meta-analysis, 5 were open label studies. 6 RCTs reported adequate randomisation procedures, 5 RCTs reported blinding and allocation concealment was only reported in 3 RCTs
[5] Downgraded 1 level - not assessable (insufficient data for reanalysis)
[6] Downgraded 1 level - significant heterogeneity >50%
[7] Downgraded 1 level - at a default minimal important difference (MID) of 25% data are consistent with no meaningful difference or appreciable harm with quinolones

Table 22: GRADE profile – short course antibiotic versus long course antibiotic in adults

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short course antibiotic	Long course antibiotic	Relative (95% CI)	Absolute		
Cure or improvement (at the test of cure time point; follow-up 10 to 36 days[1])												
12[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1845/2216[3] (83.2%)	1862/2214 (84.1%)	OR 0.95 (0.81 to 1.12) NICE analysis RR 0.99 (0.97 to 1.02)	-	⊕⊕⊕⊕ HIGH	CRITICAL
Cure or improvement (at the test of cure time point; 5 days vs. 10 days)												
7[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1155/1349 (85.6%)	1177/1366 (86.1%)	OR 0.98 (0.79 to 1.22) NICE analysis RR 1.00 (0.97 to 1.03)	-	⊕⊕⊕⊕ HIGH	CRITICAL
Cure or improvement (at the test of cure time point; beta-lactam antibiotics)												
6[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1138/1318 (86.3%)	1159/1331 (87%)	OR 0.95 (0.76 to 1.2) NICE analysis RR 0.99 (0.96 to 1.02)	-	⊕⊕⊕⊕ HIGH	CRITICAL
Relapse												
5[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	51/687 (7.4%)	54/709 (7.61%)	OR 0.95 (0.63 to 1.42) NICE analysis RR 0.95 (0.66 to 1.37)	-	⊕⊕OO LOW	CRITICAL
Relapse (5 days vs. 10 days)												
4[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	48/660 (7.2%)	53/684 (7.74%)	OR 0.91 (0.6 to 1.37) NICE analysis RR 0.92 (0.63 to 1.33)	-	⊕⊕OO LOW	CRITICAL
Relapse (beta-lactam antibiotics)												
3[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	43/524 (8.2%)	48/551 (8.7%)	OR 0.90 (0.58 to 1.39) NICE analysis RR 0.91 (0.62 to 1.34)	-	⊕⊕OO LOW	CRITICAL
Microbiological efficacy												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short course antibiotic	Long course antibiotic	Relative (95% CI)	Absolute		
3[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	168/181[5] (92.8%)	180/198 (90.9%)	OR 1.30 (0.62 to 2.74) NICE analysis RR 1.02 (0.96 to 1.08)	-	⊕⊕⊕⊕ HIGH	CRITICAL
Adverse events												
10[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	486/2083 (23.33%)	538/2089 (25.7%)	OR 0.88 (0.71 to 1.09) NICE analysis RR 0.91 (0.78 to 1.05)	-	⊕⊕⊕⊕ HIGH	CRITICAL
Adverse events (5 days vs. 10 days)												
5[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	none	209/1065 (19.24%)	252/1086 (23.2%)	OR 0.79 (0.63 to 0.98) NICE analysis RR 0.85 (0.73 to 0.99)	-	⊕⊕⊕O MODERATE	CRITICAL
Adverse events (beta-lactam antibiotics)												
5[2]	randomised trials	no serious risk of bias	serious[7]	no serious indirectness	very serious[4]	none	149/1103 (13.5%)	146/1114 (13.1%)	OR 1.03 (0.65 to 1.62) NICE analysis RR 1.02 (0.68 to 1.52)	-	⊕OOO VERY LOW	CRITICAL
Withdrawals due to adverse events												
11[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	52/2232 (2.32%)	61/2330 (2.61%)	OR 0.88 (0.61 to 1.29) NICE analysis RR 0.89 (0.62 to 1.28)	-	⊕⊕OO LOW	CRITICAL
Withdrawals due to adverse events (5 days vs. 10 days)												
6[2]	randomised trials	no serious risk of bias	serious[7]	no serious indirectness	very serious[4]	none	34/1214 (2.8%)	36/1327 (2.71%)	OR 1.02 (0.63 to 1.64) NICE analysis RR 1.02 (0.64 to 1.62)[8]	-	⊕OOO VERY LOW	CRITICAL
Withdrawals due to adverse events (beta-lactam antibiotics)												
5[2]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	19/1103 (1.7%)	29/1214 (2.38%)	OR 0.71 (0.39 to 1.27) NICE analysis RR 0.71 (0.40 to 1.26)	-	⊕⊕OO LOW	CRITICAL

Abbreviations: CI, Confidence interval; OR, Odds ratio

[1] Test of cure time point varied from 10 days to days 22 to 36

[2] Falagas et al (2009)

[3] Short course was 5 days in 8 RCTs, 3 days in 2 RCTs and 7 days in 2 RCTs. Long course was 10 days in 10 RCTs, 7 days in 1 RCT and 6 days in 1 RCT

[4] Downgraded 2 levels - at a default minimal important difference (MID) of 25% data are consistent with no meaningful difference, appreciable benefit or appreciable harm

[5] Population with bacterial isolates
[6] Downgraded 1 level - at a default MID of 25% data are consistent with no meaningful difference or appreciable benefit for short course antibiotic
[7] Downgraded 1 level - heterogeneity >50%
[8] NICE analysis using random effects model OR 0.98 (95% CI 0.41 to 2.32)

H.5.1 Data from RCTs included in systematic reviews of penicillin V (phenoxymethylpenicillin) compared with amoxicillin

Table 23: GRADE profile – penicillin V versus amoxicillin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Penicillin V	Amoxicillin	Relative (95% CI)	Absolute		
Subjective status at day 3 (cure or improvement)[1]												
1[2]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[3]	none	32/39 (82.1%)	35/44 (79.5%)[4]	RR 1.03[5] (0.84 to 1.27)	p=1.00[6]	⊕⊕⊕O MODERATE	CRITICAL
Subjective status at day 10 (cure or improvement)[1]												
1[2]	randomised trials	no serious risk of bias	N/A	no serious indirectness	no serious imprecision	none	36/39 (92.3%)	43/44 (97.7%)[7]	RR 0.94[5] (0.85 to 1.05)	p=0.19[6]	⊕⊕⊕⊕ HIGH	CRITICAL
1[8]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[3]	none	18/20 (90%)	19/22 (86.4%)[9]	RR 1.04[5] (0.84 to 1.30)	p=0.66[10]	⊕⊕⊕O MODERATE	CRITICAL
Recovery at 14 to 16 days (telephone follow-up)[11]												
1[12]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[3]	none	26/32 (81%)	18/23 (78%)[13]	RR 1.04[5] (0.79 to 1.36)	p=0.27[5]	⊕⊕⊕O MODERATE	CRITICAL
Mean [SD] clinical severity score at day 10 (Better indicated by lower values)[14]												
1[2]	randomised trials	no serious risk of bias	N/A	no serious indirectness	no serious imprecision	none	n=39 (2.9 [1.54])	n=44 (2.9 [1.64])	MD 0.0[15] (-0.68 to 0.68)	p=0.58[16]	⊕⊕⊕⊕ HIGH	CRITICAL
Mean [SD] clinical severity score at day 10 (Better indicated by lower values)[17]												
1[8]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[3]	none	20 (0.7 [0.64])	22 (0.5 [0.67])	MD 0.20[15] (-0.20 to 0.60)	p=0.66	⊕⊕⊕O MODERATE	CRITICAL
Mean [SD] symptom score at 3 and 10 days (Antibiotics compared to placebo; 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	Penicillin V	Amoxicillin	Relative (95% CI)	Absolute		
1[12]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[18]	none	88 (9.4 [4.7])	59 (11.5 [5.2])	MD -2.10[15] (-3.75 to -0.45)	p=0.01	⊕⊕⊕⊕ HIGH	CRITICAL
Duration of illness (Median duration; Better indicated by lower values)												
1[2]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[18]	none	39	44	The median duration of illness was 17 days in the placebo group, 9 days in the amoxicillin group and 11 days in the penicillin group. Both antibiotics being significantly better than placebo (p<0.001 for amoxicillin versus placebo; low quality evidence and p=0.008 for penicillin V versus placebo)		⊕⊕OO LOW	CRITICAL
1[8]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[18]	none	20	22	The median duration of illness was 10 days in the placebo and amoxicillin groups and 13.5 days in the penicillin group. There was no significant difference between the three groups (p=0.89, p=0.99 and p=0.76)		⊕⊕⊕O MODERATE	CRITICAL
Duration of illness (Mean duration; Better indicated by lower values)												
1[12]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[18]	none	88 in the antibiotic groups and 60 in the placebo group		The mean duration of illness was 6.4 days in the placebo group and 6.0 days in the antibiotic groups (amoxicillin and penicillin V).		⊕⊕⊕O MODERATE	CRITICAL
Adverse effects												
1[2]	randomised trials	no serious risk of bias	N/A	no serious indirectness	very serious[19]	none	24/41 (58.5%)	25/45 (55.5%)	RR 1.05[15] (0.73 to 1.52)	p=0.78	⊕⊕OO LOW	CRITICAL
1[8]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[18]	none	Not reported in the results; 3 patients (2 in the amoxicillin group and 1 in the penicillin group) stopped taking initial treatment after a few days due to marked gastrointestinal side effects. 2 further participants stopped treatment before 10 days (1 in amoxicillin and 1 in placebo group). 2 participants (1 in the placebo group and 1 in the amoxicillin group) required extended treatment after 10 days with amoxicillin. All participants were included in their original study groups (ITT)				⊕⊕⊕O MODERATE	CRITICAL
1[12]	randomised trials	no serious risk of bias	N/A	no serious indirectness	serious[18]	none	No significant differences were noted between antibiotics and placebo for diarrhoea, stomach pain, headache, rash, vaginal discharge and fatigue				⊕⊕⊕O MODERATE	CRITICAL
Abbreviations: CI, Confidence interval; ITT, Intention to treat; MD, Mean difference; N/A, Not applicable; OR, Odds ratio; RR, relative risk; SD, Standard deviation												

[1] The authors used a five point scale of restored, much better, somewhat better, unimproved and worse. The first three have been used to estimate cure or improvement.
[2] Lindbaek et al (1996)
[3] Downgraded 1 level – at a default minimal important difference (MID) of 25% or 0.5 SD for continuous data, data are consistent with no meaningful difference or appreciable benefit with penicillin V
[4] Also placebo arm 17/44 (39%)
[5] NICE analysis
[6] X^2 for trend

