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Respiratory tract infections – antibiotic prescribing

Prescribing of antibiotics for self-limiting respiratory tract infections in adults and children in primary care

NICE clinical guideline 69
Developed by the Centre for Clinical Practice at NICE

Prescribing of antibiotics for self-limiting respiratory tract infections in adults and children in primary care

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- The full guideline (this document) – all the recommendations, details of how they were developed, and reviews of the evidence they were based on
- A quick reference guide – a summary of the recommendations for healthcare professionals.
- 'Understanding NICE guidance' – information for patients and carers.

For printed copies of the quick reference guide or 'Understanding NICE guidance', phone NICE publications on 0845 003 7783 or email publications@nice.org.uk and quote:

- N1623 (quick reference guide)
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Foreword

Most people will develop an acute respiratory tract infection (RTI) every year. RTIs are also the commonest acute problem dealt with in primary care – the 'bread and butter' of daily practice. Management of acute RTIs in the past concentrated on advising prompt antibiotic treatment of presumptive bacterial infections. This advice was appropriate, in an era of high rates of serious suppurative and non-suppurative complications, up to and including the immediate post-war period. However, in modern developed countries, rates of major complications are now low. In addition, there is no convincing evidence, either from international comparisons or from evidence within countries, that lower rates of prescribing are associated with higher rates of complications. Therefore much of the historically high volume of prescribing to prevent complications may be inappropriate. After a fall in antibiotic use in the late 1990s, antibiotic prescribing in the UK has now reached a plateau and the rate is still considerably higher than the rates of prescribing in other northern European countries. Most people presenting in primary care with an acute uncomplicated RTI will still receive an antibiotic prescription – with many doctors and patients believing that this is the right thing to do.

There may be several problems with this. First, complications are now much less common, so the evidence for symptomatic benefit should be strong to justify prescribing; otherwise many patients may have unnecessary antibiotics, needlessly exposing them to side effects. Second, except in cases where the antibiotic is clinically necessary, patients, and their families and friends, may get the message from healthcare professionals that antibiotics are helpful for most infections. This is because patients will understandably attribute their symptom resolution to antibiotics, and thus maintain a cycle of 'medicalising' self-limiting illness. Third, international comparisons make it clear that antibiotic resistance rates are strongly related to antibiotic use in primary care. This is potentially a major public health problem both for our own and for future generations; unless there is clear evidence of benefit, we need to maintain the efficacy of antibiotics by more judicious antibiotic prescribing.

Following a review of the evidence, we have tried to produce simple, practical guidance for antibiotic prescribing for all of the common, acute,

uncomplicated, RTIs, with recommendations for targeting of antibiotics. The guideline includes suggestions for safe methods of implementing alternatives to an immediate antibiotic prescription – including the ‘delayed’ antibiotic prescription.

The Guideline Development Group (GDG) recognised the concern of GPs and patients regarding the danger of developing complications. While most patients can be reassured that they are not at risk of major complications, the difficulty for prescribers lies in identifying the small number of patients who will suffer severe and/or prolonged illness or, more rarely, go on to develop complications. The GDG struggled to find much good evidence to inform this issue. This is clearly an area where further research is needed. In the meantime, GPs need to take ‘safety-netting’ approaches in the case of worsening illness, either by using delayed prescriptions or by prompt clinical review.

This is one of the new National Institute for Health and Clinical Excellence (NICE) short clinical guidelines. The methodology is of the same rigour as for the standard NICE clinical guidelines, but the scope is narrower, and the development and consultation phases have been compressed. In particular, the detailed issues surrounding the diagnosis of acute RTIs and the use of diagnostic tests during the consultation could not be adequately dealt with in such a short timescale. We hope that the guideline will be welcomed by those who manage and experience the clinical care of acute respiratory infections.

Paul Little, Professor of Primary Care Research,

GP and Chair, Guideline Development Group

Patient-centred care

This guideline offers best practice advice on the care of adults and children (3 months and older) with RTIs, for whom immediate antibiotic prescribing is not indicated.

Treatment and care should take into account patients' needs and preferences. Adults and children (or their parents/carers) for whom immediate antibiotic prescribing is not indicated should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. If patients do not have the capacity to make decisions, healthcare professionals should follow the Department of Health (2001) guidelines – 'Reference guide to consent for examination or treatment' (available from www.dh.gov.uk). Healthcare professionals should also follow a code of practice accompanying the Mental Capacity Act (summary available from www.publicguardian.gov.uk).

If the patient is under 16, healthcare professionals should follow guidelines in 'Seeking consent: working with children' (available from www.dh.gov.uk).

Good communication between healthcare professionals and patients is essential. It should be supported by evidence-based oral or written information tailored to the patient's needs. Treatment and care, and the information patients are given about it, should be culturally appropriate. It should also be accessible to people with additional needs such as physical, sensory or learning disabilities, and to people who do not speak or read English.

If the patient agrees, families and carers should have the opportunity to be involved in decisions about treatment and care.

Families and carers should also be given the information and support they need.

Care of young people in transition between paediatric and adult services should be planned and managed according to the best practice guidance described in 'Transition: getting it right for young people' (available from www.dh.gov.uk).

Adult and paediatric healthcare teams should work jointly to provide assessment and services to young people with respiratory tract infection and any possible complications. Diagnosis and management should be reviewed throughout the transition process, and there should be clarity about who is the lead clinician to ensure continuity of care.

1 Summary

1.1 List of all recommendations

The clinical effectiveness and cost effectiveness of antibiotic management strategies for respiratory tract infections (RTIs) (section 2.2.3)

1.1.1 At the first face-to-face contact in primary care, including walk-in centres and emergency departments, adults and children (3 months and older) presenting with a history suggestive of the following conditions should be offered a clinical assessment:

- acute otitis media
- acute sore throat/acute pharyngitis/acute tonsillitis
- common cold
- acute rhinosinusitis
- acute cough/acute bronchitis.

The clinical assessment should include a history (presenting symptoms, use of over-the-counter or self medication, previous medical history, relevant risk factors, relevant comorbidities) and, if indicated, an examination to identify relevant clinical signs.

1.1.2 Patients' or parents'/carers' concerns and expectations should be determined and addressed when agreeing the use of the three antibiotic prescribing strategies (no prescribing, delayed prescribing and immediate prescribing).

1.1.3 A no antibiotic prescribing strategy or a delayed antibiotic prescribing strategy should be agreed for patients with the following conditions:

- acute otitis media
- acute sore throat/acute pharyngitis/acute tonsillitis
- common cold
- acute rhinosinusitis
- acute cough/acute bronchitis.

Depending on clinical assessment of severity, patients in the following subgroups can also be considered for an immediate antibiotic prescribing strategy (in addition to a no antibiotic or a delayed antibiotic prescribing strategy):

- bilateral acute otitis media in children younger than 2 years
- acute otitis media in children with otorrhoea
- acute sore throat/acute pharyngitis/acute tonsillitis when three or more Centor criteria[1] are present.

1.1.4 For all antibiotic prescribing strategies, patients should be given:

- advice about the usual natural history of the illness, including the average total length of the illness (before and after seeing the doctor):
  - acute otitis media: 4 days
  - acute sore throat/acute pharyngitis/acute tonsillitis: 1 week
  - common cold: 1½ weeks
  - acute rhinosinusitis: 2½ weeks
  - acute cough/acute bronchitis: 3 weeks
- advice about managing symptoms, including fever (particularly analgesics and antipyretics). For information about fever in children younger than 5 years, refer to 'Feverish illness in children' (NICE clinical guideline 47).

1.1.5 When the no antibiotic prescribing strategy is adopted, patients should be offered:

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

[1] Centor criteria are: presence of tonsillar exudate, tender anterior cervical lymphadenopathy or lymphadenitis, history of fever and an absence of cough.

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

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

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

Identifying those patients with RTIs who are likely to be at risk of developing complications (section 2.3.3)

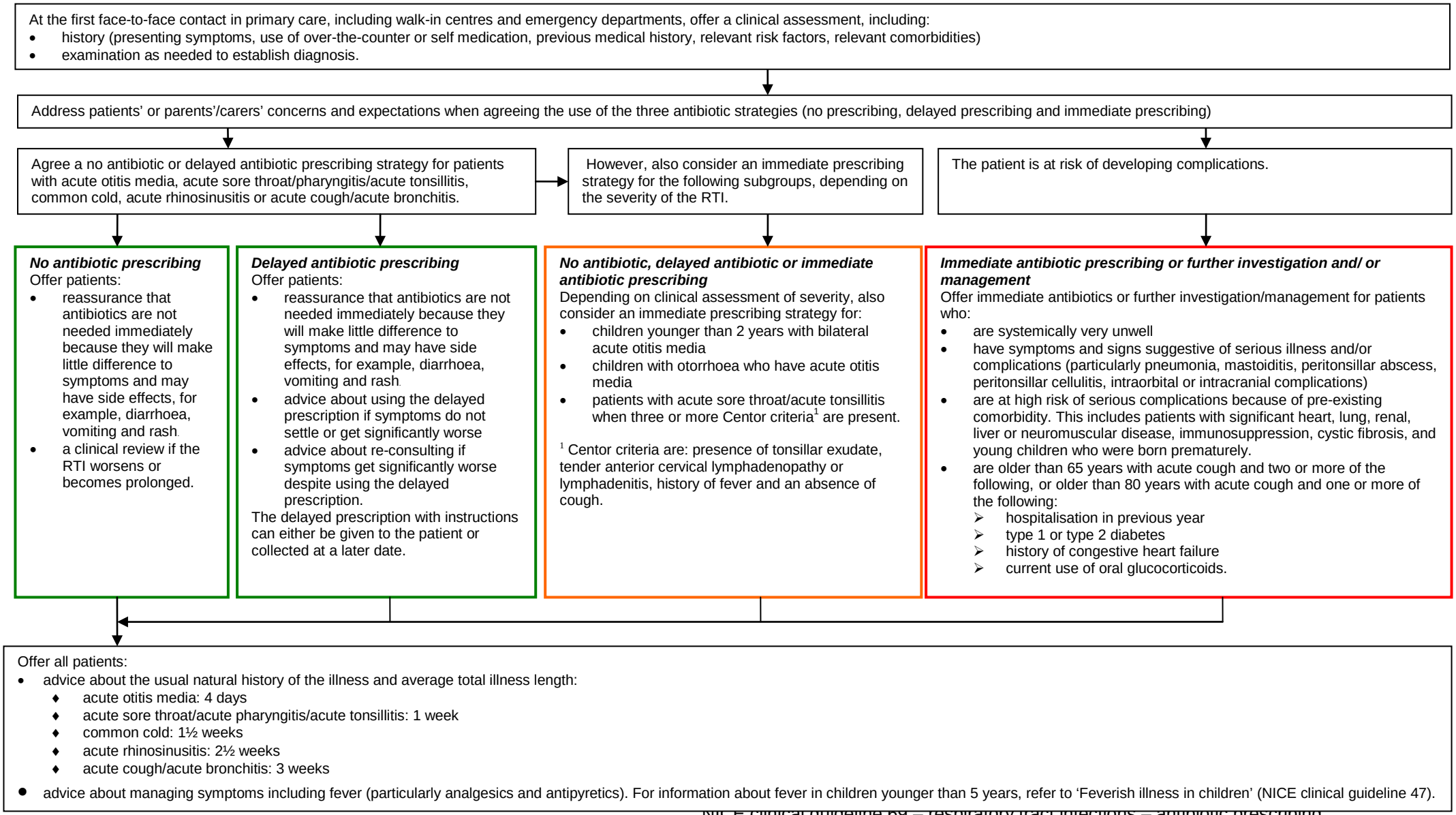
1.1.7 An immediate antibiotic prescription and/or further appropriate investigation and management should only be offered to patients (both adults and children) in the following situations:

- if the patient is systemically very unwell
- if the patient has symptoms and signs suggestive of serious illness and/or complications (particularly pneumonia, mastoiditis, peritonsillar abscess, peritonsillar cellulitis, intraorbital and intracranial complications)
- if the patient is at high risk of serious complications because of pre-existing comorbidity. This includes patients with significant heart, lung, renal, liver or neuromuscular disease, immunosuppression, cystic fibrosis, and young children who were born prematurely
- if the patient is older than 65 years with acute cough and two or more of the following criteria, or older than 80 years with acute cough and one or more of the following criteria:
  - hospitalisation in previous year
  - type 1 or type 2 diabetes
  - history of congestive heart failure

- current use of oral glucocorticoids.

For these patients, the no antibiotic prescribing strategy and the delayed antibiotic prescribing strategy should not be considered.

1.2 Care pathway for respiratory tract infections



1.3 Overview

1.3.1 Prescribing of antibiotics for self-limiting respiratory tract infections in adults and children in primary care

Respiratory tract infection (RTI) is defined as any infectious disease of the upper or lower respiratory tract. Upper respiratory tract infections (URTIs) include the common cold, laryngitis, pharyngitis/tonsillitis, acute rhinitis, acute rhinosinusitis and acute otitis media. Lower respiratory tract infections (LRTIs) include acute bronchitis, bronchiolitis, pneumonia and tracheitis. Antibiotics are commonly prescribed for RTIs in adults and children in primary care. General practice consultation rates in England and Wales show that a quarter of the population will visit their GP because of an RTI each year (Ashworth et al. 2005). RTIs are the reason for 60% of all antibiotic prescribing in general practice, and this constitutes a significant cost to the NHS. Annual prescribing costs for acute cough alone exceed £15 million (Lindbaek 2006).

There is evidence from randomised placebo-controlled trials (RCTs) that antibiotics have limited efficacy in treating a large proportion of RTIs in adults and children (see section 2). These include acute otitis media (AOM), acute cough/acute bronchitis, acute sore throat/acute pharyngitis/acute tonsillitis, acute rhinosinusitis and the common cold. These conditions are largely self-limiting and complications are likely to be rare if antibiotics are withheld. Therefore, these five common RTIs are the focus of this guideline. The inappropriate prescribing of antibiotics has the potential to cause drug-related adverse events, escalate the prevalence of antibiotic-resistant organisms in the community and increase primary care consultation rates for minor illness (Standing Medical Advisory Committee 1998).

Three different antibiotic management strategies can be used for patients with RTIs who present in primary care and other first face-to-face contact healthcare settings (such as emergency departments and walk-in centres): no antibiotic prescribing; delayed (or deferred) antibiotic prescribing (in which an antibiotic prescription is written for use at a later date should symptoms worsen); and immediate antibiotic prescribing. The decision agreed between healthcare professional and patient depends on both the healthcare

professional's assessment of the risk of complications if antibiotics are withheld and the patient's expectations regarding an antibiotic prescription (Britten N et al. 2008; Butler et al. 1998). Perceived advantages of delayed prescribing as a strategy over no prescribing are that it offers a 'safety net' for the small proportion of patients who develop a complication, and that a patient expecting antibiotics may be more likely to agree with this course of action rather than with no prescribing. Delayed prescribing has therefore been advocated as an important management strategy to reduce inappropriate antibiotic prescribing (Little 2005).

Prescribing patterns for antibiotics for RTIs vary widely among general practices. Although delayed prescribing and no prescribing strategies have been advocated since the late 1990s (Little 2005), it is unclear to what extent they have been taken up in primary care in England and Wales.

There is currently no national clinical guideline in the UK relating to antibiotic prescribing in primary care for RTIs that are likely to be self-limiting. There is therefore a need for guidance for primary care and other first-contact healthcare professionals (GPs, nurse practitioners, pharmacists and those working in emergency departments) on:

- which RTIs do not require immediate antibiotic treatment
- which antibiotic management strategies could be offered once a decision has been made that the patient does not need immediate antibiotic treatment
- the clinical and cost effectiveness of delayed prescribing or no prescribing as management strategies during the consultation to ensure the appropriate use of antibiotics for RTIs.

This short clinical guideline aims to improve the care of adults and children (3 months or older) for whom immediate antibiotic prescribing is not clinically indicated by making evidence-based recommendations on antibiotic prescribing strategies. However, this guideline does not cover details of antibiotic regimens for the above five RTIs. Healthcare professionals should refer to the British National Formulary for choice of antibiotic and its dosage.

1.3.2 The NICE short clinical guideline programme

'Prescribing of antibiotics for self-limiting respiratory tract infections in adults and children in primary care' (NICE clinical guideline 69) is a NICE short clinical guideline.

For a full explanation of the process, see www.nice.org.uk/guidelinesmanual.

1.3.3 Using this guideline

This document is intended to be relevant to primary care and community settings where face-to-face contact takes place between patients and healthcare professionals. These settings include general practices, community pharmacies, NHS walk-in centres, NHS out-of-hours services and primary medical and nursing care provided in emergency departments. The target population is adults and children (3 months and older) for whom immediate antibiotic prescribing is not indicated.

This is the full version of the guideline. It is available from www.nice.org.uk/CG069. Printed summary versions of this guideline are available: 'Understanding NICE guidance' (a version for patients and carers) and a quick reference guide (for healthcare professionals). These are also available from www.nice.org.uk/CG069.

1.3.4 Using recommendations and supporting evidence

The GDG reviewed the evidence and for each clinical question the GDG was presented with a summary of the clinical evidence and, where appropriate, economic evidence derived from the studies reviewed and appraised. From this information the GDG was able to derive the guideline recommendations. The link between the evidence and the view of the GDG in making each recommendation is made explicit in the accompanying evidence to recommendations sections.

2 Evidence review and recommendations

2.1 Overview of the efficacy of antibiotics for RTIs in primary care

2.1.1 Introduction

This short clinical guideline seeks to optimise the use of antibiotic prescribing for RTIs in adults and children presenting in primary care settings. The conditions included in the review are those common RTIs presenting in primary care where antibiotic prescribing is often considered for resolving symptoms and preventing complications. The five RTIs covered in this short clinical guideline are: acute otitis media (AOM), acute sore throat/acute pharyngitis/acute tonsillitis, the common cold, acute rhinosinusitis and acute cough/acute bronchitis. These are the five most common RTIs consulted for in UK general practice[2].

The aim of this overview section is to summarise the evidence on antibiotic efficacy for the above five RTIs. It provides the rationale for the conduct of this short clinical guideline, which is to ascertain the clinical effectiveness and cost effectiveness of specific antibiotic management strategies for RTIs (see section 2).

The overview draws on recently published systematic reviews (the Cochrane Library) and other relevant studies. The identified evidence is summarised and presented narratively.

This overview is to demonstrate the efficacy of antibiotics in treating RTIs (acute otitis media [AOM], acute sore throat/acute pharyngitis/acute tonsilitis, the common cold, acute rhinosinusitis and acute cough/acute bronchitis) in adults and children presenting in primary care settings. The term ‘acute rhinosinusitis’ is used instead of ‘acute sinusitis’ for consistency throughout

[2] Since studies and practitioners use slightly different terms for RTIs, the terminology used in this guideline for RTIs provides covers a range of acute symptoms and also a suspected diagnosis if appropriate. For example:

- Acute otitis media (AOM) is a diagnosis made from the symptoms and by examining the eardrum. Two common symptoms of AOM are otalgia (acute earache) and otorrhoea.
- Acute cough/acute bronchitis – acute cough is the main symptom of acute bronchitis.
- Diagnoses of acute sore throat include viral/bacterial pharyngitis and tonsillitis.
- Acute rhinosinusitis is also referred to as acute sinusitis in some medical literature.

this guideline because acute rhinosinusitis is the terminology that is currently internationally accepted. However, in some medical literature, studies still refer to the condition as acute sinusitis.

2.1.2 Overview

Acute otitis media (AOM)

One Cochrane systematic review on the efficacy of antibiotics for AOM was identified (Glasziou et al. 2004). This Cochrane review included 8 randomised controlled trials (RCTs) involving 2287 children (6 months to 15 years) of either gender without tympanostomy tubes, suffering from AOM, irrespective of the setting from which they were recruited. The type of intervention in the studies was any antibiotic therapy versus placebo. The studies were set in primary care (general practice) (4) and hospital (1) (randomised by hospital pharmacy). The settings of the other 3 studies were unknown.

This Cochrane review carried out meta-analyses using pooled relative risk (RR) on patient-relevant outcomes (symptoms or problems that are important to patients' sense of wellbeing) and other key outcomes. The two key patient-relevant outcomes of the reviews were duration and severity of pain and hearing problems (mid- to long-term) caused by fluid in the middle ear. The other two key outcomes were adverse events (vomiting, diarrhoea, rash) and progression of symptoms (complication – contralateral otitis media).

Outcome 1: duration and severity of pain

In the meta-analyses, duration and severity of pain was not significantly reduced by antibiotics in the first 24 hours (RR = 1.02, 95% confidence interval [CI] 0.85 to 1.22, p = 0.91) (4 studies) but was significantly reduced by antibiotics on days 2 to 7 (pooled RR = 0.70, 95% CI 0.60 to 0.81, p < 0.00001, number needed to treat[3] [NNT] = 15, 95% CI 11 to 24) (8 studies).

Generalisability to primary care settings

Within the 4 studies that reported the duration and severity of pain in the first 24 hours, only 1 was from primary care setting. The study sample in this investigation was 229 children. The result of this individual study was

[3] For a more detailed definition of number need to treat (NNT), please refer to the glossary.

RR = 0.99, 95% CI 0.75 to 1.30, which was not significant. Within the 8 studies that had outcomes for days 2 to 7, only 3 studies were set in general practice. The total study sample of these 3 studies was 586 children. The results of these 3 individual primary care studies were RR = 0.89, 95% CI 0.41 to 1.93; RR = 0.71, 95% CI 0.43 to 1.18 and RR = 0.82, 95% CI 0.68 to 0.98, respectively; (2 of the 3 studies showed nonsignificant results).

Outcome 2: hearing problems

For the outcome of hearing problems, no significant difference in the meta-analysis for tympanometry results was reported at 1 month (3 studies) or 3 months (2 studies) after the acute episode, suggesting no beneficial effect of antibiotics on hearing (1 month: pooled RR = 0.94, 95% CI 0.75 to 1.19, p = 0.6; 3 months: pooled RR = 0.80, 95% CI 0.55 to 1.16, p = 0.2).

Generalisability to primary care settings

Two studies from the analyses (at 1 month) were set in general practices with a total study sample of 323 children (RR = 0.74, 95% CI 0.49 to1.13 and RR = 1.05, 95% CI 0.74 to 1.48, respectively), and 1 study (out of 2) from the 3-month analysis was set in primary care, with a study sample of 221 children (RR = 0.65, 95% CI 0.40 to 1.07).

Outcome 3: adverse events

As well as patient-relevant outcomes, 4 studies in the Cochrane systematic review reported adverse events experienced by individual children (side effects of antibiotics such as nausea, diarrhoea and rash). When all 4 studies were combined, the results showed that children who took antibiotics were more at risk of having adverse events compared with the placebo group (pooled RR = 1.60, 95% CI 1.19 to 2.16, p = 0.002).

Generalisability to primary care settings

Out of these 4 studies, 2 were reported as primary care-based with a total study sample of 472 children. The RRs for the 2 individual studies were 1.52 (95% CI 1.09 to 2.13) and 1.75 (95% CI 0.90 to 3.42).

Outcome 4: progression of symptoms

In terms of progression of symptoms, the meta-analysis showed no beneficial effect of antibiotics in reducing contralateral otitis (3 studies) (pooled RR = 0.48, 95% CI 0.17 to 1.33, p = 0.2).

Generalisability to primary care settings

Only 1 study was from a primary care setting (RR = 0.91, 95% CI 0.60 to 1.38). In just over 2000 children studied in this Cochrane review, only one case of mastoiditis was recorded, suggesting that mastoiditis is a rare complication of AOM.

Individual patient data meta-analysis (IPDM)

Apart from the Cochrane systematic review (Glasziou et al. 2004), another meta-analysis with individual patient data on antibiotics for AOM (Rovers et al. 2006) was also identified for inclusion in this overview. Unlike the Cochrane review (Glasziou et al. 2004), which had a wide age range (6 months to 15 years), this IPDM identified subgroups of children who would and would not benefit more than others from treatment with antibiotics. A total of 6 randomised trials were included and individual patient data from 1643 children aged between 6 months and 12 years were validated and re-analysed. The primary outcome of the study was a protracted episode of AOM (consisting of pain, fever or both at 3 to 7 days).

The results showed that, relative to placebo, the overall RR for symptoms at 3 to 7 days with antibiotics was 0.83 (95% CI 0.78 to 0.89; NNT = 8). When pain and fever were analysed separately, results for both outcomes showed a modest effect of antibiotics in reducing pain at 3 to 7 days (RR = 0.86, 95% CI 0.81 to 0.91, NNT = 10) and reducing fever at 3 to 7 days (RR = 0.95, 95% CI 0.92 to 0.98, NNT = 20).

Further analyses for the primary outcome (pain, fever or both at 3 to 7 days) also showed that the effect of antibiotics was modified by age and bilateral AOM, and by otorrhoea. In children younger than 2 years with bilateral AOM, 30% of the antibiotics group and 55% of the control group still had pain, fever or both at 3 to 7 days, with RR = 0.64 (95% CI 0.62 to 0.80; NNT = 4). In contrast, in children aged 2 years or older, there was no significant difference between the two groups in pain, fever or both at 3 to 7 days (RR = 0.80, 95%

CI 0.70 to 1.02). Pain, fever or both were still reported at 3 to 7 days in 24% of children with otorrhoea in the antibiotics group and 60% of children with otorrhoea in the control group, with RR = 0.52 (95% CI 0.37 to 0.73; NNT = 3). The risk difference, which was 36%, was much greater than the risk difference for children without otorrhoea in the two groups (14%). This suggests that children with otorrhoea seemed to benefit more from treatment with antibiotics irrespective of other characteristics.

The summary findings of the Cochrane review and the IPDM are as follows. Antibiotics for AOM are effective only in reducing duration of pain in children aged between 6 months and 15 years. The NNT in order to prevent one child from having some pain after 2 days was 15, and children who took antibiotics were more at risk of having adverse events. However, despite possible adverse reactions, antibiotics seem to be beneficial in children younger than 2 years with bilateral AOM (NNT = 4), and in children with both AOM and otorrhoea (NNT = 3). However, the pain on day 3 for those children who still have pain is mild and most parents used suboptimal doses of analgesics (Little et al. 2001). Hence, it is debatable whether it is worthwhile to treat children with antibiotics, particularly when analgesic use to relieve pain has not been optimised.

Acute cough/acute bronchitis

One Cochrane systematic review on the efficacy of antibiotics for acute bronchitis was identified (Fahey et al. 2004). The authors of this review included 9 RCTs involving 750 children and adults (aged 8 years and over) with acute bronchitis or acute productive cough without underlying pulmonary disease. Both smokers and non-smokers were included in the primary analysis and the duration of illness at entry was less than 30 days. The type of intervention in the studies was any antibiotic therapy versus placebo. The review excluded trials with patients diagnosed with pre-existing chronic bronchitis (that is, acute exacerbation of chronic bronchitis). The 9 studies were set in primary care (general practice) (5), a hospital ambulatory screening clinic (1) and hospital outpatient units (3).

This Cochrane review carried out meta-analyses using the pooled RR of having a cough, improvement on clinician's global assessment, having an

abnormal lung examination, duration of cough, duration of feeling ill and adverse events.

Outcome 1: patients with cough

Overall, this Cochrane review showed that patients receiving antibiotics had better outcome for cough than the patients receiving placebo. Results from the meta-analyses showed that patients receiving antibiotics were less likely to have a cough 7 to 14 days after the initiation of treatment (4 studies) (pooled RR = 0.64, 95% CI 0.49 to 0.85, p = 0.002).

Generalisability to primary care settings

All 4 studies documenting a cough 7 to 14 days after initiating treatment were from primary care settings. The NNT in order to prevent one patient having a cough was 5, with 95% CI 3 to 14.

Outcome 2: improvement on clinician's global assessment

Results from the meta-analysis showed that patients receiving antibiotics were less likely to show no improvement on clinician's global assessment (6 studies) (pooled RR = 0.52, 95% CI 0.31 to 0.87, p not provided) but the NNT was relatively high (NNT = 14, 95% CI 8 to 50).

Generalisability to primary care settings

Of the 6 studies, 4 were from primary care settings, with a total sample of 473. The 4 studies individually showed no differences between antibiotics and placebo (RR = 0.46, 95% CI 0.18 to 1.16; RR = 0.42, 95% CI 0.11 to 1.57; RR = 0.52, 95% CI 0.25 to 1.09; RR = 1.73, 95% CI 0.16 to 18.20, respectively).

Outcome 3: abnormal lung examination

For the outcome abnormal lung examination, the meta-analysis showed that patients receiving antibiotics were less likely to have an abnormal lung examination (5 studies) (pooled RR = 0.54, 95% CI 0.41 to 0.70, p < 0.00001; NNT = 11, 95% CI 6 to 50) compared with the placebo group.

Generalisability to primary care settings

Of the 5 studies, 4 were from primary care settings, with a total sample of 270. The pooled results of the meta-analysis of the 5 studies were heavily skewed by 1 large trial from a hospital setting that constituted 77.8% of the weight of

the meta-analysis. When the 4 studies from primary care were examined separately, none showed any differences between antibiotics and placebo.

Outcome 4: durations of cough, productive cough and feeling ill

Further meta-analyses showed that patients receiving antibiotics had shorter durations of cough (5 studies) (weighted mean difference = -0.58 days, 95% CI -1.16 to -0.01 days), shorter productive cough (5 studies) (weighted mean difference = -0.52 days, 95% CI -1.03 to -0.01 days), and shorter duration of feeling ill (4 studies) (weighted mean difference = -0.58 days, 95% CI -1.16 to 0.00 days).

Generalisability to primary care settings

In total, 4 out of 5 studies on duration of cough and 4 out of 5 studies on duration of productive cough were from primary care settings, whereas all 4 studies on duration of feeling ill were from primary care settings. Although the results showed statistically significant reductions in illness durations, in practice the actual size of the reductions was small: all less than 1 day in duration.

Outcome 5: adverse events

The differences in adverse events (that is, adverse effects from antibiotics) (9 studies) were not statistically significant between the antibiotic group and the control group, with pooled RR = 1.22, 95% CI 0.94 to 1.58, p = 0.1.

Generalisability to primary care settings

Out of the 9 studies, 7 were from primary care settings with a total sample of 643 patients. None of the 7 studies showed any differences between the antibiotic group and the control group.

The summary findings of the Cochrane review are as follows. Patients receiving antibiotics are less likely to have a cough, with an NNT of 5. However, the NNTs for improvement on clinician's global assessment and the likelihood of having an abnormal lung examination were considerably higher (14 and 11, respectively). Moreover, when those studies from primary care settings were examined individually, none showed significant effects of antibiotics in improving clinician's global assessment and in reducing the likelihood of having an abnormal lung examination. Although there were

significant effects of antibiotics on the durations of cough and productive cough, and on feeling ill, these were small – a fraction of 1 day in an illness lasting several weeks.

Acute sore throat/acute pharyngitis/acute tonsillitis

One Cochrane systematic review on the efficacy of antibiotics for sore throat was identified (Del Mar et al. 2006). The authors of this Cochrane review included 27 RCTs involving 2835 cases of sore throat (in adults and children). Of these RCTs, 17 did not distinguish between bacterial and viral aetiology (that is, the patients were only clinically judged by practitioners/researchers to have suspected group A beta-haemolytic *Streptococcus* pharyngitis (GABHS); no diagnostic investigations were carried out). However, 8 studies included only GABHS-positive patients, while 2 studies excluded patients who were GABHS-positive. The type of intervention in the studies was any antibiotic therapy versus placebo. The settings of the 27 studies were: US air force bases (8), general practices (10), paediatric clinics (4), hospitals (2) and not reported (3). Of the 10 studies set in primary care, 2 studies used a GABHS-positive result as an inclusion/exclusion criterion: 1 study excluded patients with a GABHS-negative throat swab and 1 study included only patients with a GABHS-negative throat swab. The remaining 8 studies set in primary care did not use GABHS as a strict inclusion or exclusion criterion; instead, patients were included if they were clinically judged by physicians to have simple sore throat/pharyngitis or if they had three or more Centor criteria. (Centor criteria have been developed to predict bacterial infection – presence of: tonsillar exudate, fever and cervical lymphadenopathy, and an absence of cough.) Some studies carried out throat swabs at follow-up visits to confirm the aetiology of sore throat.

The review carried out meta-analysis using pooled RR on two groups of outcome measures – incidence of complications (suppurative and non-suppurative), and symptoms of sore throat.

Outcome 1: acute rheumatic fever

For non-suppurative complications, the findings from the meta-analysis (16 studies) showed that antibiotics reduced the incidence of acute rheumatic fever within 2 months (pooled RR = 0.29, 95% CI 0.18 to 0.44, $p < 0.00001$).

Generalisability to primary care settings

When the meta-analysis was further analysed, only 7 out of the 16 studies had recorded the incidence of rheumatic fever and these 7 studies were carried out between 1954 and 1961, when rheumatic fever was much more common than in later years. Moreover, only 6 out of the 16 studies were from primary care settings, with a total study sample of 2267 adults and children. None of the studies reported any cases of rheumatic fever.

Outcome 2: acute glomerulonephritis

Another non-suppurative complication in the meta-analysis was acute glomerulonephritis within 1 month (10 studies). The results showed antibiotic treatment did not reduce the incidence of acute glomerulonephritis (pooled RR = 0.22, 95% CI 0.02 to 2.02, p = 0.2). Again, only 2 studies out of the 10 recorded the incidence of acute glomerulonephritis (both studies were carried out before 1960).

Generalisability to primary care settings

Of the 8 studies that did not identify cases of acute glomerulonephritis, 4 were from primary care settings, with a total study sample of 2186 adults and children.

The incidence rates of rheumatic fever and acute glomerulonephritis have continued to decline in Western society. A recent retrospective cohort study using data from the UK General Practice Research Database between 1991 and 2001 (during which time there were 3.36 million episodes of RTI) (Petersen et al. 2007) claimed that it was difficult to examine rheumatic fever and acute glomerulonephritis as potential complications of sore throat because of the very small number of cases of these complications occurring after sore throat. Thus, any reported relative risk reduction in the efficacy trials must be viewed in the context of an extremely small absolute risk of developing both of these conditions in primary care settings after an episode of sore throat.

Outcome 3: AOM, quinsy and acute rhinosinusitis

For suppurative complications, the findings showed that antibiotics reduced the incidence of AOM within 14 days (11 studies) (pooled RR = 0.28, 95% CI 0.15 to 0.52, p = 0.00005) and quinsy within 2 months (8 studies) (pooled

RR = 0.14, 95% CI 0.05 to 0.39, p < 0.0002), but antibiotics did not reduce the incidence of acute rhinosinusitis (the study used the term acute sinusitis) within 14 days (8 studies) (pooled RR = 0.53, 95% CI 0.18 to 1.55, p = 0.2).

Generalisability to primary care settings

In the analysis of AOM, only 4 out of 11 studies were from primary care settings, with a total study sample of 1612 adults and children. Of the 1612 patients, only one case of AOM was recorded (in a control group). In the analysis of quinsy, 6 out of the 8 studies were from primary care settings, with a total study sample of 1810 adults and children. Of the 1810 patients, nine cases of quinsy were recorded (eight cases in control groups and one case in a treatment group). However, further analysis from the systematic review showed that the NNT for AOM was nearly 200. In the study by Little et al. (2002), the median annual incidence of hospital admission of quinsy (interquartile range) within the residents of the health authority who had acute uncomplicated RTIs was low, at 1.66 per 10,000.

Outcome 4: symptoms of sore throat

Results from the meta-analysis showed that antibiotics reduced the symptom of throat soreness on day 3 (15 studies) (pooled RR = 0.72, 95% CI 0.68 to 0.76, p < 0.00001) and at 1 week (13 studies) (pooled RR = 0.65, 95% CI 0.55 to 0.76, p < 0.00001). Antibiotics also reduced the symptom of headache (3 studies) (pooled RR = 0.47, 95% CI 0.38 to 0.58, p < 0.00001) and fever on day 3 (7 studies) (pooled RR = 0.69, 95% C: 0.53 to 0.88, p = 0.003). No cases of fever (3 studies) were recorded at 1 week.

Generalisability – subgroup analyses and primary care setting

When further subgroup analyses were performed in the meta-analysis (GABHS-positive compared with GABHS-negative compared with untested/inseparable), the findings showed a different picture. For instance, for the symptom of throat soreness on day 3, all three subgroups (GABHS-positive, GABHS-negative and untested/inseparable) showed beneficial effect of antibiotics over placebo (RR = 0.59, 95% CI 0.54 to 0.64, RR = 0.79, 95% CI 0.71 to 0.88, RR = 0.89, 95% CI 0.80 to 0.99, respectively). Of the 11 studies from the GABHS-positive subgroup, 4 were from primary care settings; of the 6 studies from the GABHS-negative

subgroup, 3 were from primary care settings; and all 3 studies from the untested/inseparable subgroup were from primary care settings.

However, for the symptom of throat soreness at 1 week, only the GABHS-positive subgroup showed a beneficial effect of antibiotics over placebo (RR = 0.28, 95% CI 0.17 to 0.44) but not the GABHS-negative subgroup and the untested/inseparable subgroup. Out of the 7 studies, 3 were from primary care settings.

Studies that used three or four of the Centor criteria for bacterial infection to determine eligibility (Dagnelie et al. 1996; Zwart et al. 2000) in the Cochrane review showed a little more benefit from antibiotics both for symptom resolution (of the order of 1 to 2 days at a time when symptoms are milder) and for the prevention of complications (NNT = 60). However, caution is required in generalising from these studies, which are from a setting where the level of antibiotic prescribing has traditionally been very low. A low level of antibiotic prescribing is likely to reduce consultation rates and result in a more severe illness spectrum among patients presenting in primary care.