[7] Also placebo arm 39/44 (88%)
[8] Linbaek et al (1998)
[9] Also placebo arm 18/21 (86%)
[10] Mann Whitney U-test corrected for ties (also antibiotics versus placebo arm p=0.99), additional NICE meta-analysis of subjective status at day 10, cure or improvement, (Lindbaek et al. 1996 and Lindbaek et al. 1998) penicillin V vs. amoxicillin (54/59 [91.5%] vs. 62/66 [93.9%]; RR 0.97, 95% CI 0.88 to 1.08, fixed effect model, I^2=0.0%, moderate quality evidence).
[11] Recovery as assessed by telephone follow-up using 12 subjective symptoms related to acute maxillary sinusitis (nasal obstruction, nasal discharge, headache, postnasal drip, cough, sinus pain, unilateral facial pain, maxillary toothache, hyposmia, anosmia, malaise, fever), a 3 point scale was used (no, a little, much)
[12] Varonen et al (2003)
[13] Also doxycycline 26/33 (79%) and placebo 39/59 (66%)
[14] Clinical severity score measured on a scale 0 to 13. One point for each (hyposmia or anosmia, symptom duration >7 days, unilateral face pain, pain in upper teeth, pain worsening on bending forward, two phases of illness, nasal obstruction, rhinorrhoea, sinus pain, malaise). Raised rectal temp (0.5 [37.6°C to 38°C] to 1[above 38°C]) and 2 points for purulent secretion in the nasal floor
[15] Additional analysis (SD and 95% CI for MD) by NICE
[16] Placebo arm mean symptom severity score was 4.8 at day 10
[17] Sum of four VAS (nasal obstruction, rhinorrhoea, sinus-related pain and malaise) maximum of 4.0 points
[18] Downgraded 1 level – not assessable
[19] Downgraded 2 levels – at a default minimal important difference (MID) of 25% or 0.5 SD for continuous data, data are consistent with no meaningful difference, appreciable benefit or appreciable harm

H.6 Antibiotics (children)

Table 24: GRADE profile – antibiotic versus placebo in children

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		
Improvement in symptoms (follow-up 10 to 14 days)												
4[1]	randomised trials	serious[2]	no serious inconsistency[3]	no serious indirectness	serious[4]	none	207	155	OR 2.00 (1.16 to 3.47) NICE analysis RR not estimable	-	⊕⊕OO LOW	CRITICAL
Cure or improvement												
3[5]	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	163/199 (81.9%)	95/127 (74.8%)	OR 1.66 (0.95 to 2.90) NICE analysis RR 1.09 (0.97 to 1.23)	-	⊕⊕⊕O MODERATE	CRITICAL
Adverse events												
4[1]	randomised trials	serious[2]	serious[6]	no serious indirectness	serious[6]	none	-		Adverse effects were mostly gastrointestinal (mainly diarrhoea) and were 3 times more common in children treated with an antibiotic (no analysis reported)		⊕OOO VERY LOW	CRITICAL
Abbreviations: CI, Confidence interval; RR, Relative risk; OR, Odds ratio												

[1] Cronin et al (2013)
[2] One RCT included in the meta-analysis was not intention to treat and excluded 14% of children for lack of compliance and drug toxicity
[3] Authors reported 'moderate to substantial heterogeneity', I^2 reported was 14.8%
[4] Downgraded 1 level - at a default minimal important difference (MID) of 25% data are consistent with no meaningful difference or appreciable benefit with antibiotics
[5] Falagas et al (2008)
[6] Downgraded 1 level - not assessable

Table 25: GRADE profile – antibiotic versus other antibiotic in children

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic	Other antibiotic	Relative	Absolute		
Cure												
4[1]	randomised trials	serious[2]	serious[3]	no serious indirectness	serious[3]	none	n=347[4]		Data not pooled; no significant differences between groups		⊕OOO VERY LOW	CRITICAL
Improvement in symptoms												
2[1]	randomised trials	no serious risk of bias	serious[3]	no serious indirectness	serious[3]	none	n=188[5]		Data not pooled; no significant differences between groups		⊕⊕OO LOW	CRITICAL
Adverse events												
4[1]	randomised trials	serious[6]	serious[3]	no serious indirectness	serious[3]	none	-		In 3 RCTs there were no significant differences in adverse events between groups (data on the rates or types of adverse events were not reported). There was a higher rate of diarrhoea (18.1%) in 1 RCT, in children receiving co-amoxiclav compared with those receiving cefditoren (4.5%; p=0.02). Diarrhoea was self-limiting and did not need discontinuation of the antibiotic or study withdrawal		⊕OOO VERY LOW	CRITICAL

Abbreviations: RCT, Randomised controlled trial

[1] Smith (2013)
[2] Downgraded 1 level - 3 of the 4 RCTs were very low quality (Jadad score = 1 as assessed by the study authors)
[3] Downgraded 1 level - not assessable
[4] Antibiotics included amoxicillin, erythromycin, azithromycin and brodimoprim
[5] Antibiotics were amoxicillin or co-amoxiclav
[6] Downgraded 1 level - 2 RCTs were of very low quality (Jadad score = 1 as assessed by the authors)

Appendix I: Studies not-prioritised

Study reference	Reason
Ah-See K (2011) Sinusitis (acute). BMJ clinical evidence 2011	Lower quality systematic review (limited reporting of included studies)
Arrieta JR, Galgano AS, Sakano E et al (2007) Moxifloxacin vs amoxicillin/clavulanate in the treatment of acute sinusitis. American Journal of Otolaryngology - Head and Neck Medicine and Surgery 28(2), 78-82	RCT included in a systematic review that has been prioritised
Bachert C, Meltzer EO (2007) Effect of mometasone furoate nasal spray on quality of life of patients with acute rhinosinusitis. Rhinology 45(3), 190-6	Secondary analysis of a primary RCT that has been prioritised (Meltzer et al. 2005)
Benninger MS, Sedory Holzer SE, Lau J (2000) Diagnosis and treatment of uncomplicated acute bacterial rhinosinusitis: summary of the Agency for Health Care Policy and Research evidence-based report. Otolaryngology--head and neck surgery: official journal of American Academy of Otolaryngology-Head and Neck Surgery 122(1), 1-7	Lower quality systematic review
Bucher HC, Tschudi P, Young J et al (2003) Effect of amoxicillin-clavulanate in clinically diagnosed acute rhinosinusitis: a placebo-controlled, double-blind, randomized trial in general practice. Archives of internal medicine 163(15), 1793-8	RCT included in a systematic review that has been prioritised
Burgstaller JM, Steurer J, Holzmann D et al (2016) Antibiotic efficacy in patients with a moderate probability of acute rhinosinusitis: a systematic review. European Archives of Oto-Rhino-Laryngology 273(5), 1067-1077	Lower quality systematic review
Dolor RJ, Witsell DL, Hellkamp AS et al (2001) Comparison of cefuroxime with or without intranasal fluticasone for the treatment of rhinosinusitis. The CAFFS Trial: a randomized controlled trial. JAMA 286(24), 3097-105 (see also anonymous [2004]).	RCT included in a systematic review that has been prioritised
El-Hennawi DM, Ahmed MR, Farid AM et al (2015) Comparative study of the efficacy of topical steroid and antibiotic combination therapy versus oral antibiotic alone when treating acute rhinosinusitis. The Journal of laryngology and otology 129(5), 462-7	Low relevance to current UK practice (intervention not available in the UK)
Garbutt JM, Goldstein M, Gellman E et al (2001) A randomized, placebo-controlled trial of antimicrobial treatment for children with clinically diagnosed acute sinusitis. Pediatrics 107(4), 619-25	RCT included in a systematic review that has been prioritised
Garbutt JM, Banister C, Spitznagel E et al (2012) Amoxicillin for acute rhinosinusitis: a randomized controlled trial. JAMA 307(7), 685-92	RCT included in a systematic review that has been prioritised
Gehanno P, Beauvillain C, Bobin S et al (2000) Short therapy with amoxicillin-clavulanate and corticosteroids in acute sinusitis: results of a multicentre study in adults. Scandinavian journal of infectious diseases 32(6), 679-84	RCT included in a systematic review that has been prioritised
Gelardi M, Mezzoli A, Fiorella ML et al (2009) Nasal irrigation with lavonase as ancillary treatment of acute rhinosinusitis: a pilot study. Journal of biological regulators and homeostatic agents 23(2), 79-84	Lower quality RCT (small sample size; n<30)

Study reference	Reason
Guo R, Canter PH, Ernst E (2006) Herbal medicines for the treatment of rhinosinusitis: A systematic review. Otolaryngology - Head and Neck Surgery 135(4), 496-506	Low relevance to current UK practice (intervention not available in UK)
Hadley JA, Mosges R, Desrosiers M et al (2010) Moxifloxacin five-day therapy versus placebo in acute bacterial rhinosinusitis. The Laryngoscope 120(5), 1057-62	RCT included in a systematic review that has been prioritised
Hansen JG, Schmidt H, Grinsted P (2000) Randomised, double blind, placebo controlled trial of penicillin V in the treatment of acute maxillary sinusitis in adults in general practice. Scandinavian journal of primary health care 18(1), 44-7	RCT included in a systematic review that has been prioritised
Hansen J, Schmidt H, Grinsted P (2000) [Penicillin treatment of acute maxillary sinusitis in adults. A randomized, double-blind, placebo-controlled trial from general practice]. Ugeskrift for laeger 162(40), 5351-3	RCT included in a systematic review that has been prioritised
Hauptman G, Ryan MW (2007) The effect of saline solutions on nasal patency and mucociliary clearance in rhinosinusitis patients. Otolaryngology--head and neck surgery: official journal of American Academy of Otolaryngology-Head and Neck Surgery 137(5), 815-21	Low relevance to current UK practice (strength of saline used)
Hayward G, Heneghan C, Perera R et al (2012) Intranasal corticosteroids in management of acute sinusitis: a systematic review and meta-analysis. Annals of family medicine 10(3), 241-9	Lower quality systematic review
Henry D, Riffer E, Sokol W et al (2003) Randomized double-blind study comparing 3- and 6-day regimens of azithromycin with a 10-day amoxicillin-clavulanate regimen for treatment of acute bacterial sinusitis. Antimicrobial agents and chemotherapy 47(9), 2770-4	RCT included in a systematic review that has been prioritised
Hosoien E, Lund AB, Vasseljen O (2010) Similar effect of therapeutic ultrasound and antibiotics for acute bacterial rhinosinusitis: a randomised trial. Journal of physiotherapy 56(1), 29-32	Low relevance to current UK practice (therapeutic ultrasound)
Inanli S, Ozturk O, Korkmaz M et al (2002) The effects of topical agents of fluticasone propionate, oxymetazoline, and 3% and 0.9% sodium chloride solutions on mucociliary clearance in the therapy of acute bacterial rhinosinusitis in vivo. The Laryngoscope 112(2), 320-5	Lower quality systematic review (methods not fully described)
Jund R, Mondigler M, Steindl H et al (2012) Clinical efficacy of a dry extract of five herbal drugs in acute viral rhinosinusitis. Rhinology 50(4), 417-26	Low relevance to current UK practice (intervention not available in UK)
Kaiser L, Morabia A, Stalder H et al (2001) Role of nasopharyngeal culture in antibiotic prescription for patients with common cold or acute sinusitis. European Journal of Clinical Microbiology and Infectious Diseases 20(7), 445-451	RCT included in a systematic review that has been prioritised
Kitz R, Martens U, Zieseniss E et al (2012) Probiotic E.faecalis - Adjuvant therapy in children with recurrent rhinosinusitis. Central European Journal of Medicine 7(3), 362-365	Low relevance to current UK practice (probiotics)
Kristo A, Uhari M, Luotonen J et al (2005) Cefuroxime axetil versus placebo for children with acute respiratory infection and imaging evidence of sinusitis: a randomized, controlled trial. Acta paediatrica (Oslo, and Norway: 1992) 94(9), 1208-13	RCT included in a systematic review that has been prioritised
Kutluhan A, Akdeniz H, Kaya Z et al (2002) The treatment duration of acute maxillary sinusitis: how long should it be? A nasal smear controlled study. Rhinology 40(4), 198-202	Lower quality RCT

Study reference	Reason
Lari AR, Ghaffariyeh A, Etesam N et al (2010) A randomized controlled trial of 5-day regimen of azithromycin and a 10-day regimen of co-amoxiclav for treatment of acute sinusitis. Iranian Journal of Clinical Infectious Diseases 5(3), 137-141	RCT included in a systematic review that has been prioritised
Lari AR, Alinejad F, Alaghehbandan R et al (2012) Comparison of cefuroxime and co-amoxiclav in the treatment of acute sinusitis in a sample of the Iranian population. Le infezioni in medicina : rivista periodica di eziologia, epidemiologia, diagnostica, and clinica e terapia delle patologie infettive 20(4), 251-5	Systematic review has been prioritised
Marple BF, Roberts CS, de Caprariis PJ et al (2007) Onset of symptom resolution in adults with acute bacterial rhinosinusitis treated with a single dose of azithromycin extended release compared with 10 days of levofloxacin: a retrospective analysis of a randomized, double-blind, double-dummy trial. Clinical therapeutics 29(12), 2690-8	Systematic review has been prioritised
Marple BF, Roberts CS, Frytak JR et al (2010) Azithromycin extended release vs amoxicillin/clavulanate: symptom resolution in acute sinusitis. American journal of otolaryngology 31(1), 1-8	RCT included in a systematic review that has been prioritised
Meltzer EO, Charous BL, Busse WW et al (2000) Added relief in the treatment of acute recurrent sinusitis with adjunctive mometasone furoate nasal spray. The Nasonex Sinusitis Group. The Journal of allergy and clinical immunology 106(4), 630-7	Systematic review has been prioritised; lower quality RCT
Meltzer EO, Gates D, Bachert C (2012) Mometasone furoate nasal spray increases the number of minimal-symptom days in patients with acute rhinosinusitis. Annals of allergy, asthma & immunology: official publication of the American College of Allergy, Asthma, and & Immunology 108(4), 275-9	Secondary analysis of a primary RCT that has been prioritised (Meltzer et al. 2005)
Merenstein D, Whittaker C, Chadwell T et al (2005) Are antibiotics beneficial for patients with sinusitis complaints? A randomized double-blind clinical trial. The Journal of family practice 54(2), 144-51	RCT included in a systematic review that has been prioritised
Mittmann N, Jivarj F, Wong A et al (2002) Oral fluoroquinolones in the treatment of pneumonia, bronchitis and sinusitis. The Canadian journal of infectious diseases = Journal canadien des maladies infectieuses 13(5), 293-300	Lower quality systematic review
Muhammad R, Zaman A, Khan AR et al (2015) Comparison of efficacy of amoxicillin clavulanate and levofloxacin in treatment of acute bacterial sinusitis. Journal of Medical Sciences (Peshawar) 23(2), 77-81	Systematic review has been prioritised
Murray JJ, Emparanza P, Lesinskas E et al (2005) Efficacy and safety of a novel, single-dose azithromycin microsphere formulation versus 10 days of levofloxacin for the treatment of acute bacterial sinusitis in adults. Otolaryngology--head and neck surgery: official journal of American Academy of Otolaryngology-Head and Neck Surgery 133(2), 194-200	RCT included in a systematic review that has been prioritised
Nayak AS, Settipane GA, Pedinoff A et al (2002) Effective dose range of mometasone furoate nasal spray in the treatment of acute rhinosinusitis. Annals of allergy, asthma & immunology: official publication of the American College of Allergy, Asthma, and & Immunology 89(3), 271-8	RCT included in a systematic review that has been prioritised
Ng DK, Chow PY, Leung L et al (2000) A randomized controlled trial of azithromycin and amoxycillin/clavulanate in the management of subacute childhood rhinosinusitis. Journal of paediatrics and child health 36(4), 378-81	Lower quality RCT

Study reference	Reason
Passali D, Loglisci M, Passali GC et al (2015) A prospective open-label study to assess the efficacy and safety of a herbal medicinal product (Sinupret) in patients with acute rhinosinusitis. ORL 77(1), 27-32	Low relevance to current UK practice (intervention not available in UK)
Pfaar O, Mullol J, Anders C et al (2012) Cyclamen europaeum nasal spray, a novel phytotherapeutic product for the management of acute rhinosinusitis: a randomized double-blind, placebo-controlled trial. Rhinology 50(1), 37-44	Low relevance to current UK practice (intervention not available in UK)
Ponikau JU, Hamilos DL, Barreto A et al (2012) An exploratory trial of Cyclamen europaeum extract for acute rhinosinusitis. The Laryngoscope 122(9), 1887-92	Low relevance to current UK practice (intervention not available in UK)
Poole M, Anon J, Paglia M et al (2006) A trial of high-dose, short-course levofloxacin for the treatment of acute bacterial sinusitis. Otolaryngology--head and neck surgery: official journal of American Academy of Otolaryngology-Head and Neck Surgery 134(1), 10-7	Systematic review has been prioritised
Rahmati MB, Mohebi S, Shahmohammadi S et al (2013) Fluticasone nasal spray as an adjunct to Amoxicillin for acute sinusitis in children: a randomized controlled trial. European review for medical and pharmacological sciences 17(22), 3068-72	Systematic review has been prioritised; lower quality RCT
Rakkar S, Roberts K, Towe B et al (2001) Moxifloxicin versus amoxycillin clavulanate in the treatment of acute maxillary sinusitis: a primary care experience. International journal of clinical practice 55(5), 309-15	RCT included in a systematic review that has been prioritised
Ratau NP, Snyman JR, Swanepoel C (2004) Short-course, low-dose oral betamethasone as an adjunct in the treatment of acute infective sinusitis : a comparative study with placebo. Clinical drug investigation 24(10), 577-82	Low relevance to current UK practice (oral corticosteroids)
Rechtweg JS, Moinuddin R, Houser SM et al (2004) Quality of life in treatment of acute rhinosinusitis with clarithromycin and amoxicillin/clavulanate. The Laryngoscope 114(5), 806-10	Systematic review has been prioritised
Riffer E, Spiller J, Palmer R et al (2005) Once daily clarithromycin extended-release vs twice-daily amoxicillin/clavulanate in patients with acute bacterial sinusitis: a randomized, investigator-blinded study. Current medical research and opinion 21(1), 61-70	RCT included in a systematic review that has been prioritised
Siegert R, Gehanno P, Nikolaidis P et al (2000) A comparison of the safety and efficacy of moxifloxacin (BAY 12-8039) and cefuroxime axetil in the treatment of acute bacterial sinusitis in adults. The Sinusitis Study Group. Respiratory medicine 94(4), 337-44	RCT included in a systematic review that has been prioritised
Sng WJ, Wang De-Yun (2015) Efficacy and side effects of antibiotics in the treatment of acute rhinosinusitis: a systematic review. Rhinology 53(1), 3-9	Lower quality systematic review
Tesche S, Metternich F, Sonnemann U et al (2008) The value of herbal medicines in the treatment of acute non-purulent rhinosinusitis. Results of a double-blind, randomised, controlled trial. European archives of oto-rhino-laryngology: official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS): affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery 265(11), 1355-9	Low relevance to current UK practice (intervention not available in UK)
Tugrul S, Dogan R, Eren SB et al (2014) The use of large volume low pressure nasal saline with fluticasone propionate for the treatment of pediatric acute rhinosinusitis. International journal of pediatric otorhinolaryngology 78(8), 1393-9	Low relevance to current UK practice (intervention not available in the UK)

Study reference	Reason
Varonen H, Kunnamo I, Savolainen S et al (2003) Treatment of acute rhinosinusitis diagnosed by clinical criteria or ultrasound in primary care. A placebo-controlled randomised trial. Scandinavian journal of primary health care 21(2), 121-6 [data for penicillin V vs. amoxicillin used]	RCT included in a systematic review that has been prioritised
Venekamp RP, Sachs APE, Bonten MJM et al (2010) Intranasal corticosteroid monotherapy in acute rhinosinusitis: an evidence-based case report. Otolaryngology--head and neck surgery: official journal of American Academy of Otolaryngology-Head and Neck Surgery 142(6), 783-8	Lower quality systematic review
Venekamp RP, Thompson MJ, Hayward G et al (2014) Systemic corticosteroids for acute sinusitis. The Cochrane database of systematic reviews 3, CD008115	Low relevance to current UK practice (oral corticosteroids)
Wald ER, Nash D, Eickhoff J (2009) Effectiveness of amoxicillin/clavulanate potassium in the treatment of acute bacterial sinusitis in children. Pediatrics 124(1), 9-15	RCT included in a systematic review that has been prioritised
Wan KS, Wu WF, Chen TC et al (2015) Comparison of amoxicillin + clavulanate with or without intranasal fluticasone for the treatment of uncomplicated acute rhinosinusitis in children. Minerva pediatrica 67(6), 489-94	Systematic review has been prioritised; lower quality RCT
Wang Yun-Hu, Yang Chun-Ping, Ku Min-Sho et al (2009) Efficacy of nasal irrigation in the treatment of acute sinusitis in children. International journal of pediatric otorhinolaryngology 73(12), 1696-701	RCT included in a systematic review that has been prioritised
Williamson IG, Rumsby K, Benge S et al (2007) Antibiotics and topical nasal steroid for treatment of acute maxillary sinusitis: a randomized controlled trial. JAMA 298(21), 2487-96	Systematic review has been prioritised
Yilmaz G, Varan B, Yilmaz T et al (2000) Intranasal budesonide spray as an adjunct to oral antibiotic therapy for acute sinusitis in children. European archives of oto-rhino-laryngology: official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS): affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery 257(5), 256-9	Systematic review has been prioritised; lower quality RCT