Systematic review on acute pharyngitis in adults

As well as the Cochrane review (Del Mar et al. 2006), a systematic review on appropriate antibiotic use for acute pharyngitis in adults has been carried out (Cooper et al. 2001). In this review, the findings showed that treatment with antibiotics within 2 to 3 days of symptom onset hastened symptomatic improvement by 1 to 2 days in patients with three or more Centor Criteria (Centor et al. 1981) (where throat cultures of a significant proportion of these patients ultimately grew GABHS). However, antibiotics did not have this beneficial effect in patients with a negative GABHS culture. The Centor criteria include presence of tonsillar exudate, tender anterior cervical lymphadenopathy or lymphadenitis, history of fever and an absence of cough.

The summary findings of the Cochrane review are as follows. There is evidence from studies in selected populations carried out in the 1950s and 1960s that suggests a beneficial effect of antibiotics in reducing the incidence of rheumatic fever and acute glomerulonephritis following an episode of sore throat. However, observational studies show that these two complications are now extremely rare in modern Western society. Thus, the absolute risk of

developing these complications following sore throat is now extremely small. The evidence from the Cochrane review also suggests that antibiotics confer relative benefits in preventing AOM and peritonsillar abscess (quinsy) but the NNTs are high.

The evidence from the Cochrane review also suggests that antibiotics appear to have a modest beneficial effect in reducing the symptoms of throat soreness, fever and headache. However, nearly half of the study population in the review were GABHS-positive. Since current UK general practice does not use throat swabs or rapid diagnostic tests to detect the presence or absence of GABHS, primary care clinicians rely on symptoms and signs to decide on initial treatment with antibiotics. Studies in settings where antibiotic use is low and that use three or four of the Centor criteria for bacterial infection to determine eligibility do show some benefits from antibiotics both for symptom resolution (of the order of 1 to 2 days at a time when symptoms are milder) and for the prevention of complications. The symptomatic benefits from antibiotics within this subgroup of patients (with three or more Centor criteria) were also supported by results from the systematic review (Cooper et al. 2001).

Common cold

There is one Cochrane systematic review on the efficacy of antibiotics for the common cold and acute purulent rhinitis (Arroll and Kenealy 2005). This review included 13 RCTs involving 2467 adults and children (aged 2 months and older) who had been diagnosed with an upper respiratory tract infection with symptoms for 7 days or acute purulent rhinitis of less than 10 days' duration. The type of intervention in the studies was any antibiotic therapy versus placebo. The review excluded patients diagnosed with pharyngitis and bronchitis, conforming to the 1986 International Classification of Health Problems in Primary Care (ICHPPC) definition.

The settings of the 13 studies were: general practice (4), military bases (4), hospital outpatient units (2), unspecified research unit (factory and office workers) (1), accident and emergency department (1) and unknown (1).

The review carried out a meta-analysis using pooled RR on a number of outcome measures. The key outcomes were lack of cure or persistence of

symptoms of nasopharyngeal inflammation on days 1 to 7 (rhinitis, sore throat and sneezing), acute persisting purulent rhinitis and adverse events.

Outcome 1: lack of cure or persistence of symptoms

The results from the meta-analysis showed that there were no significant findings for lack of cure or persistence of symptoms of nasopharyngeal inflammation (6 studies) (pooled RR = 0.89, 95% CI 0.77 to 1.04, p = 0.1).

Generalisability to primary care settings

Of these 6 studies, only 1 was based in a primary care setting (with a study sample of 188 children aged between 2 and 10 years). The RR of persistence of symptoms in this study was 1.83 (95% CI 0.54 to 6.24), which was not statistically significant.

Outcome 2: acute persisting purulent rhinitis

The results from the meta-analysis (5 studies) also showed no significant benefit from antibiotics (pooled RR = 0.62, 95% CI 0.38 to 1.01, p = 0.06) for acute persisting purulent rhinitis.

Generalisability to primary care settings

Out of the 5 studies, 3 were from primary care settings, with a total study sample of 554 adults and children.

Outcome 3: adverse events

In addition to persistence of symptoms and acute persisting purulent rhinitis, 6 studies in the systematic review also reported adverse events experienced by individual patients. When all 6 studies were combined, the results showed that patients who took antibiotics were more at risk of having adverse events (adverse side effects from antibiotics) compared with the control group (pooled RR = 1.80, 95% CI 1.01 to 3.21, p = 0.05). However, there was also a high level of heterogeneity. When subgroup analyses were performed for adults and children, only adult patients who took antibiotics were more at risk of having adverse events compared with the control group (4 studies) (pooled RR = 2.62, 95% CI 1.32 to 5.18, p < 0.00001); no difference was found for children (2 studies) (pooled RR = 0.91, 95% CI 0.51 to 1.63, p = 0.8).

Generalisability to primary care settings

In the adult subgroup analysis, 2 out of the 4 studies were from primary care settings, with a total study sample of 946. In the children subgroup analysis, 1 of the 2 studies was from a primary care setting, with a study sample of only 188.

The summary findings of this Cochrane systematic review are that antibiotics are not effective in reducing persistence of common cold symptoms and adult patients may experience adverse events from antibiotic use.

Persistent nasal discharge

There is also 1 Cochrane systematic review[4] that addresses the efficacy of antibiotics for persistent nasal discharge (Morris and Leach 2002). This review included 6 RCTs involving 562 children (aged between 0 months and 18 years) with persistent nasal discharge for at least 10 days. For inclusion in the review, nasal discharge had to be the primary condition requiring medical intervention. Trials that only compared or combined antibiotics with surgery or sinus puncture and lavage were excluded. Trials that only compared two or more antibiotics without a non-antibiotic comparison group were also excluded from the systematic review. The type of intervention in the 6 studies was any antibiotic therapy versus placebo or standard therapy (standard therapy included decongestants or nasal saline drops). The settings of the 6 studies were: hospital paediatric allergy clinic (1), allergy referral clinic (1), general hospital (2), paediatric primary care practice (1) and hospital ear, nose and throat clinic (1). The paediatric primary care studies were from the United States.

This Cochrane review carried out meta-analyses using pooled RR for a number of outcome measures. The two key outcomes of the reviews were overall clinical failure (proportions of patients with nasal discharge at follow-up, or those with no substantial improvement if failure to cure rates were not available) and adverse events.

[4] This review was withdrawn from The Cochrane Library, Issue 3, 2007. The authors agreed that they could no longer work towards updating the review, owing to other work demands.

Outcome 1: overall clinical failure

Results from the meta-analysis of overall clinical failure (6 studies) showed that antibiotics are modestly effective in reducing the probability of symptom persistence in children with nasal discharge of more than 10 days' duration (pooled RR = 0.75, 95% CI 0.61 to 0.92, p = 0.005; NNT = 8, 95% CI 5 to 29).

Generalisability to primary care settings

Out of the 6 studies, only 1 was from a primary care setting, with a study sample of 161 children. The results of this study showed no benefit of antibiotics in reducing nasal discharge (RR = 0.91, 95% CI 0.48 to 1.07). The fact that this result is at variance with the pooled RR could be because the patients who attended hospital or allergy clinics were more ill or had more severe symptoms than patients seeking help in primary care practices.

Outcome 2: adverse events

In terms of adverse events, results from the meta-analyses (4 studies) also showed that there were no significant harmful side effects of antibiotics in the intervention group compared with the control group (pooled RR = 1.75, 95% CI 0.63 to 4.82, p = 0.3).

Generalisability to primary care settings

Of the studies that investigated adverse events, 1 out of 4 was from a primary care setting, with a study sample of 157 children. The Cochrane review also attempted to carry out subgroup analysis of very young children. However, only 1 small study was limited to children younger than 8 years and hence there was insufficient evidence to determine whether age has an impact on the effectiveness of antibiotics in children with persistent nasal discharge.

The summary findings of this Cochrane review are that, for children with persistent nasal discharge, the evidence suggests that antibiotics are effective in reducing the probability of persistence in the short to medium term only in children with nasal discharge of more than 10 days' duration. However, the benefits appear to be modest and around eight children must be treated in order to achieve one additional cure. No long-term benefits have been documented in the review. Since only 1 study out of the total of 6 was from a primary care setting, and this particular study showed no benefit of antibiotics,

the generalisability of the results from meta-analysis to a primary care population of children is uncertain.

Acute rhinosinusitis

The term ‘acute rhinosinusitis’ is used instead of ‘acute sinusitis’ for consistency throughout this guideline because acute rhinosinusitis is the terminology that is currently internationally accepted. However, in some medical literature, studies still refer to the condition as acute sinusitis. One Cochrane systematic review on the efficacy of antibiotics for acute rhinosinusitis (the study used the term acute maxillary sinusitis) was identified (Williams Jr et al. 2003). The review included 49 studies involving 13,660 patients. However, only 3 studies (out of 49) compared antibiotics with placebo (whereas the other studies compared one antibiotic with another). Hence, only these 3 studies are discussed in this overview. The 3 studies were RCTs and involved 416 adults (aged 18 years and older) with acute rhinosinusitis confirmed radiographically or by aspiration. An additional inclusion criterion was that trials must have a sample size of at least 30 participants with acute rhinosinusitis. The type of intervention in the meta-analysis was any antibiotic therapy versus placebo or a topical decongestant. The treatment duration ranged from 3 to 15 days and the settings of the 3 studies were: primary care (2), not reported (1).

Outcome 1: clinically cured or clinically cured/much improved

Results from the meta-analysis showed that patients treated with amoxicillin were more likely to be clinically cured (2 studies) (pooled RR = 1.49, 95% CI 1.18 to 1.88, p = 0.001) or more likely to be clinically cured/much improved (2 studies) (pooled RR = 1.20, 95% CI 1.05 to 1.37, p = 0.007). Similarly, the meta-analysis showed that patients treated with penicillin V were more likely to be clinically cured (2 studies) (pooled RR = 1.79, 95% CI 1.05 to 3.05, p = 0.03) or more likely to be clinically cured/much improved (2 studies) (pooled RR = 1.25, 95% CI 1.01 to 1.54, p = 0.04).

Generalisability to primary care settings

Both studies using amoxicillin were based in primary care settings, with a total study sample of 303 adult patients. However, only 1 of the 2 studies with penicillin was set in primary care, with a study sample of 85 adult patients.

Although there were significant results for both amoxicillin and penicillin treatment, they need to be interpreted very cautiously because neither X-ray nor aspiration are routinely performed or indicated in primary care settings. Thus, these results cannot be generalised to patients presenting with sinusitis-like complaints in primary care settings where the effect of antibiotics is likely to be less. The study sample in this review was also relatively small, involving only 375 adult patients.

In order to address the small sample and generalisability issues in the Cochrane review (Williams Jr et al. 2003), a current primary care-based IPDM (Young et al. 2008) of 2547 patients aged 12 years and older (from 9 RCTs) with clinical signs and symptoms of rhinosinusitis was also identified. In this IPDM, trials were excluded if patients were recruited partly on the basis of results of imaging or laboratory tests or bacterial culture because in a primary care setting such methods are not routinely used or recommended.

The results from this IPDM showed that 15 patients would have to be given antibiotics before an additional patient was cured (95% CI NNT [benefit] 7 to NNT [harm] 190). In this analysis of individual patients' data, the estimated OR of the overall treatment effect for antibiotics relative to placebo was 1.37 (95% CI 1.13 to 1.66). Further subgroup analyses also showed that patients with the symptom of purulent discharge in the pharynx had a longer duration of illness with an NNT of 8 (95% CI NNT [benefit] 4 to NNT [harm] 47). The multiplicative of individual baseline signs or symptoms on the odds of cure if a patient remained untreated and on the OR for cure if treated were also analysed. The analyses showed that patients who were older, reported symptoms for longer, or reported more severe symptoms also took longer to cure but were no more likely to benefit from antibiotics than other patients. [age: odds of cure if untreated = 0.88 (95% CI: 0.81-0.96), OR for cure if treated = 1.04 (95% CI: 0.92-1.18); duration of symptoms: odds of cure if untreated = 0.90 (95% CI: 0.81-0.99), OR for cure if treated = 0.95 (95% CI: 0.82-1.10); symptom severity: odds of cure if untreated = 0.93 (95% CI: 0.90-0.91), OR for cure if treated = 0.99 (95% CI: 0.93-1.05)]. This IPDM showed that antibiotics are not justified for adult patients with rhinosinusitis-like complaints even if the patient reports symptoms for longer than 7–10 days. Although purulent discharge in the pharynx had some prognostic value, eight

patients with this symptom still needed to be treated before one additional patient benefited.

The summary findings of this Cochrane review are that for acute rhinosinusitis (termed as acute maxillary sinusitis in William Jr et al. 2003) confirmed by radiography or aspiration, there is evidence that antibiotics make clinical cure more likely. However, these results cannot be generalised to patients in UK primary care settings where neither radiography nor aspiration is in use or recommended. This was supported by the IPDM (Young J et al. 2008), (which had inclusion criteria that reflected primary care settings), where the results showed that antibiotics are not justified for adult patients with rhinosinusitis-like complaints, even if the patient reports symptoms for longer than 7–10 days.

2.2 Antibiotic management strategies for RTIs

2.2.1 Introduction

The previous section summarised the evidence underpinning the rationale for developing this short clinical guideline. There is good evidence that antibiotics are of limited efficacy in treating a large proportion of RTIs seen in adults and children in primary care.

The use of a no antibiotic or a delayed antibiotic prescribing strategy to reduce the inappropriate prescribing of antibiotics for RTIs has been advocated since the late 1990s (Little 2005). A potential advantage of a delayed prescribing strategy is that it offers a rapid ‘safety net’ for the small proportion of patients who develop complications or whose symptoms worsen significantly. A patient expecting antibiotics may also be more likely to agree with this course of action rather than with a no prescribing strategy, and this could help to maintain the doctor-patient relationship.

There is therefore a need to determine whether the use of a no prescribing strategy or a delayed prescribing strategy is clinically and cost effective compared with the use of an immediate antibiotic prescribing strategy. It is also important to consider whether there are benefits from using a printed

information leaflet or structured verbal information to deliver the chosen antibiotic management strategy. A delayed antibiotic prescribing strategy may be delivered in primary care settings in a number of ways: patients may be issued with a prescription at the consultation but advised to use it only if symptoms persist or worsen, or they may be asked to re-attend to collect the prescription from the general practice (surgery) reception. It is important to determine which of these delivery methods is the most effective.

In order to make the recommendations as useful as possible for clinicians it has been necessary to include specific information on likely illness duration for each of the five reviewed conditions. Expected duration of illness is a factor in the decision about when to start a delayed prescription. It is outside the scope of this short clinical guideline to conduct a systematic review of illness duration. However, the evidence from the included clinical trials together with other relevant identified studies has been used to support the consensus recommendations made by the GDG in this area.

2.2.2 Overview

We identified 2 systematic reviews and 12 published studies on the effectiveness of delayed antibiotic prescribing and/or no prescribing as strategies for managing RTIs compared with an immediate antibiotic prescribing strategy. No meta-analyses were carried out in the 2 systematic reviews because of significant heterogeneity across studies. Heterogeneity included variations in the treatment and symptoms of different RTIs and in the methods and duration of delayed prescribing. Both of these reviews therefore provide a narrative systematic review. A Cochrane review (Spurling et al. 2007) included 9 RCTs and 1 review. (Arroll et al. 2003) included 4 RCTs and 1 before-and-after controlled trial. All 4 RCTs in the review by Arroll et al. (2003) were also included in the Cochrane review.

Apart from the 2 systematic reviews, 29 published individual studies were also identified based on study abstracts. Out of these 29 studies, only 12 were included in the evidence review. (12 studies were not relevant, 4 were excluded as they were non-RCT studies and 1 lacked generalisability because it was carried out in a developing country). Of the 12 RCTs included, 8 were the same 8 RCTs presented in the Cochrane systematic review; 1 extra study

that was not included in the Cochrane review was identified and a further 3 studies looked at the use of specific information leaflets or structured explanations in antibiotic management strategies for RTIs. All 12 included studies were appraised individually and presented in the evidence tables and GRADE (Grading or Recommendations Assessment, Development and Evaluation) profiles. For the methodology of GRADE, see section 4.2.7.

Of the 12 included RCTs, 3 were on AOM (1 from UK general practice, 1 from a USA paediatric emergency department and 1 from a USA university paediatric clinic); 2 were on cough (both from UK general practice); 3 were on sore throat (1 from UK general practice and 2 from USA private paediatric practice) and 1 was on common cold (from New Zealand general practice). No studies were identified on acute rhinosinusitis. Out of these 9 studies, 4 were open pragmatic RCTs. Open pragmatic trials lack internal validity but seek to maximise external validity to ensure that the results reflect everyday practice more closely and are more generalisable (Fransen et al. 2007; Godwin et al. 2003). Open pragmatic trials are appropriate for answering questions on effectiveness and for assessing outcomes in situations where perceptions and behaviour in everyday practice and patients' knowledge of treatment are important factors. The remaining 3 RCTs (out of 12) were on the use of specific information leaflets or structured explanations in antibiotic management strategies for RTIs (2 from UK general practice and 1 from a primary care clinic in Israel).

The natural history or usual course of illness duration of the five RTIs was also identified from various sources. The average duration of AOM is about 4 days (Little et al. 2001); the average duration of acute cough/acute bronchitis is about 3 weeks (Little et al. 2005); the symptoms accompanying acute sore throat/acute pharyngitis/acute tonsillitis last on average for 1 week (Little et al. 1997); the average duration of symptoms of the common cold is around 1.5 weeks (Heikkinen and Jarvinen 2003); and the average duration of acute rhinosinusitis is around 2.5 weeks (Williamson et al. 2007).

Overall, the quality of the evidence was good and the studies provided the evidence statements that form the basis of the guideline recommendations. There were particular challenges in summarising and presenting the evidence

on the effectiveness of delayed antibiotic prescribing and/or no prescribing as strategies for managing self-limiting RTIs. This was because of significant variations in factors such as patient populations, methods of delaying antibiotic prescription, duration of delays in antibiotic prescribing and outcome measures. The use of the GRADE approach to summarising the evidence was found to be helpful in addressing these challenges. For full GRADE evidence profiles see appendix 4.

2.2.3 The clinical effectiveness and cost effectiveness of antibiotic management strategies for RTIs

Recommendation number 1.1.1

At the first face-to-face contact in primary care, including walk-in centres and emergency departments, adults and children (3 months and older) presenting with a history suggestive of the following conditions should be offered a clinical assessment:

- acute otitis media
- acute sore throat/acute pharyngitis/acute tonsillitis
- common cold
- acute rhinosinusitis
- acute cough/acute bronchitis.

The clinical assessment should include a history (presenting symptoms, use of over-the-counter or self medication, previous medical history, relevant risk factors, relevant comorbidities) and, if indicated, an examination to identify relevant clinical signs.

Recommendation number 1.1.2

Patients' or parents'/carers' concerns and expectations should be determined and addressed when agreeing the use of the three antibiotic prescribing strategies (no prescribing, delayed prescribing and immediate prescribing).

Recommendation number 1.1.3

A no antibiotic prescribing strategy or a delayed antibiotic prescribing strategy should be agreed for patients with the following conditions:

- acute otitis media
- acute sore throat/acute pharyngitis/acute tonsillitis
- common cold
- acute rhinosinusitis
- acute cough/acute bronchitis.

Depending on clinical assessment of severity, patients in the following subgroups can also be considered for an immediate antibiotic prescribing strategy (in addition to a no antibiotic or a delayed antibiotic prescribing strategy):

- bilateral acute otitis media in children younger than 2 years
- acute otitis media in children with otorrhoea
- acute sore throat/acute pharyngitis/acute tonsillitis when three or more Centor criteria[5] are present.

[5] Centor criteria are: presence of tonsillar exudate, tender anterior cervical lymphadenopathy or lymphadenitis, history of fever and an absence of cough.

Recommendation number 1.1.4

For all antibiotic prescribing strategies, patients should be given:

- advice about the usual natural history of the illness, including the average total length of the illness (before and after seeing the doctor):
- acute otitis media: 4 days
- acute sore throat/acute pharyngitis/acute tonsillitis: 1 week
- common cold: 1½ weeks
- acute rhinosinusitis: 2½ weeks
- acute cough/acute bronchitis: 3 weeks.
- advice about managing symptoms, including fever (particularly analgesics and antipyretics). For information about fever in children younger than 5 years, refer to 'Feverish illness in children' (NICE clinical guideline 47).

Recommendation number 1.1.5

When the no antibiotic prescribing strategy is adopted, patients should be offered:

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

Recommendation number 1.1.6

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

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

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

Evidence review

Acute otitis media (AOM)

Three studies were included in the review of AOM (Little et al. 2001; McCormick et al. 2005; Spiro et al. 2006). The patient population for the Spiro study was children diagnosed with AOM (aged between 6 months and 12 years) and the patient population for the study by Little was children aged between 6 months and 10 years presenting with AOM. The patient population for the study by McCormick was children aged between 6 months and 12 years with AOM (screened using an AOM severity screening index).

The 3 studies had different settings: Spiro's study was carried out in a paediatric emergency department in the United States, McCormick's study was carried out at the University of Texas Medical Branch paediatric clinic and the Little study was conducted in 42 general practices in southwest England.

The studies differed in terms of inclusion criteria. In Spiro's study, children were included if they were clinically diagnosed with AOM in an emergency department; in Little's study, children with acute earache (otalgia) and otoscopic evidence of acute inflammation of the eardrum (dullness or

cloudiness with erythema, bulging or perforation) were included. However, if children were too young for earache to be documented, then otoscopic evidence alone was a sufficient entry criterion. In McCormick's study children were included if they had symptoms of ear infection, otoscopic evidence of AOM including middle ear effusion, and non-severe AOM.

Table 1 Mode of delivery of antibiotic management strategies

Study	Spiro et al. (2006)	Little et al. (2001)	McCormick el al. (2005)
Antibiotic prescribing strategy	Delayed	Delayed	Delayed
Duration of delay	2 days	3 days	2 days
Methods of delay	Prescription was given to parents during the consultation with the healthcare professional.	Parents were asked to come back to collect the prescription (prescription left at the reception).	Prescription was given to parents during the consultation with the healthcare professional.
Verbal advice	No	Parents were also advised to use the prescription if their child had a discharge for 10 days or more. GPs were supported by standardised advice sheets. Advice on antibiotics given: that antibiotics do not work very well and have disadvantages such as adverse events and development of antibiotic resistance.	Parents of children received an educational intervention on definition of ear infection, causes of ear infection, characteristics of non-severe and severe AOM, antibiotic resistance, costs of antibiotics, rate of symptom response to antibiotics, possible adverse outcomes associated with immediate antibiotics versus delayed including the risk of mastoiditis.
Use of information leaflet	No	No	No
Use of analgesics	All patients received ibuprofen (100 mg/5 ml) and otic analgesic drops (4 drops every 2 hours if needed).	Advice on full doses of paracetamol for relief of pain and fever. Ibuprofen as well if child already taking full doses of paracetamol and is aged over 1 year.	Symptom medication provided (ibuprofen).

Study	Spiro et al. (2006)	Little et al. (2001)	McCormick el al (2005)
	Immediate	Immediate	Immediate
Duration of delay	N/A	N/A	N/A
Methods of delay	N/A	N/A	N/A
Verbal advice	No	GPs were supported by standardised advice sheets. Advice on benefit of antibiotics in helping symptoms to settle and prevent complications; importance of taking the full course.	Parents of children received an educational intervention on definition of ear infection, causes of ear infection, characteristics of non-severe and severe AOM, antibiotic resistance, costs of antibiotics, rate of symptom response to antibiotics, possible adverse events associated with immediate antibiotic versus delayed antibiotic prescribing, including the risk of mastoiditis.
Use of information leaflet	No	No	No
Use of analgesics	All patients received ibuprofen (100 mg/5 ml) and otic analgesic drops (4 drops every 2 hours if needed; each ml contains 54 mg antipyrene, and 14 mg benzocaine).	Advice on full doses of paracetamol for relief of pain and fever. Ibuprofen as well if child already taking full doses of paracetamol is aged over 1 year.	Symptom medication provided (ibuprofen).

Table 2 GRADE profile – outcomes

The effectiveness of delayed antibiotic prescribing as a strategy for managing acute otitis media

Summary of findings

Outcome	No. of studies (total patients)	Design	Intervention[b]	Control[c]	Relative risk	Quality
Use of antibiotics after consultation [S, L & M]	3 (758)	RCT	Delayed 120/382 (31%)	Immediate 357/376 (94%)	0.33 (0.29, 0.39)	High
Otalgia[g] [S & L]	2 (550)	RCT	Delayed 130/282 (46%)	Immediate 108/268 (40%)	1.18 (0.99, 1.40)	High
Daily pain score (1 to 10) – daily diary (severity) (over 1 week) [L]	1 (285)	RCT	Delayed 150	Immediate 135	Mean difference = -0.16 (-0.42, 0.11) t = 1.18, p = 0.24	High
Night disturbances – daily diary (over 1 week) [L]	1 (285)	RCT	Delayed 150	Immediate 135	Mean difference = -0.72 (-0.30, -1.13) t = 3.41, p < 0.01	High
Diarrhoea [S&L]	2 (550)	RCT	Delayed 24/282 (9%)	Immediate 56/268 (21%)	0.41 (0.26, 0.65)	High
Belief antibiotics are effective [L]	1 (271)	RCT	Delayed 64/140 (46%)	Immediate 100/131 (76%)	0.59 (0.48, 0.73)	High

Very satisfied with treatment approach (parents/carers) [L]	1 (284)	RCT	Delayed 115/150 (77%)	Immediate 123/134 (91%)	0.84 (0.75, 0.93)	High
Parents'/carers' satisfaction[i] [M]	1 (209)	RCT	Delayed 100	Immediate 109	Total satisfaction scores: On day-12: I = 44.0, C = 44.4 On day-30: I = 44.6, C = 44.6 (not significant; p value not reported)	Moderate

[b] intervention = delayed antibiotics

[c] control = immediate antibiotics

[g] presence of earache/otalgia: [S] data collected at follow-up (4 to 6 days); [L] data collected through daily diary (at 1 week).

[i] total satisfaction scores (4-point-scale). Data on [L] and [M] were not pooled owing to different methods of measurements.

S = Spiro et al. (2006)

L = Little et al. (2001)

M = McCormick et al. (2005)

Evidence statements

Three large trials provide good evidence supporting the effectiveness of delayed antibiotic prescribing as a strategy for managing suspected AOM.

- *In children with AOM a delayed prescribing strategy reduced the consumption of antibiotics by 63% compared with an immediate prescribing strategy.*
- *One large, good quality trial found that there was no significant difference between an immediate and a delayed antibiotic prescribing strategy in reducing the 'severity' of earache in children. The pooled results from 2 other trials suggest that an immediate prescribing strategy has moderate benefit in reducing the number of children with earache compared with a delayed prescribing strategy. However, the benefit of antibiotics might be confounded by the use of analgesics in 1 trial and both analgesics and otic analgesic drops in another trial.*

- *Children with suspected AOM are 12% less likely to develop diarrhoea when a delayed prescribing strategy is used, compared with an immediate prescribing strategy (NNT = 8).*
- *An immediate prescribing strategy reduces night disturbances in children with suspected AOM compared with a delayed prescribing strategy.*
- *Two trials provide evidence on patient (parents/carers) satisfaction. Overall, parents/carers of children in 1 trial (in which they were asked to come back to collect the delayed prescription) were satisfied with both strategies (77% with delayed; 91% with immediate). In another trial (in which a delayed prescription was given during consultation) the results suggested that parents/carers of children with AOM were equally satisfied with both delayed and immediate prescribing strategies.*
- *Parents/carers of children offered an immediate prescribing strategy were 30% more likely to believe that antibiotics are effective compared with parents/carers of children offered a delayed prescribing strategy.*

Evidence to recommendations

The GDG acknowledged that the 3 included studies were of reasonably good quality but that the study population was limited to children. Based on the evidence statements presented above, the GDG came to the conclusion that, compared with a delayed prescribing strategy, an immediate prescribing strategy provided modest benefits in reducing earache and night disturbances but increased the consumption of antibiotics and potentially might medicalise a self-limiting illness. However, the GDG also considered that the benefits of an immediate antibiotic prescription were very limited because by day 3, the pain of those children who still had earache was mild and it is debatable whether these limited benefits would outweigh the likelihood of having diarrhoea if immediate antibiotics were used. The GDG also discussed the outcome of parents'/carers' satisfaction and noted that the overall satisfaction rates were high for both strategies. However, the GDG considered that the high satisfaction rate for an immediate prescribing strategy compared with that for a delayed prescribing strategy in 1 trial (Spiro et al. 2006) could be a result of the method of delivery (in which parents were given the delayed prescription during the consultation instead of being asked to come back to collect it at the surgery reception). The GDG agreed that this conclusion is

tentative and remains a point for speculation, and that further research needs to be carried out on the mode of delivery of delayed prescribing strategies in order to clarify advice about practice. Overall, by weighing both the modest benefits and the risk of diarrhoea, the GDG thought that a delayed or no prescribing strategy should be offered to children with AOM who are not at risk of developing complications. However, owing to the lack of trials among important subgroups comparing an immediate and/or delayed prescribing strategy with a no prescribing strategy, the GDG thought that a consensus recommendation on the likely symptomatic benefits of antibiotics for particular subgroups of patients should be made. The GDG agreed that, based on the meta-analysis with individual patient data (Rovers et al. 2006) presented in section 2.1.2, an immediate prescribing strategy may be considered for two subgroups of patients depending on clinical assessment of severity and patient preference. The two subgroups are: children younger than 2 years with bilateral acute otitis media, and children with acute otitis media and otorrhoea.

Acute cough/acute bronchitis

Two studies were included in the review of acute cough/acute bronchitis: Dowell et al. (2001)and Little et al. (2005). The population in Dowell's study consisted of patients aged over 16 years presenting with acute cough as the primary complaint. The patient population in Little's study consisted of children aged 3 years and older with uncomplicated acute LRTI (duration 21 days or less). Both studies were set in UK primary care (general practice): Dowell's study was set in 22 general practices with 48 GPs in Scotland; Little's study involved 37 GPs in southwest England.

The inclusion criteria differed in the studies. In Dowell's study patients with acute cough with or without coryza, shortness of breath, sputum, fever, sore throat or chest tightness were included. In Little's study patients with cough (with a duration of 21 days or less) as the main symptom and with at least one symptom or sign localising to the lower respiratory tract (sputum, chest pain, dyspnoea, wheeze) were included.

Table 3 The mode of delivery of antibiotic prescribing management strategies

Study	Dowell et al. (2006)	Little et al. (2005)	Little et al. (2005)
Antibiotic prescribing strategy	Delayed	Delayed	No
Duration of delay	1 week	2 weeks	N/A
Methods of delay	Patients were asked to come back to collect the prescription for antibiotic (prescription left at the surgery reception).	Patients were asked to come back to collect the prescription for antibiotic (prescription left at the surgery reception).	
Verbal advice	No	All patients, irrespective of whether they had the leaflet, were given brief verbal information about the likely course of the illness and supporting the proposed prescribing strategy.	All patients, irrespective of whether they had the leaflet, were given brief verbal information about the likely course of the illness and supporting the proposed prescribing strategy.
Use of information leaflet	Information (patient information sheet) was given at consultation during recruitment. Content not reported.	50% of patients received information leaflet, 50% did not. Leaflet included information about natural history, addressed patients' major worries and provided advice about when to seek further help (for example, if persistent fever, worsening shortness of breath).	50% of patients received info leaflet, 50% did not. Leaflet included information about natural history, addressed patients' major worries and provided advice about when to seek further help (for example, persistent fever, worsening shortness of breath).
Use of analgesics	No	Advice to take an analgesic	Advice to take an analgesic

Study	Dowell et al. (2006)	Little et al. (2005)	
Antibiotic prescribing strategy	Immediate	Immediate	
Duration of delay	N/A	N/A	
Methods of delay	N/A	N/A	
Verbal advice	No	All patients, irrespective of whether they had the leaflet, were given brief verbal information about the likely range of natural history of the illness and supporting the proposed prescribing strategy.	
Use of information leaflet	Information (patient information sheet) was given at consultation during recruitment. Content not reported.	50% of patients received information leaflet, 50% did not. Leaflet included information about natural history, addressed patients' major worries and provided advice about when to seek further help (for example, persistent fever, worsening shortness of breath).	
Use of analgesics	No	Advice to take an analgesic	

Table 4 GRADE profile – outcomes

The effectiveness of delayed antibiotic prescribing and/or no prescribing as strategies for managing acute cough/acute bronchitis

Summary of findings

Outcome	No. of studies (total patients)	Design	Intervention[b]	Control[c]	Relative risk	Quality
Collection of antibiotic prescription[a] [D]	1 (187)	RCT	Delayed 43/95 (45%)	Immediate 92/92 (100%)	0.45 (0.36, 0.56)	High
Use of antibiotics [L]	1 (390)	RCT	Delayed 39/197 (20%)	Immediate 185/193 (96%)	0.20 (0.15, 0.27)	High
Use of antibiotics [L]	1 (375)	RCT	No AB 29/182 (16%)	Immediate 185/193 (96%)	0.16 (0.11, 0.23)	High
Use of antibiotics [L]	1 (379)	RCT	No AB 29/182 (16%)	Delayed 39/197 (20%)	0.80 (0.52, 1.24)	High
Outcome	No. of studies (total patients)	Design	Intervention[b]	Control[c]	Mean difference	Quality
Symptom duration[e] (cough) [D]	1 (148)	RCT	Delayed unknown	Immediate unknown	Log-rank [Mantel-Haenszel] test (result not reported), with p value > 0.4	Moderate
Symptom duration[g] (cough) [L]	1 (426)	RCT	Delayed 214	No antibiotic 212	Mean difference = 0.75 (-0.37, 1.88) p = 0.19	High
Symptom duration[g] (cough) [L]	1 (426)	RCT	Immediate 214	No antibiotic 212	Mean difference = 0.11 (-1.01, 1.24) p = 0.19	High
Symptom duration[g] (cough) [L]	1 (428)	RCT	Immediate 214	Delayed 214	Mean difference = -0.46 (-1.76, 0.48) p = 0.265	High
Outcome	No. of studies (total patients)	Design	Intervention[b]	Control[c]	Mean difference	Quality
Adjusted severity of symptoms[h][L]	1 (426)	RCT	Delayed 214	No antibiotic 212	Adjusted mean difference = -0.02 p = 0.86	High
Adjusted	1	RCT	Immediate	No	Adjusted mean	High

severity of symptoms[h][L]	(426)		214	antibiotic 212	difference = -0.07 p = 0.49	
Outcome	No. of studies (total patients)	Design	Intervention[b]	Control[c]	Odds ratio	Quality
Diarrhoea [L]	1 (426)	RCT	Delayed	No antibiotic	0.17 (0.67, 2.03)	High
Diarrhoea [L]	1 (426)	RCT	Immediate	No antibiotic	1.22 (0.70, 2.12)	High
Outcome	No. of studies (total patients)	Design	Intervention[b]	Control[c]	Relative risk	Quality
Re-attendance within 1 month [L]	1 (389)	RCT	Delayed 24/199 (12%)	No antibiotic 41/190 (22%)	0.55 (0.35, 0.88)	High
Re-attendance within 1 month [L]	1 (386)	RCT	Immediate 26/196 (13%)	No antibiotic 41/190 (22%)	0.61 (0.39, 0.96)	High
Re-attendance within 1 month [L]	1 (395)	RCT	Delayed 24/199 (12%)	Immediate 26/196 (13%)	0.90 (0.54, 1.52)	High
Outcome	No. of studies (total patients)	Design	Intervention[b]	Control[c]	Relative risk	Quality
Belief antibiotics are effective [L]	1 (306)	RCT	Delayed 57/141 (40%)	Immediate 123/165 (75%)	0.54 (0.43, 0.67)	High
Belief antibiotics are effective [L]	1 (296)	RCT	No AB 61/131 (47%)	Immediate 123/165 (75%)	0.62 (0.50, 0.76)	High
Belief antibiotics are effective [L]	1 (272)	RCT	No AB 61/131 (47%)	Delayed 57/141 (40%)	1.15 (0.87, 1.51)	High
Outcome	No. of studies (total patients)	Design	Intervention[b]	Control[c]	Relative risk	Quality
Patient satisfaction[i][D]	1 (148)	RCT	Delayed 40/73 (54%)	Immediate 55/75 (73%)	0.74 (0.58, 0.95)	High
Patient satisfaction[k][L]	1 (384)	RCT	Delayed 147/190	Immediate 166/194	0.90 (0.82, 0.99)	High

			(77%)	(86%)		
Patient satisfaction[k] [L]	1 (375)	RCT	No antibiotic 130/181 (72%)	Immediate 166/194 (86%)	0.83 (0.75, 0.93)	High
Patient satisfaction[k] [L]	1 (371)	RCT	No antibiotic 130/181 (72%)	Delayed 147/190 (77%)	0.92 (0.82, 1.04)	High

[a] rates of consumption unknown

[b] intervention = delayed antibiotics

[c] control = immediate antibiotics

[e] probability of recovery from cough over days 1 to 13

[g] duration of cough – days (until very little problem)

[h] on a point scale 0 to 6 on six symptoms (adjusted on baseline variables): cough, dyspnoea, sputum production, wellbeing, sleep disturbance, activity disturbance

[l] 'very satisfied' with the consultation

[k] 'very satisfied' with overall management.

L = Little et al. (2005)

D = Dowell et al. (2001)

Evidence statements

One large and one smaller trial provide good evidence on the effectiveness of delayed antibiotic prescribing and/or no prescribing as strategies for managing acute cough.