Appendix J: Excluded studies

Study reference	Reason for exclusion
Abdalgani M, Hajjar J, Edelman K et al. (2014) Evaluation of oral antibiotics versus placebo for the treatment of rhinosinusitis with neutrophilia on nasal cytology. Journal of allergy and clinical immunology 133(2 suppl. 1), Ab128	Inappropriate or unclear methodology
Adelman A (2001) Are the antibiotics appropriate for the treatment of acute sinusitis in adults? Journal of Family Practice 50(6), 489	Inappropriate or unclear methodology
Ah-See K (2003) Acute sinusitis. Clinical evidence (10), 567-73.	Updated systematic review available
Ah-See KW, and Evans AS (2007) Sinusitis and its management. BMJ (Clinical research ed.) 334(7589), 358-61.	Updated systematic review available
Ahovuo-Saloranta A, Borisenko OV, Kovanen N et al (2008) Antibiotics for acute maxillary sinusitis. Cochrane Database of Systematic Reviews (2)	Updated systematic review available
Akhaddar A, Elasri F, Elouennass M et al. (2010) Orbital abscess associated with sinusitis from odontogenic origin. Internal Medicine 49(5), 523-524	Inappropriate or unclear methodology
Alagic-Smailbegovic J, Saracevic E, Sutalo K (2006) Azythromicin versus amoxicillin-clavulanate in the treatment of acute sinusitis in children. Bosnian journal of basic medical sciences 6(4), 76-8	Publication/study type (not an RCT)
Ali M, Baraniuk Jn, and Petrie K (2005) "Baseline" nasal symptoms and secretions do not change following acute sinusitis despite standard treatment and a nasal steroid [Abstract] Journal of Allergy and Clinical Immunology 115(2 (Suppl 1)), S200, Abstract No. 800	Abstract only
Anon (2004) Erratum: Comparison of cefuroxime with or without intranasal fluticasone for the treatment of rhinosinusitis: The CAFFS trial: A randomized controlled trial (Journal of the American Medical Association (2001) 286 (3097-3105)). Journal of the American Medical Association 292(14), 1686 (see also Dolor et al. [2001]).	Publication/study type (erratum only)
Anon JB (2005) Current management of acute bacterial rhinosinusitis and the role of moxifloxacin. Clinical Infectious Diseases 41(2 SUPPL.), S167-S176	Not a clinical study
Anon JB (2005) Current management of acute bacterial rhinosinusitis and the role of moxifloxacin. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 41 Suppl 2, S167-76	Not a clinical study
Anon JB, Berkowitz E, Breton J et al. (2006) Efficacy/safety of amoxicillin/clavulanate in adults with bacterial rhinosinusitis. American journal of otolaryngology 27(4), 248-54	Inappropriate or unclear methodology
Anon JB, Ferguson B, Twynholm M etal. (2006) Pharmacokinetically enhanced amoxicillin/clavulanate (2,000/125 mg) in acute bacterial rhinosinusitis caused by Streptococcus pneumoniae, including penicillin-resistant strains. Ear, nose, and & throat journal 85(8), 500-passim	Inappropriate or unclear methodology
Anon JB, Jacobs MR, Poole MD et al. (2004) Antimicrobial treatment guidelines for acute bacterial rhinosinusitis. Otolaryngology--head and neck surgery: official journal of American Academy of Otolaryngology-Head and Neck Surgery 130(1 Suppl), 1-45.	Not a clinical study

Study reference	Reason for exclusion
Anonymous (2001) Current approaches to community-acquired acute maxillary rhinosinusitis or sinusitis in France and literature review. Rhinology 39(SUPPL. 17), 1-38	Unable to source study
Anonymous (2001) Steroid therapy of acute ENT infections: rarely indicated. Prescrire international 10(56), 185-7	Not a clinical study
Anonymous (2003) Fluoroquinolones in ambulatory ENT and respiratory tract infections: rarely appropriate. Prescrire international 12(63), 26-7	Not a clinical study
Anonymous (2005) Azithromycin extended-release (Zmax) for sinusitis and pneumonia. The Medical letter on drugs and therapeutics 47(1218), 78-80	Not a clinical study
Anonymous (2006) Acute sinusitis. MeReC Bulletin 17(3), 6-8.	Not a clinical study
Anonymous (2006) Azithromycin extended-release (Zmax) for sinusitis and pneumonia. Obstetrics and gynecology 107(1), 180-2	Inappropriate or unclear methodology
Anonymous (2006) Intranasal steroids alone effective for acute uncomplicated sinusitis. The Journal of family practice 55(3), 190	Not a clinical study
Anonymous (2008) Are fluoroquinolones better than beta-lactams for acute bacterial sinusitis? Journal of Family Practice 57(9), 577	Not a clinical study
Anonymous (2008) Can nasal irrigation help relieve nasal and sinus congestion? Mayo Clinic women's healthsource 12(6), 8	Not a clinical study
Anonymous (2008) Sinusitis. Getting rid of a stuffy problem. Mayo Clinic women's healthsource 12(10), 4-5	Not a clinical study
Anonymous (2014) Acute rhinosinusitis: no tangible benefit with antibiotic therapy. Prescrire international 23(151), 191	Not a clinical study
Anselmo-Lima WT, Sakano E, Araripe Nunes, AA et al. (2015) Rhinosinusitis: Evidence and experience. October 18 and 19, 2013-Sao Paulo. Brazilian Journal of Otorhinolaryngology 81, S1-S49	Inappropriate or unclear methodology
Anselmo-Lima WT, Sakano E, Tamashiro E et al. (2015) Rhinosinusitis: Evidence and experience. A summary. Brazilian Journal of Otorhinolaryngology 81(1), 8-18	Inappropriate or unclear methodology
Anzai Y, Jarvik JG, Sullivan SD et al. (2007) The cost-effectiveness of the management of acute sinusitis. American journal of rhinology 21(4), 444-51.	Inappropriate or unclear methodology
Ariza H, Rojas R, Johnson P et al. (2006) Eradication of common pathogens at days 2, 3 and 4 of moxifloxacin therapy in patients with acute bacterial sinusitis. BMC ear, nose, and throat disorders 6, 8	Inappropriate or unclear methodology
Arroll B (2005) Antibiotics for upper respiratory tract infections: an overview of Cochrane reviews. Respiratory medicine 99(3), 255-61	Inappropriate or unclear methodology
Bachert C, Hormann K, Mosges R et al. (2003) An update on the diagnosis and treatment of sinusitis and nasal polyposis. Allergy: European Journal of Allergy and Clinical Immunology 58(3), 176-191.	Not a clinical study
Bahtouee M, Adibi H, and Langroodi Mm (2011) Acetylcysteine in treatment of subacute sinusitis: A double blind placebo controlled clinical trial study. Otolaryngology - Head and Neck Surgery 145, 251	Does not reflect usual UK practice
Bailey J, Change J (2009) Antibiotics for acute maxillary sinusitis. American family physician 79(9), 757-8	Not a clinical study
Balfour JA, Figgitt DP (2001) Telithromycin. Drugs 61(6), 815-1	Does not reflect usual UK practice
Balfour JA, Lamb HM (2000) Moxifloxacin: a review of its clinical potential in the management of community-acquired respiratory tract infections. Drugs 59(1), 115-39	Not a clinical study

Study reference	Reason for exclusion
Balk EM, Zucker DR, Engels EA et al. (2001) Strategies for diagnosing and treating suspected acute bacterial sinusitis: a cost-effectiveness analysis. Journal of general internal medicine 16(10), 701-11.	Inappropriate or unclear methodology
Baraniuk JN (2001) Addition of intranasal glucocorticoids to standard antibiotic therapy for sinusitis. Current allergy and asthma reports 1(3), 191-192	Not a clinical study
Barnett M (2012) Do intranasal steroids improve symptoms of acute sinusitis? American Family Physician 86(7), 680-682	Not a clinical study
Barron JJ, Grochulski WD, Merchant S et al. (2004) Treatment costs associated with commonly used branded antibiotics for the management of acute sinusitis, chronic bronchitis and pneumonia. Journal of Applied Research 4(1), 24-36	Inappropriate or unclear methodology
Bastier PL, Lechot A, Bordenave L et al. (2015) Nasal irrigation: From empiricism to evidence-based medicine. A review. European annals of otorhinolaryngology, and head and neck diseases 132(5), 281-5	Inappropriate or unclear methodology
Bax R (2007) Development of a twice daily dosing regimen of amoxicillin/clavulanate. International Journal of Antimicrobial Agents 30(SUPPL. 2), 118-121	Inappropriate or unclear methodology
Bazuhair A, Alawadhi A, Alreefy H (2016) Role of balloon sinuplasty in the treatment of frontal sinusitis. Bahrain Medical Bulletin 38(1), 44-45	Inappropriate or unclear methodology
Behm J, Corcoran G, Li-McLeod J et al. (2002) Health resource utilization: moxifloxacin compared to levofloxacin and amoxicillin clavulanate in reducing "practice time use" in the treatment of sinusitis. American journal of respiratory and critical care medicine 165(8 (Suppl)), A107	Unable to source study.
Bergogne-Berezin E (2003) Rhinosinusitis: New treatment strategies. Otorinolaringologia 53(3), 99-107	Not a clinical study
Bird J, Biggs TC, Thomas M et al. (2013) Adult acute rhinosinusitis. BMJ (Clinical research ed.) 346, f2687	Not a clinical study
Bjerrum L, Gahrn-Hansen B, Munck AP (2004) C-reactive protein measurement in general practice may lead to lower antibiotic prescribing for sinusitis. The British journal of general practice: the journal of the Royal College of General Practitioners 54(506), 659-62.	Inappropriate or unclear methodology
Blin P, Blazejewski S, Lignot S et al. (2010) Effectiveness of antibiotics for acute sinusitis in real-life medical practice. British journal of clinical pharmacology 70(3), 418-28.	Inappropriate or unclear methodology
Block SL (2006) Comparative tolerability, safety and efficacy of tablet formulations of twice-daily clarithromycin 250 mg versus once-daily extended-release clarithromycin 500 mg in pediatric and adolescent patients. Clinical pediatrics 45(7), 641-8	Inappropriate or unclear methodology
Blomgren K, Eliander L, Hytonen M et al. (2015) How patients experience antral irrigation. Clinical medicine insights. Ear, and nose and throat 8, 13-7	Inappropriate or unclear methodology (intervention)
Bolt P, Barnett P, Babl FE et al. (2008) Topical lignocaine for pain relief in acute otitis media: results of a double-blind placebo-controlled randomised trial. Archives of disease in childhood 93(1), 40-4	Poor relevance against search terms (population)

Study reference	Reason for exclusion
Braun JM, Schneider B, Beuth HJ (2005) Therapeutic use, efficiency and safety of the proteolytic pineapple enzyme Bromelain-POS in children with acute sinusitis in Germany. In Vivo 19(2), 417-422	Inappropriate or unclear methodology (intervention)
Brook I (2002) Antimicrobial management of acute sinusitis: A review of therapeutic recommendations. Infections in Medicine 19(5), 231-237	Not a clinical study
Brook I (2016) Microbiology and choice of antimicrobial therapy for acute sinusitis complicated by subperiosteal abscess in children. International Journal of Pediatric Otorhinolaryngology 84, 21-26	Not a clinical study
Brook I (2007) Current issues in the management of acute bacterial sinusitis in children. International journal of pediatric otorhinolaryngology 71(11), 1653-61	Not a clinical study
Brook I, Hausfeld JN (2006) Effect of telithromycin and azithromycin on nasopharyngeal bacterial flora in patients with acute maxillary sinusitis. Archives of otolaryngology--head & neck surgery 132(4), 442-5	Does not reflect usual UK practice
Brook I, Foote PA, Hausfeld JN (2008) Increase in the frequency of recovery of meticillin-resistant Staphylococcus aureus in acute and chronic maxillary sinusitis. Journal of medical microbiology 57(Pt 8), 1015-7	Poor relevance against search terms (population)
Brook I, Foote PA, Hausfeld JN (2005) Eradication of pathogens from the nasopharynx after therapy of acute maxillary sinusitis with low- or high-dose amoxicillin/clavulanic acid. International journal of antimicrobial agents 26(5), 416-9	Publication/study type (not an RCT)
Buchanan P, Roos K, Tellier G et al. (2005) Bacteriological efficacy of 5-day therapy with telithromycin in acute maxillary sinusitis. International journal of antimicrobial agents 25(3), 237-46	Does not reflect usual UK practice
Buchanan PP, Stephens TA, Leroy B (2003) A comparison of the efficacy of telithromycin versus cefuroxime axetil in the treatment of acute bacterial maxillary sinusitis. American journal of rhinology 17(6), 369-77	Does not reflect usual UK practice
CADTH (2013) Intranasal triamcinolone versus intranasal beclomethasone for acute and chronic sinus inflammation: a review of comparative clinical effectiveness and safety (Structured abstract). Health Technology Assessment Database (4)	Poor relevance against search terms (population)
Cals JWL, Schot MJC, de Jong SAM et al (2010) Point-of-care C-reactive protein testing and antibiotic prescribing for respiratory tract infections: a randomized controlled trial. Annals of family medicine 8(2), 124-33	Not relevant population
Casiano RR, Cohn S, Villasuso IE et al. (2001) Comparison of antral tap with endoscopically directed nasal culture. Laryngoscope 111(8), 1333-1337	Inappropriate or unclear methodology
Castellano F, Mautone G (2002) Decongestant activity of a new formulation of xylometazoline nasal spray: a double-blind, randomized versus placebo and reference drugs controlled, dose-effect study. Drugs under experimental and clinical research 28(1), 27-35	Poor relevance against search terms (population)
Cauwenberge P, Norcross L (2001) Fluticasone Propionate Aqueous nasal spray as an adjunct to antibiotic therapy in the treatment of recurrent sinusitis (FLTB3052). Journal of Allergy and Clinical Immunology 107(2 (Pt 2)), S311	Inappropriate or unclear methodology

Study reference	Reason for exclusion
Chadha NK, Chadha R (2007) Sinusitis. British Medical Journal 334(7604), 1165	Inappropriate or unclear methodology
Charous B, Zinreich S, Meltzer E et al. (2001) Prevention of recurrent acute episodes of sinusitis with prophylactic mometasone furoate nasal spray (MFNS). Journal of Allergy and Clinical Immunology 107(2 (Pt 2)), S166	Inappropriate or unclear methodology
Chaudry R, Stroebel RJ, McLeod TG et al. (2006) Nurse-based telephone protocol versus usual care for management of URI and acute sinusitis: A controlled trial. Managed Care Interface 19(8), 26-31	Inappropriate or unclear methodology (intervention)
Chauhan P, Sood A, Jain M et al. (2013) Serum PCT and CRP levels in upper respiratory tract infections as a marker of infection. Clinical Rhinology 6(1), 1-4	Inappropriate or unclear methodology
Chmielik LP, Ryczer T, Chmielik M (2011) The efficacy of antibiotic therapy in the treatment of complicated acute sinusitis in children - The initial report. New Medicine 2011-January (4), 113-115	Inappropriate or unclear methodology
Cho Y, Kim M, Chun Y et al. (2010) A Prospective Randomized Open Trial of Nasal Irrigation and Nasal Decongestant for Sinusitis in Children. Pediatric Allergy and Respiratory Disease 20(4), 232-7	Unable to source study
Chow J, Russell M, Volk S et al. (2000) Efficacy of Cefditoren Pivoxil (CDTR) Vs. Amoxicillin/Clavulanate (AMX/CLV) in Acute Maxillary Sinusitis (AMS). Intersci Conf Antimicrob Agents Chemother 40, 495	Unable to source study
Ciervo CA, Shi J (2005) Pharmacokinetics of telithromycin: application to dosing in the treatment of community-acquired respiratory tract infections. Current medical research and opinion 21(10), 1641-50	Does not reflect usual UK practice
Cohen R, Levy C, Rocque F et al. (2003) Efficacy and safety of cefpodoxime proxetil compared to amoxicillin-clavulanate in acute maxillary rhinosinusitis, in children. [French]. Medecine et maladies infectieuses 33(1), 20-6	Non-English language
Contopoulos-Ioannidis DG, Ioannidis JPA, Lau J (2003) Acute sinusitis in children: current treatment strategies. Paediatric drugs 5(2), 71-80	Not a clinical study
Cook C, Meltzer E, Goode-sSlers St et al. (2002) Fluticasone propionate aqueous nasal spray decreases frequency of recurrence and increases time to recurrence of acute sinusitis [Abstract]. Journal of Allergy and Clinical Immunology 109(Suppl 1), Abstract No. 223	Abstract only.
Costa ML, Psaltis AJ, Nayak JV et al. (2015) Medical therapy vs surgery for recurrent acute rhinosinusitis. International forum of allergy & rhinology 5(8), 667-73	Inappropriate or unclear methodology
Danzig M, Meltzer Eo, and Gates D (2008) Mometasone furoate nasal spray increases the number of days with minimal symptoms in patients with acute rhinosinusitis. Journal of Allergy and Clinical Immunology 121(2 (Suppl 1)), S52, Abstract No. 202	Abstract only
de Bock GH, van Erkel AR, Springer MP et al. (2001) Antibiotic prescription for acute sinusitis in otherwise healthy adults. Clinical cure in relation to costs. Scandinavian journal of primary health care 19(1), 58-63	Inappropriate or unclear methodology
de la Poza Abad, M, Mas Dalmau G, Moreno B et al. (2013) Rationale, design and organization of the delayed antibiotic prescription (DAP) trial: a randomized controlled trial of the efficacy and safety of delayed antibiotic prescribing strategies in the non-	Inappropriate or unclear methodology

Study reference	Reason for exclusion
complicated acute respiratory tract infections in general practice. BMC family practice 14, 63	
de Moor C, Reardon G, McLaughlin J et al. (2012) A retrospective comparison of acute rhinosinusitis outcomes in patients prescribed antibiotics, mometasone furoate nasal spray, or both. American journal of rhinology & allergy 26(4), 308-14	Inappropriate or unclear methodology
De Sutter A, Lemiengre M, Van Maele G et al. (2006) Predicting prognosis and effect of antibiotic treatment in rhinosinusitis. Annals of family medicine 4(6), 486-93	Inappropriate or unclear methodology
Debska M, Brozek E, Bielicka A et al. (2003) Complications of sinusitis in children hospitalised between 1994 and 2002. New Medicine 6(2), 26-29	Inappropriate or unclear methodology
DeMuri GP, Wald ER (2011) Complications of acute bacterial sinusitis in children. Pediatric Infectious Disease Journal 30(8), 701-702	Inappropriate or unclear methodology
DeMuri G, Wald ER (2013) Acute bacterial sinusitis in children. Pediatrics in review / American Academy of Pediatrics 34(10), 429-437	Not a clinical study
Desrosiers M, Ferguson B, Klossek JM et al. (2008) Clinical efficacy and time to symptom resolution of 5-day telithromycin versus 10-day amoxicillin-clavulanate in the treatment of acute bacterial sinusitis. Current medical research and opinion 24(6), 1691-702	Does not reflect usual UK practice
Dharod A (2016) Delayed prescriptions for reducing antibiotic use. Journal of Clinical Outcomes Management 23(3), 106-108	Inappropriate or unclear methodology
Di Cicco M, Alicandro G, Claut L et al. (2014) Efficacy and tolerability of a new nasal spray formulation containing hyaluronate and tobramycin in cystic fibrosis patients with bacterial rhinosinusitis. Journal of cystic fibrosis: official journal of the European Cystic Fibrosis Society 13(4), 455-60	Inappropriate or unclear methodology (intervention)
Di Pierro F, Zanvit A, Colombo (2016) Role of a proprietary propolis-based product on the wait-and-see approach in acute otitis media and in preventing evolution to tracheitis, bronchitis, or rhinosinusitis from nonstreptococcal pharyngitis. International journal of general medicine 9, 409-414	Inappropriate or unclear methodology (intervention)
Dimartino C (2012) Amoxicillin does not improve symptoms of acute rhinosinusitis. American Family Physician 86(3), 282-291	Inappropriate or unclear methodology
Dolor R, Witsell DI, Hellkamp A et al. (2001) Treatment of rhinosinusitis with or without intranasal steroids. Otolaryngology - Head and Neck Surgery 125(2), P102	Inappropriate or unclear methodology
Dosh SA, Hickner JM, Mainous AG et al. (2000) Predictors of antibiotic prescribing for nonspecific upper respiratory infections, acute bronchitis, and acute sinusitis. An UPRNet study. Upper Peninsula Research Network. The Journal of family practice 49(5), 407-14	Inappropriate or unclear methodology
Dubreuil C, Gehanno P, Goldstein F et al. (2001) Treatment of acute maxillary sinusitis in adult outpatients: Comparison of a five versus ten day-course of cefuroxime axetil. Medecine et Maladies Infectieuses 31(2), 70-78	Non-English language
Dunmore F (2002) Acute bacterial rhinosinusitis. Care and treatment modalities. Advance for nurse practitioners 10(8), 28-31	Unable to source study