- *There are no significant differences in reducing symptom duration (cough) and the severity of symptoms among the three antibiotic management strategies (no prescribing, delayed prescribing and immediate prescribing) in adults and children.*
- *Compared with an immediate prescribing strategy, both delayed and no prescribing strategies significantly reduce the consumption of antibiotics for acute cough in adults and children (by 76% and 80%, respectively). There is no significant difference in antibiotic consumption between a delayed prescribing strategy and a no prescribing strategy.*
- *Patients offered immediate antibiotics and a delayed prescribing strategy do not develop diarrhoea significantly more often compared with patients offered a no antibiotic prescribing strategy.*
- *Overall, adult patients and parents/carers of children with acute cough are satisfied with all three strategies (immediate, delayed and no prescribing) (86%, 77% and 72% satisfied, respectively). When compared with an immediate prescribing strategy, adult patients and parents/carers of*

children offered a delayed or a no prescribing strategy are significantly less satisfied (9% and 14% less satisfied). However, there is no significant difference in satisfaction between a no prescribing strategy and a delayed prescribing strategy.

- *Adult patients and parents/carers of children offered a delayed or a no prescribing strategy are less likely to believe that antibiotics are effective compared with those offered an immediate prescribing strategy (35% and 28% less likely to believe, respectively). However, there is no significant difference in belief between those offered a delayed or a no prescribing strategy.*
- *There are fewer re-attendances within 1 month with acute cough among patients offered a delayed prescribing strategy or an immediate prescribing strategy compared with a no prescribing strategy. There are no significant differences in re-attendance between delayed and immediate prescribing strategies.*

Evidence to recommendations

The GDG acknowledged that the 2 included studies were both of good quality. Based on the evidence statements presented above, the GDG concluded that delayed and no antibiotic prescribing strategies significantly reduced the consumption of antibiotics and lessened beliefs that antibiotics were effective in patients with acute cough. There were no significant differences in managing symptom duration/severity compared with an immediate prescribing strategy. The GDG also considered that the evidence statement on patient satisfaction showed that overall, patients with cough are satisfied with all three management strategies (all with satisfaction rates above 70%). The GDG thought that the differences in satisfaction rates between delayed/no prescribing and immediate prescribing could be confounded by the methods of delivery (such as ways of collecting delayed prescriptions, verbal advice provided or the amount of information provided on symptomatic treatment) rather than reflecting differences in the antibiotic management strategies per se. However, the GDG recognised that currently there are no specific studies that address the issue of the best way to deliver a delayed prescribing strategy. In conclusion, the GDG considered that a delayed or no prescribing

strategy should be offered to patients with acute cough who are not at an increased risk of developing complications.

Acute sore throat/acute pharyngitis/acute tonsillitis

Three studies were included in the review of acute sore throat (suspected pharyngitis or tonsillitis): Gerber et al. (1990), Little et al. (1997) and; Pichichero et al. (1987). The 3 included studies had different patient populations. The study population in Little consisted of patients aged 4 years and older with sore throat and an abnormal physical sign in the throat (84% had tonsillitis or pharyngitis). In contrast, the other 2 studies included only patients who were culture positive for GABHS pharyngitis: in the Pichichero study patients were aged between 4 and 18 years, and in the Gerber study patients were aged between 2 and 22 years.

In terms of study setting, only 1 (Little) was based in UK primary care (general practice – 25 GPs). The other 2 studies were based in a single paediatric clinic in the USA There are also differences in study design among the 3 studies: in the delayed arm of 1 study, (Little et al. 1997), patients were asked to return after 3 days to collect the prescription, which had been left at the surgery reception. In the delayed arms of the other 2 studies, placebo tablets were used as a method of delay for the first 48 hours and followed by a 10-day course of antibiotics.

The inclusion criteria in Little's study were sore throat, either as principal or subsidiary symptom, and an abnormal physical sign localising to the throat (inflamed tonsils or pharynx, purulent exudate, faucial or palatal inflammation or cervical adenopathy). For children younger than 12 years, who were less likely to complain of sore throat, abnormal signs in the throat were sufficient.

The inclusion criteria for the children in the study by Pichichero were three of the following signs or symptoms compatible with the diagnosis of GABHS pharyngitis:

- sore throat associated with difficulty in swallowing
- exudate on tonsils or a beefy red throat
- cervical lymph node tenderness
- history of fever of 100.6°F or higher rectally or 99.6°F or higher orally

- systemic toxicity characterised by insomnia, malaise, lethargy and other symptoms
- a Breese score of 32 or above.

The inclusion criteria in the study by Gerber were a positive Q test *Streptococcus* result and a positive throat culture.

Table 5 Mode of delivery of antibiotic management strategies

Study	Little et al. (1997)	Pichichero et al. (1987)	Gerber et al. (1990)	Little et al. (1997)
Antibiotic prescribing strategy	Delayed	Delayed	Delayed	No
Duration of delay	3 days	2 days	2 days	N/A
Methods of delay	Patients were asked to return to collect the prescription for antibiotic (prescription left at the surgery).	Use of placebo tablets	Use of placebo tablets	N/A
Verbal advice	The advice package given to patients (in each group) had six or seven standard statements supporting the particular strategy.	No	No	The advice package given to patients (in each group) had six or seven standard statements supporting the particular strategy.
Use of information leaflet	No	No	No	No
Use of analgesics	Advice to take analgesics or antipyretics.	Encouraged to take aspirin or acetaminophen (paracetamol) ad libitum every 4 hours as needed to control fever and discomfort.	No	Advice to take analgesics or antipyretics.
	Little (97)	Pichichero (87)	Gerber (90)	
	Immediate	Immediate	Immediate	
Duration of delay	N/A	N/A	N/A	
Methods of delay	N/A	N/A	N/A	
Verbal advice	The advice package given to patients (in each group) had six or seven standard statements supporting the particular strategy	No	No	
Use of information leaflet	No	No	No	

Use of analgesics	Advice to take analgesics or antipyretics.	Encouraged to take aspirin or acetaminophen ad libitum every 4 hours as needed to control fever and discomfort.	No	

Table 6 GRADE profile – outcomes

The effectiveness of delayed antibiotic prescribing and/or no prescribing as strategies for managing acute sore throat/acute pharyngitis/acute tonsillitis

Summary of findings

Outcome	No. of studies (total patients)	Design	Intervention	Control	Relative risk	Quality
Use of antibiotics [L]	1 (385)	RCT	No 23/174 (13%)	Immediate 210/211 (99%)	0.13 (0.09, 0.19)	High
Use of antibiotics [L]	1 (387)	RCT	Delayed 55/176 (31%)	Immediate 210/211 (99%)	0.31 (0.25, 0.39)	High
Use of antibiotics [L]	1 (350)	RCT	No 23/174 (13%)	Delayed 55/176 (31%)	0.42 (0.27, 0.65)	High
Outcome	No. of studies (total patients)	Design	Kruskal-Wallis, X2			Quality
Resolution of symptoms by 3 days[a] [L]	1 (561)	RCT	No = 35%; immediate = 37%; delayed = 30% X2 = 2.50, p = 0.28			High
Outcome	No. of studies (total patients)	Design	Student t-test Kruskal-Wallis, X2			Quality
Sore throat[c] (severity) [P]	1 (114)	RCT	Mean score, student t-test Delayed = 1.6, Immediate = 1.3, p = 0.006			Moderate
Sore throat[d] (duration) [L]	1 (561)	RCT	Median (IQR), Kruskal-Wallis, X2 Delayed = 5(3-7), No AB = 5(3-7), Immediate = 4(3-6) X2 = 1.9, p = 0.39			High
Outcome	No. of studies (total patients)	Design	Intervention[b]	Control[c]	Relative risk	Quality
Diarrhoea [L]	1 (394)	RCT	Delayed 23/179 (13%)	Immediate 23/215 (11%)	1.02 (0.69, 2.06)	High
Diarrhoea [L]	1 (401)	RCT	No 16/186 (9%)	Immediate 23/215 (11%)	0.80 (0.43, 1.47)	High
Diarrhoea [L]	1 (365)	RCT	No 16/186 (9%)	Delayed 23/179 (13%)	0.66 (0.36, 1.22)	High
Outcome	No. of studies	Design	Intervention[b]	Control[c]	Relative risk	Quality

	(total patients)					
Re-consultation with sore throat (within 1 month) [L]	1 (484)	RCT	Delayed 12/238 (5%)	Immediate 22/246 (9%)	0.56 (0.28, 1.11)	High
Re-consultation with sore throat (within 1 month) [L]	1 (478)	RCT	No 22/232 (9%)	Immediate 22/246 (9%)	1.06 (0.60, 1.86)	High
Re-consultation wit sore throat (within 1 month) [L]	1 (470)	RCT	No 22/232 (9%)	Delayed 12/238 (5%)	1.88 (0.95, 3.71)	High
Outcome	No. of studies (total patients)	Design	Intervention[b]	Control[c]	Relative risk	Quality
Re-consultation with sore throat (within 12 months) [L]	1 (317)	RCT	Delayed 50/169 (30%)	Immediate 90/148 (61%)	0.48 (0.37, 0.63)	High
Re-consultation with sore throat with(in 12 months) [L]	1 (297)	RCT	No 70/149 (47%)	Immediate 90/148 (61%)	0.77 (0.62, 0.95)	High
Re-consultation with sore throat (within 12 months) [L]	1 (318)	RCT	No 70/149 (47%)	Delayed 50/169 (30%)	1.58 (1.19, 2.11)	High
Outcome	No. of studies (total patients)	Design	Intervention[b]	Control[c]	Relative risk	Quality
Belief antibiotics are effective [L]	1 (372)	RCT	Delayed 99/165 (60%)	Immediate 181/207 (87%)	0.68 (0.59, 0.78)	High
Belief antibiotics are effective [L]	1 (380)	RCT	No 95/173 (55%)	Immediate 181/207 (87%)	0.62 (0.54, 0.72)	High
Belief AB are effective [L]	1 (338)	RCT	No 95/173 (55%)	Delayed 99/165 (60%)	0.91 (0.76, 1.09)	High
Outcome	No. of studies (total patients)	Design	Intervention[b]	Control[c]	Relative risk	Quality
Patient satisfaction[k] [L]	1 (388)	RCT	Delayed 165/177 (93%)	Immediate 202/211 (96%)	0.97 (0.92, 1.02)	High
Patient	1	RCT	No	Immediate	0.94	High

satisfaction[k] [L]	(395)		166/184 (90%)	202/211 (96%)	(0.89, 0.99)	
Patient satisfaction[k] [L]	1 (361)	RCT	No 166/184 (90%)	Delayed 165/177 (93%)	0.96 (0.90, 1.02)	High

[a] symptoms included sore throat, cough, headache, feeling unwell and fever
[c] the presence and severity of symptom from checklist scale 1 to 3 (day 3).
[d] median (interquartile range) duration of symptom (days) after 3 days
[c, d] data were not pooled owing to different methods of measurements
[k] satisfaction with consultation (scoring 'very' or 'moderate')
L = Little et al. (1997)
P = Pichichero et al. (1987)
G = Gerber et al. (1990)

Evidence statements

Two large trials and one small trial provide mixed qualities of evidence on the effectiveness of delayed antibiotic prescribing and/or no prescribing as strategies for managing acute sore throat. The evidence suggests the following.

- *Both a no prescribing strategy and a delayed prescribing strategy reduce the consumption of antibiotics for sore throat in adults and children compared with an immediate prescribing strategy (by 13% and 31%, respectively). In addition, a no prescribing strategy further reduces the consumption of antibiotics by 18% compared with a delayed prescribing strategy.*
- *There are no differences regarding resolution of symptoms by 3 days between the three antibiotic management strategies for sore throat in adults and children.*
- *A large, high quality trial suggests that there are no differences in reducing the duration of sore throat between the three antibiotic management strategies in adults and children.*
- *One small trial gives moderate quality evidence that an immediate prescribing strategy is moderately beneficial in reducing the severity of symptoms of sore throat compared with a delayed prescribing strategy among children with more severe (GABHS-confirmed) pharyngitis.*

- *The evidence suggests that there are no significant differences in the incidence of diarrhoea between the three antibiotic management strategies for adults and children when using narrow-spectrum antibiotics.*
- *Most adult patients and parents/carers of children with sore throat are satisfied with the three antibiotic management strategies (with satisfaction rates above 90%).Adult patients and parents/carers of children offered a no prescribing strategy are slightly (6%) less satisfied than those offered an immediate prescribing strategy. However, there are no differences between a delayed and an immediate prescribing strategy or between a delayed and a no prescribing strategy in terms of patient satisfaction.*
- *Adult patients and parents/carers of children with sore throat are less likely to believe that antibiotics are effective if they are offered a delayed prescribing or a no prescribing strategy compared with those offered an immediate prescribing strategy (27% and 32% less likely, respectively). However, there is no difference between delayed and no prescribing strategies in terms of the belief that antibiotics are effective.*
- *One large trial with a high quality of evidence shows that there are no significant differences in re-consultation rates for sore throat within 1 month between the three antibiotic management strategies in adults and children. However, adults and children offered an immediate prescribing strategy are more likely to re-consult with sore throat within 1 year compared with those offered a delayed or no prescribing strategy (31% and 14% more likely, respectively), and adults and children offered a no prescribing strategy are 17% more likely to re-consult with sore throat within 1 year compared with those offered a delayed prescribing strategy.*

Evidence to recommendations

The GDG acknowledged that the 3 included studies were of mixed quality. Based on the evidence statements presented above, the GDG concluded that in patients with acute sore throat, a delayed and a no prescribing strategy significantly reduced the consumption of antibiotics and lessened beliefs that antibiotics were effective. The GDG also reviewed the effectiveness of different antibiotic prescribing strategies and concluded that delayed and no prescribing strategies showed no significant differences in managing symptom duration or resolution compared with an immediate prescribing strategy. The

GDG thought that the only study providing evidence of a modest beneficial effect of immediate antibiotics in reducing the severity of symptoms of acute sore throat related to a study population of patients with confirmed GABHS pharyngitis. The GDG thought that this could not be generalised to UK primary care settings because diagnostic tests to determine the cause of sore throat are not currently routinely used. Nevertheless, the GDG considered the results from the two-way sensitivity analysis undertaken as part of the economic evaluation (see section 4.2.9 and appendix 5). In that analysis both the baseline probability of developing quinsy and the efficacy of immediate antibiotic prescribing (as determined by the probability of symptoms resolving after 3 days) were varied simultaneously in the model. The GDG noted that the relative risk of developing complications remained constant (that is, at its baseline values) in the analysis. While the analysis indicated that there were situations in which immediate antibiotic prescribing could be considered cost effective, these situations depended on making arguably extreme assumptions. The GDG also considered that these results should be interpreted with caution for two main reasons. First, the lack of relevant utility estimates was an important limitation of the economic evaluation. Second, the absence of evidence on the rate of complications resulting from a strategy of delayed antibiotic prescribing made the interpretation of the results problematic. Consequently, the GDG thought that there could be exceptional scenarios in which immediate prescribing could be an option, in addition to strategies involving delayed or no antibiotic prescribing. In these situations, the choice of strategy should be based on a discussion between the healthcare professional and the patient/carer. Based on the two studies from the Cochrane review (Dagnelie et al. 1996), (Zwart et al. 2000) and the systematic review (Cooper et al. 2001) in section 2.1.2 that suggested symptomatic benefits of antibiotics for subgroups of patients with sore throat, the GDG considered that the Centor criteria could be a useful means of identifying individuals with acute sore throat who may benefit from immediate prescribing. At the same time the GDG acknowledged that this means of risk stratification was not explored in the economic model because of data limitations.

In conclusion, the GDG came to the consensus that a delayed or a no prescribing strategy should be offered to patients with acute sore throat who are not at an increased risk of developing complications. However, depending on patient preference and clinical assessment of severity, an immediate prescribing strategy may be considered for subgroups of patients with three or more Centor criteria in addition to the reasonable options of a no antibiotic strategy or a delayed prescribing strategy.

Health economics

Published health economics literature

A literature review was conducted to identify cost-effectiveness evidence on the five relevant RTIs (see section 2 for details).

A number of potentially useful studies were identified (Anzai et al. 2007; Balk et al. 2001; Coco 2007; Davey 1994; de Bock et al. 2001; Dippel et al. 1992; Hillner and Centor 1987; Koskinen et al. 2006; Neuner et al. 2003; Singh et al. 2006; Tsevat and Kotagal 1999; Van Howe and Kusnier 2006). Three studies examined the cost effectiveness of management strategies for sinusitis (Anzai et al. 2007; Balk et al. 2001; de Bock et al. 2001) and 2 studies examined strategies for managing otitis media (Coco 2007 and Koskinen et al. 2006). Hillner and Centor (1987), Neuner et al. (2003) and Singh et al. (2006) examined the cost effectiveness of the diagnosis and management of adults with pharyngitis. Dippel et al. (1992), Tsevat and Kotagal (1999) and Van Howe and Kusnier (2006) looked at the diagnosis and management of children with pharyngitis.

Only 1 study specifically examined delayed prescribing versus no prescribing in a full cost-utility analysis (Coco 2007). This study was quality assessed and data extracted into evidence tables (see appendix 6). The majority of studies examined strategies for the diagnosis of RTIs and did not follow up patients after a result was obtained. No UK-based studies examining delayed versus immediate or no antibiotic prescribing for RTIs were identified and no studies were identified that examined cold or acute cough/acute bronchitis.

Coco (2007) examined the cost effectiveness of treatment options for AOM. The objective of this USA-based study was to evaluate the costs and utility of four treatment options for children with AOM aged from 6 months to 12 years.

The setting was primary care offices. Four intervention strategies were included: watchful waiting, delayed prescription, 5 days of immediate amoxicillin, and 7 to 10 days of immediate amoxicillin. A decision analytic model was used to evaluate the incremental cost effectiveness of the four strategies by comparing short-term outcomes and cost utilities. The analysis adopted a societal perspective and included non-healthcare costs associated with parental work loss and transportation. The time horizon of the analysis was 30 days. The authors state that this reflects the lack of evidence on long-term outcomes for otitis media such as recurrent AOM and tympanic membrane rupture.

Effectiveness estimates for the clinical parameters, including non-attendance, clinical failure with attendance, clinical failure without attendance, probability of complications (mastoiditis), probability of experiencing gastrointestinal adverse effects owing to amoxicillin and probability of experiencing dermatologic adverse effects were taken from various sources.
Non-attendance rates were based on data from a cross-national study and a clinical trial. Clinical failure data were obtained from a RCT, a pragmatic RCT and a cross-national study. The probabilities of developing mastoiditis were based on national statistics and the probabilities of adverse events were derived from 4 studies, 3 of which were clinical trials. The design of the fourth study was unclear. The watchful waiting strategy considered current practice in the Netherlands and included estimates of the percentage of parents not seeking consultation and the probability of clinical failure based on studies conducted in the Netherlands.

Utility estimates were obtained from a cost-utility analysis of second-line antibiotics conducted in Canada by Oh et al. (1996). Utilities were derived from responses of physicians to a standardised scenario of AOM with combinations of adverse events measured on a visual analogue scale on which 1 represented perfect health and 0 represented death. Utilities from this paper represented 1 day of being in each particular health state. Lost quality-adjusted life days (QALDs) were presented separately for each pathway in the model by combining the utility weights in Oh et al. with the number of days spent in each health state. QALYs were also presented using the utilities presented by Oh et al.

Costs were estimated for antibiotics including amoxicillin, amoxicillin-clavulanate and ceftriaxone (for mastoiditis only). Resource use and costs were estimated for mastoiditis treatment and included hospitalisation, medication and outpatient costs. The cost of outpatient consultations was also included. Non-healthcare costs such as babysitting, day care, travel, parking and other expenses related to an episode of simple AOM were included.

The strategy with the highest benefit in terms of QALYs was 7–10 days of amoxicillin. This strategy had an incremental cost-utility ratio (ICUR) of $55,900 per QALY (£42,700[6]), compared with the least costly option, which was delayed prescribing. The watchful waiting strategy was extendedly dominated by the delayed antibiotic prescribing strategy and the 7–10-day antibiotic prescribing strategy. The 5–day amoxicillin strategy was dominated (more costly and less effective) by the 7–10-day antibiotic prescribing strategy. In one-way sensitivity analysis the 7–10-day antibiotic prescribing strategy was compared with the delayed antibiotic prescribing strategy; the costs that had the greatest effect on the ICUR were amoxicillin prescribing, non-healthcare items, office consultations and work loss. Other variables that had the greatest effect on the ICUR were probability of clinical failure, probability of gastrointestinal events, probability of non-attendance, probability of prescription redemption and the utility of a day of treatment failure. The authors reported that a probabilistic sensitivity analysis had been undertaken demonstrating that 7–10 days of amoxicillin was associated with a 61% probability of the ICUR being under $50,000 per QALY gained compared with a delayed antibiotic prescribing strategy. No cost-effectiveness acceptability curves were presented.

An important limitation of this study is that it did not consider the cost implications of antibiotic resistance. The authors concluded that delayed prescription is the least costly option. Adopting such a strategy, it was argued, would lead to substantial savings for payers and would promote a decrease in

[6] Converted for clarity from 2001 US dollars to 2006/7 pounds sterling using a purchasing power parity (PPP) exchange rate of 0.626 (www.oecd.org/std/ppp) then adjusted by inflation factor of 22% (www.pssru.ac.uk/pdf/uc/uc2006/uc2006.pdf).

the use of antibiotics for a common, primarily self-limiting RTI, potentially reducing the impact of antibiotic resistance.

In summary, there is a clear lack of evidence on the cost effectiveness of delayed antibiotic prescribing strategies compared with immediate and no antibiotic prescribing strategies for all of the RTIs examined. In particular, there is a complete lack of evidence for sore throat, cough, sinusitis and cold.

De novo economic evaluation

Given the scarcity of economic evaluations of delayed versus no antibiotic prescribing strategies for RTIs in primary care, it was considered appropriate to carry out a de novo economic analysis. A model was developed to estimate the cost effectiveness of a delayed antibiotic prescribing strategy compared with immediate or no antibiotic prescribing strategies for the management of one of the RTIs covered in the guideline, acute sore throat. The decision to use sore throat as the basis of the economic analysis reflects the fact that sore throat has a high prevalence and that there is sufficient clinical evidence available.

The economic evaluation consisted of a decision-tree analysis incorporating a care pathway for the management of patients with sore throat. This was based on an open randomised trial by Little et al. (1997). This trial investigated three prescribing strategies for sore throat. Patients aged 4 years and older (no upper age limit was specified) were randomised to three groups: prescription for antibiotics, no prescription and prescription for antibiotics if symptoms were not starting to settle after 3 days. The decision tree was built and analysed using TreeAge Pro 2007 Suite (TreeAge Software, Inc) and adopts a 1-year time horizon. The study was conducted within a UK primary care setting (general practice) and so provides direct evidence on which to base the economic model. As differences in utility are likely to be very small owing to the acute nature of sore throat, the base-case analysis assumes that all antibiotic strategies were of equal effectiveness in terms of utility, and is therefore presented as a cost minimisation analysis. Full details of the modelling are presented in appendix 5.

The model suggests that the least costly option is to adopt a delayed antibiotic strategy. This strategy is associated with an expected cost of £14 per patient

compared with £16 and £45.50 for the no antibiotic and immediate antibiotic prescribing strategies, respectively. The difference was mostly attributable to the reduced costs of prescribing antibiotics in the delayed strategy and the effectiveness of antibiotics at lowering the rate of complications. The probability of complications was assumed to be the same in the delayed and the immediate antibiotic prescribing strategies. In the base case, some patients in the no antibiotics arm received immediate antibiotics, as reflected in the trial outcomes on which the model was based. This was examined in the sensitivity analysis.

When utilities are considered in the model, incremental benefits realised between the strategies are small. The evidence on utilities for sore throat is poor and therefore the base-case analysis did not consider the impact of health-related quality of life. One sensitivity analysis applied the utilities used by Neuner et al. (2003) for pharyngitis. The results showed that there were no QALY differences above 0.0001 and therefore the results were not clinically significant. The ICER for an immediate antibiotic prescribing strategy over a delayed prescribing strategy was £3,628,772 per QALY gained. The delayed antibiotic strategy dominated the no antibiotic strategy (was less costly and more effective) in the base case.

In sensitivity analysis, the results are most sensitive to the baseline risk of developing quinsy. A one-way sensitivity analysis was carried out to assess the impact on model results of varying the underlying baseline risk of complications. This analysis shows that patients' baseline risk of quinsy must be approximately 6 times higher before immediate antibiotics can be considered cost effective. A two-way analysis combining the underlying baseline risk of complications and the probability of symptoms resolving following a prescription of antibiotics shows that when symptom resolution at 3 days following antibiotic prescription is between 30% and 60%, the baseline probability for developing quinsy has to be greater than 0.12 (12%) for immediate antibiotic prescribing to become the optimal strategy (requires a sixfold increase in baseline risk of complications).

A separate analysis was carried out to look at the potential difference in cost effectiveness of each of the strategies in adult and child populations, as the

probability of developing complications and the resulting cost implications are likely to differ between these groups.

Evidence to recommendations

The GDG considered that the presented cost-effectiveness analyses demonstrated that it was cost effective to offer a delayed prescribing strategy for adults and children presenting with acute sore throat. It was also noted that a no prescribing strategy is an acceptable alternative if the patient's/carer's preference is to have no antibiotics prescribed. The GDG considered that an immediate prescribing strategy may be considered cost effective for patients with a high baseline risk of quinsy.

Common cold

Only 1 study was included in the review of the common cold (Arroll et al. 2002). The patient population was patients of any age presenting with the common cold who requested antibiotics or whose physicians thought they wanted them. The study was based in primary care: 15 family physicians (general practitioners) in a family practice in New Zealand.

The inclusion criterion for this particular study was diagnosis of the common cold (URTI) based on the ICHPPC-2 (International Classification of Health Problems in Primary Care): the presence of acute inflammation of the nasal or pharyngeal mucosa in the absence of other specifically defined respiratory infection.

Table 7 Mode of delivery of antibiotic management strategies

Study	Arroll et al. (2002)	Arroll et al. (2002)
Antibiotic prescribing strategy	Delayed	Immediate
Duration of delay	3 days	N/A
Methods of delay	Prescription was given at consultation.	N/A
Verbal advice	Patients were advised to return to see their doctor if symptoms worsened.	No
Use of information leaflet	No	No
Use of analgesics	No	No

Table 8 GRADE profile – outcomes

The effectiveness of delayed antibiotic prescribing and/or no prescribing as strategies for managing common cold

Summary of findings

Outcome	No. of studies (total patients)	Design	Intervention[b]	Control [c]	Relative risk	Quality
Use of antibiotics	1 (123)	RCT	Delayed 27/62 (43%)	Immediate 54/61 (89%)	0.49 (0.36, 0.66)	Moderate
Temperature (°C) (day 3)	1 (129)	RCT	Mean score (°C): delayed = 36.7, immediate = 36.9 (analysis of comparison not provided)			Moderate
Symptom scores[e] (day 3)	1 (129)	RCT	Mean score: delayed = 5.4, immediate = 5.1 (analysis of comparison not provided)			Moderate
Belief antibiotics are effective	1 (129)	RCT	Delayed 51/67 (76%)	Immediate 47/62 (76%)	1.00 (0.82, 1.21)	Moderate
Patient satisfaction[f] (day 3)	1 (129)	RCT	Delayed 64/67 (96%)	Immediate 58/62 (94%)	1.02 (0.93, 1.10)	Moderate

[b] intervention = delayed antibiotics
[c] control = immediate antibiotics
[e] 1 point scored for each of 15 symptoms (dry cough, night cough, sneezing, sore throat, pain on inspiration, pain when coughing, hoarse voice, headache, staying home from work or unable to do normal daily tasks, unwell, diarrhoea, vomiting, nausea without vomiting, runny nose, blocked nose
[f] patient satisfaction with the consultation measured on 'very or moderately satisfied'

Evidence statements

The evidence suggests that a delayed prescribing strategy reduces the consumption of antibiotics by 46% compared with an immediate prescribing strategy for adults and children with the common cold.

The evidence suggests that there are no clinically significant differences in temperature and incidence of common cold symptoms between adults and children offered a delayed prescribing strategy and adults and children offered an immediate prescribing strategy.

There are no differences in patient satisfaction and belief in antibiotics being effective between a delayed prescribing strategy and an immediate prescribing strategy for adults and parents/carers of children with the common cold.

Evidence to recommendations

The GDG acknowledged that the evidence was only of moderate quality. Based on the evidence statements presented above, the GDG concluded that antibiotics have no beneficial effect on the common cold and that the common cold is a self-limiting condition. Therefore, an immediate prescribing strategy should not be offered to patients with no increased risk of developing complications.

Acute rhinosinusitis

No studies addressing the clinical effectiveness of the three different antibiotic management strategies were identified for acute rhinosinusitis.

Evidence to recommendations

The GDG considered that although there was no evidence on the effectiveness of antibiotic management strategies for acute rhinosinusitis[7], there is limited evidence for the efficacy of antibiotics for acute rhinosinusitis (termed acute maxillary sinusitis in the study) from a systematic review of randomised placebo-controlled trials. (Williams Jr et al. 2003). However, based on the individual patient data meta-analysis on rhinosinusitis (Young et al. 2008) (see section 2.1.2), the GDG reached a consensus opinion that this condition should be treated in the same way as the other four types of RTI included in this guideline, that is, a delayed or a no antibiotic prescribing strategy should be offered to patients with acute rhinosinusitis who are not at increased risk of developing complications.

Information leaflet or structured verbal explanation

Four studies were also included in the review of the use of specific information leaflets or structured explanations when delivering the antibiotic management strategies. The leaflets included information on the likely course of a chesty cough, what is meant by a 'chesty cough', when the patient should use the

[7] Acute rhinosinusitis can also be referred as acute sinusitis in some medical literature.

prescription, what patients should look out for and four ways to relieve a chesty cough (plenty of fluids, analgesics, cough linctus or lozenges and steam or vapour). For AOM, the structured explanation was short and included the likely course of AOM, reassurance that in most cases children would recover regardless of antibiotic prescription, the information that late complications may occur regardless of whether antibiotics are administered, and that parents are advised in cases of high fever or severe pain to administer paracetamol prescribed according to the child's weight. The 5 studies were (Gerber et al. 1990; Little et al. 2005; Macfarlane et al. 2002; Macfarlane et al. 1997; Pshetizky et al. 2003)). The study by Little was on cough, Macfarlane's (2002) was on acute bronchitis, Pshetizky looked at AOM, and Marfarlane (1997) studied LRTI.

The patient population in the Little study was children 3 years and older with uncomplicated acute LRTI (21 days or below in duration) who presented in primary care. The patient population in Macfarlane's study was adults 16 years and older presenting with 'acute bronchitis' defined as a 'new, acute lower respiratory tract illness in a previously well adult' (including smokers). Pshetizky's study included children aged between 3 months and 4 years visiting family practice clinics and diagnosed with AOM; Macfarlane's (1997) study included previously well adults (16 years and older including smokers) presenting with an illness defined as an LRTI. Three studies (Little et al. 2005, Macfarlane et al. 2002 and Macfarlane et al. 1997) were based in primary care general practices in the UK. Pshetizky's study was based in two primary care clinics in Israel.

The inclusion criteria in the study on cough by Little were cough (21 days or less in duration) as the main symptom and at least one symptom or sign localising to the lower respiratory tract (sputum, chest pain, dyspnoea or wheeze). The inclusion criteria for Macfarlane's study (acute bronchitis) were age 16 years or older, previously well and not under supervision or management for an underlying disease (for example, no pre-existing asthma, COPD, heart disease or diabetes). Further requirements for inclusion were cough as the main symptom; at least one other lower respiratory tract symptom (sputum production, dyspnoea, wheeze, chest discomfort or pain)

and no alternative explanation (for example, not sinusitis, pharyngitis or a new presentation of asthma).

The inclusion criteria for Macfarlane's (1997) study on LRTI were previously well adults (not under supervision or treatment for an underlying disease) who consulted with an LRTI (defined as a new cough and at least one other lower respiratory tract symptom, including sputum production, dyspnoea, wheeze, or chest pain, for which there was no explanation). In the Pshetuzky study of AOM, the inclusion criteria were children aged between 3 months and 4 years diagnosed with AOM (for example, fever of 38°C or higher, purulent ear discharge and opacity or bulging of the eardrum).

Table 9 GRADE profile – outcomes

The use of specific information leaflet or structured explanation in antibiotic management strategies for respiratory tract infections

Summary of findings

Outcome	No. of studies (total patients)	Design	Intervention	Control	Relative risk	Quality
Use of antibiotics (next 2 weeks) [M2]	1 (205)	RCT	Delayed (leaflet) 49/104 (47%)	Delayed (no leaflet) 63/101 (62%)	0.76 (0.59, 0.97)	High
Use of antibiotics (next 2 weeks) [M2]	1 (150)	RCT	Delayed (leaflet) 49/104 (47%)	Immediate (no leaflet) 44/46 (96%)	0.49 (0.39, 0.60)	High
Use of antibiotics (at 1 week) [P]	1 (81)	RCT	Delayed (structured explanation) 18/44 (41%)	Delayed (no structured explanation) 32/37 (86%)	0.47 (0.32, 0.68)	Moderate
Use of antibiotics (at 3 week) [L]	1 (572)	RCT	Leaflet[d] 160/281 (57%)	No leaflet[d] 159/291 (55%)	1.04 (0.90, 1.20)	High
Outcome	No. of studies (total patients)	Design	Intervention	Control	Relative risk	Quality
Re-consultation (within 4 weeks) [M2]	1 (209)	RCT	Delayed (leaflet) 11/104 (11%)	Delayed (no leaflet) 14/105 (13%)	0.79 (0.37, 1.66)	High
Re-consultation (within 4 weeks) [M1]	1 (283)	RCT	No (leaflet) 15/136 (11%)	No (no leaflet) 26/147 (18%)	0.62 (0.34, 1.12)	High
Re-consultation (within 4 weeks) [M1]	1 (723)	RCT	Immediate (leaflet) 60/369 (16%)	Immediate (no leaflet) 81/354 (23%)	0.71 (0.52, 0.95)	High
Re-attendance (within 1 month) [L]	1 (572)	RCT	No leaflet as control vs. leaflet Incidence rate ratio estimate = 1.63 (95% CI 1.07-2.49),			High

[d] leaflet factor: both leaflet and no leaflet included all three groups – delayed, no antibiotic prescribing and immediate antibiotic prescribing

L = Little et al. (2005)

M1 = Macfarlane et al. (1997)

M2 = Macfarlane et al. (2002)

P = Pshetizky et al. (2003)

Evidence statements

One large trial with a high quality of evidence suggested that the use of an information leaflet in general (when used with any of the three antibiotic management strategies) does not affect the consumption of antibiotics. Two smaller trials show that within a delayed prescribing strategy, the use of information leaflets and structured verbal explanations reduced the consumption of antibiotics.

The use of an information leaflet in an immediate prescribing strategy reduced repeat consultation rates in one trial but not in another larger trial where all patients received structured verbal information.

Evidence to recommendation

The GDG thought that the evidence on the use of an information leaflet or structured verbal explanation to deliver a chosen antibiotic management strategy remained inconclusive, since the included studies showed inconsistent findings across different strategies within various comparisons (that is, leaflet versus no leaflet across all three prescribing strategies; leaflet in delayed arm versus no leaflet in immediate arm; study of the effect of leaflet and verbal explanation only in the delayed arm but not others). The GDG decided that, owing to inconsistent evidence, no recommendation could be made regarding the efficacy of information leaflets as opposed to structured verbal explanations.

2.3 Identifying those patients with RTIs who are likely to be at risk of developing complications

2.3.1 Introduction

It is clear from the previous overview of antibiotic efficacy and the review of the effectiveness of antibiotic management strategies that antibiotics are, in general, ineffective in treating RTIs. However, antibiotics may still be beneficial for a subgroup of patients who present with an RTI in primary care settings and who are likely to be at risk of developing complications.

The first group is adults and children who present with a complicated infection such as pneumonia. The diagnosis and management of complicated RTIs is outside the scope of this short clinical guideline. However, it is important that this guideline clearly signposts that such complicated infections should not be managed using a delayed or no antibiotic prescribing strategy.

The second group is adults and children who present with an uncomplicated infection, but who are at a high risk of developing complications. For this group, the use of a delayed or a no antibiotic prescribing strategy may potentially lead to an increased risk of developing complications, although in the case of delayed prescribing this risk may be reduced by offering the patient advice on when the antibiotic should be started. It is therefore important that for each of the RTIs covered in this guideline evidence is sought as to whether specific clinical symptoms, signs and risk factors can predict which patients seen in primary care and other first-contact care settings are more likely to develop complications. For the purposes of this guideline, the following complications of RTIs were considered to lead to significant morbidity and were therefore the focus of the review.

- For sore throat/acute pharyngitis/acute tonsillitis:
  - quinsy, cellulitis/impetigo, acute AOM, contralateral AOM, acute rhinosinusitis

- For acute otitis media:
  - mastoiditis, deafness, contralateral AOM

- For acute cough/acute bronchitis:
  - pneumonia

- For acute rhinosinusitis and common cold:
  - frontal abscess.

2.3.2 Overview

We identified 24 published individual studies based on study abstracts. After further assessment, only 6 studies that provided evidence on clinical symptoms, signs and risk factors that predict which patients with RTIs are likely to develop complications were included in the evidence review (15 studies were not relevant, 1 study had an inappropriate study population and 1 study was excluded as statistical analysis was inappropriate). All 6 studies were appraised individually using the NICE prognostic study checklist (see appendix 4) and presented in the evidence tables and narrative summary.

Of the 6 included studies, 1 case control study was on acute sore throat/acute pharyngitis/acute tonsillitis (from UK primary care data) (level of evidence +); 2 prospective studies and 1 retrospective cohort study were on acute cough/acute bronchitis (2 from UK primary care settings with level of evidence + and ++ respectively; and 1 from a Netherlands primary care setting with level of evidence ++). One prospective cohort and 1 analysis of RCT cohort were on AOM (1 from a Netherlands primary care setting and 1 from a UK primary care setting, both with level of evidence +). No studies were identified on acute rhinosinusitis or the common cold.

Overall, the quality of the evidence was good. However, 3 out of the 6 included studies need cautious interpretation as the evidence of clinical prediction criteria reported in these 3 studies has not been validated in other primary care populations.

2.3.3 Identifying those patients with RTIs who are likely to be at risk of developing complications

Recommendation number 1.1.7

An immediate antibiotic prescription and/or further appropriate investigation and management should only be offered to patients (both adults and children) in the following situations:

- if the patient is systemically very unwell
- if the patient has symptoms and signs suggestive of serious illness and/or complications (particularly pneumonia, mastoiditis, peritonsillar abscess, peritonsillar cellulitis, intraorbital and intracranial complications)
- if the patient is at high risk of serious complications because of pre-existing comorbidity. This includes patients with significant heart, lung, renal, liver or neuromuscular disease, immunosuppression, cystic fibrosis, and young children who were born prematurely
- if the patient is older than 65 years with acute cough and two or more of the following criteria, or older than 80 years with acute cough and one or more of the following criteria:
  - hospitalisation in previous year
  - type 1 or type 2 diabetes
  - history of congestive heart failure
  - current use of oral glucocorticoids.

For these patients, the no antibiotic prescribing strategy and the delayed antibiotic prescribing strategy should not be considered.

Evidence review

Acute sore throat/acute pharyngitis/acute tonsillitis

One reasonably good quality retrospective case control study was included as the basis for recommendations (Dunn et al. 2007). It was based on UK-wide primary care data from the General Practice Research Database between 1995 and 1997. The aim of this study was to identify clinical symptoms, signs and risk factors that were associated with the development of quinsy after initial presentation of uncomplicated sore throat. The study identified 606 cases of quinsy within the study period, of which only 192 cases developed following initial uncomplicated sore throat. These 192 patients with quinsy formed the study group and another 198,124 patients of sore throat without quinsy formed the control group for the analysis. The prevalence of quinsy within the study period was 96 cases per 100,000 patients with sore throat (per annum between 1995 and 1997).

Outcome 1: development of quinsy after initial uncomplicated sore throat

Logistic regression was used to calculate odds ratios (ORs) for the risk of quinsy following a sore throat for different variables such as age, sex, smoking status, type of diagnosis, exposure to antibiotics and lung disease. Results for the analysis showed that only age (21 to 40 years) (adjusted OR = 3.4, 95% CI 2.1 to 5.5), smoking (adjusted OR = 2.5, 95% CI 1.8 to 3.5) and male gender (adjusted OR = 1.6, 95% CI 1.1 to 2.2) were significantly associated with the development of quinsy following a sore throat.

Outcome 2: exposure to antibiotics and the development of quinsy following different types of diagnosis

Further analysis was also carried out based on different diagnoses of sore throat, such as tonsillitis and sore throat/pharyngitis (adjusted for age, sex, smoking status, lung disease at patient level and clustering at practice level). The interval between diagnosis of a sore throat and development of quinsy was a median of 2 days (interquartile range 1 to 6 days) for tonsillitis, and 3 days (interquartile range 2 to 5 days) for sore throat/pharyngitis. Results from this further analysis showed that prescription of antibiotics after recording a diagnosis of a sore throat generally did not seem to reduce the risk of

developing quinsy (antibiotic given after all diagnoses [adjusted OR = 1.2, 95% CI 0.7 to 1.8]; antibiotics given after tonsillitis [adjusted OR = 0.6, 95% CI 0.3 to 1.3]; antibiotics given after sore throat/pharyngitis [adjusted OR = 1.2, 95% CI 0.7-2.2]). However, considerable caution is needed in estimating the effect of antibiotics in this study owing to confounding by indication in routine databases (individuals with more severe illness are more likely to be given antibiotics than individuals with less severe illness).

Evidence statements

Patients aged between 21 and 40 years who are male and are smokers are significantly more likely to develop quinsy after initial presentation of uncomplicated sore throat in primary care settings.

Evidence to recommendations

The GDG noted both that quinsy is a rare complication of sore throat in the UK (with an annual incidence of 96 cases per 100,000 patients) and therefore the absolute risk of developing quinsy is low (Dunn et al. 2007), and that the predictive value of the risk factors for the development of quinsy was not sufficient to make a recommendation to prescribe immediate antibiotics. It was also noted that the included study did not offer a validated clinical prediction rule, although the study did document the same risk factors in those presenting with a prior RTI and those presenting with de novo quinsy. The GDG came to the conclusion that patients with sore throat should not be excluded from delayed or no prescribing strategies based on the three risk factors identified (aged 21 to 40 years, male and smoker). Hence, no recommendation on exclusion criteria for antibiotic management strategies for patients with sore throat was generated from the evidence statement. Nevertheless, the GDG acknowledged that quinsy is a serious complication and came to the consensus conclusion that immediate antibiotic prescription and/or further appropriate investigation and management should be offered to adults and children who appear unwell and with symptoms and signs suggestive of peritonsillar abscess (quinsy).

Evidence review

Acute cough/acute bronchitis

Three good quality studies were included as the basis of the recommendations. Two were prospective cohort studies from the same research team (a derivation study and the further validation study). The studies were based in UK primary care settings (Dunn et al. 2007; Hay 2004; Hay et al. 2007) and aimed at identifying and validating a clinical rule for predicting complications of acute cough in pre-school children. The third study was a retrospective cohort study based on patient data from the Netherlands General Practice Research Network and the second Dutch National Survey of General Practice (Bont 2007). The aim of this study was to identify and validate a prediction rule for complications of LRTIs in elderly primary care patients.

Outcome 1: complications and hospital admission before cough resolution

A derivation study and a further validation study (Hay 2004; Hay et al. 2007) on a clinical rule for predicting complications of acute cough in pre-school children (aged between 0 years and 4 years) were identified. Complications in these two studies were defined as new sign/symptoms/conditions identified after initial consultation, which were bronchiolitis, possible asthma, vomiting, bronchitis, viral illness, cough and wheeze, conjunctivitis, LRTI, baby asthma, chest infection, chicken pox, viral induced wheeze, pharyngitis and otitis media. Hospital admission was defined as hospital admission before cough resolution owing to bronchiolitis, pneumonia, whooping cough and viral-induced wheeze.

In the derivation study (Hay 2004), multivariate analysis showed that only the presence of a chest sign (OR = 2.78, 95% CI 1.04 to 7.35, p = 0.048) and the presence of fever (OR = 4.65, 95% CI 1.63 to 13.3, p = 0.007) were significant independent predictors of complications and hospital admission before cough resolution in pre-school children. Further logistic regression also showed that lack of fever and chest signs was a good predictor for ruling out complications in children with cough, with a likelihood ratio (LHR) of 0.56 (95% CI 0.35 to 0.91). Fever only or both fever and chest sign LHR = 3.54 (95% CI 1.62 to 7.68) and only fever and chest sign LHR = 5.39 (95% CI 0.95 to 30.6) were

found to be good predictors for complications in children with cough. However, the discriminatory ability of this particular prediction model was weak, with an area under receiver operating characteristic (ROC) below 0.70 (ROC = 0.68). A further validation study by Hay (2007) of the earlier derivation study (Hay 2004) was also identified. In the further validation study, however, chest sign and fever were not found to be significant predictors of complications and hospital admission in children with cough. Instead, chest sign and fever were found to be protective against complications and hospital admission (post-test probability: neither fever nor chest sign = 13.7 [95% CI 7.5 to 22.3]; chest sign only = 13.8 [95% CI 3.9 to 32.0]; fever only = 9.1 [95% CI 0.0 to 41.0]; both fever and chest sign = 0.0 [95% CI 0.0 to 37.0]). A completely different set of variables were found to be significant independent predictors of complications and hospital admission: age (OR = 0.95, 95% CI 0.90 to 0.99, p = 0.03); deprivation (OR = 0.79, 95% CI 0.64 to 0.97, p = 0.02); number of GP visits in previous year (OR = 1.14, 95% CI 1.02 to 1.27, p = 0.02). The authors commented that the contradictory findings from the validation study compared with the derivation study could be a result of spectrum bias (that is, sociodemographic differences, possible reduced levels of circulating influenza-like illness between the derivation and validation cohorts) and confounding by indication (that is, clinicians' antibiotic prescriptions tended to be targeted at children with chest signs or fever). Thus, the evidence provided by these two studies needs cautious interpretation.

Outcome 2: 30-day hospitalisation or death

Another retrospective cohort study (Bont 2007) that derived and validated a prediction rule for complications of LRTIs in elderly primary care patients was also identified. The derivation cohort of this study was from the Netherlands General Practice Research Network and the validation study cohort was from the second Dutch National Survey of General Practice. Patients included in this study were 65 years or older. Logistic regression in the derivation cohort showed that after initial diagnosis, the following variables were significant predictors of 30-day hospitalisation and death (table 10) and a scoring system was derived based on regression coefficients.

Table 10 Significant predictors and scoring system

Predictors after initial diagnosis	Regression coefficient	Score
Acute bronchitis	0.000	0
Exacerbation of chronic obstructive pulmonary disease	0.643	2
Pneumonia	1.608	4
Aged 65–79	0.000	0
Aged ≥80	0.575	2
Congestive heart failure	0.364	1
Diabetes	0.629	2
Using oral glucocorticoids	0.966	3
Hospitalisation in previous year:		
0 hospitalisation	0.000	0
1 hospitalisation	0.676	2
≥ 2 hospitalisations	1.239	3
Use of antibiotics in previous month	0.615	2

The scoring system was separated into three risk groups: low risk (score ≤ 2), medium risk (score 3–5) and high risk (score ≥ 7). The discriminatory abilities of this prediction scoring system in the derivation cohort were: low risk – sensitivity = 0.82, specificity = 0.52, percentage of risk of endpoint 3.2%; medium risk – sensitivity/specificity = not reported, percentage of risk of endpoint = 9.9%; high risk – sensitivity = 0.35, specificity = 0.92, percentage of risk of endpoint = 30.9%, with good discriminatory power (area under ROC = 0.75 [95% CI 0.72 to 0.78]).

The prediction scoring system was also validated in a separate cohort with similar results: low risk – sensitivity = 0.42, specificity = 0.81, percentage of risk of endpoint = 5.3%; medium risk – sensitivity/specificity = not reported, percentage of risk of endpoint = 14.5%; high risk – sensitivity = 0.06, specificity = 0.98, percentage of risk of endpoint = 22.0%, with good discriminatory power (area under ROC = 0.74 [95% CI 0.71 to 0.78]). However, the limitation of the validation study is that it did not include exacerbation of chronic obstructive pulmonary disease (COPD) among the predictors.

Evidence statements

There is inconsistent evidence on the utility of clinical rules for predicting complications of acute cough in pre-school children.

The following clinical signs/symptoms and risk factors are significant predictors of the development of complications of LRTIs in elderly primary care patients:

- *suspected or diagnosed pneumonia at the presence of consultation*
- *history of:*
  - *congestive heart failure*
  - *diabetes*
  - *COPD or exacerbation of COPD*
- *80 years or older*
- *present use of oral glucocorticoids*
- *hospitalisation in previous year*
- *use of antibiotics in previous month.*

Evidence to recommendations

The GDG discussed the evidence on predicting complications in elderly primary care patients with LRTIs. The GDG agreed the evidence statement but questioned the validity of the full prediction model provided by the study since this model was based on a single study; moreover, a large proportion of the study population had comorbidities. In addition, the study was conducted in the Netherlands, where the level of antibiotic prescribing is low and thus patients are more likely to present with a more severe illness.

The GDG also recognised that there is inconsistent and inconclusive evidence on predicting which children with acute cough are likely to develop complications.

Evidence review

Acute otitis media (AOM)

Two good quality studies were included as the basis of recommendations. One was a prospective cohort study (Damoiseaux et al. 2006) on long-term prognosis of AOM in infancy (6 months to 24 months) with a prediction model for complication (recurrent AOM). The setting of this study was family practices in the Netherlands. The other study was a follow-up secondary

analysis study of an RCT cohort (Little et al. 2006). This was a UK primary care-based study looking for clinical predictors of complications (recurrent AOM and hearing impairment) from AOM in children (6 months to 10 years). No studies were identified regarding the complication mastoiditis. Based on Hospital Episode Statistics (2006–07) there were 952 finished consultant episodes of mastoiditis and in relation to GP-registered populations (GP Registered Populations 2007), there were 50,542,505 registered patients in England. These constituted a crude rate of 144 cases of mastoiditis per 1,000,000 patients per annum, indicating that mastoiditis is a rare complication. A large Dutch cohort study also showed that mastoiditis is likely to be very rare when using a 72-hour wait-and-see policy before prescribing antibiotics (van Buchem et al. 1985).

Outcome 1 – recurrent AOM/recurrent episodes of earache (otalgia) and functional hearing impairment

In the Damoiseaux's (2006) study, logistic regression showed that the variables listed in table 11 were significant predictors of recurrent AOM within 6 months in infants. A scoring system was derived based on regression coefficients (table 11).

Table 11 Significant predictors and scoring system

Predictors after initial diagnosis	Regression coefficient	Score*
Male	0.60	6
Passive smoking	-0.76	-8
Winter season	0.86	9
Persistent symptoms	0.82	8

*baseline score starts from -9

The scoring system was then separated into three cut-off points: below -8, below -1 and below 5. The discriminatory abilities of this prediction scoring system were: below -8 – sensitivity = 93%, specificity = 23%, positive predictive value (PPV) = 54%, negative predictive value (NPV) = 77%); below -1 – sensitivity = 72%, specificity = 56%, PPV = 62%, NPV = 67%; below 5 – sensitivity = 51%, specificity = 76%, PPV = 68%, NPV = 61%. The discriminatory power of the model was weak, with an area under ROC of 0.69

(95% CI 0.62 to 0.76), and this particular model was not validated in different primary care populations.

In Little's study, logistic regression showed that ear discharge (otorrhoea) (LHR = 7.04, p = 0.004) and bulging eardrum (LHR = 5.50, p = 0.019) were significant predictors of recurrent episodes of otalgia within 3 months in children aged between 6 months and 10 years, whereas past history or previous episodes of AOM (LHR = 8.04, p = 0.005) were the significant predictors of recurrent episodes of otalgia within 1 year.

Little (2006) also investigated predictors of functional hearing impairment following initial AOM in children in their study. Functional hearing impairment in this study was measured by a child function score (in which a score of 9 or above indicates hearing impairment) based on 14 descriptions of how hearing impairment with chronic secretory otitis media presents. Results from logistic regression showed that only past history or previous episodes of otitis media were significant predictors of functional hearing impairment in children aged between 6 months and 10 years within both 3 months (LHR = 4.95, p = 0.026) and 1 year (LHR = 4.56, p = 0.033) of initial presentation of AOM. Further analysis also showed that, compared with an immediate antibiotic prescribing strategy, a delayed antibiotic prescribing strategy did not significantly increase the risk of recurrent AOM after 3 months (OR = 0.89, 95% CI 0.48 to 1.65) or after 1 year (OR = 1.03, 95% CI 0.60 to 1.78). Additionally, there was no significant increase in the risk of functional hearing impairment in children after 3 months (OR = 1.37, 95% CI 0.72 to 2.60) or after 1 year (OR = 1.16, 95% CI 0.61 to 2.23). Moreover, the study showed that a delayed prescribing strategy did not significantly increase the risk of otalgia at 3 months (OR = 0.89, 95% CI 0.48 to 1.65) or at 1 year (OR = 1.03, 95% CI 0.60 to 1.78), nor did it significantly increase the risk of a poor child (hearing) function score at 3 months (OR = 1.37, 95% CI 0.72 to 2.60) or 1 year (OR = 1.16, 95% CI 0.61 to 2.23). However, as noted by the authors, this is a secondary analysis and there was no validation study. Moreover, since recurrent AOM or recurrent episodes of otalgia are not serious complications, the evidence requires cautious interpretation.

Evidence statements

In children aged between 6 months and 10 years, ear discharge and bulging eardrum are significant predictors of recurrent episodes of otalgia within 3 months of the initial consultation. However, the predictors are no longer significant after 1 year.

In children aged between 6 months and 10 years, a history of previous episodes of AOM is a significant predictor of recurrent episodes of otalgia only 1 year after the initial consultation.

In infants aged between 6 months and 24 months, male gender, passive smoking, winter season and persistent symptoms are significant predictors of recurrent AOM within 6 months of the initial consultation.

Delayed prescribing does not significantly increase the risk of otalgia or poor child (hearing) function at 3 months or at 1 year

Evidence to recommendations

Mastoiditis was considered by the GDG to be a rare but potentially serious complication of AOM, but no mastoiditis studies were identified that met the inclusion criteria for the review. The GDG recognised that the outcome measures reported in the included studies (recurrent AOM and recurrent episodes of otalgia) were not considered to be serious complications of AOM. Moreover, the GDG considered that the evidence merited a cautious interpretation as it was a secondary analysis from a previous RCT. The GDG considered that these three factors precluded the use of this evidence as the basis for making recommendations. The GDG concluded that it was not possible to identify subgroups of patients presenting with AOM who should be excluded from the offer of a delayed or no prescribing strategy.

However, the GDG acknowledged that mastoiditis is a serious complication of AOM and came to the consensus conclusion that immediate antibiotic prescription and/or further appropriate investigation and management should be offered to adults and children who appear unwell and with symptoms and signs suggestive of mastoiditis.

Evidence review

Acute rhinosinusitis

No studies were identified for acute rhinosinusitis.

Evidence statement

No evidence was identified for acute rhinosinusitis.

Evidence to recommendations

The GDG noted the lack of evidence in this area and concluded that it was not possible to identify subgroups of patients presenting with acute rhinosinusitis who should be excluded from the offer of a delayed or no prescribing strategy.

However, the GDG acknowledged that intraorbital and intracranial complications are serious complications of acute rhinosinusitis. Hence, the GDG came to the consensus conclusion that immediate antibiotic prescription and/or further appropriate investigation and management should be offered to adults and children who appear unwell and with symptoms and signs suggestive of intraorbital and intracranial complications.

Evidence review

Common cold

No studies were identified for common cold.

Evidence statement

No evidence was identified for common cold.

Evidence to recommendation

The GDG noted the lack of evidence in this area and concluded that it was not possible to identify subgroups of patients presenting with common cold who should be excluded from the offer of a delayed or no prescribing strategy.

2.4 Patients and parents/carers' preferences regarding antibiotic management strategies for RTIs (no antibiotic prescribing, delayed antibiotic prescribing and immediate antibiotic prescribing)

2.4.1 Introduction

A central task of the healthcare professional during the patient consultation is to address the patient's ideas, concerns and expectations regarding treatment before agreeing a management plan (Fraser 1999). This is particularly important in consultations for RTIs, when there may be an expectation on the part of the patient that an antibiotic will be required, whereas the opinion of the healthcare professional is that an antibiotic prescription is not clinically indicated. Conversely, there may be an expectation on the part of the healthcare professional that the patient has attended specifically with a view to obtaining an antibiotic prescription whereas the patient is seeking only advice and/or reassurance (Butler et al. 1998). Indeed, there is evidence that GPs overestimate the proportion of patients who attend with RTIs expecting an antibiotic prescription (Altiner 2004). The perceived advantage of delayed prescribing as a strategy over no prescribing is that a patient expecting antibiotics may be more likely to agree with this course of action than with a no prescribing strategy.

The issue of patients' preferences regarding the three antibiotic management strategies (immediate, delayed or no prescribing) is therefore extremely important. In the overview presented in section 2.4.2, the included RCTs assessed patients' preferences using satisfaction rating scales and the results are presented in the relevant GRADE tables and evidence statements by condition. Patients reported a high level of satisfaction (above 70% overall) with the use of a delayed or a no antibiotic prescribing strategy. The included studies, however, did not report whether patient preferences regarding the three antibiotic management strategies differed across ethnic and socioeconomic groups.

There is a body of literature suggesting that variations in prescribing in primary care may be a result, at least in part, of patient ethnicity and

socioeconomic status. A secondary analysis (Gill et al. 1996) of data from the General Household Survey that examined the association between being given a prescription and ethnicity found that people of Pakistani or Indian origin were significantly more likely to receive a prescription from their GP than people of white or West Indian origin. Another study (Gill and Roalfe 2001) found that patients from manual classes and patients from the most deprived areas received significantly more antibiotics during primary care consultations than patients from other socioeconomic classes. There is also evidence that people's knowledge of and attitudes toward antibiotics may vary according to their ethnicity. A large-scale household survey in Britain (McNulty et al. 2007) of the public's knowledge of and attitudes to antibiotics showed that people of Asian/Asian British or Caribbean/black British origin were less knowledgeable about and had different attitudes toward antibiotics than people of white British origin.

Given the above findings, it is important to determine whether there is any additional evidence that reports patient preferences for the three antibiotic management strategies, in particular whether there is evidence pertaining to specific black and minority ethnic and socioeconomic groups.

2.4.2 Overview

We identified 10 published individual qualitative studies based on study abstracts. After further assessment, only 2 studies that provided information on patients' preferences regarding antibiotic management strategies for RTIs were included in the evidence review (8 excluded studies were not relevant). Both studies were appraised individually and presented in the evidence tables and narrative summary.

Both of the 2 included studies were survey questionnaire studies. One (Edwards et al. 2003) explored patients' responses to delayed antibiotic prescribing for acute URTIs in a UK primary care setting. The other (Couchman et al. 2000) studied patients' self-reported satisfaction with a delayed prescribing strategy for common respiratory symptoms. Qualitative studies including survey questionnaires were assigned evidence level 3 in accordance with NICE technical guidance.

2.4.3 Patients and parents/carers' preferences regarding antibiotic management strategies for RTIs

See Recommendation number 1.1.2.

Evidence review

Patients/parents' satisfaction and expectations

In Edwards' survey questionnaire study that investigated patients' responses to delayed antibiotic prescribing for acute URTIs, the results showed that of the 256 patients who received a delayed prescription, 92.5% were satisfied and would choose to receive a delayed prescription again in the future. Further analysis from Edwards' study showed that of the 256 patients who received a delayed prescription, approximately two-thirds (65.2%) had expected to receive an immediate antibiotic prescription, 37% had expected advice, 2.0% had expected tests or a hospital referral and 4.7% had anticipated a sickness certificate. Patients' expectations were not associated with whether they had consumed the delayed prescription or not.

The study by Couchman of 286 patients who received a delayed prescription for common respiratory symptoms found that patients' self-reported satisfaction was 96.1%. The overall delayed prescription fill rate of this study was 50.2% and the fill rates did not differ significantly by patient characteristics or their self-reported satisfaction with the care received.

Evidence statement

For patients who were expecting to receive immediate antibiotics during consultation, over 90% of those who then received a delayed prescription for acute URTIs were satisfied and would choose to receive a delayed prescription again in the future.

No studies were identified that reported patient preferences for the three antibiotic management strategies in black and minority ethnic and differing socioeconomic groups.

Evidence to recommendation

The GDG noted that the evidence presented here was consistent with that presented in the RCTs on different antibiotic management strategies (see

section 2.2.2). They also noted that no specific evidence was identified that reported on patient preferences by specific black and minority ethnic and socioeconomic groups.

In view of the lack of evidence in this area, the GDG considered that a general recommendation should be made on the need for patient concerns and expectations regarding antibiotic use to be determined during healthcare consultations with adults and children with RTIs in primary care settings. This should apply for all ethnic and socioeconomic groups.

2.5 Research recommendations

- Which subgroups of adults and children with RTIs presenting in primary care settings are most likely to benefit from an immediate antibiotic prescribing strategy in terms of symptomatic management and prevention of complications?
- What is the clinical and cost effectiveness of a delayed antibiotic prescribing strategy compared with both a no antibiotic prescribing strategy and an immediate antibiotic prescribing strategy for acute rhinosinusitis?
- What is the clinical and cost effectiveness of differing methods of delivering a delayed antibiotic prescribing strategy in primary care for adults and children presenting with RTIs?
- What are the rates of prescription, dispensing and complications in adults and children with RTIs when different delayed prescribing strategies or no prescribing are used, and how does any potential difference in risk of developing complications affect the cost effectiveness of a delayed antibiotic prescribing strategy or a no prescribing strategy?
- Which clinical features of children and adults presenting in primary care with RTIs are associated with the development of serious complications and need for hospitalisation?
- Do patients and parents/carers' preferences regarding antibiotic management strategies (immediate, delayed and no prescribing strategy) for RTIs differ according to ethnicity and socioeconomic status?

Health economics

- How does a delayed prescribing strategy affect the risk of patients developing complications after an initial episode of RTI and how does this potential difference in risk affect the cost effectiveness of a delayed prescribing strategy?
- Research is needed in assessing the health-related quality of life of people with RTIs, in particular when using generic measures such as the EQ-5D. In addition, further research is needed in applying health-related quality of life weights when investigating interventions for short-term illnesses such as RTIs.

3 References, glossary and abbreviations

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3.2 Glossary

Respiratory tract infection (RTI)

RTI is defined as any infectious disease of the upper or lower respiratory tract. Upper respiratory tract infections (URTIs) include the common cold, laryngitis, pharyngitis/tonsillitis, rhinitis, rhinosinusitis/sinusitis and otitis media. Lower respiratory tract infections (LRTIs) include bronchitis, bronchiolitis, pneumonia and tracheitis. The five common respiratory tract infections that are covered by this guideline are: the common cold, pharyngitis/tonsillitis, rhinosinusitis/sinusitis, acute otitis media and acute cough/acute bronchitis.

Centor criteria

The Centor criteria have been developed to predict bacterial infection in acute sore throat. The four Centor criteria are: presence of tonsillar exudate, tender anterior cervical lymphadenopathy or lymphadenitis, history of fever and an absence of cough. (Centor et al. 1981).

Before-and-after study

A study design that involves intervention and control groups chosen other than by random process, and inclusion of a baseline period of assessment of main outcomes. There are two minimum criteria for this study design: that the pre- and post-intervention periods for the study sites and the control sites are the same, and that second sites used as control sites are comparable with the control sites in terms of dominant reimbursement system, level of care, setting of care and academic status.

Case control study

A comparative observational study in which the investigator selects individuals who have experienced an event (for example, developed a disease) and

others who have not (controls), and then collects data to determine previous exposure to a possible cause.

Cohort study

An observational study in which a defined group of people (the cohort) is followed over time (also known as a follow-up, incidence, longitudinal or prospective study). Outcomes are compared in subsets of the cohort who were exposed or not exposed (or exposed at different levels) to an intervention or other factor of interest.

Comorbidity

Two or more diseases or conditions occurring at the same time, such as depression and anxiety.

Confidence interval

The range within which the ‘true‘ values (for example, size of effect of an intervention) are expected to lie with a given degree of certainty (for example, 95% or 99%). (Note: confidence intervals represent the probability of random errors, but not systematic errors or bias.)

Cost-effectiveness analysis

An economic evaluation that compares alternative options for a specific patient group, looking at a single effectiveness dimension measured in a non-monetary (natural) unit. It expresses the result in the form of an incremental (or average or marginal) cost-effectiveness ratio.

Economic evaluation

A technique developed to assess both the costs and the consequences of alternative health strategies and to provide a decision-making framework.

Extendedly dominated

A term used in health economics. An extendedly dominated strategy has an ICER (incremental cost-effectiveness ratio) higher than that of the next most effective strategy; therefore an extendedly dominated strategy produces additional gains in effectiveness at incremental costs higher than those of the next most effective strategy.

Guideline Development Group

A group of healthcare professionals, patients, carers and members of the Short Clinical Guidelines Technical Team who develop the recommendations for a short clinical guideline. The group writes draft guidance, and then revises it after a consultation with organisations registered as stakeholders.

Generalisability

The degree to which the results of a study or systematic review can be extrapolated to other circumstances, particularly routine healthcare situations in the NHS in England and Wales.

GRADE

Grading of Recommendations Assessment, Development and Evaluation is a system for grading the quality of evidence and the strength of recommendations that can be applied across a wide range of interventions and contexts.

Heterogeneity

A term used to illustrate the variability or differences between studies in the estimates of effects.

Kappa

Kappa coefficient is a statistical measure of inter-rater reliability. It is generally thought to be a more robust measure than simple per cent agreement calculation because kappa takes into account the agreement occurring by chance.

Likelihood ratio

The likelihood ratio incorporates both the sensitivity and specificity of the test and provides a direct estimate of how much a test result will change the odds of having a disease. The likelihood ratio for a positive result (LR+) tells you how much the odds of the disease increase when a test is positive. The likelihood ratio for a negative result (LR-) tells you how much the odds of the disease decrease when a test is negative.

Negative predictive value

The proportion of patients with negative test results who are correctly diagnosed.

Number needed to treat (NNT)

The number needed to treat (NNT) is defined as the expected number of people who need to receive the experimental rather than the comparator intervention for one additional person to either incur (or avoid) an event in a given time frame. Thus, for example, an NNT of 10 can be interpreted as 'it is expected that one additional (or less) person will incur an event for every 10 participants receiving the experimental intervention rather than control over a given time frame'. It is important to be clear that:

- since the NNT is derived from the risk difference, it is still a comparative measure of effect (experimental versus a certain control) and not a general property of a single intervention; and
- the NNT gives an 'expected value'. For example, NNT = 10 does not imply that one additional event will occur in each and every group of ten people.

Odds ratio

A measure of treatment effectiveness. The odds of an event happening in the intervention group, divided by the odds of it happening in the control group. The 'odds' is the ratio of non-events to events.

Positive predictive value

The proportion of people with a positive test result who actually have the disease.

Purposive sampling

A purposive sample is one that is selected by the researcher subjectively. The researcher attempts to obtain a sample that appears to him/her to be representative of the population and will usually try to ensure that a range from one extreme to the other is included.

Quality-adjusted life year (QALY)

A statistical measure, representing 1 year of life, with full quality of life.

Randomised controlled trial

A form of clinical trial to assess the effectiveness of medicines or procedures. Considered reliable because it tends not to be biased.

Relative risk

Also known as risk ratio; the ratio of risk in the intervention group to the risk in the control group. The risk (proportion, probability or rate) is the ratio of people with an event in a group to the total in the group. A relative risk (RR) of 1 indicates no difference between comparison groups. For undesirable outcomes, an RR below 1 indicates that the intervention was effective in reducing the risk of that outcome.

Receiver operating characteristic (ROC)

Receiver operating characteristic (ROC), or simply ROC curve, is a graphical plot of the sensitivity vs. (1 – specificity) for a classifier system as its discrimination threshold is varied. The ROC can also be represented equivalently by plotting the fraction of true positives (TPR = true positive rate) vs. the fraction of false positives (FPR = false positive rate).

Sensitivity (of a test)

The proportion of people classified as positive by the gold standard who are correctly identified by the study test.

Specificity (of a test)

The proportion of people classified as negative by the gold standard who are correctly identified by the study test.

Systematic review

Research that summarises the evidence on a clearly formulated question according to a predefined protocol using systematic and explicit methods to identify, select and appraise relevant studies, and to extract, collate and report their findings. It may or may not use statistical meta-analysis.

3.3 Abbreviations

AOM	Acute otitis media
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
GABHS	Group A beta-haemolytic *Streptococcus*

GPRD	General Practice Research Database
GRADE	Grading of Recommendations Assessment, Development and Evaluation
ICHPPC-2	International Classification of Health Problems in Primary Care - 2
IPDM	Individual patient data meta-analysis
LR	Likelihood ratio
LRTI	Lower respiratory tract infection
NPV	Negative predictive value
NS	Not significant
NNT	Number needed to treat
PPV	Positive predictive value
OR	Odds ratio
QALY	Quality-adjusted life year
RTI	Respiratory tract infection
ROC	Receiver operating characteristic
RCT	Randomised controlled trial
RR	Relative risk
SD	Standard deviation
URTI	Upper respiratory tract infection

4 Methods

4.1 Aim and scope of the guideline

4.1.1 Scope

NICE guidelines are developed in accordance with a scope that defines what the guideline will and will not cover (see appendix 1). The scope of this guideline is available from www.nice.org.uk/CG069.

The aim of this guideline is to provide evidence-based recommendations to guide healthcare professionals in the appropriate prescribing of antibiotics for self-limiting respiratory tract infections in adults and children in primary care.

4.2 Development methods

This section sets out in detail the methods used to generate the recommendations for clinical practice that are presented in the previous sections of this guideline. The methods used to develop the recommendations are in accordance with those set out by the National Institute for Health and Clinical Excellence ('NICE' or 'the Institute') in 'The guidelines manual 2007' (available from www.nice.org.uk).

4.2.1 Developing the guideline scope

The draft scope, which defined the areas the guideline would and would not cover, was prepared by the Short Clinical Guidelines Technical Team on the basis of the remit from the Department of Health, consultation with relevant experts and a preliminary search of the literature to identify existing clinical practice guidelines, key systematic reviews and other relevant publications. The literature search gave an overview of the issues likely to be covered by the guideline and helped define key areas. It also informed the Short Clinical Guidelines Technical Team of the volume of literature likely to be available in the topic area, and therefore the amount of work required.

The draft scope was tightly focused and covered five clinical topic areas.

The draft scope was the subject of public consultation.

4.2.2 Forming and running the Short Clinical Guideline Development Group

The short clinical guideline on the prescribing of antibiotics for self-limiting respiratory tract infections in adults and children in primary care was developed by a Guideline Development Group (GDG) consisting of nine full members and the Short Clinical Guidelines Technical Team. The GDG had a chair, healthcare professional members and patient/carer members who were recruited through open advertisement. Development took 5 months and the GDG met on five occasions, every 3 to 5 weeks.

4.2.3 Developing key clinical questions

The third step in the development of the guideline was to refine the scope into a series of key clinical questions. The key clinical questions formed the starting point for the subsequent evidence reviews and facilitated the development of recommendations by the GDG.

The key clinical questions were developed by the GDG with assistance from the Short Clinical Guidelines Technical Team. As necessary, the questions were refined into specific research questions by the project teams to aid literature searching, appraisal and synthesis. The full list of key clinical questions is shown in appendix 2.

The GDG and Short Clinical Guidelines Technical Team agreed appropriate review parameters (inclusion and exclusion criteria) for each question or topic area. A full table of the included and excluded studies is shown in appendix 4.

4.2.4 Developing recommendations

For each key question, recommendations were derived from the evidence summaries and statements presented to the GDG.

4.2.5 Literature search

The reviews used to develop the guideline recommendations were underpinned by systematic literature searches, following the methods described in ‘The guidelines manual 2007.’ The purpose of systematically searching the literature is to attempt to comprehensively identify the published

evidence to answer the review questions developed by the GDG and Short Clinical Guidelines Technical Team.

The search strategies for the reviews on the prescribing of antibiotics for self-limiting respiratory tract infections in adults and children in primary care were developed by the Short Clinical Guidelines Technical Team, in consultation with the GDG. Review questions were developed using the PICO model, and reflecting the inclusion criteria, which were translated in to search strategies using subject heading and free text terms. The strategies were run across a number of databases (e.g. MEDLINE, EMBASE and CINAHL) with no date restrictions imposed on the searches.

To identify economic evaluations the NHS Economic Evaluation Database (NHS EED) and the Health Economic Evaluations Database (HEED) were searched. Reports of economic evaluations added to bibliographic databases (e.g. MEDLINE) from 2006 onwards, and quality of life data, were also sought using search filters.

In addition to the systematic literature searches, the GDG was asked to alert the Short Clinical Guidelines Technical Team to any additional evidence, published, unpublished or in press, that met the inclusion criteria.

The searches were undertaken between August 2007 and December 2007. Full details of the systematic search, including the sources searched and the MEDLINE search strategy for each review, are presented in appendix 3.

4.2.6 Reviewing the evidence

The aim of the literature review was to systematically identify and synthesise relevant evidence in order to answer the specific key clinical questions developed from the guideline scope. The guideline recommendations were evidence based if possible; if evidence was not available, informal consensus of opinion within the GDG was used. The need for future research was also specified. This process required four main tasks: selection of relevant studies; assessment of study quality; synthesis of the results; and grading of the evidence. The Technical Analyst had primary responsibility for reviewing the evidence but was supported by the Project Lead, Information Scientist and Health Economist.

After the scope was finalised, searches based on individual key clinical questions were undertaken. The searches were first sifted by the Short Clinical Guidelines Technical Team using title and abstract to exclude papers that did not address the specified key clinical question. After selection based on title and abstract, the full text of the papers were obtained and reviewed by the Short Clinical Guidelines Technical Team in order to determine which studies should be included in the literature review. Studies suggested or submitted by the GDG and expert advisers were also reviewed for relevance to the key clinical questions and included if they met the inclusion criteria.

The papers chosen for inclusion were then critically appraised by the Short Clinical Guidelines Technical Team for their methodological rigour against a number of criteria that determine the validity of the results. These criteria differed according to study type and were based on the checklists included in 'The guidelines manual 2007'.

The data were extracted to standard evidence table templates. The findings were summarised by the Short Clinical Guidelines Technical Team into both a series of evidence statements and an accompanying narrative summary.

4.2.7 Grading the evidence

Intervention studies

Studies that meet the minimum quality criteria were ascribed a level of evidence to help the guideline developers and the eventual users of the guideline understand the type of evidence on which the recommendations have been based.

There are many different methods of assigning levels to the evidence and there has been considerable debate about what system is best. A number of initiatives are currently under way to find an international consensus on the subject. NICE has previously published guidelines using different systems and is now examining a number of systems in collaboration with the National Collaborating Centres and academic groups throughout the world to identify the most appropriate system for future use.