Study reference	Reason for exclusion
Edwards M, Dennison J, Sedgwick P (2003) Patients' responses to delayed antibiotic prescription for acute upper respiratory tract infections. British Journal of General Practice 53(496), 845-850	Inappropriate or unclear methodology
El-Hennawi DM, Abou-Halawa AS, Zaher SR (2006) Management of clinically diagnosed subacute rhinosinusitis in children under the age of two years: a randomized, controlled study. The Journal of laryngology and otology 120(10), 845-8	Not relevant population
Elies W (2001) Short course therapy with cefuroxime axetil for five days in comparison to ten days of therapy with clarithromycin in acute sinusitis. [German]. Chemotherapie Journal 10(3), 105-9	Non-English language
Elies W, Lemmnitz G, Landwehr J et al. (2005) Comparison of efficacy and tolerability of amoxicillin/flucloxacillin (Flanamox 500) and amoxicillin/clavulanate in patients with acute purulent sinusitis. [German]. Chemotherapie Journal 14(5), 168-73	Non-English language
EUCTR (2004) A prospective, randomized, open-label, active-controlled study in adult subjects with acute bacterial sinusitis comparing the clinical efficacy of telithromycin (KETEK®) 800 mg once a day for 5 days versus amoxicillin-clavulanic acid (AUGMENTIN®) 875/125 mg twice a day for 10 days. EUCTR [www.clinicaltrialsregister.eu]	Does not reflect usual UK practice
EUCTR (2014) Efficacy and safety of Sinusitis Hevert SL tablets compared to placebo in adult patients with acute, uncomplicated rhinosinusitis: A multicenter, randomized, double-blind, placebo-controlled, parallel group phase IV study - Sinusitis Study. EUCTR [www.clinicaltrialsregister.eu]	Unable to source study
EUCTR (2009) A randomized, double-blind, placebo controlled, parallel group, multi-centre, 2-week treatment study to evaluate the safety and efficacy of fluticasone furoate nasal spray (FFNS) 110 mcg, administered either once daily or twice daily, compared with placebo, as effective monotherapy in the treatment of uncomplicated acute rhinosinusitis (ARS) in adult and adolescent subjects 12 years of age and older. EUCTR [www.clinicaltrialsregister.eu]	Inappropriate or unclear methodology (intervention)
EUCTR (2006) Prospective, multicenter, randomized, double blind, parallel arm study to evaluate the efficacy and safety of Moxifloxacin 400 mg OD for 7 days versus amoxicillin clavulanate/claritromycin for 10 days in the treatment of Acute Bacterial Rhino Sinusitis. EUCTR [www.clinicaltrialsregister.eu]	Inappropriate or unclear methodology (intervention)
Fahey T, Howie J (2001) Re-evaluation of a randomized controlled trial of antibiotics for minor respiratory illness in general practice. Family practice 18(3), 246-8	Inappropriate or unclear methodology
Farrer F (2014) Sinusitis and allergic rhinitis. SA Pharmaceutical Journal 81(8), 11-12	Not a clinical study
Ferguson B, Anon J, Hendrick K et al. (2000) Efficacy of Once Daily Gemifloxacin for 7 Days Compared with Cefuroxime Twice Daily for 10 Days in the Treatment of Acute Bacterial Sinusitis. Intersci Conf Antimicrob Agents Chemother 40, 475	Inappropriate or unclear methodology (intervention)
Ferguson BJ, Anon J, Poole MD et al. (2002) Short treatment durations for acute bacterial rhinosinusitis: Five days of gemifloxacin versus 7 days of gemifloxacin. Otolaryngology--head and neck surgery: official journal of American Academy of Otolaryngology-Head and Neck Surgery 127(1), 1-6	Inappropriate or unclear methodology (intervention)
Ferguson BJ, Guzzetta RV, Spector SL et al. (2004) Efficacy and safety of oral telithromycin once daily for 5 days versus moxifloxacin	Inappropriate or unclear methodology (intervention)

Study reference	Reason for exclusion
once daily for 10 days in the treatment of acute bacterial rhinosinusitis. Otolaryngology--head and neck surgery: official journal of American Academy of Otolaryngology-Head and Neck Surgery 131(3), 207-14	
Fiocchi A, Sarratud T, Bouygue GR et al. (2007) Topical treatment of rhinosinusitis. Pediatric allergy and immunology: official publication of the European Society of Pediatric Allergy and Immunology 18 Suppl 18, 62-7	Not a clinical study
Foden N, Burgess C, Shepherd K et al. (2013) A guide to the management of acute rhinosinusitis in primary care: management strategy based on best evidence and recent European guidelines. The British journal of general practice: the journal of the Royal College of General Practitioners 63(616), 611-3	Not a clinical study
Fogarty CM, Buchanan P, Aubier M et al. (2006) Telithromycin in the treatment of pneumococcal community-acquired respiratory tract infections: a review. International journal of infectious diseases: IJID: official publication of the International Society for Infectious Diseases 10(2), 136-47	Does not reflect usual UK practice
Fokkens W, Lund V, Bachert C et al (2005) EAACI position paper on rhinosinusitis and nasal polyps executive summary. Allergy: European Journal of Allergy and Clinical Immunology 60(5), 583-601	Not a clinical study
Fukazawa K, Takayasu S, Hashimoto Y et al. (2004) A clinical study of azithromycin hydrate for acute sinusitis with special regard to methods of oral administration. [Japanese]. Practica oto-rhino-laryngologica 97(9), 833-8	Non-English language
Garbutt J, Spitznagel E, Piccirillo J (2011) Use of the modified SNOT-16 in primary care patients with clinically diagnosed acute rhinosinusitis. Archives of otolaryngology--head & neck surgery 137(8), 792-7	Not a clinical study
Gehanno P, Berche P, Hercot O et al. (2004) [Efficiency of a four-day course of pristinamycin compared to a five-day course of cefuroxime axetil for acute bacterial maxillary sinusitis in adult outpatients]. Médecine et maladies infectieuses 34(7), 293-302	Does not reflect usual UK practice
Gehanno P, Dubreuil C, Berche P et al. (2002) Treatment of acute bacterial maxillary sinusitis in adult outpatients: Comparison of a 5 versus 10 days course of cefpodoxime proxetil. Medecine et Maladies Infectieuses 32(12), 662-677	Non-English language
Gehanno P, Goldstein F, Gutmann L et al. (2000) Efficacy of twice-daily dosing of Augmentin (1 g/125 mg) in acute maxillary sinusitis. [French]. Medecine et maladies infectieuses 30(11), 703-13	Non-English language
Gehanno P, Loncle-Provot V, Kerneau J (2004) Efficacy of cefotiam hexetil in acute maxillary sinusitis, with a short five day vs ten day treatment. Médecine et maladies infectieuses 34(10), 455-9	Non-English language
Granizo JJ, Gimenez MJ, Barberan J et al. (2008) Efficacy of cefditoren in the treatment of upper respiratory tract infections: a pooled analysis of six clinical trials. Revista espanola de quimioterapia : publicacion oficial de la Sociedad Espanola de Quimioterapia 21(1), 14-21	Inappropriate or unclear methodology (intervention)
Gurdogan K, Senol E (2001) Comparison of 3-day course of azithromycin with penicillin V and amoxicillin+clavulonate in the treatment of upper respiratory tract infections. [Turkish]. Mikrobiyoloji bulteni 35(2), 239-43	Non-English language

Study reference	Reason for exclusion
Gwaltney Jr, JM, Wiesinger BA, Patrie JT (2004) Acute Community-Acquired Bacterial Sinusitis: The Value of Antimicrobial Treatment and the Natural History. Clinical Infectious Diseases 38(2), 227-233	Not a clinical study
Harris AM, Hicks LA, Qaseem A et al. (2016) Appropriate Antibiotic Use for Acute Respiratory Tract Infection in Adults: Advice for High-Value Care From the American College of Physicians and the Centers for Disease Control and Prevention. Annals of internal medicine 164(6), 425-34	Not a clinical study
Hasibi M, Mohraz M, Haji-Abdolbaghi M et al. (2007) Low-dose sultamicillin versus amoxicillin-clavulanic acid in the treatment of acute bacterial sinusitis in adults: A randomized clinical trial. Infectious Diseases in Clinical Practice 15(2), 104-105	Does not reflect usual UK practice
Haxel BR, Woywode C, Mewes T et al. (2004) Myeloperoxidase in nasal secretion as a cell-activation marker in acute sinusitis. American journal of rhinology 18(2), 93-8	Inappropriate or unclear methodology (intervention)
Henderson J, Stevermer JJ (2001) Are antibiotics effective in the treatment of acute sinusitis in children and adolescents? Journal of Family Practice 50(8), 717	Not a clinical study
Henry DC, Kapral D, Busman TA et al. (2004) Cefdinir versus levofloxacin in patients with acute rhinosinusitis of presumed bacterial etiology: a multicenter, randomized, double-blind study. Clinical therapeutics 26(12), 2026-33	Inappropriate or unclear methodology (intervention)
Hitzeman N, Shoemaker J (2014) Intranasal corticosteroids for acute bacterial rhinosinusitis. American Family Physician 90(5), 286-287	Not a clinical study
Ioannidis JP, Contopoulos-Ioannidis DG, Chew P et al. (2001) Meta-analysis of randomized controlled trials on the comparative efficacy and safety of azithromycin against other antibiotics for upper respiratory tract infections. The Journal of antimicrobial chemotherapy 48(5), 677-89	Inappropriate or unclear methodology (population)
IRCT, 2012111511470N (2013) Comparison of amoxicillin and sodium chloride 0.9% in the treatment of sinusitis. IRCT [www.irct.ir]	Inappropriate or unclear methodology (population)
ISRCTN (2009) A primary care randomised controlled trial of nasal irrigation and steam inhalation for recurrent sinusitis. ISRCTN [www.controlled-trials.com]	Inappropriate or unclear methodology
Ivanchenko O, Chuchueva N, Lopatin A (2007) Avelox efficacy in the treatment of acute purulent rhinosinusitis. Terapevticheskii arkhiv 79(8), 41-4	Non-English language
Jackson EA (2003) Amoxicillin-clavulanate ineffective for suspected acute sinusitis. Journal of Family Practice 52(12), 930-932	Not a clinical study
Jacobs M, Anon JB (2010) Amoxicillin/potassium clavulanate is effective treatment for acute bacterial sinusitis in children. Journal of Pediatrics 156(1), 166	Not a clinical study
Jareoncharsri P, Bunnag C, Fooanant S et al. (2004) An open label, randomized comparative study of levofloxacin and amoxicillin/clavulanic acid in the treatment of purulent sinusitis in adult Thai patients. Rhinology 42(1), 23-9	Inappropriate or unclear methodology (population)
Jehl F, Klossek J, Peynegre R et al. (2002) Sinusal penetration of amoxicillin-clavulanic acid. Formulation 1 g/125 mg, twice daily versus formulation 500 mg/125 mg. three times daily. Presse médicale (Paris, and France: 1983) 31(34), 1596-603	Non-English language
Jurkiewicz D, Zielnik-Jurkiewicz B (2004) Intranasal corticosteroid in the treatment of acute sinusitis. 5th European Congress of Oto Rhino	Inappropriate or unclear methodology