Until a decision is reached on the most appropriate system for the NICE guidelines, the Short Clinical Guidelines Technical Team will use the system for evidence shown in table 12.

Table 12 Levels of evidence for intervention studies

Reproduced with permission from the Scottish Intercollegiate Guidelines Network

Level of evidence	Type of evidence
1^{++}	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1^{+}	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias[a]
2^{++}	High-quality systematic reviews of case control or cohort studies High-quality case control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2^{+}	Well-conducted case control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2^{-}	Case control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal[a]
3	Non-analytic studies (for example, case reports, case series)
4	Expert opinion, formal consensus

[a] studies with a level of evidence '–' should not be used as a basis for making a recommendation

It was the responsibility of the GDG to endorse the final levels given to the evidence.

Presenting intervention studies with GRADE

The reader of a guideline should be able to follow a clear path from the question posed, through the summary of the evidence collected to address the question (linking to detailed evidence tables if desired), to the consideration of the evidence and the formulation of appropriate recommendations.

Grading or Recommendations Assessment, Development and Evaluation (GRADE) is a system for grading the quality of evidence and the strength of recommendations that can be applied across a wide range of interventions

and contexts. The system is a useful way to summarise evidence of effectiveness by the outcomes for which data have been collected. This approach uses an 'evidence profile' that combines presentation of quality assessment and outcome data. This then followed by a short evidence statement summarising what the evidence has shown.

In the GRADE system, the quality of evidence indicates the extent to which one can be confident that an estimate of effect is correct. The strength of a recommendation indicates the extent to which one can be confident that adherence to the recommendation will do more good than harm. The steps in this approach, which follow these judgements, are to make sequential judgements about:

- the quality of evidence across studies for each important outcome
- which outcomes are critical to a decision
- the overall quality of evidence across these critical outcomes
- the balance between benefits and harms
- the strength of recommendations.

A systematic and explicit approach to making judgements about the quality of evidence and the strength of recommendations can help to prevent errors, facilitate critical appraisal of these judgements, and improve communication of this information. More information about GRADE and its utilisation is available from www.grade.workinggroup.org

Diagnostic studies

The system described above covers studies of treatment effectiveness. However, it is less appropriate for studies reporting diagnostic tests of accuracy. In the absence of a validated ranking system for this type of test, NICE has developed a hierarchy for evidence of accuracy of diagnostic tests that takes into account the various factors likely to affect the validity of these studies (table 13). Since this hierarchy has not been systematically tested, NICE recommends that the National Collaborating Centres use the system when appropriate, on a pilot basis, and report their experience to us.

This evidence grading system was applied to the evidence reviews.

Table 13 Hierarchy for evidence of accuracy of diagnostic tests

Level of evidence	Type of evidence
Ia	Systematic review (with homogeneity)[a] of level 1 studies[b]
Ib	Level 1 studies[b]
II	Level 2 studies[c] Systematic reviews of level 2 studies
III	Level 3 studies[d] Systematic reviews of level 3 studies
IV	Consensus, expert committee reports or opinions and/or clinical experience without explicit critical appraisal; or based on physiology, bench research or 'first principles'

[a] homogeneity means there are no or minor variations in the directions and degrees of results between individual studies that are included in the systematic review.

[b] level 1 studies are studies:
- that use a blind comparison of the test with a validated reference standard (gold standard)
- in a sample of patients that reflects the population to whom the test would apply.

[c] level 2 studies are studies that have **only one** of the following:
- narrow population (the sample does not reflect the population to whom the test would apply)
- use a poor reference standard (defined as that where the 'test' is included in the 'reference', or where the 'testing' affects the 'reference')
- the comparison between the test and reference standard is not blind
- case control studies.

[d] level 3 studies are studies that have **at least two or three** of the features listed for level 2 studies.

Prognostic studies

Studies that are reviewed for questions about prognosis were addressed using the newly developed pilot checklist for prognostic studies (see appendix 4. This checklist is based on a checklist for the quality appraisal of prognostic studies developed by Hayden et al (Hayden JA et al. 2006) and is designed to answer questions about prognosis and address the likelihood of an outcome, for patients from a population at risk for that outcome, based on the presence of a proposed prognostic factor. Prognostic factors may be disease-specific (for example, presence/absence of particular disease feature), demographic (for example, age or sex), or may be the likely response to treatment or the presence of comorbidities.

A well designed and validated approach to summarising a body of evidence on prognosis does not currently exist. In the absence of such a system, a

narrative summary of the quality of the evidence should given, based on the quality appraisal criteria from the checklist (appendix 4) that were considered to be most important for the question addressed. Clinical input (such as from a GDG member) may be needed to identify the most appropriate quality criteria. This should be followed by a short evidence statement summarising what the evidence has shown. Finally, there should be a clear description of how the GDG has interpreted the evidence in reaching its recommendations.

4.2.8 Evidence to recommendations

The evidence tables and narrative summaries for the key clinical questions being discussed were made available to the GDG 1 week before the scheduled GDG meeting.

All GDG members were expected to have read the evidence tables and narrative summaries before attending each meeting. The review of the evidence had three components. First, the GDG discussed the evidence tables and narrative summaries or GRADE profiles and corrected any factual errors or incorrect interpretation of the evidence. Second, evidence statements, which had been drafted by the Short Clinical Guidelines Technical Team, were presented to the GDG and the GDG agreed the correct wording of these. Third, from a discussion of the evidence statements and the experience of GDG members recommendations were drafted. The Short Clinical Guidelines Technical Team explicitly flagged up with the GDG that it should consider the following criteria (considered judgement) when developing the guideline recommendations from the evidence presented:

- internal validity
- consistency
- generalisability (external validity)
- clinical impact
- cost effectiveness
- ease of implementation
- patient's perspective
- equalities
- overall synthesis of evidence.

The GDG was able to agree recommendations through informal consensus. The process by which the evidence statements informed the recommendations is summarised in an 'evidence to recommendations' section in the relevant evidence review. Each recommendation was linked to an evidence statement if possible. If there was a lack of available evidence of effectiveness, but the GDG was of the view that a recommendation was important based on the GDG members' own experience, this was noted in the 'evidence to recommendations' section.

4.2.9 Health economics

An economic evaluation aims to integrate data on the benefits (ideally in terms of quality-adjusted life years, or QALYs), harms and costs of alternative options. An economic appraisal will not only consider whether a particular course of action is clinically effective, but also whether it is cost effective (that is, value for money). If a particular treatment strategy is found to yield little health gain relative to the resources used, then it could be advantageous to redirect resources to other activities that yield greater health gain.

A systematic review of the economic literature relating to RTIs was conducted. In addition, the GDG and expert advisers were questioned over any potentially relevant unpublished data. The search of the published literature yielded one relevant economic study. This was the only study to specifically examine delayed prescribing versus no prescribing in a full cost-utility analysis for AOM (Coco 2007). The majority of studies identified examined strategies for the diagnosis of RTI and did not follow up patients after a result was obtained. No UK-based studies were identified and no studies were identified that examined the common cold or acute cough/acute bronchitis.

Given the potentially large resource implications of antibiotic use, the cost of complications of RTIs and the potential for development of antimicrobial resistance as a result of overuse of antibiotics, a de novo model was developed that considered strategies for the prescribing of antibiotics for acute sore throat in the UK.

Health economics statements are made in the guideline in sections where the use of NHS resources is considered.

4.2.10 Consultation

The draft of the full guideline was available on the website for consultation, and registered stakeholders were informed by NICE that the documents were available. Non-registered stakeholders could view the guideline on the NICE website.

4.2.11 Piloting and implementation

It is beyond the scope of the work to pilot the contents of this guideline or validate any approach to implementation. These limitations excepted, every effort has been made to maximise the relevance of recommendations to the intended audience through the use of a guideline development group with relevant professional and patient involvement, by use of relevant experienced expert reviewers and the stakeholder process facilitated by the NICE Short Clinical Guidelines Technical Team. Implementation support tools for this guideline will be available from the Implementation Team at NICE.

4.2.12 Audit methods

The guideline recommendations have been used to develop clinical audit support for monitoring local practice. This is an essential implementation tool for monitoring the uptake and impact of guidelines, and thus needs to be clear and straightforward for organisations and professionals to use.

NICE develops audit support for all its guidance programmes as part of its implementation strategy.

4.2.13 Scheduled review of this guideline

The guidance has been developed in accordance with the NICE guideline development process for short clinical guidelines. This has included allowing registered stakeholders the opportunity to comment on the draft guidance. In additional the first draft was reviewed by an independent Guideline Review Panel established by NICE.

The comments made by stakeholders, peer reviewers and the Guideline Review Panel were collated and presented anonymously for consideration by the GDG. All comments were considered systematically by the GDG and the Project Team recorded the agreed responses.

This guideline will be considered for an update following the current process (chapter 15 of 'The guidelines manual'). However, if the evidence available has not changed the guideline will not be updated. Any agreed update would be carried out by the Short Clinical Guidelines Technical Team in conjunction with the Guideline Development Group. Alternatively the topic may be referred to the NICE Topic Selection Panel for it to consider developing a standard clinical guideline.

5 Contributors

5.1 The Guideline Development Group

The GDG was composed of relevant healthcare professionals, patient representatives and NICE technical staff.

The members of the GDG are listed below.

Paul Little – Professor of Primary Care Research and General Practitioner (GDG Chair)

Nicky Coote – Consultant Paediatrician

Anne Joshua – Associate Director of Pharmacy, NHS Direct

Cliodna McNulty – Consultant Microbiologist

Cheryl Salmon – Patient/carer Representative

Mike Sharland – Consultant Paediatrician

Genine Riley – Senior Pharmaceutical Adviser

Matthew Thompson – General Practitioner and Clinical Lecturer in Primary Health Care

Mark Woodhead – Consultant in Respiratory Medicine

The following individual was not a full member of the GDG but was co-opted onto the group as an expert adviser:

Matt Griffiths – Professor of Prescribing and Medicines Management

5.1.1 The Short Clinical Guidelines Technical Team

The Short Clinical Guidelines Technical Team was responsible for this guideline throughout its development. It was responsible for preparing information for the GDG, for drafting the guideline and for responding to consultation comments. The following people, who are employees of NICE, made up the technical team working on this guideline.

Dr Tim Stokes – Guideline Lead and Associate Director

Emma Banks – Coordinator

Janette Boynton – Senior Information Specialist

Nicole Elliott –Commissioning Manager

Michael Heath – Project Manager

Ruth McAllister – Analyst, Health Economics

Francis Ruiz – Technical Adviser in Health Economics

Toni Tan – Technical Analyst

5.1.2 Guideline review panel

Robert Walker – General Practitioner, Workington (Chair)

Ailsa Donnelly – Lay member

Mark Hill – Head of Medical Affairs, Novartis Pharmaceuticals UK Ltd

John Harley – Clinical Governance and Prescribing Lead and General Practitioner, North Tees Primary Care Trust

5.1.3 List of stakeholders

Abbott Laboratories Ltd

ARHAI

Association of Medical Microbiologists

Association of the British Pharmaceuticals Industry (ABPI)

AstraZeneca UK Ltd

Barnsley PCT

Barts & the London NHS Trust

Bayer PLC

Bedfordshire PCT

Bio-Stat Diagnostic Systems

Boehringer Ingelheim Ltd

Bolton Council

Bournemouth and Poole PCT

BRAHMS AG

British Geriatrics Society

British In Vitro Diagnostics Association

British Infection Society

British National Formulary (BNF)

British Paediatric Respiratory Society

British Paramedic Association

British Rhinological Society

British Association for Paediatric Otorhinolaryngology

British Society for Antimicrobial Chemotherapy

British Society of Otology (ENT UK)

British Thoracic Society

Calderdale PCT

Cambridge University Hospitals NHS Foundation Trust

CASPE

Cephalon

Cheshire PCT

Commission for Social Care Inspection

Connecting for Health

Cornwall & IoS PCT

Daiichi Sankyo UK

Department of Health

Der Norske Veritas – NHSLA Schemes

Derbyshire County PCT

Derbyshire Mental Health Services NHS Trust

General Practice Airways Group

Genzyme Diagnostics

Harrogate & District NHS Foundation Trust

Health Commission Wales

Health Protection Scotland

Healthcare Commission

Heatherwood & Wexham Park Hospitals NHS Trust

Hill-Rom

Institute of Biomedical Science

Kirklees PCT

Launch Diagnostics

Leeds PCT

Luton & Dunstable Hospital NHS Foundation Trust

NCCHTA

NHS Clinical Knowledge Summaries Service

Medicines and Healthcare Products Regulatory Agency

Menarini Diagnostics

Milton Keynes PCT

MRSA Action UK

National Patient Safety Agency

National Pharmacy Association

National Public Health Service - Wales

NHS Direct

NHS Health and Social Care Information Centre

NHS Plus

NHS Quality Improvement Scotland

North Cumbria Acute Hospitals NHS Trust

North Tees PCT

North Yorkshire and York PCT

Nottingham University Hospitals NHS Trust

PAGB

PERIGON Healthcare Ltd

Powys Local Health Board

Primary Care Pharmacists Association

Q-Med UK Ltd

Respironics UK

Roche Diagnostics Ltd

Rotherham PCT

Royal Brompton & Harefield NHS Trust

Royal College of General Practitioners

Royal college of Midwives

Royal College of Nursing

Royal College of Paediatrics and Child Health

Royal College of Pathologists

Royal College of Physicians of London

Royal College of Radiologists

Royal Liverpool and Broadgreen NHS Trust

Royal Pharmaceutical Society of Great Britain

Royal Society of Medicine

Salford PCT

Sandwell PCT

Sanofi-Aventis

Schering-Plough Ltd

Scottish Intercollegiate Guidelines Network (SIGN)

Sedgefield PCT

Sefton PCT

Sheffield PCT

Sheffield Teaching Hospitals NHS Foundation Trust

Social Care Institute for Excellence (SCIE)

Solihull PCT

South Staffordshire PCT

Specialist Advisory Committee on Antimicrobial Resistance (SACAR)

St Mary's Hospital, Isle of Wight Healthcare NHS Trust

Trafford PCT

University Hospital of South Manchester

University of Wales, Bangor

Warrington PCT

Welsh Assembly Government

Welsh Scientific Advisory Committee

West & East & North Hertfordshire PCTs

West Midlands Ambulance Service NHS Trust

Whipps Cross Hospitals NHS Trust

Wiltshire PCT

Wyeth Pharmaceuticals

Yorkshire Ambulance Service

5.2 Declarations

5.2.1 Authorship and citation

Authorship of this full guideline document is attributed to the NICE Short Clinical Guidelines Technical Team and members of the GDG under group authorship.

The guideline should be cited as: NICE Short Clinical Guidelines Technical Team (2008). Respiratory tract infections – antibiotic prescribing. Prescribing of antibiotics for self-limiting respiratory tract infections in adults and children in primary care. London: National Institute for Health and Clinical Excellence.

5.2.2 Declarations of interest

A full list of all declarations of interest made by this GDG is available on the NICE website (www.nice.org.uk).

6 Appendices

Available as a separate document:

6.1 Appendix 1 – Scope

6.2 Appendix 2 – Key clinical questions

6.3 Appendix 3 – Search strategy

6.4 Appendix 4 – Inclusion and exclusion criteria and evidence tables

6.5 Appendix 5 – Health economic evidence

6.6 Appendix 6 – Health economic evidence tables

NICE clinical guideline 69 – Antibiotic prescribing – respiratory tract infections

6 Appendices

6. 1 Appendix 1 – Scope

NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

SCOPE

1 Guideline title

Prescribing of antibiotics for self-limiting respiratory tract infections in adults and children in primary care

1.1 Short title

Respiratory tract infections – antibiotic prescribing

2 Background

The National Institute for Health and Clinical Excellence ('NICE' or 'the Institute') will develop an optimal practice review on prescribing of antibiotics for self-limiting respiratory tract infections in adults and children in primary care. The guideline will provide recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness.

3 Clinical need for the guideline

a) Antibiotics are commonly prescribed in primary care for respiratory tract infections (RTIs) in both adults and children. General practice consultation rates in England and Wales show that a quarter of the population will visit their GP because of an RTI each year. RTIs are the reason for 60% of all antibiotic prescribing in general practice, and this constitutes a significant cost to the NHS. The cost of acute cough alone, in terms of antibiotic prescribing costs, is greater than £15 million a year.

b) There is good evidence that antibiotics offer little benefit in treating a large proportion of RTIs in adults and children in primary care. These RTIs include the common cold, sore throat, acute sinusitis, acute otitis media and acute bronchitis. These conditions are largely self-limiting, and complications are likely to be rare if

antibiotics are withheld. The inappropriate prescribing of antibiotics has the potential to cause drug-related adverse events, to increase the prevalence of antibiotic-resistant organisms in the community and to increase primary care consultation rates for minor illness.

c) Three different antibiotic management strategies can be used to deal with RTIs within the primary care consultation: no antibiotic prescribing; delayed (or deferred) antibiotic prescribing (in which an antibiotic prescription is written for use at a later date should symptoms worsen); and immediate antibiotic prescribing. The decision negotiated between practitioner and patient depends on both the practitioner's assessment of the risk of complications if antibiotics are withheld and on the patient's expectations regarding an antibiotic prescription. Perceived advantages of delayed prescribing as a strategy over no prescribing are that it offers a 'safety net' for the small proportion of cases that develop into complicated infections, and a patient expecting antibiotics is more likely to agree with this course of action rather than with no prescribing. There is also evidence that delayed antibiotic prescribing reduces the use of antibiotics for the common cold, acute otitis media, sore throat, sinusitis and acute bronchitis.

d) Prescribing patterns for antibiotics for RTIs vary widely among different general practices. Furthermore, although delayed prescribing strategies have been advocated as a method of optimising antibiotic use since the late 1990s, it is unclear to what extent they have been taken up in primary care in England and Wales.

e) There is currently no national clinical guideline in the UK relating to antibiotic prescribing for self-limiting RTIs in primary care. There is therefore a need for guidance for primary care practitioners (chiefly GPs, nurse practitioners and pharmacists) on:

- which RTIs do not require immediate antibiotic treatment
- which antibiotic management strategies could be offered once a decision has been made that the patient does not need immediate antibiotic treatment
- the clinical and cost effectiveness of delayed prescribing or no prescribing as a management strategy to be used in the consultation to ensure the appropriate use of antibiotics for RTIs.

4 The guideline

a) This document is the scope. It defines exactly what this guideline will (and will not) examine, and what the guideline developers will consider.

b) The areas that will be addressed by the guideline are described in the following sections.

4.1 Population

4.1.1 Groups that will be covered

Adults and children (3 months and older) in whom immediate antibiotic prescribing is not indicated (see section 4.3 a).

4.1.2 Groups that will not be covered

Adults and children with RTIs in whom further investigation and/or immediate antibiotic prescribing is appropriate.

4.2 Healthcare setting

Primary care and community settings. These will include general practices, community pharmacies, NHS walk-in centres and primary medical and nursing care provided in emergency departments.

4.3 Clinical management (including key interventions)

4.3.1 Areas covered by the guideline

a) Definitions, using clinical symptoms and signs, for the following RTIs considered suitable for delayed prescribing or no prescribing:

- earache (suspected acute otitis media)

- sore throat (suspected pharyngitis or tonsillitis)
- acute cough (suspected acute bronchitis)
- acute sinusitis
- common cold/rhinosinusitis.

This will include consideration of the evidence relating to the ability of symptom/sign clusters for each condition to predict likely benefit or not from immediate prescription of antibiotics.

b) Assessment of the above conditions within the primary care consultation, in order to decide what antibiotic management strategies should be offered.

c) For patients for whom antibiotics are not indicated immediately, the following antibiotic management strategies will be considered.

- Delayed treatment with antibiotics, including methods and duration of delay (antibiotic prescription written for collection or use at a later date should symptoms worsen or persist for a defined period of time).
- No treatment with antibiotics (patients may be asked to reconsult if symptoms worsen or persist for a defined period of time).

d) The mode of delivery of the strategies in 4.3.1 c – brief verbal advice from the practitioner compared with the use of patient information leaflets.

e) Advice on the use of analgesics (paracetamol/aspirin and/or ibuprofen) for patients in 4.3.1 c.

4.3.2 Areas not covered by the guideline

a) Details of diagnosis and management of specific RTIs.

b) Details of antibiotic regimens.

c) The use of rapid diagnostic tests.

d) Management of individuals with comorbidities that will affect the decision to prescribe antibiotics (for example, asthma or chronic obstructive pulmonary disease – COPD).

4.4 Key outcome measures

Key outcomes that will be considered when reviewing the evidence include:

a) the presence, duration and severity of symptoms such as fever, pain and malaise
b) the risk of complications from not prescribing antibiotics
c) adverse events from prescribing antibiotics (for example, diarrhoea, vomiting, rashes, abdominal pain)
d) the level of antibiotic prescribing, including antibiotic prescriptions consumed or collected
e) resource use (including reconsultation rates and rates of referral to secondary care)
f) patient satisfaction and health-related quality of life.

4.5 Status

4.5.1 Scope

This is the final scope.

Related NICE guidance

Feverish illness in children: assessment and initial management in children younger than 5 years. NICE clinical guideline 47 (2007). Available from: www.nice.org.uk/CG047

Medicines concordance and adherence: involving adults and carers in decisions about prescribed medicines. NICE clinical guideline. Publication expected December 2008. See www.nice.org.uk

4.5.2 Guideline

The development of the guideline recommendations began in October 2007.

5 Further information

Information on the guideline development process is provided in:

- 'The guideline development process: an overview for stakeholders, the public and the NHS'
- 'The guidelines manual'
- 'Background and overview of the short guidelines programme'
- 'The short guideline process – consultation document'.

These booklets are available as PDF files from the NICE website (www.nice.org.uk/guidelinesmanual). Information on the progress of the guideline will also be available from the website.

The development group will work in accordance with the methods set out in the documents above.

6.2 Appendix 2 – Key clinical questions

6.2.1 Topic areas and structured clinical questions

Topic 1: Antibiotic management strategies for RTIs

1. *The effectiveness and cost effectiveness of delayed antibiotic prescribing and/or no prescribing as strategies for managing RTIs and how they should be delivered?*

Topic 2: Identifying patients with RTIs who are likely to be at risk of developing complications

2. *What are the clinical symptoms, signs and risk factors that predict which patients with RTIs are likely to develop complications?*

Topic 3: Patients' preferences regarding antibiotic management strategies for RTIs (no prescribing, delayed prescribing and immediate prescribing strategies)

3. *What are patients' preferences regarding antibiotic management strategies for RTIs (no prescribing, delayed prescribing and immediate prescribing strategies)?*

6.3 Appendix 3 – Search strategy

6.3.1 Scoping searches

Scoping searches were undertaken in April 2007. The following websites and databases (listed in alphabetical order) were browsed and/or searched to identify existing clinical practice guidelines, key systematic reviews and other relevant information for the purposes of scope development and project planning.

Guidance/guidelines	**Systematic reviews**
• Agency for Healthcare Research and Quality (US) • British Thoracic Society • Canadian Medical Association Infobase • Department of Health • European Respiratory Society • Guidelines International Network (GIN) • Health Protection Agency • National Guideline Clearinghouse (US) • National Health and Medical Research Council (Australia) • National Institute for Health and Clinical Excellence (NICE) • National Library for Health - Clinical Knowledge Summaries - National Library of Guidelines - Protocols and Care Pathways Library - Specialist Libraries • New Zealand Guidelines Group • Royal College of General Practitioners • Royal College of Paediatrics and Child Health • Royal College of Physicians • Scottish Intercollegiate Guidelines Network (SIGN) • World Health Organization (WHO)	• Clinical Evidence • Cochrane Database of Systematic Reviews (CDSR) • Database of Abstracts of Reviews of Effects (DARE) • Health Technology Assessment (HTA) Database • National Coordinating Centre for Health Technology Assessment (NCCHTA) • NHS R&D Service Delivery and Organisation Programme • TRIP Database

6.3.2 Main searches

Overview of the efficacy of antibiotics for RTIs in primary care

For the overview of the efficacy of antibiotics for RTIs in primary care (section 2.1 in the main guideline) systematic reviews were sought from the Cochrane Database of Systematic Reviews (Cochrane Library 2007, Issue 3). The search was undertaken on 22 August 2007 using the strategy presented below.

#1 MeSH descriptor Anti-Bacterial Agents explode all trees
#2 (antibiotic*):ti,ab,kw
#3 (anti-bacterial*):ti,ab,kw
#4 (antibacterial*):ti,ab,kw
#5 (bacteriocid*):ti,ab,kw
#6 (bactericid*):ti,ab,kw
#7 (antimycobacterial*):ti,ab,kw
#8 (anti-mycobacterial* or antimicrobial* or anti-microbial*):ti,ab,kw
#9 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)
#10 MeSH descriptor Respiratory Tract Infections, this term only
#11 (respiratory near/2 infection*):ti,ab,kw
#12 MeSH descriptor Common Cold, this term only
#13 (cold* or coryza or rti* or urti* or lrti*):ti,ab,kw
#14 MeSH descriptor Cough, this term only
#15 (cough*):ti,ab,kw
#16 MeSH descriptor Pharyngitis, this term only
#17 (pharyngitis):ti,ab,kw
#18 ("sore throat" or "sore throats"):ti,ab,kw
#19 MeSH descriptor Rhinitis explode all trees
#20 (rhinitis or rhinitic*):ti,ab,kw
#21 MeSH descriptor Sinusitis explode all trees
#22 (sinusit*):ti,ab,kw
#23 (rhinosinusit*):ti,ab,kw
#24 MeSH descriptor Tonsillitis, this term only
#25 (tonsillitis):ti,ab,kw
#26 MeSH descriptor Laryngitis, this term only
#27 (laryngitis):ti,ab,kw
#28 MeSH descriptor Bronchitis explode all trees
#29 (bronchitis or bronchitic*):ti,ab,kw
#30 (bronchiolitis or bronchiolitic*):ti,ab,kw
#31 MeSH descriptor Otitis Media explode all trees
#32 (otitis media):ti,ab,kw
#33 MeSH descriptor Earache, this term only

#34 (earache* or otalgia*):ti,ab,kw
#35 (ear near/2 ache*):ti,ab,kw
#36 (ear near/2 infect*):ti,ab,kw
#37 (ear near/2 inflammat*):ti,ab,kw
#38 (#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37)
#39 (#9 AND #38)

Antibiotic management strategies for RTIs

Literature searches were undertaken on 22 August 2007 to answer the question: 'Are delayed and no antibiotic prescribing strategies more effective compared with immediate antibiotic prescribing for managing RTIs?' (see also section 2.2.3 in the main guideline).

The sources searched included:

- Cochrane Database of Systematic Reviews – CDSR (Wiley)
- Database of Abstracts of Reviews of Effects – DARE (Wiley and CRD website)
- Health Technology Assessment (HTA) Database – (Wiley and CRD website)
- Cochrane Central Register of Controlled Trials – CENTRAL (Wiley)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)
- EMBASE (Ovid)
- CINAHL (Ovid)
- Science Citation Index (Dialog DataStar)
- National Research Register – NRR
- Clinicaltrials.gov
- *meta*Register of Controlled Trials – *m*RCT

The MEDLINE search strategy presented below was used and translated for use in all other databases.

1. Respiratory Tract Infections/
2. Common Cold/
3. exp Otitis Media/
4. Earache/
5. Pharyngitis/
6. exp Laryngitis/
7. exp Tonsillitis/
8. exp Bronchitis/
9. Cough/
10. Rhinitis/
11. exp Sinusitis/
12. (respiratory adj3 (infection$ or inflamm$)).tw.
13. (RTI$ or URTI$ or LRTI$).tw.
14. cold$.tw.
15. coryza$.tw.
16. (otitis adj2 media$).tw.
17. otalgia.tw.
18. earache$.tw.
19. (ear$ adj3 (ache$ or infect$ or inflamm$)).tw
20. pharyngitis.tw.
21. laryngitis.tw.
22. tonsillitis.tw.
23. (sore$ adj3 throat$).tw.
24. (throat$ adj3 infect$).tw.
25. bronchit$.tw.
26. bronchiolit$.tw.
27. cough$.tw.
28. rhiniti$.tw.
29. rhinosinusit$.tw.
30. sinusit$.tw.
31. or/1-30
32. exp Anti-Bacterial Agents/
33. antibiotic$.tw.
34. (anti-bacterial$ or antibacterial$).tw.
35. (anti-microbial$ or antimicrobial$).tw.
36. (anti-mycobacterial$ or antimycobacterial$).tw.
37. (bacteriocid$ or bactericid$).tw.
38. or/32-37
39. Unnecessary Procedures/
40. (prescription$ adj5 (strateg$ or appropriat$ or inappropriat$ or unnecessary or delay$ or defer$ or no or non or behaviour$ or behavior$ or immediate$ or optimal or optimi?$ or reduc$ or decreas$ or declin$ or rate$ or improv$ or back-up$)).tw.

41. (prescrib$ adj5 (strateg$ or appropriat$ or inappropriat$ or unnecessary or delay$ or defer$ or no or non or behaviour$ or behavior$ or immediate$ or optimal or optimi?$ or reduc$ or decreas$ or declin$ or rate$ or improv$ or back-up$)).tw.
42. (delay$ adj3 (treat$ or therap$)).tw.
43. (immediate$ adj3 (treat$ or therap$)).tw.
44. 42 and 43
45. (wait adj2 see).tw.
46. watchful$ wait$.tw.
47. or/39-41, 44-46
48. 31 and 38 and 47

Identifying patients with RTIs who are likely to be at risk of developing complications

Literature searches were undertaken on 13 November 2007 to answer the question: 'What are the clinical symptoms, signs and risk factors that predict which patients with RTIs are likely to develop complications?' (see also section 2.2.3 in the main guideline).

The MEDLINE search strategy presented below was used. It was translated for use in all other databases listed in section 1.1.3 in the main guideline.

1. "signs and symptoms"/
2. ((sign or signs) adj5 symptom$).tw.
3. risk factors/
4. factor$.tw.
5. predict$.tw.
6. or/1-5
7. Ambulatory Care/
8. Family Practice/
9. Physicians, Family/
10. Primary Health Care/
11. Emergency Service, Hospital/
12. Community Health Services/
13. Outpatient Clinics, Hospital/
14. ((general or family) adj (practice$ or practitioner$ or physician$ or doctor$)).tw.
15. GP$.tw.
16. (primary adj2 care).tw.
17. primary healthcare.tw.
18. (ambulatory adj2 care).tw.
19. ((walk-in or walk in) adj2 centre$).tw.
20. (accident and emergency).tw.
21. (emergency adj2 department$).tw.

22. (community health adj2 (care or service$)).tw.
23. ((outpatient or hospital) adj2 clinic$).tw.
24. or/7-23
25. Pharyngitis/
26. exp Tonsillitis/
27. exp Laryngitis/
28. pharyngitis.tw.
29. tonsillitis.tw.
30. laryngitis.tw.
31. (sore$ adj3 throat$).tw.
32. (throat$ adj3 infect$).tw.
33. or/25-32
34. Rheumatic Fever/
35. Glomerulonephritis/
36. Otitis Media/
37. Sinusitis/
38. Peritonsillar Abscess/
39. Impetigo/
40. Cellulitis/
41. (rheumatic adj2 fever$).tw.
42. glomerulonephritis.tw.
43. (otitis adj2 media).tw.
44. sinusitis.tw.
45. (peritonsillar adj2 abscess$).tw.
46. quinsy.tw.
47. impetigo.tw.
48. cellulitis.tw.
49. poor outcome$.tw.
50. complication$.tw.
51. Co.fs
52. Rheumatic Heart Disease/
53. (rheumatic adj2 carditis).tw.
54. Scarlet Fever/
55. (scarlet fever or scarletiniform rash$ or scarlatina).tw.
56. Tonsillectomy/
57. tonsillectom$.tw.
58. (illness$ adj3 duration$).tw.
59. Prognosis/
60. prognosis.tw.
61. or/34-60
62. 6 and 24 and 33 and 61
63. Earache/
64. Otitis Media/
65. earache$.tw.
66. (ear$ adj3 (ache$ or infect$ or inflamm$)).tw.
67. (otitis adj2 media$).tw.
68. otalgia.tw.
69. or/63-68

70. Mastoiditis/
71. Intracranial Thrombosis/
72. Brain Abscess/
73. Otitis Media, Suppurative/
74. Deafness/
75. exp Sinus Thrombosis, Intracranial/
76. Epidural Abscess/
77. Tympanic Membrane Perforation/
78. mastoiditis.tw.
79. ((cerebral or intracranial or brain) adj2 (thrombosis or thrombus)).tw.
80. ((cerebral or brain) adj2 abscess$).tw.
81. (sinus adj2 (thrombosis or thrombus or thrombophlebitis)).tw.
82. ((epidural or subperiosteal or cerebellar or sundural) adj2 abscess$).tw.
83. (otitis adj2 media adj2 (suppurative or purulent$ or contralateral or contra-lateral)).tw.
84. deafness.tw.
85. (hearing adj2 (loss or impair$)).tw.
86. poor outcome$.tw.
87. complication$.tw.
88. (illness$ adj3 duration$).tw.
89. Prognosis/
90. prognosis.tw.
91. Co.fs.
92. ((tympanic membrane or eardrum) adj2 (perforat$ or rupture$)).tw.
93. or/70-92
94. 6 and 24 and 69 and 93
95. Cough/
96. exp Bronchitis/
97. cough$.tw.
98. bronchit$.tw.
99. bronchiolit$.tw.
100. or/95-99
101. Pneumonia/
102. exp Empyema/
103. pneumonia.tw.
104. empyema.tw.
105. pyothorax.tw.
106. poor outcome$.tw.
107. complication$.tw.
108. Co.fs.
109. (illness$ adj3 duration$).tw.
110. Prognosis/
111. prognosis.tw.
112. or/101-111
113. 6 and 24 and 100 and 112
114. exp Sinusitis/
115. sinusit$.tw.
116. or/114-115

117. Brain Abscess/
118. ((cerebral or brain) adj2 abscess$).tw.
119. ((epidural or subperiosteal or cerebellar or sundural) adj2 abscess$).tw.
120. poor outcome$.tw.
121. complication$.tw.
122. Co.fs.
123. (illness$ adj3 duration$).tw.
124. Prognosis/
125. prognosis.tw.
126. or/117-125
127. 6 and 24 and 116 and 126
128. Common Cold/
129. Rhinitis/ and Sinusitis/
130. cold$.tw.
131. coryza$.tw.
132. rhinosinusit$.tw.
133. or/128-132
134. Otitis Media with Effusion/
135. Eustachian Tube/
136. (otitis adj2 media adj2 (effusion or serous or secretory)).tw.
137. (eustachian tube adj (dysfunction or inflamm$)).tw.
138. poor outcome$.tw.
139. complication$.tw.
140. Co.fs.
141. (illness$ adj3 duration$).tw.
142. Prognosis/
143. prognosis.tw.
144. or/134-143
145. 6 and 24 and 133 and 144
146. animals/
147. humans/
148. 146 not (146 and 147)
149. 62 not 148
150. 94 not 148
151. 113 not 148
152. 127 not 148
153. 145 not 148

Patients' preferences regarding antibiotic management strategies for RTIs (delayed antibiotic prescribing, no prescribing and immediate prescribing)

Literature searches were undertaken on 13 December 2007 to answer the following question 'What are patients' preferences regarding antibiotic management strategies for RTIs (no antibiotic prescribing, delayed antibiotic

prescribing and immediate antibiotic prescribing strategies)?' (see also section 2.4.3 in the main guideline).

The MEDLINE search strategy presented below was used. It was translated for use in all other databases listed in section 1.1.3 in the main guideline. The Social Science Citation Index (Dialog DataStar) was searched in place of the Science Citation Index (Dialog DataStar).

1. Respiratory Tract Infections/
2. Common Cold/
3. exp Otitis Media/
4. Earache/
5. Pharyngitis/
6. exp Laryngitis/
7. exp Tonsillitis/
8. exp Bronchitis/
9. Cough/
10. Rhinitis/
11. exp Sinusitis/
12. (respiratory adj3 (infection$ or inflamm$)).tw.
13. (RTI$ or URTI$ or LRTI$).tw.
14. cold$.tw.
15. coryza$.tw.
16. (otitis adj2 media$).tw.
17. otalgia.tw.
18. earache$.tw.
19. (ear$ adj3 (ache$ or infect$ or inflamm$)).tw.
20. pharyngitis.tw.
21. laryngitis.tw.
22. tonsillitis.tw.
23. (sore$ adj3 throat$).tw.
24. (throat$ adj3 infect$).tw.
25. bronchit$.tw.
26. bronchiolit$.tw.
27. cough$.tw.
28. rhiniti$.tw.
29. rhinosinusit$.tw.
30. sinusit$.tw.
31. or/1-30
32. exp Anti-Bacterial Agents/
33. antibiotic$.tw.
34. (anti-bacterial$ or antibacterial$).tw.
35. (anti-microbial$ or antimicrobial$).tw.
36. (anti-mycobacterial$ or antimycobacterial$).tw.
37. (bacteriocid$ or bactericid$).tw.
38. or/32-37

39. Ambulatory Care/
40. Family Practice/
41. Physicians, Family/
42. Primary Health Care/
43. Emergency Service, Hospital/
44. Community Health Services/
45. Outpatient Clinics, Hospital/
46. ((general or family) adj (practice$ or practitioner$ or physician$ or doctor$)).tw.
47. GP$.tw.
48. (primary adj2 care).tw.
49. primary healthcare.tw.
50. (ambulatory adj2 care).tw.
51. ((walk-in or walk in) adj2 centre$).tw.
52. (accident and emergency).tw.
53. (emergency adj2 department$).tw.
54. (community health adj2 (care or service$)).tw.
55. ((outpatient or hospital) adj2 clinic$).tw.
56. or/39-55
57. Qualitative Research/
58. Nursing Methodology Research/
59. exp Interviews/
60. Questionnaires/
61. Narration/
62. Health Care Surveys/
63. (qualitative$ or interview$ or focus group$ or questionnaire$ or narrative$ or narration$ or survey$).tw.
64. (ethno$ or emic or etic or phenomenolog$ or grounded theory or constant compar$ or (thematic$ adj3 analys$) or theoretical sampl$ or purposive sampl$).tw.
65. (hermeneutic$ or heidegger$ or husser$ or colaizzi$ or van kaam$ or van manen$ or giorgi$ or glaser$ or strauss$ or ricoeur$ or spiegelberg$ or merleau$).tw.
66. (metasynthes$ or meta-synthes$ or metasummar$ or meta-summar$ or metastud$ or meta-stud$).tw.
67. or/57-66
68. exp Patients/px
69. Outpatients/px
70. exp Parents/px
71. exp Family/px
72. exp Consumer Satisfaction/
73. exp Consumer Participation/
74. exp Decision Making/
75. Professional-Patient Relations/
76. Physician-Patient Relations/
77. exp Attitude to Health/
78. Attitude/
79. Perception/

80. Emotions/
81. Anxiety/
82. ((patient$ or outpatient$ or out-patient$ or parent$ or famil$ or consumer$ or user$) adj2 (satisf$ or participat$ or decision$ or choice$ or attitud$ or perception$ or perceiv$ or expectation$ or prefer$ or view$ or opinion$ or accept$ or perspective$ or issue$ or belief$ or believ$ or feeling$ or felt$ or thought$ or anxi$ or know$ or understand$ or concern$ or confiden$ or uncertain$ or unsure)).tw.
83. or/68-82
84. 31 and 38 and 56 and (67 or 83)

Economic evaluations and quality of life data

The following sources were searched on 22 November 2007 to identify economic evaluations:

- NHS Economic Evaluation Database – NHS EED (Wiley and CRD website)
- Health Economics Evaluation Database – HEED
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)
- EMBASE (Ovid).

Economic evaluations were sought for all years from NHS EED and HEED. In addition, economic evaluations were sought from MEDLINE, MEDLINE In-Process and EMBASE from 2006 onwards to allow for any indexing time lags associated with NHS EED and HEED. The NHS EED and MEDLINE strategies are presented below; they were translated for use in all other databases.

NHS EED

1. MeSH Otitis Media EXPLODE 1
2. MeSH Earache
3. otitis NEAR media
4. otalgia
5. earache*
6. ear NEAR ache*
7. ear NEAR infect*
8. ear NEAR inflamm*
9. #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8
10. MeSH Pharyngitis
11. MeSH Laryngitis EXPLODE 1 2 3
12. MeSH Tonsillitis EXPLODE 1 2 3
13. pharyngitis
14. laryngitis
15. tonsillitis
16. sore NEAR throat*
17. throat NEAR infect*

18. #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17
19. MeSH Bronchitis EXPLODE 1 2 3
20. MeSH Cough
21. bronchit*
22. bronchiolit*
23. cough*
24. #19 or #20 or #21 or #22 or #23
25. MeSH Common Cold EXPLODE 1 2
26. MeSH Rhinitis EXPLODE 1 2 3
27. MeSH Sinusitis EXPLODE 1 2 3
28. #26 and #27
29. cold*
30. coryza*
31. rhinit*
32. rhinosinusit*
33. #25 or #28 or #29 or #30 or #31 or #32
34. MeSH Sinusitis EXPLODE 1 2 3
35. sinusit*
36. #34 or #35
37. MeSH Anti-Bacterial Agents EXPLODE 1
38. antibiotic*
39. antibacterial* OR anti-bacterial*
40. antimicrobial* OR anti-microbial*
41. antimycobacterial* OR anti-mycobacterial*
42. bacteriocid* OR bactericid*
43. #37 or #38 or #39 or #40 or #41 or #42
44. #9 and #43
45. #18 and #43
46. #24 and #43
47. #33 and #43
48. #36 and #43
49. #44 or #45 or #46 or #47 or #48

MEDLINE

1. Common Cold/
2. Rhinitis/
3. exp Sinusitis/
4. 2 and 3
5. cold$.tw.
6. coryza$.tw.
7. rhinit$.tw.
8. rhinosinusit$.tw.
9. or/1,4-8
10. exp Otitis Media/
11. Earache/
12. (otitis adj2 media$).tw.
13. otalgia.tw.

14. earache$.tw.
15. (ear$ adj3 (ache$ or infect$ or inflamm$)).tw.
16. or/10-15
17. Pharyngitis/
18. exp Laryngitis/
19. exp Tonsillitis/
20. pharyngitis.tw.
21. laryngitis.tw.
22. tonsillitis.tw.
23. (sore$ adj3 throat$).tw.
24. (throat$ adj3 infect$).tw.
25. or/17-24
26. exp Bronchitis/
27. Cough/
28. bronchit$.tw.
29. bronchiolit$.tw.
30. cough$.tw.
31. or/26-30
32. exp Sinusitis/
33. sinusit$.tw.
34. 32 or 33
35. exp Anti-Bacterial Agents/
36. antibiotic$.tw.
37. (anti-bacterial$ or antibacterial$).tw.
38. (anti-microbial$ or antimicrobial$).tw.
39. (anti-mycobacterial$ or antimycobacterial$).tw.
40. (bacteriocid$ or bactericid$).tw.
41. or/35-40
42. Economics/
43. exp "Costs and Cost Analysis"/
44. Economics, Dental/
45. exp Economics, Hospital/
46. exp Economics, Medical/
47. Economics, Nursing/
48. Economics, Pharmaceutical/
49. Budgets/
50. exp models, economic/
51. markov chains/
52. monte carlo method/
53. Decision Trees/
54. econom$.tw.
55. cba.tw.
56. cea.tw.
57. cua.tw.
58. markov$.tw.
59. (monte adj carlo).tw.
60. (decision adj2 (tree$ or analys$)).tw.
61. (cost or costs or costing$ or costly or costed).tw.

62. (price$ or pricing$).tw.
63. budget$.tw.
64. expenditure$.tw.
65. (value adj2 (money or monetary)).tw.
66. (pharmacoeconomic$ or (pharmaco adj economic$)).tw.
67. or/42-66
68. 9 and 41 and 67 (100)
69. limit 68 to yr="2006 - 2008"
70. 16 and 41 and 67 (307)
71. limit 70 to yr="2006 - 2008"
72. 25 and 41 and 67 (192)
73. limit 72 to yr="2006 - 2008"
74. 31 and 41 and 67 (261)
75. limit 74 to yr="2006 - 2008"
76. 34 and 41 and 67 (161)
77. limit 76 to yr="2006 - 2008"

Quality of life data were sought from MEDLINE and MEDLINE In-Process for all years by appending the following search filter to lines 1–41 of the MEDLINE search for economic evaluations.

1. "Quality of Life"/
2. quality of life.tw.
3. "Value of Life"/
4. Quality-Adjusted Life Years/
5. quality adjusted life.tw.
6. (qaly$ or qald$ or qale$ or qtime$).tw.
7. disability adjusted life.tw.
8. daly$.tw.
9. Health Status Indicators/
10. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
11. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
12. (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
13. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
14. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
15. (euroqol or euro qol or eq5d or eq 5d).tw.
16. (qol or hql or hqol or hrqol).tw.
17. (hye or hyes).tw.
18. health$ year$ equivalent$.tw.
19. utilit$.tw.

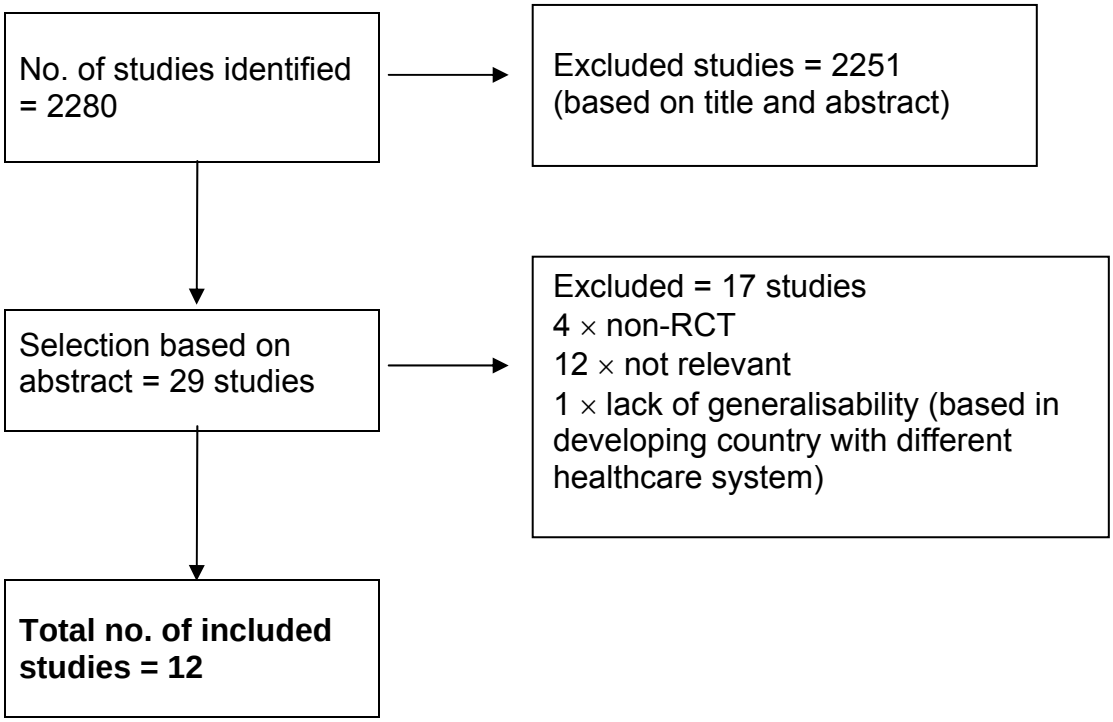
20. (hui or hui1 or hui2 or hui3).tw.
21. disutili$.tw.
22. rosser.tw.
23. quality of wellbeing.tw.
24. quality of well-being.tw.
25. qwb.tw.
26. willingness to pay.tw.
27. standard gamble$.tw.
28. time trade off.tw.
29. time tradeoff.tw.
30. tto.tw.
31. or/1-30

6.4 Appendix 4 – Inclusion and exclusion criteria and evidence tables

6.4.1 Chapter 1 – Antibiotic management strategies for RTIs

Language	English
Status	Published papers (full papers only)
Study design	Randomised controlled trial
Contents of papers *(inclusion/exclusion criteria)*	Intervention studies comparing the effectiveness of delayed and/or no antibiotic prescribing strategies with immediate prescribing strategy in primary care settings. Conditions included are: • acute otitis media • acute cough/bronchitis • acute sore throat • acute sinusitis • common cold. As well as the clinical effectiveness, the modes of delivery of delayed and no prescribing strategies were also explored and include: • duration of delay for the five types of RTIs • brief verbal advice from the practitioner • patient information leaflet • advice on the use of analgesics (paracetamol/aspirin and/or ibuprofen). Studies that looked only at the efficacy of antibiotic regimens compared with placebo or studies based on specific subgroup populations with specific comorbidities (i.e. COPD, asthma, etc.) were excluded. Studies based in developing countries where there are significant differences in terms of epidemiology, healthcare systems and primary care practices were also excluded because of lack of generalisability.

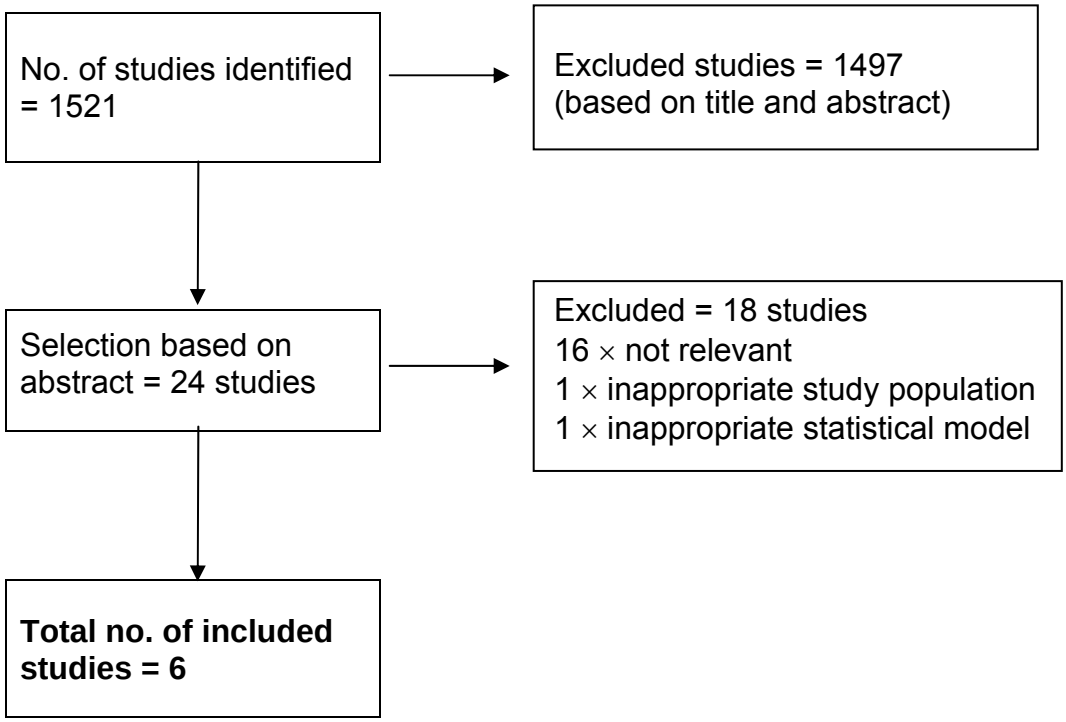
Flow chart 1 Volume of evidence for chapter 1



6.4.2 Chapter 2 – Identifying patients with RTIs who are likely to be at risk of developing complications

Language	English
Status	Published papers (full papers only)
Study design	• Prospective/retrospective cohort studies and case–control studies were included. • Uncontrolled studies, including case series of those with complications, were excluded.
Population	All adults and children in primary care settings excluding: • children aged under 3 months • individuals with defined comorbidities • those not presenting in primary care and first contact (emergency department) settings.
Contents of papers *(inclusion/exclusion criteria)*	Studies that explore clinical symptoms, signs and/or prediction rule models that predict serious complications in those presenting with: • acute otitis media • acute cough/bronchitis • acute sore throat • acute sinusitis • common cold. Complications were explored for: • acute sore throat (acute otitis media, contralateral AOM, acute sinusitis, peritonsillar abscess/quinsy and cellulitis/impetigo) • acute otitis media (mastoiditis, contralateral AOM and deafness) • acute cough/bronchitis (pneumonia and emphysema) • acute sinusitis (frontal abscess) • common cold (frontal abscess). Studies that specifically looked at derivation or validation of diagnostic tools/assessments for the above complications were excluded.

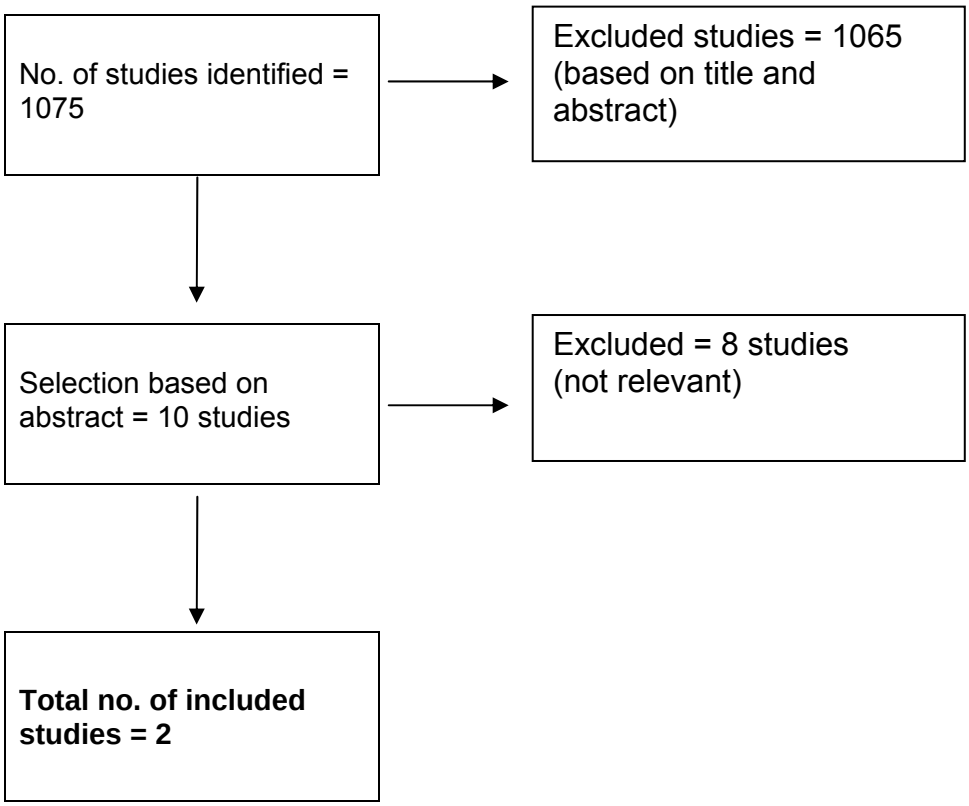
Flow chart 2 Volume of evidence for chapter 2



6.4.3 Chapter 3 – Patients' preferences regarding antibiotic management strategies for RTIs (no prescribing, delayed prescribing and immediate prescribing strategies)

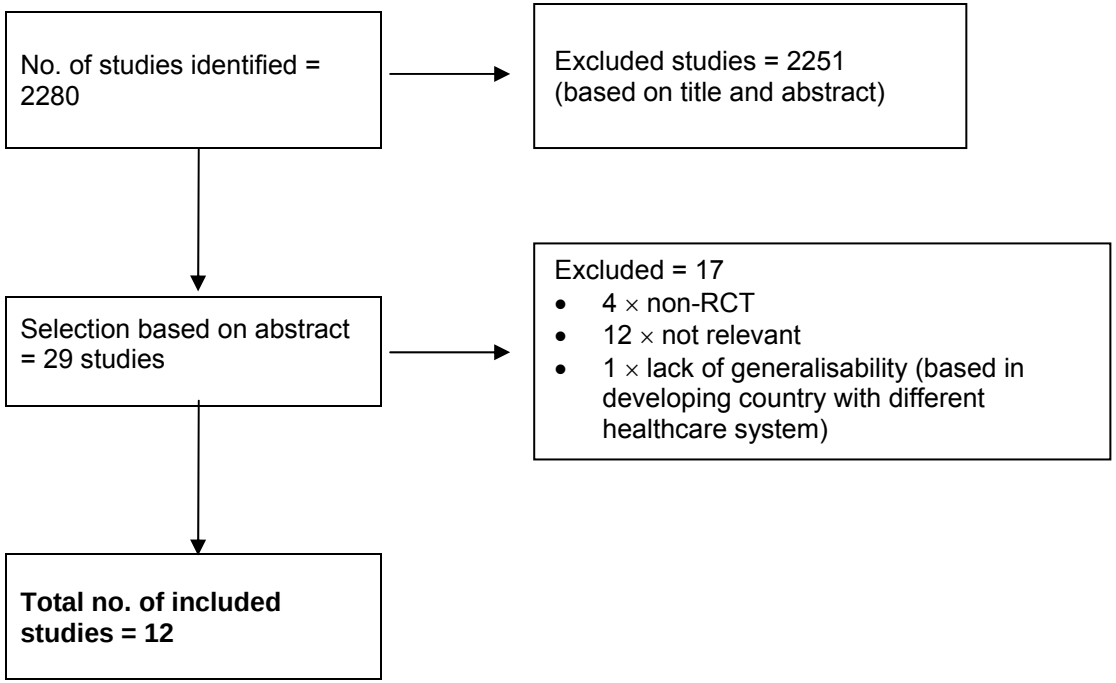
Language	English
Status	Published papers (full papers only)
Study design	Qualitative study and questionnaire survey
Population	All adults and children/parents in primary care and first contact (emergency department) settings consulting with the RTIs defined in the scope excluding: • parents of children aged under 3 months • individuals with specific comorbidities (e.g. asthma, COPD). Evidence from population subgroups (e.g. BME) who may have differing preferences than the population included in the antibiotic management trials will be sought.
Contents of papers *(inclusion/exclusion criteria)*	Studies that explored expectation, satisfaction and preferences of adult patients or parents of children on no prescribing, delayed prescribing and immediate prescribing strategies. Conditions included: • acute otitis media • acute cough/bronchitis • acute sore throat • acute sinusitis • common cold. Studies that specifically explored differing preferences of subgroups (e.g. BME) on antibiotic management strategies were included. Studies that reported general attitudes or expectations regarding antibiotic use were excluded.

Flow chart 3 Volume of evidence for chapter 3



6.4.3 – Evidence Table

Volume of evidence (key clinical question 1)



Topic 1 Antibiotic management strategies for RTIs

Key clinical question 1
The effectiveness and cost effectiveness of delayed antibiotic prescribing and/or no prescribing as strategies for managing RTIs and how they should be delivered?

Wait-and-see prescription for the treatment of acute otitis media							
Level of evidence	Patient population/ characteristics	Selection/inclusion criteria	Intervention	Comparison	Follow-up	Outcome	Effect size
ID: 453 Level of evidence: (1+) Study type: RCT (single blinded) Authors: Spiro et al. (2006)	Children diagnosed with AOM (aged 6 months to 12 years) <u>No. of participants (completed trial):</u> Total = 265 I = 132 C = 133 <u>At baseline (based on I = 138, C = 145, total = 283):</u> *(I Group)* Male = 57% Median age = 3.6 Mean temp at triage = 37.1 *(C Group)* Male = 52% Median age = 3.2 Mean temp at triage = 36.9	<u>Inclusions:</u> Children diagnosed with AOM at emergency department <u>Exclusions:</u> • Children with severe AOM • Appeared 'toxic' determined by clinician • Patient was hospitalised • Patient was immunocompromised • Patient was treated with AB in the preceding 7 days • Had either myringotomy tubes or a perforated tympanic membrane • Uncertain access to medical care • Primary language not English nor Spanish <u>Study period:</u> 12/07/04–11/07/05 <u>Settings:</u> Paediatric emergency department in US	Wait-and-see AB prescription (Parents asked to fill the prescription if the child either is not better or is worse in 48 hours [2 days]) <u>Mode of delivery:</u> • Prescription was given at consultation • No other forms of advice or information leaflets <u>Analgesics:</u> All patients received ibuprofen (100 mg/5 ml) and otic analgesics drops (4 drops every 2 hours if needed)	Immediate AB prescription <u>Analgesics:</u> All patients received ibuprofen (100 mg/5 ml) and otic analgesics drops (4 drops every 2 hours if needed)	At 4–6 days 11–14 days 30–40 days **Analysis adjusted for race/ ethnicity, insurance status, baseline symptoms*	**Primary outcome** <u>*1) 4–6 days*</u> Did not utilise AB prescription within 3 days after consultation **Secondary outcomes** <u>*1) 4–6 days*</u> Otalgia Fever Diarrhoea Vomiting Unscheduled visits <u>*2) 11–14 days*</u> Otalgia Fever Diarrhoea Vomiting Unscheduled visits	I = 62%, C = 13% Adj RR = 4.80 (95% CI: 3.57–5.85), p < 0.001 Adj RR = 1.01 (95% CI: 0.83–1.17), p = 0.96 Adj RR = 1.04 (95% CI: 0.70–1.44), p = 0.85 Adj RR = 0.30 (95% CI: 0.14–0.64), p < 0.001 Adj RR = 1.24 (95% CI: 0.59–2.41), p = 0.56 Adj RR = 1.17 (95% CI: 0.51–2.51), p = 0.70 Adj RR = 1.19 (95% CI: 0.98–1.34), p = 0.07 Adj RR = 1.20 (95% CI: 0.79–1.68), p = 0.37 Adj RR = 0.44 (95% CI: 0.21–0.83), p = 0.01 Adj RR = 1.13 (95% CI: 0.48–2.47), p = 0.79 Adj RR = 1.27 (95% CI: 0.62–2.39), p = 0.51

						3) 30–40 days Unscheduled visits **Further analysis within the intervention group (AB filled vs. AB not filled)** Willingness to withhold AB for future episodes of AOM *4–6 days* Otalgia Fever Diarrhoea Vomiting	I = 22%, C = 21%, p = 0.85 *4–6 days* AB filled = 28% AB not filled = 63%, p < 0.001 *11–14 days* AB filled = 31% AB not filled = 65%, p < 0.001 *40 days* AB filled = 26% AB not filled = 66%, p < 0.001 RR = 1.62 (95% CI: 1.26–2.03), p < 0.001 RR = 2.95 (95% CI: 1.75–4.99), p < 0.001 RR = 2.46 (95% CI: 0.73–8.29), p = 0.13 RR = 3.28 (95% CI: 1.19–9.04), p = 0.01

Chief findings/comments:

- A well conducted RCT single-blind study (researcher blinded). This RCT has provided evidence that the wait-and-see (delayed) prescribing strategy significantly reduces the use of AB in children with AOM in an urban population presenting to a US emergency department.
- There were no differences in terms of the severity of symptoms between intervention and control group. This indicated that delaying the use of AB does not worsen disease symptoms significantly apart from 'diarrhoea' which was significantly higher in the control group (immediate AB) compared with the intervention group. This indicated the benefit of delayed strategy over immediate AB prescribing on diarrhoea.
- Moreover, within the intervention group, parents who did not fill the prescription were substantially more likely to indicate that they would be willing to withhold AB for future episodes of AOM.

Potential confounder/bias:

- Parents were not blinded to group designation since the primary outcome was based on the treatment choice of the parent.
- The use of otic analgesic drops was not quantified and hence may have been underestimated in the intervention group for symptoms control.

Generalisability:

• Results may not be generalisable to all primary care settings as this was a single-centre study performed in an urban US emergency department.							
Pragmatic randomised controlled trial of two prescribing strategies for childhood acute otitis media							
Level of evidence	Patient population/ characteristics	Selection/inclusion criteria	Intervention	Comparison	Follow-up	Outcome	Effect size
ID: 424 Level of evidence: (1+) Study type: pragmatic open RCT Authors: Little et al. (2001)	Children aged between 6 months and 10 years presenting with AOM <u>No. of participants (completed trial):</u> Total = 285 I = 150 C = 135 <u>At baseline (based on I = 164, C = 151, total = 315):</u> *(I Group)* Mean prior duration of illness (days) = 1.46 Aged > 3 = 57% Perforated ear drum = 7% Bulging ear drum = 47% Red ear drum = 82% *(C Group)* Mean prior duration of illness (days) = 1.48 Aged > 3 = 62% Perforated ear drum = 9% Bulging ear drum = 46% Red ear drum = 78% **No statistical differences* **No evidence of*	<u>Inclusions:</u> Children aged between 6 months and 10 years who attended their doctor with acute otalgia and otoscopic evidence of acute inflammation of the ear drum (dullness or cloudiness with erythema, bulging or perforation). When children were too young for otalgia to be documented then otoscopic evidence alone was a sufficient entry criterion <u>Exclusions:</u> Otoscopic appearances consistent with crying or a fever alone; appearances and history more suggestive of OM with effusion and chronic suppurative OM; serious chronic disease; use of AB within the previous 2 weeks; previous complications; child too unwell to be left to wait and see <u>Study period:</u> Not stated <u>Settings:</u>	Delayed prescription (Patients asked to fill the prescription if symptoms failed to improve after 3 days) <u>Mode of delivery:</u> • Parents were asked to come back to collect the prescription for AB (prescription left at the reception) • Parents were also advised to use the prescription if their child had a discharge for 10 days or more • GPs were supported by standardised advice sheets • Advice on AB that AB do not work very well and have disadvantages such as side effects and resistance <u>Analgesics:</u> Advice on full doses of paracetamol for relief of pain and fever Ibuprofen as well if child already using full doses of paracetamol and over 1 year old	Immediate AB prescription <u>Mode of delivery:</u> • GPs were supported by standardised advice sheets • Advice on benefit of AB in helping symptoms settling, prevent complications and the importance of taking the full course <u>Analgesics:</u> Advice on full doses of paracetamol for relief of pain and fever Ibuprofen as well if child already using full doses of	At 1 week	Usage of AB **<u>Immediate vs. delayed</u>** **Daily diary of presence of symptoms* 1) Earache 2) Ear discharge 3) Night disturbance 4) Crying 5) No. school days missed 6) Daily no. of episodes of distress 7) Daily no. of spoons of paracetamol consumed 8) Daily pain score (1–10)	C = 132/134 (99%), I = 36/150 (24%) Mean diff = –1.10 (95% CI: –0.54 to –1.48), t = 4.24, p < 0.01 Mean diff = –0.66 (95% CI: –0.19 to –1.13), t = 2.75, p < 0.01 Mean diff = –0.72 (95% CI: –0.30 to –1.13), t = 3.41, p < 0.01 Mean diff = –0.69 (95% CI: –0.31 to –1.08), t = 3.56, p < 0.01 Mean diff = –0.18 (95% CI: –0.76 to 0.41), t = 0.59, p = 0.56 Mean diff = –0.12 (95% CI: –0.34 to 0.11), t = 1.02, p = 0.31 Mean diff = –0.52 (95% CI: –0.79 to –0.26), t = 3.42, p < 0.01 Mean diff = –0.16 (95% CI: –0.42 to 0.11), t = 1.18, p = 0.24

	interaction between treatment and age	GP practices (42 GPs) in southwest England 62% from training practices 60% managed their own budgets 33% were in mixed urban and rural practice settings		paracetamol and over 1 year old		*Adverse events:* 1) Rash 2) Diarrhoea *Other outcomes:* 1) Not better after 3 days 2) Belief AB are effective 3) Very satisfied with treatment approach 4) Very likely to consult doctor in the future	 Immediate = 6/133 Delayed = 8/149 Diff: χ^2 = 0.1, p = 0.74 Immediate = 25/135 Delayed = 14/150 Diff: χ^2 = 5.2, p = 0.02 Immediate = 19/135 Delayed = 45/150 Diff: χ^2 = 10.3, p < 0.01 Immediate = 100/131 Delayed = 64/140 Diff: χ^2 = 19.3, p < 0.01 Immediate = 123/135 Delayed = 115/150 Diff: χ^2 = 10.8, p < 0.01 Immediate = 109/132 Delayed = 92/147 Diff: χ^2 = 13.81, p < 0.01

Chief findings/comments:

- A well conducted open RCT with detailed information.
- Study found that delayed strategy reduced AB consumption.
- Results from this trial suggested that immediate AB prescription provided symptomatic benefit (earache, ear discharge, night disturbance and crying). No differences were found for no. of school days missed, daily no. of episodes of distress and daily pain score. Moreover, the benefit occurred mainly after the first 24 hours when symptoms were already resolving.
- Immediate prescribing also increased adverse events (i.e. diarrhoea), increased parents' belief in the effectiveness of AB and their intention to consult their doctor with the same problem in the future.

Methodology/potential confounder/bias:

- Open pragmatic trials are claimed to be lacking internal validity compared with double-blinded RCTs and prone to placebo effect (favouring AB). However, open pragmatic trials also seek to maximise external validity to ensure that the results can be generalised and therefore they are designed specifically to investigate how effective a treatment strategy is in everyday practice (i.e. delayed strategy). Hence, they are appropriate for assessing the effectiveness of treatment strategies.
- Potential selection bias as the recruitment rates of individual GPs varied widely. However, statistical analyses showed no significant differences between high recruiters and low recruiters.

Generalisability:

- UK-based GP practices, highly generalisable to UK population.

Non-severe acute otitis media: a clinical trial comparing outcomes of watchful waiting with immediate antibiotic treatment							
Level of evidence	Patient population/ characteristics	Selection/inclusion criteria	Intervention	Comparison	Follow-up	Outcome	Effect size
ID: 430 Level of evidence: (1+) Study type: single-blinded RCT Authors: McCormick et al. (2005)	Children 6 months to 12 years old with AOM (screened by an AOM-severity screening index) <u>No. of participants (completed trial):</u> On day 12: I = 108 C = 110 On day 30: I = 100 C = 109 <u>At baseline (based on I = 111, C = 112, total = 223):</u> *(I Group)* Male = 52% 0.5 ≤age<1 = 31% 1.0 ≤age<2 = 21% 2.0 ≤age<13 = 48% No. of prior AOM: 0 = 14% 1–3 = 58% 4–6 = 19% >6 = 9% *(C Group)* Male = 48% 0.5 ≤age<1 = 32% 1.0 ≤age<2 = 29% 2.0 ≤age<13 = 39% No. of prior AOM: 0 = 21% 1–3 = 47% 4–6 = 20% >6 = 12%	<u>Inclusions:</u> To enrol patients were required to have symptoms of ear infection, otoscopic evidence of AOM, including middle ear effusion, and nonsevere AOM <u>Exclusions:</u> Children who had comorbidity requiring AB, anatomic defect of ear or nasopharynx, allergy to study medication, and/or indwelling tympanostomy tube or draining otitis in the affected ear(s) <u>Study period:</u> May 2000 to March 2003 <u>Settings:</u> University of Texas Medical Branch paediatric clinic	Delayed prescription (Patients asked to fill the prescription if symptoms failed to improve after 2 days) <u>Mode of delivery:</u> • Prescription was given at consultation • Parents of children received an educational intervention on definition of ear infection, causes of ear infection, characteristics of nonsevere and severe AOM, AB resistance, costs of AB, rate of symptom response to AB, possible adverse outcomes associated with immediate AB vs. delayed, including the risk of mastoiditis <u>Analgesics:</u> Symptom medication provided (ibuprofen)	Immediate AB prescription <u>Mode of delivery:</u> Parents of children received an educational intervention on definition of ear infection, causes of ear infection, characteristics of nonsevere and severe AOM, AB resistance, costs of AB, rate of symptom response to AB, possible adverse outcomes associated with immediate AB vs. delayed, including the risk of mastoiditis <u>Analgesics:</u> Symptom medication provided (ibuprofen)	On days 12 and 30	<u>AB consumption</u> <u>Symptoms (OM-3) (mean and SD)</u> Day 0 Day 12 Day 30 <u>Failure (day 0–12)</u> < 2 years ≥ 2 years <u>Recurrence (day 13–30)</u> < 2 years ≥ 2 years <u>Cure</u> < 2 years ≥ 2 years AB-related adverse events (allergy, diarrhoea, candidal infection) Extra office visit (AOM related) <u>Patient satisfaction</u> (total satisfaction scores – 4-point scale) On day 12 On day 30 <u>*Note:*</u> *OM-3: earache, fever, poor balance, irritability, frustration,*	I = 34/100 (34%), C = 100% I = 8.1±2.5, C = 8.3±2.7 p = 0.68 I = 5.2±3.1, C = 4.7±2.9 p = 0.24 I = 4.3±2.5, C = 4.5±2.6 p = 0.76 I = 12/50, C = 4/65 I = 9/50, C = 1/44 I = 10/50, C = 11/65 I = 3/50, C = 9/44 I = 28/50, C = 50/65 I = 38/50, C = 34/44 I = 5/108, C = 13/111 p = 0.06 I = 22/108, C = 14/111 p = 0.15 I = 44.0, C = 44.4 I = 44.6, C = 44.6 (not significant, actual analysis not reported)

	**No statistical differences*					*sadness, restlessness, poor appetite, limitation in activity, attending school or day care (7-point scale, from not present to extreme problem)* *Failure: returned to doctor (day 0–12) with acute ear symptoms* *Recurrence: returned to doctor (day 13–30) with acute ear symptoms* *Cure: without a failure or recurrence episode before the day 30 visit were considered cured*	

Chief findings/comments:

- A well conducted single-blinded RCT with detailed information.
- Study found that delayed strategy reduced AB consumption but not on other outcomes.

Methodology/potential confounder/bias:

- Did not investigate diverse events.

Generalisability:

- US-based university paediatric clinic; might not be generalisable to UK primary care population.