Study reference	Reason for exclusion
Laryngology Head and Neck Surgery (EUFOS), 2004, 11-16 September, Rhodes, Kos, and Greece	
Kaiser L, Morabia A, Stalder H et al (2001) Role of nasopharyngeal culture in antibiotic prescription for patients with common cold or acute sinusitis. European journal of clinical microbiology & infectious diseases: official publication of the European Society of Clinical Microbiology 20(7), 445-51	Publication/study type (duplicate)
Kaper NM, Breukel L, Venekamp RP et al (2013) Absence of evidence for enhanced benefit of antibiotic therapy on recurrent acute rhinosinusitis episodes: a systematic review of the evidence base. Otolaryngology--head and neck surgery: official journal of American Academy of Otolaryngology-Head and Neck Surgery 149(5), 664-7	Publication/study type (no data reported)
Keith T, Saxena S, Murray J et al. (2010) Risk-benefit analysis of restricting antimicrobial prescribing in children: what do we really know? Current opinion in infectious diseases 23(3), 242-8	Inappropriate or unclear methodology
Khianey R, Oppenheimer J (2012) Is nasal saline irrigation all it is cracked up to be? Annals of allergy, asthma & immunology: official publication of the American College of Allergy, Asthma, and & Immunology 109(1), 20-8	Publication/study type (systematic review includes observational studies)
Khoshdel A, Panahande GR, Noorbakhsh MK et al (2014) A comparison of the efficacy of amoxicillin and nasal irrigation in treatment of acute sinusitis in children. Korean journal of pediatrics 57(11), 479-83	No relevant comparator
Kim AS (2009) Sinusitis (acute). American Family Physician 79(4), 320-322	Not a clinical study
Klossek JM, Siegert R, Nikolaidis P et al. (2003) Comparison of the efficacy and safety of moxifloxacin and trovafloxacin for the treatment of acute, bacterial maxillary sinusitis in adults. The Journal of laryngology and otology 117(1), 43-51	Does not reflect usual UK practice
Klossek JM, Desmonts-Gohler C, Deslandes B et al. (2004) Treatment of functional signs of acute maxillary rhinosinusitis in adults. Efficacy and tolerance of administration of oral prednisone for 3 days. Presse médicale (Paris, and France: 1983) 33(5), 303-9	Non-English language
Kristo A, Uhari M (2009) Timing of rhinosinusitis complications in children. The Pediatric infectious disease journal 28(9), 769-71	Inappropriate or unclear methodology
Kunel'skaya N, Gurov A, Kudriavtseva IS et al. (2008) Study of the efficacy of cefixime (suprax) in patients with acute and recurrent chronic purulent sinusitis. Vestnik Otorinolaringologii (6), 55-8	Non-English language
Lacroix JS, Ricchetti A, Lew D et al. (2002) Symptoms and clinical and radiological signs predicting the presence of pathogenic bacteria in acute rhinosinusitis. Acta oto-laryngologica 122(2), 192-6	Inappropriate or unclear methodology
Lal D, Jategaonkar AA, Borish L et al. (2016) Management of rhinosinusitis during pregnancy: systematic review and expert panel recommendations. Rhinology 54(2), 99-104	Inappropriate or unclear methodology
Lee Ji-Eun, Han Doo Hee, Won Tae-Bin et al. (2011) A Randomized, Double-blinded, Open Label Study of the Efficacy and Safety of Cefcapene Pivoxil and Amoxicillin Clavulanate in Acute Presumed Bacterial Rhinosinusitis. Clinical and experimental otorhinolaryngology 4(2), 83-7	Inappropriate or unclear methodology (intervention)
Lee S, Woodbury K, Ferguson BJ (2013) Use of nasopharyngeal culture to determine appropriateness of antibiotic therapy in acute	Inappropriate or unclear methodology (intervention)

Study reference	Reason for exclusion
bacterial rhinosinusitis. International forum of allergy & rhinology 3(4), 272-5	
Lehrer-Coriat E, Marino-Sanchez F, Alobid I et al. (2013) Quality of life measures in patients on rhinosinusitis trials. Clinical Investigation 3(3), 251-263	Not a clinical study
Lindbaek M (2006) Mometasone furoate nasal spray was more effective for symptom relief of acute rhinosinusitis than amoxicillin or placebo. Evidence-Based Medicine 11(4), 114	Not a clinical study
Little P, Stuart B, Mullee M et al (2016) Effectiveness of steam inhalation and nasal irrigation for chronic or recurrent sinus symptoms in primary care: a pragmatic randomized controlled trial. CMAJ: Canadian Medical Association journal = journal de l'Association medicale canadienne 188(13), 940-9	Poor relevance against search terms (population)
Lund VJ (2008) Therapeutic targets in rhinosinusitis: infection or inflammation? Medscape journal of medicine 10(4), 105	Not a relevant study
Macchi A, Terranova P, Castelnuovo P (2012) Recurrent acute rhinosinusitis: a single blind clinical study of N-acetylcysteine vs ambroxol associated to corticosteroid therapy. International journal of immunopathology and pharmacology 25(1), 207-17	Does not reflect usual UK practice
Maiese E, Moor C, McLaughlin J et al. (2011) The impact of antibiotic and mometasone furoate nasal spray therapy on healthcare resource utilisation among acute rhinosinusitis patients in the United Kingdom. Allergy 66, 243	Inappropriate or unclear methodology
Mandal R, Patel N, and Ferguson BJ (2012) Role of antibiotics in sinusitis. Current opinion in infectious diseases 25(2), 183-92	Not a clinical study
McConaghy JR (2001) Is mometasone furoate aqueous nasal spray (MFNS) effective in reducing symptoms in acute recurrent sinusitis? The Journal of family practice 50(2), 107	Inappropriate or unclear methodology
Morris PS, Leach AJ (2008) Antibiotics for persistent nasal discharge (rhinosinusitis) in children. Cochrane Database of Systematic Reviews (2)	Unable to source study
Mosges R, Spaeth J, Berger K et al. (2002) Topical treatment of rhinosinusitis with fusafungine nasal spray. A double-blind, placebo-controlled, parallel-group study in 20 patients. Arzneimittel-Forschung 52(12), 877-83	Does not reflect usual UK practice
Murray JJ, Solomon E, McCluskey D et al. (2000) Phase III, randomized, double-blind study of clarithromycin extended-release and immediate-release formulations in the treatment of adult patients with acute maxillary sinusitis. Clinical therapeutics 22(12), 1421-32	Does not reflect usual UK practice
NCT (2005) A Multicenter, Randomized Study to Compare the Safety and Efficacy of Oral Levofloxacin With Amoxicillin/Clavulanate Potassium in the Treatment of Acute Sinusitis in Adults. Clinicaltrials.gov [www.clinicaltrials.gov]	Inappropriate or unclear methodology
NCT (2005) Prospective, Multicenter, Randomized, Double-Blind, Placebo Controlled Trial to Evaluate the Efficacy and Safety of Moxifloxacin 400 mg QD for 5 Days Versus Placebo in the Treatment of Acute Bacterial Sinusitis. Clinicaltrials.gov [www.clinicaltrials.gov]	Inappropriate or unclear methodology
NCT (2006) A multicenter, randomized, open label comparative study of azithromycin extended release (zmax) versus amoxicillin/clavulanate potassium in subjects with acute bacterial sinusitis (ABS) in a physician practice environment [completed]. Clinicaltrials.gov [www.clinicaltrials.gov] ClinicalTrials.gov ID: NCT00367120	Inappropriate or unclear methodology

Study reference	Reason for exclusion
NCT (2007) A Randomized, Double-blind, Placebo Controlled, Parallel Group Trial of Cyclamen Europaeum Extract Nasal Spray 10% (v/v) in the Treatment of Subjects With Acute Sinusitis. Clinicaltrials.gov [www.clinicaltrials.gov]	Does not reflect usual UK practice
NCT (2008) A Multicenter, Randomized, Double-Blind, Double-Dummy Comparative Trial of Azithromycin SR Versus Levofloxacin for the Treatment of Acute Bacterial Maxillary Sinusitis in Adults Undergoing Diagnostic Sinus Aspiration. Clinicaltrials.gov [www.clinicaltrials.gov]	Does not reflect usual UK practice
NCT (2009) Efficacy of Azithromycin Prophylaxis in Preventing Recurrent Acute Sinusitis in Children: A Prospective, Randomized, Double-blind, Placebo Controlled Trial. Clinicaltrials.gov [www.clinicaltrials.gov]	Inappropriate or unclear methodology
NCT (2013) Evaluation of Inhaled Corticosteroid Treatment in Sinusitis. Clinicaltrials.gov [www.clinicaltrials.gov]	Inappropriate or unclear methodology
NCT (2014) Clinical Trial of the Treatment of Acute Sinusitis With Standard-dose Versus High-dose Amoxicillin/Clavulanate. Clinicaltrials.gov [www.clinicaltrials.gov]	Unable to source study
Nielsen IR, Seim A, Bentzen N (2013) Chloramphenicol eye drops in the treatment of conditions indicative of maxillary sinusitis. Tidsskrift for den Norske laegeforening: tidsskrift for praktisk medicin, and ny raekke 133(20), 2146-8	Non-English language
Orlandi RR, Kingdom TT, Hwang PH (2016) International Consensus Statement on Allergy and Rhinology: Rhinosinusitis Executive Summary. International Forum of Allergy and Rhinology 6, S3-S21	Not a clinical study
Ovchinnikov A, Dzhenzhera G, Lopatin A (2009) Efficiency of sinuforte in combined therapy of acute suppurative rhinosinusitis. Vestnik otorinolaringologii (5), 59-62	Non-English language
Passali D, Damiani V, Passali FM et al. (2005) Atomized nasal douche vs nasal lavage in acute viral rhinitis. Archives of otolaryngology--head & neck surgery 131(9), 788-90	Inappropriate or unclear methodology (population)
Passali D, Spinosi MC, Crisanti A et al. (2016) Mometasone furoate nasal spray: a systematic review. Multidisciplinary respiratory medicine 11, 18	Inappropriate or unclear methodology
Patel NA, Garber D, Hu S et al. (2016) Systematic review and case report: Intracranial complications of pediatric sinusitis. International journal of pediatric otorhinolaryngology 86, 200-12	Inappropriate or unclear methodology
Pessey JJ, Gehanno P, Dabernat H (2001) Pristinamycin versus cefuroxime axetil in the treatment of acute sinusitis in adults. Medecine et Maladies Infectieuses 31(6), 425-432	Non-English language
Piccirillo JF (2004) Acute bacterial sinusitis. New England Journal of Medicine 351(9), 902	Inappropriate or unclear methodology
Pichichero ME, Brixner DI (2006) A review of recommended antibiotic therapies with impact on outcomes in acute otitis media and acute bacterial sinusitis. American Journal of Managed Care 12(SUPPL. 10), S292-S302	Not a clinical study
Poachanukoon O, Kitcharoensakkul M (2008) Efficacy of cefditoren pivoxil and amoxicillin/clavulanate in the treatment of pediatric patients with acute bacterial rhinosinusitis in Thailand: a randomized, investigator-blinded, controlled trial. Clinical therapeutics 30(10), 1870-9	Inappropriate or unclear methodology (intervention)