A randomised controlled trial of delayed antibiotic prescribing as a strategy for managing uncomplicated RTIs (cough) in primary care							
Level of evidence	Patient population/ Characteristics	Selection/inclusion criteria	Intervention	Comparison	Follow-up	Outcome	Effect size
ID: 400 Level of evidence: (1+) Study type: open RCT Authors: Dowell et al. (2001)	Patients aged over 16 years old presenting with acute cough as the primary complaint <u>No. of participants (returned questionnaire):</u> Total = 148 I = 72 C = 76 (Response rate = 78%) <u>At baseline (based on I = 99, C = 92, total = 191)</u> *(I Group)* Male = 34% Mean age = 43.8 Symptoms at baseline (mean number) = 3.4 Believe AB to be effective for cough = 63% *(C Group)* Male = 43% Mean age = 39.3 Symptoms at baseline (mean number) = 3.7 Believe AB to be effective for cough = 70% **No significant differences*	<u>Inclusions:</u> Patients with acute cough with or without coryza, shortness of breath, sputum, fever, sore throat or chest tightness <u>Exclusions:</u> • Patients whose GPs would not consider offering AB • Patients expressed strong preference for AB • Toxic patients perceived to require treatment • Patients with chest signs, immunosuppression, pre-existing lung disease, diabetic or patients for whom a return visit was unusually difficult <u>Study period:</u> Dec 1997 to Nov 1998 <u>Settings:</u> 22 Scottish general practices with 48 GPs in total	Delayed prescription (Patients asked to fill the prescription if symptoms failed to improve after 7 days/1 week) <u>Mode of delivery:</u> • Patients were asked to come back to collect the prescription for AB (prescription left at the reception) • Information (patient information sheet) was given at consultation during recruitment. <u>Analgesics:</u> Not included	Immediate AB prescription <u>Mode of delivery:</u> Information (patient information sheet) was given at consultation during recruitment <u>Analgesics:</u> Not included	On day 14	1) Symptom duration (probability of recovery from cough over days 1–13) <u>*2) Patients satisfaction:*</u> a) Consultation ('very satisfied') b) Treatment ('very satisfied ') c) Advice ('very satisfied') d) Information ('very satisfied') 3) Patient enablement index (mean and interquartile range) <u>*Note:*</u> *Pick up of AB prescription* *I = 43/95 (45%)* *C = 92/92 (100%)* **No. of patients who actually cashed in the prescription not reported*	Log-rank (Mantel–Haenszel) test (result not reported), with p > 0.4 (not significant) I = 40/73 (54%), C = 55/75 (73%) I = 31/73 (42%), C = 51/75 (68%) I = 34/73 (47%), C = 48/75 (64%) I = 44/73 (60%), C = 47/75 (63%) I = mean 2.4 (IQR: 0–4), C = mean 3.3 (IQR: 1–6) Mann–Whitney U = 2221, p = 0.04
<u>Chief findings/comments:</u> • A well conducted open RCT with limited detailed information. • The study found that there was no difference between immediate AB and delayed strategy in terms of symptom duration for cough, while delayed strategy was effective at reducing the pick up of AB prescription. • However, patients treated with delayed strategy were less satisfied (in terms of consultation and treatment) and less enabled as a result.							

Methodology/potential confounder/bias:

- Relatively small sample size.
- Potential selection bias as more patients selected by low recruiters were more satisfied (consultation, advice and treatment) than those from high recruiters.
- Results and analyses were not well reported.

Generalisability:

- UK-based GP practices, highly generalisable to UK population.

Information leaflet and antibiotic prescribing strategies for acute lower respiratory tract infection (cough)							
Level of evidence	Patient population/ characteristics	Selection/inclusion criteria	Intervention	Comparison	Follow-up	Outcome	Effect size
ID: 425 Level of evidence: (1+) Study type: open RCT Authors: Little et al. (2005)	Patients aged 3 years or older with uncomplicated acute lower respiratory tract infection (≤ 21 days) who presented in primary care <u>A 2 × 3 factorial design:</u> Factor 1 = info leaflet, no leaflet Factor 2 = AB strategies (immediate AB, delayed AB, no AB) <u>No. of participants (completed trial):</u> Total = 639 No leaflet/no AB = 100 No leaflet/delayed = 107 No leaflet/AB = 112 Leaflet/no AB = 100 Leaflet/delayed = 107 Leaflet/AB = 113 <u>At baseline (based on N = 807):</u> Children = 17% Adults = 66% Older patients = 17% <u>Leaflet</u> Mean age = 39 Prior duration of cough (mean days) = 9.6 Mean temperature = 36.6 <u>No leaflet</u> Mean age = 38 Prior duration of cough (mean days) = 9.5	<u>Inclusions:</u> Patients with (≤ 21 days) cough as the main symptom and with at least one symptom or sign localizing to the lower tract (sputum, chest pain, dyspnoea, wheeze) <u>Exclusions:</u> • Patients with a history and physical examination suggestive of pneumonia based on British Thoracic Society guideline • Patients clinically diagnosed with asthma; other chronic or acute lung diseases including cystic fibrosis, cardiovascular disease, major current psychiatric diagnosis, mental subnormality, dementia • Patients with previous episodes of LRTIS (e.g. hospital admission for pneumonia) <u>Study period:</u> 18/08/98–30/07/03	<u>(Factor 2)</u> 1) Delayed prescription (Patients asked to fill the prescription if symptoms failed to improve after 14 days] 2) Immediate AB prescription <u>(Factor 1)</u> Information leaflet (info about natural history and also addressed patients' major worries and provided advice about when to seek further help, (e.g. persistent fever, worsening shortness of breath) <u>Mode of delivery:</u> • All patients, irrespective of whether they had the leaflet, were given brief verbal information about the likely range of natural history of the illness and supporting the proposed prescribing strategy • For delayed prescription, parents were asked to come back to collect the prescription for AB (prescription left at the reception)	<u>(Factor 2)</u> No AB prescription *(as control)* <u>(Factor 1)</u> No information leaflet *(as control)* <u>Mode of delivery:</u> • All patients, irrespective of whether they had the leaflet, were given brief verbal information about the likely range of natural history of the illness and supporting the proposed prescribing strategy	At 3 weeks	**<u>Daily symptom diary: Primary outcomes (1):</u>** (No AB as control) *– controlling effect of leaflet* <u>1) Delayed AB vs. no AB</u> Duration of cough – day (until very little problem) Duration of moderately bad cough – day Severity of symptoms (point scale 0–6) <u>2) Immediate AB vs. no AB</u> Duration of cough – day (until very little problem) Duration of moderately bad cough – day Severity of symptoms (point scale 0–6) <u>Adjusted severity of symptoms – point scale 0–6 on 6 symptoms (adjusted baseline variables):</u> 1) Delayed AB vs. no AB 2) Immediate AB vs. no AB 3) Leaflet vs. no leaflet	 Mean diff = 0.75 (95% CI: –0.37 to 1.88), p = 0.19 Mean diff = 0.13 (95% CI: –1.70 to 2.00), p = 0.89 Mean diff = 0.06 (95% CI: –0.15 to 0.27), p = 0.56 Mean diff = 0.11 (95% CI: –1.01 to 1.24), p = 0.19 Mean diff = 0.52 (95% CI: –1.30 to 2.40), p = 0.19 Mean diff = -0.10 (95% CI: –0.31 to 0.11), p = 0.11 Adj mean diff = –0.02, p = 0.86 Adj mean diff = –0.07, p = 0.49 Adj mean diff = –0.05, p = 0.58

	Mean temperature = 36.7 <u>No AB</u> Mean age = 39 Prior duration of cough (mean days) = 9.9 Mean temperature = 36.7 <u>Delayed AB</u> Mean age = 38 Prior duration of cough (mean days) = 9.4 Mean temperature = 36.6 <u>Immediate AB</u> Mean age = 40 Prior duration of cough (mean days) = 9.4 Mean temperature = 36.6 **No significant differences at baseline comparisons*	<u>Settings:</u> 37 physicians in primary settings in the region of southwest England	<u>Analgesics:</u> Advice to take an analgesic	<u>Analgesics:</u> Advice to take an analgesic		<u>Adverse events (Diarrhoea):</u> 1) Delayed AB vs. no AB 2) Immediate AB vs. no AB **<u>Primary outcomes (2):</u>** (No leaflet as control) – *controlling effect of AB strategies* Duration of cough (until very little problem) Duration of moderately bad cough Severity of symptoms **<u>Questionnaire outcomes:</u>** <u>1) AB strategies</u> Used AB Believed in AB Very satisfied <u>2) Info leaflet:</u> Used AB	 OR = 1.17 (95% CI: 0.67–2.03), p = 0.58 OR = 1.22 (95% CI: 0.70–2.12), p = 0.48 Mean diff = 0.26 (95% CI: –0.66 to 1.18), p = 0.58 Mean diff = 0.20 (95% CI: –0.16 to 2.00), p = 0.83 Mean diff = -0.03 (95% CI: –0.20 to 0.15), p = 0.77 No AB (16%), delayed AB (20%), immediate AB (96%), p < 0.01 No AB (47%), Delayed AB (40%), Immediate AB (75%), P < 0.01 No AB (72%), delayed AB (77%), immediate AB (86%), p = 0.05 No leaflet (57%), leaflet provided (55%) p = 0.58

						Believed in AB	No leaflet (56%), leaflet provided (54%) p = 0.73
						Very satisfied	No leaflet (76%), leaflet provided (78%) p = 0.24
						Re-attendance within 1 month	
						(No AB as control) 1) Delayed AB	Incidence rate ratio estimate = 0.65 (95% CI: 0.40–1.04), p = 0.08
						2) Immediate AB	Incidence rate ratio estimate = 0.55 (95% CI: 0.33–0.91), p = 0.02
						(No leaflet as control) Leaflet provided	Incidence rate ratio estimate = 1.63 (95% CI: 1.07–2.49), p = 0.02

Chief findings/comments:

- A well conducted open RCT with 2 × 3 factorial designs with large sample size.
- The study found that no AB prescription or a delay offer of AB only associated with little nonsignificant difference in symptom resolution of lower respiratory tract infection (cough).
- No AB prescription and a delay offer of AB also likely to reduce AB use and beliefs in the effectiveness of antibiotics.
- The study also suggested that one advantage of delayed or immediate AB is fewer re-attendances with cough in the month after the physician visit.
- However, there was lack of effect of an information leaflet. The lack of effect could be diluted by the verbal information provided.

Methodology/potential confounder/bias:

- Individual recruitment rates not reported.

Generalisability:

- UK-based GP practices, highly generalisable to UK population.

Open randomised trial of prescribing strategies in managing sore throat							
Level of evidence	Patient population/ characteristics	Selection/inclusion criteria	Intervention	Comparison	Follow-up	Outcome	Effect size
ID: 422 Level of evidence: (1+) Study type: open RCT Authors: Little et al. (1997)	Patients aged 4 years and over with sore throat and an abnormal physical sign in the throat (84% had tonsillitis or pharyngitis) <u>No. of participants (completed trial):</u> Total = 714 I1 (no AB) = 230 I2 (delayed AB) = 238 C = 246 Response rate = 582/716 (81%) <u>At baseline (based on 582 responders):</u> *(I1 Group – no AB)* Age > 12 years = 73% Male = 35% Duration > 3 days before seeing doctor = 40% Tonsillitis or pharyngitis = 85% Initial temp >37.5°C = 19% *(I2 Group – delayed AB)* Age > 12 years = 75% Male = 37% Duration > 3 days before seeing doctor = 41% Tonsillitis or pharyngitis = 83% Initial temp >37.5°C = 24% *(C Group)* Age > 12 years = 75% Male = 39% Duration > 3 days before	<u>Inclusions:</u> Patients aged 4 and over with sore throat either as principal or subsidiary symptom and showed an abnormal physical sign localising to the throat (inflamed tonsils or pharynx, purulent exudate, facial or palatal inflammation, cervical adenopathy). For children under 12 years old, who are less likely to complain of sore throat, abnormal signs in the throat were sufficient <u>Exclusions:</u> Excluded if patients had other explanation of sore throat (drugs, aphthous ulcers, Candida, etc.); were very ill; had suspected or previous rheumatic fever; had had multiple attacks of tonsillitis; had had severe local complication (quinsy); or were pregnant <u>Study period:</u> Sept 1994 to May 1996 <u>Settings:</u> 25 GPs (in 11 GP practices) on the Wessex research	1) No antibiotic 2) Delayed prescription (Patients asked to fill the prescription if symptoms failed to improve after 3 days) <u>Mode of delivery:</u> • The advice package given to patients (in each group) had 6 or 7 standard statements supporting the particular strategy • For delayed prescription, patients were asked to come back to collect the prescription for AB (prescription left at the surgery) <u>Analgesics:</u> Advice to take analgesics or antipyretics (included in the advice package)	Immediate AB prescription <u>Mode of delivery:</u> • The advice package given to patients (in each group) had 6 or 7 standard statements supporting the particular strategy <u>Analgesics:</u> Advice to take analgesics or antipyretics (included in the advice package)	On day 3 following initiation of treatment	Antibiotics use Median duration of AB use (days) Delayed group who did not use their AB prescription The resolution of symptoms by 3 days <u>Median (interquartile range) duration of individual symptom (days):</u> 1) Sore throat 2) Cough 3) Headache 4) Unwell 5) Fever (>37.0°C) 6) Time off work or school	Immediate = 210/211 (99%) No AB = 23/174 (13%) Delayed = 55/176 (31%) Immediate = 10 No AB = 0, delayed = 0 $p < 0.001$ = 69% Immediate = 37%, No AB = 35%, delayed = 30% $\chi^2 = 2.50$, p = 0.28 Immediate = 4 (3–6) No AB = 5 (3–7), delayed = 5 (3–7), $\chi^2 = 1.9$, p = 0.39 Immediate = 3 (0–7) No AB = 3 (0–7), delayed = 3 (0–7), $\chi^2 = 0.1$, p = 0.97 Immediate = 2 (1–4) No AB = 2 (0–4), delayed = 2 (1–4), $\chi^2 = 0.6$, p = 0.74 Immediate = 4 (2–5) No AB = 3 (2–5), Delayed = 3 (2–5), $\chi^2 = 1.7$, P = 0.43 Immediate = 1 (0–3) No AB = 2 (0–4), delayed = 2 (0–4), $\chi^2 = 6.6$, p = 0.04 Immediate = 2 (0–4) No AB = 2 (0–6), delayed = 1

	seeing doctor = 34% Tonsillitis or pharyngitis = 84% Initial temp >37.5°C = 25% **No significant differences at baseline comparisons*	network expressing an interest in ENT research				<u>No. of (%) with event:</u> 1) Diarrhoea 2) Stomach ache 3) Vomiting 4) Rash <u>Satisfaction, belief and intention of patients (scoring 'very' or 'moderate'):</u> 1) Satisfaction with consultation 2) GP dealt with worries 3) Likely to consult in future (sore throat) 4) AB are effective	(0–4), χ^2 = 4.0, p = 0.13 Immediate = 23/215 (11%), no AB = 16/186 (9%), delayed = 23/179 (13%) χ^2 = 1.7, p = 0.43 Immediate = 66/215 (31%), no AB = 52/186 (28%), delayed = 48/179 (27%) χ^2 = 0.9, p = 0.62 Immediate = 18/215 (8%), no AB = 22/186 (12%), delayed = 15/179 (8%) χ^2 = 1.7, p = 0.42 Immediate = 14/215 (7%), no AB = 21/186 (12%), delayed = 11/179 (6%) χ^2 = 4.0, p = 0.61 Immediate = 202/211 (96%), no AB = 166/184 (90%), delayed = 165/177 (93%) χ^2 = 4.7, p = 0.09 Immediate = 201/211 (95%), no AB = 165/184 (90%), delayed = 164/177 (93%) χ^2 = 4.5, p = 0.1 Immediate = 148/187 (79%), no AB = 87/162 (54%), delayed = 92/162 (57%) χ^2 = 27.0, p = 0.001 Immediate = 181/207 (87%), no AB = 95/173 (55%), delayed = 99/165 (60%) χ^2 = 55.0, p = 0.001

						<u>Legitimation of illness:</u> 1) Work or school	Immediate = 128/209 (61%), no AB = 117/184 (64%), delayed = 96/177 (54%) χ^2 = 3.56, p = 0.17
						2) Family or friends	Immediate = 75/210 (36%), no AB = 69/183 (38%), delayed = 67/176 (38%) χ^2 = 0.27, p = 0.9
						Subgroup analyses for duration of sore throat (in days): <u>*Selected subgroups (median and IQR):*</u>	
						i) Enlarged cervical glands (n = 309)	Immediate = 4(3–7), no AB = 4(3–6), delayed = 5(3–6), χ^2 = 0.67, p = 0.7
						ii) Pharyngitis (n = 374)	Immediate = 5(3–7), no AB = 5(3–7), delayed = 5(3–7), χ^2 = 0.05, p = 0.98
						iii) Age under 12 (n = 149)	Immediate = 3(2–5), no AB = 4(2–6), delayed = 4(3–5), χ^2 = 4.5, p = 0.11
						iv) Dysphagia (n = 395)	Immediate = 5(3–6), no AB = 5(3–7), delayed = 5(3–7), χ^2 = 5.5, p = 0.06
						v) Temperature >37.5°C (n = 285)	Immediate = 4(2–5), no AB = 3(2–5), delayed = 5(4–7), χ^2 = 10.0, p = 0.01
						vi) Tonsilitis	Immediate = 4(3–6), no AB = 4(3–6), delayed = 5(4–7), χ^2 = 2.7, p = 0.25
						vii) Purulent exudate	Immediate = 4(3–6), no AB = 4(3–6), delayed =

							5(4–7), χ^2 = 2.2, p = 0.33

Chief findings/comments:

- Prescribing AB for sore throat only marginally affects the resolution of symptoms but enhances belief in AB and intention to consult in future when compared with the acceptable strategies of no AB or delayed AB.
- In terms of individual symptoms, only fever showed marginal differences between groups in duration of symptoms.
- The study found no differences on satisfaction with consultation and 'worries' being dealt with. However, significantly more patients in immediate AB group were likely to reconsult for the same problem in the future and more patients believe AB are effective.
- In general, most results from subgroup analyses suggest that identifying broad subgroups is unlikely to predict antibiotic response.

Methodology/potential confounder/bias:

- Open RCT, potential placebo effect.
- The trial excluded very ill patients and thus cannot show the efficacy of AB prescribing strategies for them.

Generalisability:

- UK-based GP practices, highly generalisable to UK population.

Adverse and beneficial effects of immediate treatment of group A beta-haemolytic streptococcal pharyngitis with penicillin							
Level of evidence	Patient population/ characteristics	Selection/inclusion criteria	Intervention	Comparison	Follow-up	Outcome	Effect size
ID: 439 Level of evidence: (1+) Study type: double-blinded RCT Authors: Pichichero et al. (1987)	Children aged between 4 and 18 years old with culture positive of GABHS pharyngitis <u>No. of participants (completed trial):</u> Total = 114 I = 55 C = 59 <u>At baseline (based on total 114):</u> *(I Group)* Mean age ± SE = 7.83±2.3 Mean days ill before enrolment ± SE = 1.44±0.69 Breese score > 32 = 43% Defined symptom complex = 57% *(C Group)* Mean age ± SE = 7.47±2.6 Mean days ill before enrolment ± SE = 1.47±0.73 Breese score > 32 = 37% Defined symptom complex = 63% **No significant differences*	<u>Inclusions:</u> Children who were acutely ill with 3 of the following 5 signs or symptoms compatible with the diagnosis of GABHS pharyngitis: • Sore throat associated with difficulty in swallowing • Exudate on tonsils or a beefy red throat • Cervical lymph node tenderness • History of fever at least to >100.6°F rectally or 99.6°F orally • Systemic toxicity characterised by insomnia, malaise, lethargy and others • Also, Breese scores > 32 <u>Exclusions:</u> • Allergic to penicillin • Received AB in the preceding 7 days • An acute illness in the preceding 7 days • A GABHS infection in the preceding month • Concurrent infection requiring treatment with an AB <u>Study period:</u> Sept–June in the years 1980, 1981, 1982, 1983 <u>Settings:</u> Elmwood Paediatric Group – private practice located in suburban Rochester, NY (5 physicians)	Delayed prescription (Patients were provided placebo tablets for the first 2 days then 10-day course of AB provided after 48–56 hours) <u>Mode of delivery:</u> N/A <u>Analgesics:</u> Encouraged to use aspirin or acetaminophen ad libitum every 4 hours as needed to control fever and discomfort	Immediate AB prescription (2-day course, then further 8-day course) <u>Analgesics:</u> Encouraged to use aspirin or acetaminophen ad libitum every 4 hours as needed to control fever and discomfort	Symptoms of both groups were assessed for 2 days using symptom diary following the initiation of treatment. Physician follow-up examination on day 3. Also 3-week follow-up visit??	<u>Collected by symptom diary – on day 3:</u> Fever (°F) **<u>Clinical symptoms – the presence and severity (mean score from checklist scale 1–3)</u>** Sore throat Dysphagia Lethargy Tender glands Irritable Hoarseness <u>Adverse effects:</u> Abdominal pain Vomiting <u>Relapse and Recurrences –</u>	I = 98.875°F, C = 98.25°F, p = 0.022 I = 1.6, C = 1.3, p = 0.006 I = 1.55, C = 1.25, p = 0.004 I = 1.3, C = 1.1, p = 0.008 I = 1.4, C = 1.25, p = 0.093 I = 1.25, C = 1.1, p = 0.173 I = 1.1, C = 1.05, p = 0.320 I = 1.15, C = 1.0, p = 0.004 I = 1.1, C = 1.0, p = 0.475

						<u>confirmed by positive throat culture:</u> Relapse (at 3-week follow-up) Early recurrence (within 1 month after the 3-week follow-up) Late recurrences (between 1 and 4 months after the 3-week follow-up)	 I = 8/55 (15%), C = 10/59 (17%), p = 0.382 I = 8/55 (15%), C = 14/59 (24%), p = 0.115 I = 1/55 (2%), C = 8/59 (14%), p = 0.035

<u>Chief findings/comments:</u>

- A well conducted double-blinded RCT with limited detailed information. However, the main aim of the study is to determine whether recurrence rates for GABHS pharyngitis are related to the time of initiation of AB therapy, but not the effectiveness of antibiotic management strategies.
- This study found that fever severity was reduced with immediate AB compared to delayed AB. Immediate AB was also found beneficial for improving symptoms of sore throat, lethargy but not hoarseness, irritability and tender glands.
- In terms of side effects, the study found that the delayed AB group had more abdominal pain but there was no difference on vomiting between the two groups.
- However, the study's aim is to investigate whether immediate AB might impact the body's immune system response and predispose the patient to a relapse of pharyngitis or not.

<u>Methodology/potential confounder/bias</u>:

- Had rigid protocol with the use of placebo tablets, does not reflect the realistic situation in primary care.
- Relatively small sample size.
- Population were all culture positive and all these do not reflect the actual primary care consultation.

<u>Generalisability</u>:

- Private paediatric care in NY, lack generalisability to UK primary care practices and population.

Lack of impact of early antibiotic therapy for streptococcal pharyngitis on recurrence rates

Level of evidence	Patient population/characteristics	Selection/inclusion criteria	Intervention	Comparison	Follow-up	Outcome	Effect size
ID: 406 Level of evidence: (1+) Study type: RCT Authors: Gerber et al. (1990)	Patients aged between 2 and 22 years with a positive Q Test Strep result and a positive throat culture <u>No. of participants (completed trial):</u> Total = 113 I = 63 C = 50 <u>At baseline (based on total 113):</u> *(I Group)* Male = 46% Mean age = 9.5 Duration of illness <24 hour = 73% Fever = 83% Cervical lymphadenitis = 68% Sore throat = 95% Headache = 73% Abdominal pain = 37% *(C Group)* Male = 60% Mean age = 8.1 Duration of illness <24 hour = 80% Fever = 88% Cervical lymphadenitis = 78% Sore throat = 100% Headache = 86% Abdominal pain = 44% **No significant differences*	<u>Inclusions:</u> Only patients with a positive Q Test Strep result and a positive throat culture were included <u>Exclusions:</u> • Any patient with a positive Q Test Strep result who was subsequently found to have a negative throat culture was excluded from the study • Patients with a history of hypersensitivity to penicillin and patients who had received antibiotic therapy within the previous 72 hours were excluded <u>Study period:</u> Winter and spring of 1988–1989 <u>Settings:</u> A private paediatric office in Danbury, University of Connecticut School of Medicine	Delayed prescription (Patients were provided placebo tablets for the first 2 days then 10-day course of AB provided after 48 hours) <u>Mode of delivery:</u> N/A <u>Analgesics:</u> Not reported	Immediate AB prescription (2-day course, then further 8-day course) <u>Analgesics:</u> Not reported	Between day 4 and day 6 after the completion of antibiotic therapy. Also at 2 months and 4 months and 4–5 months	No. of positive throat cultures after completion (4 days to 2 month) <u>Cumulative no. of positive follow-up throat cultures (after 4–5 months):</u> Recurrences (same serotype as initial isolate) New acquisition (different serotype from initial isolate) Total Symptomatic episodes (after 4–5 months)	I = 18/63 (29%) C = 17/50 (34%) p > 0.05 I = 9/63 (14%), C = 6/50 (12%) I = 17/63 (27%), C = 12/50 (24%) I = 26/63 (41%), C = 18/50 (36%), p > 0.05 I = 12/63 (19%), C = 10/50 (20%) **Only reported 'no significant difference'. Results/analysis not provided*

<u>Chief findings/comments:</u>

- A reasonably well conducted double-blinded RCT with very limited detailed information. However, the main aim of the study is to determine whether recurrence rates for GABHS pharyngitis are related to the time of initiation of AB therapy, but not the effectiveness of antibiotic management strategies.
- The study found no significant differences in recurrence cases and symptomatic recurrences between immediate AB group and delayed AB group.
- However, the study's aim is to investigate whether immediate AB might impact the body's immune system response and predispose the patient to a relapse of pharyngitis or not.

<u>Methodology/potential confounder/bias</u>:

- Had rigid protocol with the use of placebo tablets, does not reflect the realistic situation in primary care.
- Lack of blinding might cause potential placebo effect.

- Relatively small sample size.
- Population were all culture positive and all these do not reflect the actual primary care consultation.

Generalisability:
- Private paediatric care in USA, lack generalisability to UK primary care practices and population.

Do delayed prescriptions reduce the use of antibiotics for the common cold?							
Level of evidence	Patient population/ characteristics	Selection/inclusion criteria	Intervention	Comparison	Follow-up	Outcome	Effect size
ID: 378 Level of evidence: (1+) Study type: RCT Authors: Arroll et al. (2002)	Patients of any age presenting with the common cold who requested AB or whose physicians thought they wanted them <u>No. of participants (completed trial):</u> Total = 123 I = 62 C = 61 <u>At baseline (based on I = 67, C= 62):</u> *(I Group)* Male = 39% Mean age = 23.6 Mean temp = 36.7 Days of illness before visit = 5.0 Total symptom score = 5.4 *Feeling unwell = 56 (84%) *(C Group)* Male = 35% Mean age = 27.9 Mean temp = 36.9 Days of illness before visit = 4.5 Total symptom score = 5.1 *Feeling unwell = 44 (71%) **Feeling unwell:* $\chi^2 = 9.134$ (df = 1),	Patients of any age diagnosed with the common cold (URTIS) based on the ICHPPC-2 (International Classification of Health Problems in Primary Care): • Presence of acute inflammation of the nasal or pharyngeal mucosa in the absence of other specifically defined respiratory infection <u>Exclusions:</u> • Suspected streptococcal tonsillitis, sinusitis, bronchitis, pneumonia • Patients with lower respiratory signs, needed an x-ray, past history of rheumatic fever, who had experienced a serious illness, any AB treatment in the previous 2 weeks. <u>Study period:</u> Winter 2000 <u>Settings:</u> 15 family physicians in a family practice in New Zealand	Delayed prescription (Patients asked to fill the prescription if symptoms failed to improve after 3 days) <u>Mode of delivery:</u> • Prescription was given at consultation • Patients were advised to return to see their doctor if symptoms worsened <u>Analgesics:</u> Not included	Immediate AB prescription <u>Analgesics:</u> Not included	On Day 3 Day 7 Day 10	1) Utilisation of AB prescription 2) OR for not using AB <u>*Symptoms:*</u> 3) Temperature (ºC) Baseline Day 3 Day 7 Day 10 **General linear model, repeated measures* 4) Symptom scores – 1 point for each of 15 symptoms *<u>(Mean scores)</u>* Baseline Day 3 Day 7 Day 10 **General linear model, repeated measures* **There were no significant adverse effects from taking AB or not (analysis and results not provided)* <u>*Satisfaction, attitude and beliefs:*</u> 1) satisfaction with the consultation	C = 54/61 (89%), I = 27/62 (43%) OR = 0.12 (95% CI: 0.05–0.09) p value not provided C = 36.9, I = 36.7 C = 36.4, I = 36.2 C = 36.4, I = 36.1 C = 36.3, I = 36.1 *0.2ºC higher in C group, p = 0.039 (actual figures or analysis not provided)* C = 5.1, I = 5.4 C = 2.9, I = 3.6 C = 1.8, I = 2.0 C = 1.4, I = 1.5 *No significant difference, p = 0.29 (actual figures or analysis not provided)* C = 58/62 (94%), I = 64/67 (96%), p = 0.71

	p = 0.0025					2) doctors dealt with worries 3) likely to see doctors for next common cold 4) AB are effective	C = 58/62 (94%), I = 64/67 (96%), p = 0.71 C = 40/62 (65%), I = 49/67 (73%), p = 0.343 C = 47/62 (76%), I = 51/67 (76%), p = 1.0

Chief findings/comments:

- A reasonably well conducted single-blinded RCT. However, the level of details on analysis in the results section was not appropriately provided.
- There was a significant reduction in the consumption of AB in the delayed group compared with the immediate AB group.
- The lack of difference in the symptom score in this study between the two groups suggests that there is no danger in delaying AB prescriptions for the common cold.
- AB prescribing strategies (delayed vs. immediate AB) had no significant impact on patient satisfaction, patient's perception that the doctors had dealt with their worries, patient's perspective of AS effectiveness for the common cold and the likelihood to see doctors again for future episodes of common cold.
- Clarification of patient expectations for AB may result in a lower prescription rate.

Potential confounder/bias:

- Only patients were blinded. This could reduce internal validity.
- Relatively small sample.

Generalisability:

- Only single practice with 15 family physicians, and the recruitment rates of individual physicians varied widely.

Reducing antibiotic use for acute bronchitis in primary care: blinded, randomised controlled trial of patient information leaflet							
Level of evidence	Patient population/ characteristics	Selection/inclusion criteria	Intervention	Comparison	Follow-up	Outcome	Effect size
ID: 427 Level of evidence: (1+) Study type: RCT Authors: Macfarlane et al. (2002)	Recruited consecutive adults ≥ 16 years presenting with 'acute bronchitis' defined as a 'new, acute lower respiratory tract illness in a previously well adult' (including smokers) <u>No. of participants (completed trial):</u> Total = 251 I = 104 C1 = 101 C2 = 46 <u>At baseline (based on group I and C1, total 212):</u> *(I Group)* Women = 57% Median (range) age = 45 (16–84) Smoker (current) = 25% Smoker (former or never) = 75% Median (range) duration of cough (days) = 7 (1–21) Chest examination: Clear = 80% General signs = 18% Focal signs = 2% *(C1 Group)* Women = 60% Median (range) age = 44 (17–84) Smoker (current) = 27% Smoker (former or never) = 73% Median (range) duration of cough (days) = 7 (1–21) Chest examination:	<u>Inclusions:</u> • Patients ≥ 16 years who were previously well and not under supervision or management for an underlying disease (e.g. no pre-existing asthma, COPD, heart disease, diabetes) • LRTIS required all of: – Acute illness present for 21 days or less – Cough as the main symptom – At least 1 other LRT symptom (sputum production, dyspnoea, wheeze, chest discomfort or pain) – No alternative explanation (e.g. not sinusitis, pharyngitis, a new presentation of asthma) <u>Study period:</u> Sept 1999 to Aug 2000 (excluding a moth over Christmas and the millennium period) <u>Settings:</u> 3 GP practices in Nottingham, UK	Delayed prescribing with an information leaflet (no. of days delay not reported, only stated '…if you feel you are getting worse after a while, considering taking antibiotics then would be reasonable') Information leaflet included: • Natural history of cough • The use of AB for cough • Advice and suggestions on how to manage cough without AB • Advice on when should reconsult and seek further help <u>Mode of delivery:</u> • Prescription was given at consultation • Standard verbal reassurance/information (based on a prompt card) **Delayed or immediate based on clinical decision made without additional guidance or investigations.*	1) Delayed prescribing (no leaflet) <u>Mode of delivery:</u> • Prescription was given at consultation • Standard verbal reassurance/information (based on a prompt card) 2) Immediate prescribing (no leaflet) (patients were encouraged to use the prescription)	Between 1 and 2 weeks after consultation, and then 1 month later	*<u>Primary outcome:</u>* AB usage in the next 2 weeks *<u>Secondary outcome:</u>* Reconsultation for the same symptoms in the next month Kaplan–Meier plot (I vs. C1)	I = 49/104 (47%), C1 = 63/101 (62%) RR = 0.76 (95% CI: 0.59–0.97), p =0.04, NNT = 6.7 C2 = 44/46 (96%) I = 11/104 (11%) C1 = 14/105 (13%) C2 = not stated Rate ratio = 0.66 (95% CI: 0.46–0.96)

	Clear = 79% General signs = 17% Focal signs = 4% **No significant differences by age, sex, smoking status, whether patients paid for their prescriptions, descriptions of cough or sputum, presence of chest signs, or general practice*		<u>Analgesics:</u> Not reported	<u>Analgesics:</u> Not reported			

<u>Chief findings/comments:</u>

- Sharing the patient's uncertainty, providing reassurance and information leaflet supported by verbal advice is a safe strategy and reduces AB use.
- Rates of reconsultation were not significant higher in the leaflet group.

<u>Methodology/potential confounder/bias</u>:

- Methods of delay, i.e. no. of days not clear and not as a controlled variable.

<u>Generalisability</u>:
UK GP practices, generalisable to UK population.

Acute otitis media – a brief explanation to parents and antibiotic use

Level of evidence	Patient population/ characteristics	Selection/inclusion criteria	Intervention	Comparison	Follow-up	Outcome	Effect size
ID: 1726 Level of evidence: (1+) Study type: RCT Authors: Pshetizky et al. (2003)	Children aged 3 months to 4 years visiting the family practice clinics and diagnosed with AOM No. of participants (completed trial): Total = 81 I = 44 C = 37 **Patient's characteristics not reported. Only stated that 'no significant differences were found between the socio-demographic variables of the children and parents in both groups'*	Inclusions: Children aged 3 months to 4 years diagnosed with AOM (high fever [>38°C], purulent ear discharge, opacity or bulging of the eardrum) Exclusions: Children exhibiting a toxic child appearance, a temperature of ≥ 39.5 °C, extreme restlessness/irritability or vomiting, or where there was uncertainty of the diagnosis Study period: The winter of 1998–1999 Settings: 2 primary care clinics belonging to HMO-Clalit Health services (CHS) in the southern district of Israel	Delayed prescribing with a structured explanation (Parents were advised to administer AB if there was no improvement or a worsening in the child's condition over the next 24–48 hours) The structured explanation included: • Natural history of AOM • Possible complications from AOM • Advice on the use of analgesics Mode of delivery: Prescription was given at consultation Analgesics: Parents were recommended in cases of high fever or severe pain to administer paracetamol prescribed according to the child's weight	Delayed prescribing without a structured explanation (Parents were advised to administer AB if there was no improvement or a worsening in the child's condition over the next 24–48 hours) Mode of delivery: Prescription was given at consultation Analgesics: No advice on analgesics	1 week after the consultation	Parents administration of AB Day of AB administration: Day 1 Day 2+	I = 18/44 (41%) C = 32/37 (86%) I = 9/18 (50%) C = 30/31 (97%) I = 9/18 (50%) C = 1/31 (3%)

Chief findings/comments:

- A brief explanation to the child's parents about the disease and the expected spontaneous recovery could reduce AB consumption.

Methodology/potential confounder/bias:

- Relatively small sample, no significant findings on socio-demographic variables might be due to Type II error.
- The use of analgesics in the intervention group but not the control group could be a proxy for the actual structured explanation that had an impact on AB administration.

Generalisability:

- Only based on two non-UK primary care practices, questions regarding generalisability could be raised.