Study reference	Reason for exclusion
Polonovski J, Mellah M (2006) Treatment of acute maxillary sinusitis in adults. Comparison of cefpodoxime-proxetil and amoxicillin-clavulanic acid. Presse médicale (Paris, and France: 1983) 35(1 Pt 1), 33-8	Non-English language
Polonovski J, Mellah M, Cabrillac S et al. (2005) Efficacy and tolerability of 5-day course of cefpodoxim proxetil (CPD) versus 8-day course of co-amoxiclav (AAC) in acute maxillary sinusitis (AMS). XVIII IFOS World Congress, 2005, 25-30 June, Rome, and Italy	Unable to source study
Pynnonen MA, Kim HM, Terrell JE (2009) Validation of the Sino-Nasal Outcome Test 20 (SNOT-20) domains in nonsurgical patients. American journal of rhinology & allergy 23(1), 40-5	Not a clinical study
Quadri N, Lloyd A, Keating KN et al. (2013) Psychometric evaluation of the Sinonasal Outcome Test-16 and activity impairment assessment in acute bacterial sinusitis. Otolaryngology--head and neck surgery: official journal of American Academy of Otolaryngology-Head and Neck Surgery 149(1), 161-7	Inappropriate or unclear methodology
Rabago D, Zgierska A, Mundt M et al. (2002) Efficacy of daily hypertonic saline nasal irrigation among patients with sinusitis: a randomized controlled trial. The Journal of family practice 51(12), 1049-55	Inappropriate or unclear methodology (population)
Ragab A, Farahat T, Al-Hendawy G et al (2015) Nasal saline irrigation with or without systemic antibiotics in treatment of children with acute rhinosinusitis. International journal of pediatric otorhinolaryngology 79(12), 2178-86	No relevant comparator
Rahmati M, Razaghi A, Doostdar H et al. (2014) Comparison of azithromycin, amoxicillin and amoxicillin/clavulanic acid in the treatment of children with acute bacterial sinusitis. [Persian]. Journal of Mazandaran University of Medical Sciences 23(110), 182-90	Non-English language
Rakkar S, Roberts K, Towe BF et al. (2001) Moxifloxacin versus amoxicillin clavulanate in the treatment of acute maxillary sinusitis: a primary care experience. International journal of clinical practice 55(5), 309-15	Inappropriate or unclear methodology (intervention)
Reed M (2012) Amoxicillin for Acute Rhinosinusitis. Pharmacy Times 78(6)	Not a clinical study
Rosenfeld RM (2016) CLINICAL PRACTICE. Acute Sinusitis in Adults. The New England journal of medicine 375(10), 962-70	Inappropriate or unclear methodology
Runkle K (2016) Decongestants, antihistamines and nasal irrigation for acute sinusitis in children. Paediatrics & child health 21(3), 143-4	Inappropriate or unclear methodology
Satdhabudha A, Utispan K, Monthanapisut P et al. (2016) A randomized-controlled study comparing the efficacy of positive pressure nasal saline irrigation device versus syringe use in children with acute rhinosinusitis. Asian Pacific journal of allergy and immunology	Inappropriate or unclear methodology (intervention)
Scarupa MD, Kaliner MA (2007) Adjuvant therapies in the treatment of acute and chronic rhinosinusitis. Clinical allergy and immunology 20, 251-62	Not a clinical study
Schmidt RS, Dodson KM, Goldman RA (2015) Prophylactic antibiotic therapy for fractures of the maxillary sinus. Ear, nose, and & throat journal 94(4-5), 170-7	Inappropriate or unclear methodology (intervention)
Shaikh N, Wald ER (2014) Decongestants, antihistamines and nasal irrigation for acute sinusitis in children. The Cochrane database of systematic reviews 10, CD007909	No RCTs met the systematic review inclusion criteria

Study reference	Reason for exclusion
Sharma V, Saxena RK, Sharma S et al (2011) Comparative Efficacy and Safety of Various Anti-Microbials in Patients of Acute Rhinosinusitis at Tertiary-Care Hospital in Uttarakhand (UK). Indian journal of otolaryngology and head and neck surgery: official publication of the Association of Otolaryngologists of India 63(4), 364-9	Publication/study type (not an RCT)
Sharma S, Josephson GD (2014) Orbital complications of acute sinusitis in infants: A systematic review and report of a case. JAMA Otolaryngology - Head and Neck Surgery 140(11), 1070-1073	Inappropriate or unclear methodology
Sher LD, McAdoo MA, Bettis RB et al. (2002) A multicenter, randomized, investigator-blinded study of 5- and 10-day gatifloxacin versus 10-day amoxicillin/clavulanate in patients with acute bacterial sinusitis. Clinical therapeutics 24(2), 269-81	Does not reflect usual UK practice
Sher LD, Poole MD, Von Seggern K et al. (2002) Community-based treatment of acute uncomplicated bacterial rhinosinusitis with gatifloxacin. Otolaryngology--head and neck surgery: official journal of American Academy of Otolaryngology-Head and Neck Surgery 127(3), 182-9	Does not reflect usual UK practice
Siegert R, Berg O, Gehanno P et al. (2003) Comparison of the efficacy and safety of faropenem daloxate and cefuroxime axetil for the treatment of acute bacterial maxillary sinusitis in adults. European archives of oto-rhino-laryngology: official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS) : affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery 260(4), 186-94	Inappropriate or unclear methodology
Sih TM, Bricks LF (2008) Optimizing the management of the main acute infections in pediatric ORL: Tonsillitis, sinusitis, otitis media. Brazilian Journal of Otorhinolaryngology 74(5), 755-762	Not a clinical study
Simon MW (2000) Cefprozil vs. Amoxicillin in the treatment of childhood acute sinusitis. International Pediatrics 15(2), 93-96	Does not reflect usual UK practice
Soni-Jaiswal A, Philpott C, Hopkins C (2015) The impact of commissioning for rhinosinusitis in England. Clinical otolaryngology: official journal of ENT-UK, and official journal of Netherlands Society for Oto-Rhino-Laryngology & Cervico-Facial Surgery 40(6), 639-45	Not a clinical study
Sperber SJ, Turner RB, Sorrentino JV et al (2000) Effectiveness of pseudoephedrine plus acetaminophen for treatment of symptoms attributed to the paranasal sinuses associated with the common cold. Archives of family medicine 9(10), 979-85	Not relevant population
Spurling GKP, Del Mar CB, Dooley L et al. (2004) Delayed antibiotics for symptoms and complications of respiratory infections. The Cochrane database of systematic reviews (4), CD004417	Inappropriate or unclear methodology (population)
Steurer M, Schenk P (2000) Efficacy and safety of cefdinir in the treatment of maxillary sinusitis. European archives of oto-rhino-laryngology: official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS): affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery 257(3), 140-8	Does not reflect usual UK practice
Svensson J, Lundberg J, Olsson P et al. (2012) Cost-effectiveness of mometasone furoate nasal spray in the treatment of acute rhinosinusitis. Primary care respiratory journal: journal of the General Practice Airways Group 21(4), 412-8	Inappropriate or unclear methodology
Thunberg U, Engstrom K, Olaison S et al. (2013) Anterior rhinoscopy and middle meatal culture in acute rhinosinusitis. Journal of Laryngology and Otology 127(11), 1088-1092	Inappropriate or unclear methodology

Study reference	Reason for exclusion
Topuz B, Katircioglu O, Bayramoglu I et al. (2002) Low dose sultamicillin in acute sinusitis. Le infezioni in medicina : rivista periodica di eziologia, epidemiologia, diagnostica, and clinica e terapia delle patologie infettive 10(1), 45-8	Inappropriate or unclear methodology (intervention)
Tsar'kova S, Firstova O, Kaspirova N (2013) The potential of prophylaxis and optimization of the treatment of rhinosinusitis in the children presenting with stenosing laryngotracheitis. Vestnik otorinolaringologii (6), 62-6	Does not reflect usual UK practice
Upchurch J, Rosemore M, Tosiello R et al. (2006) Randomized double-blind study comparing 7- and 10-day regimens of faropenem medoxomil with a 10-day cefuroxime axetil regimen for treatment of acute bacterial sinusitis. Otolaryngology--head and neck surgery: official journal of American Academy of Otolaryngology-Head and Neck Surgery 135(4), 511-7	Inappropriate or unclear methodology (intervention)
van Driel ML, Coenen S, Dirven K et al. (2007) What is the role of quality circles in strategies to optimise antibiotic prescribing? A pragmatic cluster-randomised controlled trial in primary care. Quality & safety in health care 16(3), 197-202	Inappropriate or unclear methodology (intervention)
van Loon JWL, van Harn RP, Venekamp RP et al (2013) Limited evidence for effects of intranasal corticosteroids on symptom relief for recurrent acute rhinosinusitis. Otolaryngology--head and neck surgery: official journal of American Academy of Otolaryngology-Head and Neck Surgery 149(5), 668-73	Publication/study type (systematic review includes observational studies)
Varonen H, Rautakorpi U-M, Nyberg S et al. (2007) Implementing guidelines on acute maxillary sinusitis in general practice--a randomized controlled trial. Family practice 24(2), 201-6	Inappropriate or unclear methodology (intervention)
Varonen H, Savolainen S, Kunnamo I et al. (2003) Acute rhinosinusitis in primary care: a comparison of symptoms, signs, ultrasound, and radiography. Rhinology 41(1), 37-43	Inappropriate or unclear methodology (intervention)
Via RM (2004) Azithromycin (3 days) better than amoxicillin-clavulanate (10 days) for sinusitis? Journal of Family Practice 53(2), 98	Inappropriate or unclear methodology (intervention)
Vishnyakov VV, Sinkov DE (2013) Herbal medicine as add-on therapy in acute Rhinosinusitis: Results of an open randomized cohort study with the herbal combination Sinupret. Zeitschrift fur Phytotherapie 34(6), 262-265	Does not reflect usual UK practice
Wald ER, Applegate KE, Bordley C et al. (2013) Clinical practice guideline for the diagnosis and management of acute bacterial sinusitis in children aged 1 to 18 years. Pediatrics 132(1), e262-80	Not a clinical study
Wang Yun-Hu, Ku Min-Sho, Sun Hai-Lun et al (2014) Efficacy of nasal irrigation in the treatment of acute sinusitis in atopic children. Journal of microbiology, immunology, and and infection = Wei mian yu gan ran za zhi 47(1), 63-9	Not relevant population
Wasserfallen JB, Livio F, Zanetti G (2004) Acute rhinosinusitis: A pharmacoeconomic review of antibacterial use. PharmacoEconomics 22(13), 829-837	Inappropriate or unclear methodology
Westlund R, Cook C, Rickard K et al. (2000) A summary of the reduction in clinician-rated total sinusitis symptom scores at the end of cefuroxime axetil treatment with and without intranasal fluticasone propionate. Annals of allergy, and asthma & immunology 84, 129	Inappropriate or unclear methodology
Williams Jr, JW, Aguilar C, Makela M (2000) Review: Penicillin V or amoxicillin is better than placebo and equal to non-penicillins for acute maxillary sinusitis. Evidence-Based Medicine 5(2), 43	Not a clinical study

Study reference	Reason for exclusion
Williamson IG, Rumsby K, Benge S et al. (2008) Are antibiotics or nasal steroids effective for acute sinusitis? Journal of Family Practice 57(3), 156	Not a clinical study
Winn RJ (2002) Do intranasal corticosteroids aid treatment of acute sinusitis in patients with a history of recurrent sinus symptoms? The Journal of family practice 51(4), 386	Not a clinical study
Young J, Tschudi P, Periat P et al. (2005) Patients' expectations about the benefit of antibiotic treatment: Lessons from a randomised controlled trial. Forschende Komplementarmedizin und Klassische Naturheilkunde 12(6), 347-349	Inappropriate or unclear methodology
Young J, Bucher H, Tschudi P et al. (2003) The clinical diagnosis of acute bacterial rhinosinusitis in general practice and its therapeutic consequences. Journal of clinical epidemiology 56(4), 377-84	Inappropriate or unclear methodology
Zalmanovici A, Yaphe J (2007) Steroids for acute sinusitis. The Cochrane database of systematic reviews (2), CD005149	Publication/study type (updated systematic review available)