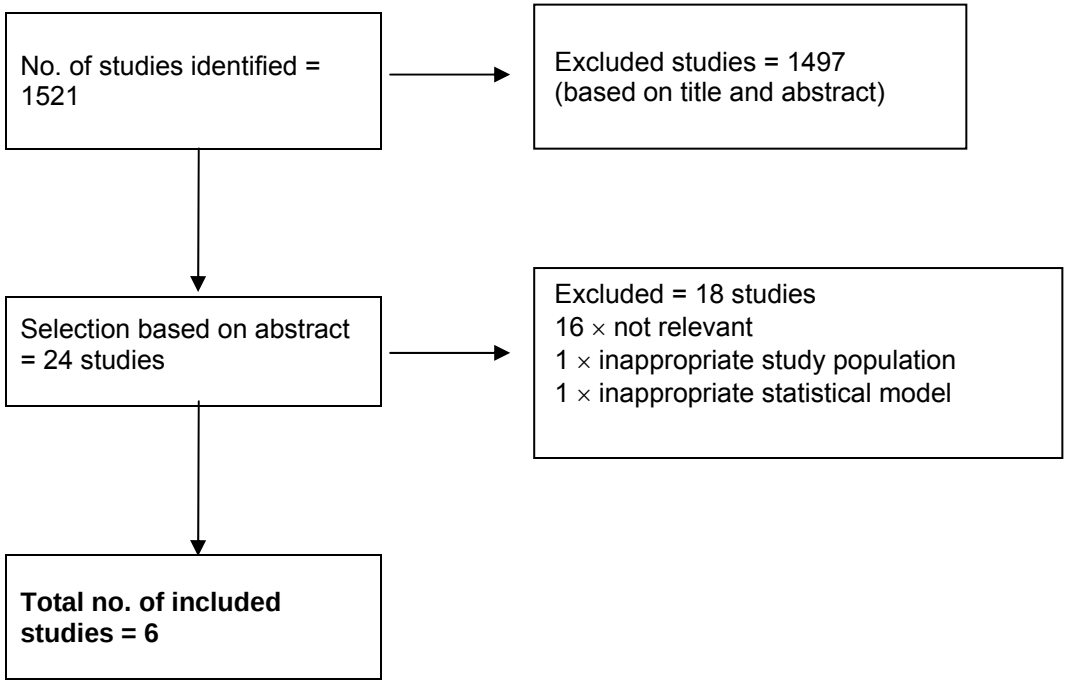
Reducing reconsultations for acute lower respiratory tract illness with an information leaflet: a randomised controlled study of patients in primary care							
Level of evidence	Patient population/characteristics	Selection/inclusion criteria	Intervention	Comparison	Follow-up	Outcome	Effect size
ID: 428 Level of evidence: (1+) Study type: RCT Authors: Macfarlane et al. (1997)	Previously well adults (aged 16 or over) presenting with an illness defined as a lower respiratory tract illness (including smokers) <u>No. of participants (completed trial):</u> Total = 1006 I1 = 136, I2 = 369 I total = 505 C1 = 147, C2 = 354 C total = 501 <u>At baseline:</u> *<u>(leaflet group)</u>* Median (range) age = 45 (16–88) Male = 39% Current smokers = 31% Symptoms (median duration in days – IQR) = 7 (4–14) Chest examination: Clear = 66% Generalised signs = 21% Focal signs = 9% Chest not examined = 4% *<u>(No leaflet group)</u>* Median (range) age = 46 (16–89) Male = 41% Current smokers = 32% Symptoms (median duration in days – IQR) = 7 (5–14) Chest examination: Clear = 64% Generalised signs = 24% Focal signs = 10% Chest not examined = 2%	<u>Inclusions:</u> Previously well adults (who were not under supervision or treatment for an underlying disease) who consulted with a lower respiratory tract illness defined as a new cough and at least one other LRT symptom, including sputum production, dyspnoea, wheeze, or chest pain, for which there was no explanation <u>Exclusions:</u> Excluding patients with conditions such as asthma and COPD, which may affect the initial diagnosis and management and reconsultation rates <u>Study period:</u> Not stated <u>Settings:</u> 76 GP practices in UK	1) No antibiotic with information leaflet describing the natural history of acute cough and respiratory symptoms 2) Immediate antibiotic with information leaflet describing the natural history of acute cough and respiratory symptoms Information leaflet included: • Natural history of cough • The use of AB for cough • Advice and suggestions on how to manage cough without AB • Advice on when to reconsult and seek further help <u>Mode of delivery:</u> N/A <u>Analgesics:</u> Not stated	1) No antibiotic without information leaflet 2) Immediate antibiotic without information leaflet <u>Mode of delivery:</u> N/A <u>Analgesics:</u> Not stated	4 weeks following the consultation	<u>Reconsultation within 4 weeks</u> 1) No AB 2) Immediate AB 3) No AB vs. immediate AB as whole	 I1 = 15/136 (11%) C1 = 26/147 (18%) I2 = 60/369 (16%) C2 = 81/354 (23%) OR = 1.53 (95% CI: 1.03-2.26), p = 0.02 I1 + C1 = 41/283 (14.5%) I2 + C2 = 141/723 (19.5%)
<u>Chief findings/comments:</u> • The findings suggested that informing patients about the natural history of acute lower respiratory tract symptoms is an effective strategy for reducing the need for patients to return for a second consultation.							

Generalisability:

- UK GP practices, generalisable to UK population.

Topic 2 Identifying patients with RTIs who are likely to be at risk of developing complications

Volume of evidence (key clinical question 2)



Topic 2 Identifying patients with RTIs who are likely to be at risk of developing complications

Key clinical question 2
What are the clinical symptoms, signs and risk factors that predict which patients with RTIs are likely to develop complications?

Use of antibiotics for sore throat and incidence of quinsy (no further validation)

Study type	No. of patients	Patient characteristics	Prognostic/diagnostic factor(s)	Follow-up	Outcome measures	Results
ID: 2312 Level: (+) Retrospective case–control Author: Dunn et al. (2001)	Study group: Cases of quinsy following initial uncomplicated sore throat = 192 **total cases of quinsy = 606* Control group: Cases of sore throat without quinsy = 198124 Study period: 1995 – 1997 Setting: UK-wide primary care data from the General Practice Research database (GPRD)	Inclusion (study group): Case events were identified as any event recorded as quinsy (or other similar diagnostic codes) and control events as those without such diagnosis, following a diagnosis of sore throat. To be included in the analysis, the case event must have occurred within 30 days of a sore throat record; that is, cases arising on first presentation to the GP were not included Characteristics of cases: (Case events) Male = 48.4% Median age (IQR) = 27 (20–36) Smoker = 38.5% Tonsillitis = 46.9% Sore throat/pharyngitis = 53.1% Exposure to AB = 88.0% (Control events) Male = 38.0% Median age (IQR) = 23 (12–38) Smoker = 18.4% Tonsillitis = 22.0% Sore throat/pharyngitis = 78.0% Exposure to AB = 84.7%	Prevalence of quinsy = 15.8 per 1000 patients with sore throat, per annum Clinical variables: Age, sex, smoking status, type of diagnosis, exposure to AB, lung disease Outcome of interest: The development of quinsy after initial uncomplicated sore throat **Note:* *Logistic regression adjusted for confounding factors at patient level (chronic diseases, comorbidities, recent prescriptions for immunosuppressive drugs) and at practice level (practice deprivation index, tonsillitis, RTIs for which AB were prescribed)*	Use of 30 days of sore throat record	After logistic regression: Age (21–40 years old) Smoking Male *OR for quinsy by exposure to AB following different types of RTIs (adjusted for age, sex smoking, lung disease at patient level and clustering at practice level)* AB given after all events AB given after 'tonsillitis' AB given after 'sore throat/pharyngitis' **There was similar level of AB exposure in quinsy cases (88.0%) and controls (84.7%).* **The interval between diagnosis of a sore throat and development of quinsy was a median of 2 days (IQR = 1–6) for tonsillitis, and 3 days (IQR = 2–5) for sore throat/pharyngitis*	 Adj OR = 3.4 (95%CI: 2.1–5.5) Adj OR = 2.5 (95%CI: 1.8–3.5) Adj OR = 1.6 (95%CI: 1.1–2.2) No. of cases = 169 Adj OR = 1.2 (95%CI: 0.7–1.8) No. of cases = 81 Adj OR = 0.6 (95%CI: 0.3–1.3) No. of cases = 88 Adj OR = 1.2 (95%CI: 0.7–2.2)

Additional comments:
The majority of cases of quinsy seem to arise without the patient having presented previously with any warning symptoms.
Prescription of AB after recording a diagnosis of a sore throat generally does not seem to reduce the risk of developing quinsy, although there is a suggestion that when doctors use the term 'tonsillitis', AB may have protective effect BUT the results are not statistically significant.
The use of retrospective data, and there are some missing data (i.e. on smoking), and data were not collected on compliance with AB prescriptions (i.e. patients might not be taking the course as

prescribed).

Predicting complications from acute cough in pre-school children in primary care: a prospective cohort study (derivation study)

Study type	No. of patients	Patient characteristics	Prognostic/diagnostic factor(s)	Follow-up	Outcome measures	Results
ID: 2403 Level: (+) Prospective cohort Author: Hay et al. (2004)	<u>Study group:</u> Total no. of patients = 256 Where follow-up completed = 222 <u>Study period:</u> Nov 1999 to Apr 2001 <u>Setting:</u> 8 GP practices in Leicestershire, UK	<u>Inclusion:</u> Preschool children aged 0–4 with cough for up to 28 days presenting to a GP or nurse practitioners, and without asthma or other chronic disease <u>Study group:</u> Most children under 2 years Male = 51% Prescribed = 18% Reconsulted = 19% Recorded as having complication = 10%	<u>Clinical predictive variables:</u> The use of a validated symptom diary Socio-demographic factors <u>Outcome of interest:</u> <u>Complications:</u> New signs/symptoms identified at a parent initiated reconsultation: bronchiolitis, possible asthma, vomiting, bronchitis, viral illness, cough and wheeze, conjunctivitis, LRTIs, baby asthma, chest infection, chicken pox, viral-induced wheeze, pharyngitis, otitis media <u>Hospital admission before cough resolution:</u> Bronchiolitis, pneumonia, whooping cough, viral induced wheeze	Validated symptom diary collected either after symptoms resolution (2 consecutive days without cough) or during parent initiated reconsultation	<u>Multivariate model (independent predictors):</u> Chest sign Fever <u>Predictive model (predicting complications):</u> Neither fever nor chest sign Fever only or both fever and chest sign Both fever and chest sign <u>Post-test probability:</u> Neither sign Chest sign only Fever only Both signs	 OR = 2.78 (95%CI: 1.04–7.35), p = 0.048 OR = 4.65 (95%CI: 1.63–13.3), p = 0.007 LHR = 0.56 (95%CI: 0.35–0.91) LHR = 3.54 (95%CI: 1.62–7.68) LHR = 5.39 (95%CI: 0.95–30.6) **Area under ROC = 0.68* Post-test probability = 6.5 (95%CI: 3.1–11.7) Post-test probability = 18.2 (95%CI: 6.9–35.0) Post-test probability = 27.8 (95%CI: 9.6–53.0) Post-test probability = 40.0 (95%CI: 5.2–85.0)

<u>Additional comments:</u>
Parent had to initiate reconsultation and reconsultation assessment was not standardised, leading to a broad range of diagnostic labels.
Deprivation and ethnicity measures were not regionally or nationally representative.

Validation of a clinical rule to predict complications of acute cough in pre-school children: a prospective study in primary care (validation study)

Study type	No. of patients	Patient characteristics	Prognostic/diagnostic factor(s)	Follow-up	Outcome measures	Results
ID: 2687 Level: (++) Prospective cohort Author: Hay et al. (2007)	<u>Study group:</u> Total no. of patients = 164 Where follow-up completed = 154 <u>Study period:</u> Oct 2004 to May 2005. <u>Setting:</u> 13 general practices in Bristol and Tayside, UK	<u>Inclusion:</u> Preschool children aged 0–4 with cough for up to 28 days presenting to a GP or nurse practitioners, and without asthma or other chronic disease <u>Study group:</u> Median age, month (IQR) = 24 (12–37) Male = 54% Prescribed = 24% Reconsulted = 23% Recorded as having complication = 12%	<u>Clinical predictive variables:</u> The use of a validated symptom diary Socio-demographic factors <u>Outcome of interest:</u> <u>Complications:</u> New signs/symptoms identified at a parent initiated reconsultation: bronchiolitis, possible asthma, vomiting, bronchitis, viral illness, cough and wheeze, conjunctivitis, LRTIs, baby asthma, chest infection, chicken pox, viral-induced wheeze, pharyngitis, otitis media <u>Hospital admission before cough resolution:</u> Bronchiolitis, pneumonia, whooping cough, viral induced wheeze	Validated symptom diary collected either after symptoms resolution (2 consecutive days without cough) or during parent initiated reconsultation	<u>Multivariate model (independent predictors):</u> Age Deprivation No. of GP visits in previous year **Note:* *Chest sign and fever that were found as a significant model of prediction in the derivation study were not significant predictors in this validation study* <u>Post-test probability:</u> Neither sign Chest sign only Fever only Both signs	 OR = 0.95 (95%CI: 0.90–0.99), p = 0.03 OR = 0.79 (95%CI: 0.64–0.97), p = 0.02 OR = 1.14 (95%CI: 1.02–1.27), p = 0.02 Derivation = 6.5 (95%CI: 3.1–11.7) Validation = 13.7 (95%CI: 7.5–22.3) Derivation = 18.2 (95%CI: 6.9–35.0) Validation =13.8 (95%CI: 3.9–32.0) Derivation = 27.8 (95%CI: 9.6–53.0) Validation = 9.1 (95%CI: 0.0–41.0) Derivation = 40.0 (95%CI: 5.2–85.0) Validation = 0.0 (95%CI: 0.0–37.0)

<u>Additional comments:</u>
In this validation study, chest sign and fever were not found to predict complications, instead they were found to be protective for complications.
The authors commented that this could be due to spectrum bias (i.e. socio-demographic differences, possible reduced levels of circulating influenza-like illness between the derivation and validation cohorts) and confounding by indication (i.e. clinician's AB prescriptions tended to be targeted at children with chest sign/or fever).

A prediction rule for elderly primary-care patients with lower RTIs (derivation and validation study – two separate cohorts)

Study type	No. of patients	Patient characteristics	Prognostic/diagnostic factor(s)	Follow-up	Outcome measures	Results
ID: 2712 Level: (+) Retrospective cohort (GP database) Author: Bont et al. (2007)	Study group 1 (derivation cohort): Total no. of patients = 1693 (3166 episodes) Study group 2 (Validation cohort): Total no. of patients = 2465 episodes of LRTIs Study period: Jan 1997 to Feb 2003 Setting: (Derivation cohort) Patient data stored in the database of the Utrecht GP research network in the Netherlands (35 GPs) (Validation cohort) Data of patients from the 2nd Dutch National Survey of General Practice in 2001, included 163 GPs in 85 practices	Inclusion (derivation cohort): Patients aged ≥65 years visiting the general practitioner with LRTIS. LRTIS defined as episodes of pneumonia, acute bronchitis and COPD Exclusion (derivation cohort): Patients who were treated with AB for another RTI within the previous 3 weeks, if at the moment of presentation, the patient was known to have lung cancer, a haematological malignancy or an infection with HIV, used immunosuppressive medication or was hospitalised during the 2 weeks preceding the diagnosis Inclusion (validation cohort): Patients aged ≥65 years visiting the general practitioner with episodes of pneumonia and acute bronchitis Study group: (Derivation cohort): Acute bronchitis = 1120 episodes Exacerbation of COPD = 1523 episodes Pneumonia = 523 30-day hospitalization or death = 274 Death = 76 Mean age = 75.5 Male = 45% With 1 or more comorbid conditions = 85% (Validation cohort): Acute bronchitis = 1736 episodes Pneumonia = 729 30-day hospitalization or death = 178 Death = 59	Clinical predictive variables: Increasing age, hospitalisation in the 12 months prior to diagnosis, heart failure, use of insulin, use of oral glucocorticoids, use of AB in the month prior to diagnosis, type of diagnosis After logistic regression: Diagnosis (score): Acute bronchitis (0) Exacerbation of COPD (2) Pneumonia (4) Age: 65–79 (0) ≥80 (2) Congestive heart failure (1) Diabetes (2) Using oral glucocorticoids (3) Hospitalisation in previous year: 0 (0) 1 (2) ≥2 (3) use of AB in previous month (2) Management: Separate into low (score ≤2), medium (score 3–5) and high risk (score ≥7) group Outcome of interest: 30-day hospitalization or death	N/A Retrospective study of databases	Predictive model (predicting 30-day hospitalisation or death): Derivation study: Low risk (score ≤2) Medium risk (score 3–5) High risk (score ≥7) Validation study: Low risk (score ≤2) Medium risk (score 3–5) High risk (score ≥7)	 Sensitivity = 0.82, specificity = 0.52 % of risk of end point = 3.2% Sensitivity/specificity = not reported % of risk of end point = 9.9% Sensitivity = 0.35, specificity = 0.92 % of risk of end point = 30.9% Area under ROC = 0.75 (95%CI: 0.72–0.78) Sensitivity = 0.42, specificity = 0.81 % of risk of end point = 5.3% Sensitivity/specificity = not reported % of risk of end point = 14.5% Sensitivity = 0.06, specificity = 0.98 % of risk of end point = 22.0% Area under ROC = 0.74 (95%CI: 0.71–0.78)

Additional comments: Retrospective study of databases, both derivation and validation. Validation study did not include COPD.						

Long-term prognosis of AOM in infancy: determinants of recurrent AOM and persistent middle ear effusion (derivation study, not validated)

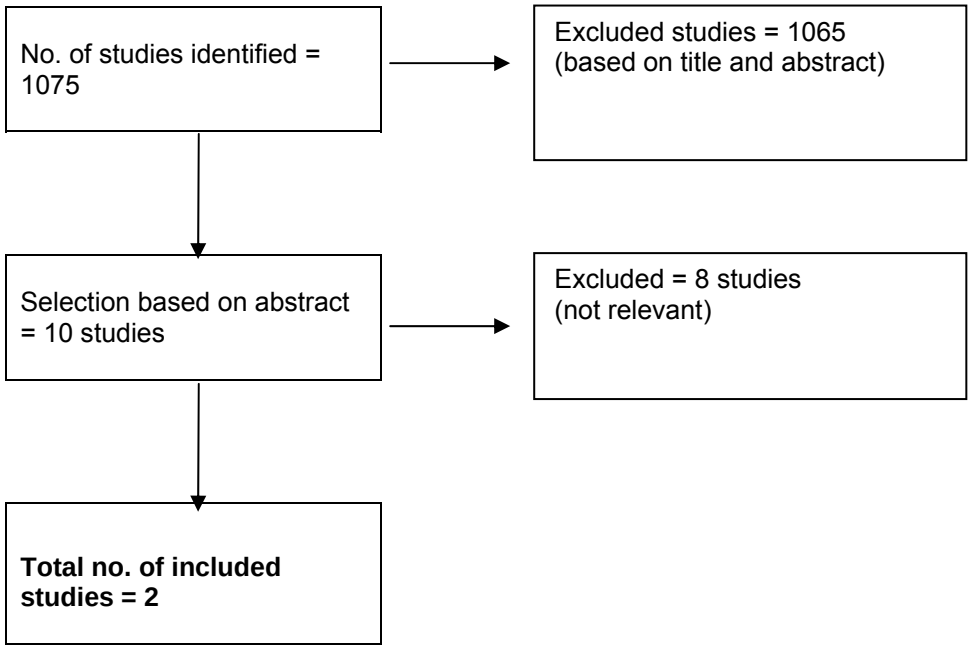
Study type	No. of patients	Patient characteristics	Prognostic/diagnostic factor(s)	Follow-up	Outcome measures	Results
ID: 2346 Level: (+) Prospective cohort Author: Damoiseaux et al. (2005)	<u>Study group:</u> Total no. of patients = 210 (recurrent AOM cohort); 190 (persistent middle ear effusion cohort) <u>Study period:</u> Feb 1996 to Dec 1998 <u>Setting:</u> Family practice in the Netherlands (within the framework of a RCT study of AB vs placebo for AOM)	<u>Inclusion:</u> Children aged between 6 and 24 months were eligible if they presented with AOM at the office of their family doctor, diagnosis: otoscopy (red eardrum, bulging or otorrhoea), presence of acute signs of infection according to the guidelines of the Dutch College of General Practitioners <u>Exclusion:</u> Children with a known immunological disorder, craniofacial abnormality, or Down's syndrome were excluded from the study <u>Study group:</u> <u>Recurrent AOM cohort:</u> Age < 1 = 42.4% Male = 54.3% Bilateral AOM = 61.0% Persistent symptoms (>10 days) = 36.7% AB treatment = 51.0% At least 1 recurrent AOM within 6 months = 105 (50%) <u>Persistent middle ear effusion cohort:</u> Age < 1 = 41.2% Male = 56.3% Bilateral AOM = 60.0% Persistent symptoms (>10 days) = 35.3% AB treatment = 51.6%	<u>Clinical predictive variables:</u> Age, sex, history of AOM, day care, history of recurrent RTIs, allergy, no. of siblings, smoking in household, season, breastfeeding, bilateral disease, duration of symptoms, treatment at entry <u>After logistic regression:</u> <u>Recurrent AOM:</u> Male (score 6), passive smoking (score –8), winter season (score 9), persistent symptoms (score 8) (baseline score starts from –9) <u>Persistent middle ear effusion:</u> Winter season (score 7), bilateral AOM (score 7), sibling history of AOM (score 7), recurrent AOM (score 7). (baseline score starts from –18) <u>Outcome of interest:</u> Recurrent AOM (at least 1 episode of AOM within 6 months of their initial AOM) and persistent middle ear effusion (uni- or bilateral middle ear effusion at all follow-up visits)	During the 10 days of treatment (AB or placebo) – 2 visits; 6-week visit; 3-month visit (those with uni- or bilateral effusion at 6-week); 6-month visit (those with uni- or bilateral effusion at 3-month); 6-month telephone contact for all children	<u>Predictive model (predicting Recurrent AOM and persistent middle ear effusion):</u> <u>Cut-off in score for predicting recurrent AOM:</u> < –8 < –1 < 5 <u>Cut-off in score for predicting persistent middle ear effusion:</u> < –11 < 2 **Note: authors concluded that no sufficient discriminatory prognostics model could be constructed for either outcome measure*	Sensitivity = 93%, specificity = 23%, PPV = 54%, NPV = 77% Sensitivity = 72%, specificity = 56%, PPV = 62%, NPV = 67% Sensitivity = 51%, specificity = 76%, PPV = 68%, NPV = 61% Area under ROC = 0.69 (95%CI: 0.62–0.76) Sensitivity = 78%, specificity = 47%, PPV = 48%, NPV = 77% Sensitivity = 49%, specificity = 85%, PPV = 67%, NPV = 73% Area under ROC = 0.69 (95%CI: 0.60–0.79)
<u>Additional comments:</u> The authors commented that the performance of the discriminatory predictive model was poor (AUC < 0.70) and the number of false-positive and/or false-negative was too high to be of value in clinical practice.						

Longer-term outcomes from a randomised trial of prescribing strategies in otitis media (not validated)

Study type	No. of patients	Patient characteristics	Prognostic/diagnostic factor(s)	Follow-up	Outcome measures	Results
ID: 3105 Level: (+) Follow-up secondary analysis of RCT cohort Author: Little et al. (2006)	<u>Study group:</u> Total no. of patients (completed follow-up) = 219 <u>Study period:</u> Not stated <u>Setting:</u> GP practices (42 GPs) in southwest England: 62% from training practices 60% managed their own budgets 33% were in mixed urban and rural practice settings	<u>Inclusion:</u> Children aged between 6 months and 10 years attended their doctor with acute otalgia and otoscopic evidence of acute inflammation of the ear drum (dullness or cloudiness with erythema, bulging or perforation) When children were too young for otalgia to be documented then otoscopic evidence alone was a sufficient entry criterion <u>Exclusion:</u> Otoscopic appearances consistent with crying or a fever alone; appearances and history more suggestive of OM with effusion and chronic suppurative OM; serious chronic disease; use of AB within the previous 2 weeks; previous complications; child too unwell to be left to wait and see <u>Study group (based on 315 patients):</u> Under AB treatment = 151 Under delayed treatment = 164 *(AB group)* Mean prior duration of illness (days) = 1.46 Aged > 3 = 57% Perforated ear drum = 7% Bulging ear drum = 47% Red ear drum = 82% *(Delayed group)* Mean prior duration of illness (days) = 1.48 Aged > 3 = 62% Perforated ear drum = 9% Bulging ear drum = 46% Red ear drum = 78%	<u>Clinical predictive variables:</u> High temperature on day 1 (>37.5°C), vomiting, ear discharge, bulging drum, previous episodes of RTIs, family/social factors <u>Outcome of interest:</u> Episodes of earache and poor score on child function (9 or more, based on 14 descriptions of how hearing impairment with chronic secretory otitis media presents)	3 months and 1 year	<u>After logistic regression, the significant independent predictors (out of 10 variables) were:</u> <u>1) Episodes of earache (after 3 months)</u> ear discharge bulging drum <u>2) Episodes of earache (after 1 year)</u> past history – previous episodes of otitis media <u>3) Poor score (9 or more) on child function (after 3 months)</u> past history – previous episodes of otitis media <u>4) Poor score (9 or more) on child function (after 1 year)</u> past history – previous episodes of otitis media <u>Prescribing strategies:</u> *The delayed prescribing strategy did not significantly increase risk of:* Earache (after 3 months) Earache (after 1 year) Poor score on function (after 3 months) Poor score on function (after 1 year)	 LHR =7.04, p = 0.004 LHR = 5.50, p = 0.019 LHR = 8.04, p = 0.005 LHR = 4.95, p = 0.026 LHR = 4.56, p = 0.033 OR = 0.89 (95%CI: 0.48–1.65) OR = 1.03 (95%CI: 0.60–1.78) OR = 1.37 (95%CI: 0.72–2.60) OR = 1.16 (95%CI: 0.61–2.23)
<u>Additional comments:</u> This is a secondary analysis that requires cautious interpretation. No area under ROC for discriminatory ability.						

Topic 3 Patients' preferences regarding antibiotic management strategies for RTIs (no prescribing, delayed prescribing and immediate prescribing strategies)

Volume of evidence (key clinical question 3)



Topic 3 Patients' preferences regarding antibiotic management strategies for RTIs (no prescribing, delayed prescribing and immediate prescribing strategies)

Key clinical question 3

What are patients' preferences regarding antibiotic management strategies for RTIs (no prescribing, delayed prescribing and immediate prescribing strategies)?

Patients' responses to delayed antibiotic prescription for acute upper RTIs			
Study type	Patient population, setting and period	Methodology	Outcomes
ID: 3995 Level of evidence: (3) Survey questionnaire Edwards et al. (2003)	Total no. of patients/parents responded = 256 (68.4% response rate) <u>Patient population:</u> Eligible subjects were those of any age presenting with a URTI (coryza, sore throat, acute sinusitis, acute otitis media, or cough without chest signs) for whom the doctor would under normal circumstances offer a delayed antibiotic prescription <u>Setting:</u> Patients were recruited from 13 general practices in southeast England that were members of the STaRNet or Lewisham Primary Care Research Consortium research networks. Six of these practices cover a predominantly mixed inner city/suburban population, and seven are predominantly suburban <u>Period:</u> Feb to Oct 2000.	<u>Methodology:</u> Patients who had received a delayed antibiotic prescription for URTIs from their GP were posted a questionnaire 2 days after their consultation In order to provide a degree of standardisation, the patients received a leaflet briefly detailing the rationale of the technique and relevant instructions	<u>Patients' expectations of the consultation:</u> Approximately two thirds (n = 167 [65.2%]) of responders had expected to receive a prescription for antibiotics, 37% (n = 96) had expected advice alone, 2.0% (n = 5) expected tests or a hospital referral, and 4.7% (n = 12) anticipated a sickness certificate. <u>Patient expectations during consultation:</u> *(those took AB: n = 136, those didn't take AB: n = 120)* <u>Antibiotic prescription:</u> Those took AB = 89 (66.4%); those didn't take AB = 78 (66.1%), p = 1.00 <u>Other prescription:</u> Those took AB = 13 (9.7%); those didn't take AB = 11 (9.3%), p = 1.00 <u>Advice:</u> Those took AB = 43 (32.1%); those didn't take AB = 53 (44.5%), p = 0.05 <u>Tests or referral:</u> Those took AB = 2 (1.5%); those didn't take AB = 3 (2.5%), p = 0.67 <u>Sick note:</u> Those took AB = 5 (3.7%); those didn't take AB = 7 (5.9%), p = 1.00 <u>No expectations:</u> Those took AB = 25 (18.7%); those didn't take AB = 19 (16.0%), p = 0.57 <u>AB consumption:</u> Just over half (n = 136 [53.1%]; 95% CI = 47.0–59.2) of the responders chose to consume their antibiotics. Of these, 82.4% (n = 112) claimed to have taken all

			the antibiotics they were prescribed, while the remaining responders claimed that they only took some of them. Satisfaction: Most patients (92.5% [n = 237]) would choose to receive a delayed prescription again in the future as the vast majority of patients were very or fairly confident about their decision-making
Additional comments: No comparisons between immediate, delayed and no prescribing strategy.			

Back-up antibiotic prescriptions for common respiratory symptoms			
Study type	Patient population, setting and period	Methodology	Outcomes
ID: 4604 Level of evidence: (3) Survey questionnaire Couchman et al. (2000)	Total no. of patients/parents = 947 Those prescribed delayed AB and responded = 255 (89.2% response rate). <u>Patient population:</u> Patients presenting with complaints of common respiratory symptoms: Patients were enrolled in the study if they had head congestion, sinus congestion, fever, headache, cough, chest congestion, or sore throat. Patients were only excluded if they had one dominant symptom and physical finding, such as earache <u>Setting:</u> 28 physicians and 2 physician extenders (a nurse practitioner and a physician assistant) in 3 family practice clinics. These clinics are part of the Scott and White Healthcare System and are located in Temple (Santa Fe Clinic), Waco, and Killeen, Texas <u>Period:</u> January and April 1999	<u>Methodology:</u> The patients who were given back-up antibiotic prescriptions were each given a patient survey to complete with instructions to return the form in a provided preaddressed envelope 7 days after their initial appointment The patient survey included questions about: (1) patient satisfaction with the care received; (2) whether they received a written back-up antibiotic prescription; (3) whether they filled the back-up prescription	<u>From the 947 enrolled patients:</u> • No AB = 441 (46.6%) • Delayed AB = 286 (30.2%) • Immediate AB = 220 (23.2%) The overall delayed AB fill rate = 50.2% **Fill rates did not differ significantly by patient characteristics or their self-reported satisfaction with the care received* Patients' self-reported satisfaction with delayed AB = 96.1%
<u>Additional comments:</u> No comparisons between immediate, delayed and no prescribing strategy.			

Topic 1 Antibiotic management strategies for RTIs

GRADE profiles

6.4.4 – GRADE profiles

Key clinical question 1

The effectiveness and cost effectiveness of delayed antibiotic prescribing and/or no prescribing as strategies for managing RTIs and how they should be delivered?

GRADE profile – outcomes

The effectiveness of delayed antibiotic prescribing as strategy for managing acute otitis media												
Quality assessment								**Summary of findings**				
Outcome	No. of studies	Design	Limitations	Inconsistency	Directness	Sparse data	Other considerations	Intervention[b]	Control[c]	Relative risk	NNT	Quality
Usage of antibiotics after consultation [S, L and M]	3	RCT	No serious	No important	Uncertainty[a]	No	No/1+[f]/No/No	Delayed 120/382 (31%)	Immediate 357/376 (94%)	0.33 (0.29, 0.39)	1.58 (1.47, 1.72)	High
Otalgia[g] [S and L]	2	RCT	No serious	No important	No uncertainty	No	No/No/No/No	Delayed 130/282 (46%)	Immediate 108/268 (40%)	1.18 (0.99, 1.40)	14.2 (7.14, 100.0)	High
Daily pain score (1–10) – daily diary (severity) (at 1 week) [L]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	Delayed 150	Immediate 135	Mean difference = –0.16 (–0.42, 0.11) t = 1.18, p = 0.24		High
Night disturbances – daily diary (over 1 week) [L]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	Delayed 150	Immediate 135	Mean difference = –0.72 (–0.30, –1.13) t = 3.41, p < 0.01		High
Diarrhoea [S and L]	2	RCT	No serious	No important	No uncertainty	No	No/1+[f]/No/No	Delayed 24/282 (9%)	Immediate 56/268 (21%)	0.41 (0.26, 0.65)	8.33 (5.26, 16.66)	High
Belief AB are	1	RCT	No serious	No important	No	No	No/No/No/No	Delayed	Immediate	0.59	3.22	High

effective [L]					uncertainty			64/140 (46%)	100/131 (76%)	(0.48, 0.73)	(2.43, 5.00)	
Very satisfied with treatment approach (parents/carers) [L]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	Delayed 115/150 (77%)	Immediate 123/134 (91%)	0.84 (0.75, 0.93)	7.14 (4.54, 16.66)	High
Parents/carers satisfaction[h] [M]	1	RCT	No serious	No important	Uncertainty[j]	No	No/No/No/No	Delayed 100	Immediate 109	Total satisfaction scores: On day 12: I = 44.0, C = 44.4 On day 30: I = 44.6, C = 44.6 (not significant, p value not reported)		Moderate

[a] Only one out of three studies was from primary care setting, 1 from US paediatric emergency department and 1 from university paediatric clinic.
[b] Intervention = delayed antibiotics
[c] Control = immediate antibiotics
[f] Strong association
[g] Episodes of earache/otalgia: [S] data collected at follow-up (4–6 days); [L] data collected through daily diary (at 1 week).
[h] Total satisfaction scores – 4-point scale. Data on [L] and [M] were not pooled due to different methods of measurements
[j] Setting in US university paediatric clinic, study did not specify whether the clinic is community based with open access
S = Spiro et al. (2006)
L = Little et al. (2001)
M = McCormick et al. (2005)

GRADE profile – outcomes

The effectiveness of delayed antibiotic prescribing and/or no prescribing as strategies for managing acute cough/bronchitis												
Quality assessment								**Summary of findings**				
Outcome	No. of studies	Design	Limitations	Inconsistency	Directness	Sparse data	Other considerations	Intervention[b]	Control[c]	Relative risk	NNT	Quality
Pick up of antibiotic prescription[a] [D]	1	RCT	No serious	No important	No uncertainty	No	No/1+[d]/No/No	Delayed 43/95 (45%)	Immediate 92/92 (100%)	0.45 (0.36, 0.56)	2.00 (1.66, 2.50)	High
Usage of antibiotics [L]	1	RCT	No serious	No important	No uncertainty	No	No/1+[d]/No/No	Delayed 39/197 (20%)	Immediate 185/193 (96%)	0.20 (0.15, 0.27)	1.31 (1.21, 1.44)	High
Usage of antibiotics [L]	1	RCT	No serious	No important	No uncertainty	No	No/1+[d]/No/No	No AB 29/182 (16%)	Immediate 185/193 (96%)	0.16 (0.11, 0.23)	1.26 (1.17, 1.35)	High
Usage of antibiotics [L]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	No AB 29/182	Delayed 39/197	0.80 (0.52, 1.24)	33.33 (9.09, 33.33)	High

								(16%)	(20%)			
Outcome	No. of studies	Design	Limitations	Inconsistency	Directness	Sparse data	Other considerations	Intervention	Control	Mean difference		Quality
Symptom duration[e] (cough) [D]	1	RCT	No serious	No important	No uncertainty	Imprecise or sparse data[f]	No/No/No/No	Delayed Unknown	Immediate Unknown	*Log-rank [Mantel-Haenszel] test (result not reported), with p value > 0.4*		Moderate
Symptom duration[g] (cough) [L]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	Delayed 214	No AB 212	Mean difference = 0.75 (–0.37, 1.88) p = 0.19		High
Symptom duration[g] (cough) [L]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	Immediate 214	No AB 212	Mean difference = 0.11 (–1.01, 1.24) p = 0.19		High
Symptom duration[g] (cough) [L]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	Immediate 214	Delayed 214	Mean difference = –0.46 (–1.76, 0.48) p = 0.265		High
Outcome	No. of studies	Design	Limitations	Inconsistency	Directness	Sparse data	Other considerations	Intervention	Control	Mean difference		Quality
Adjusted severity of symptoms[h] [L]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	Delayed 214	No AB 212	Adj mean difference = –0.02 p = 0.86		High
Adjusted severity of symptoms[h] [L]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	Immediate 214	No AB 212	Adj mean difference = –0.07 p = 0.49		High
Outcome	No. of studies	Design	Limitations	Inconsistency	Directness	Sparse data	Other considerations	Intervention	Control	Odds ratio		Quality
Diarrhoea [L]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	Delayed	No AB	0.17 (0.67, 2.03)		High
Diarrhoea [L]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	Immediate	No AB	1.22 (0.70, 2.12)		High
Outcome	No. of studies	Design	Limitations	Inconsistency	Directness	Sparse data	Other considerations	Intervention	Control	Relative risk	NNT	Quality
Re-attendance within 1 month [L]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	Delayed 24/199 (12%)	No AB 41/190 (22%)	0.55 (0.35, 0.88)	–0.09 (–0.16, –0.02)	High
Re-attendance within 1 month [L]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	Immediate 26/196 (13%)	No AB 41/190 (22%)	0.61 (0.39, 0.96)	–0.08 (–0.15, –0.01)	High
Re-attendance within 1 month [L]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	Delayed 24/199 (12%)	Immediate 26/196 (13%)	0.90 (0.54, 1.52)	–0.01 (–0.07, 0.04)	High
Outcome	No. of studies	Design	Limitations	Inconsistency	Directness	Sparse data	Other considerations	Intervention	Control	Relative risk	NNT	Quality
Belief AB are effective [L]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	Delayed 57/141	Immediate 123/165	0.54 (0.43, 0.67)	2.94 (2.27, 4.34)	High

								(40%)	(75%)			
Belief AB are effective [L]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	No AB 61/131 (47%)	Immediate 123/165 (75%)	0.62 (0.50, 0.76)	3.70 (2.63, 5.88)	High
Belief AB are effective [L]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	No AB 61/131 (47%)	Delayed 57/141 (40%)	1.15 (0.87, 1.51)	16.6 (5.88, 20.0)	High
Outcome	No. of studies	Design	Limitations	Inconsistency	Directness	Sparse data	Other considerations	Intervention	Control	Relative risk	NNT	Quality
Patient satisfaction[i] [D]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	Delayed 40/73 (54%)	Immediate 55/75 (73%)	0.74 (0.58, 0.95)	5.55 (3.03, 33.33)	High
Patient satisfaction[j] [L]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	Delayed 147/190 (77%)	Immediate 166/194 (86%)	0.90 (0.82, 0.99)	12.5 (6.66, 100.0)	High
Patient satisfaction[j] [L]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	No AB 130/181 (72%)	Immediate 166/194 (86%)	0.83 (0.75, 0.93)	7.69 (4.76, 20.0)	High
Patient satisfaction[j] [L]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	No AB 130/181 (72%)	Delayed 147/190 (77%)	0.92 (0.82, 1.04)	20 (7.14, 33.33)	High

[a] Rates of consumption unknown
[b] Intervention = delayed antibiotics
[c] Control = immediate antibiotics
[d] Strong association
[e] Probability of recovery from cough over days 1–13
[f] Limited data provide.
[g] Duration of cough – day (until very little problem).
[h] On a point scale 0–6 on six symptoms (adjusted to baseline variables). The six symptoms are: cough, dyspnoea, sputum production, well-being, sleep disturbance, activity disturbance
[i] 'Very satisfied' with the consultation
[j] 'Very satisfied' with overall management
L = Little et al. (2005)
D = Dowell et al. (2001)

GRADE profile – outcomes

The effectiveness of delayed antibiotic prescribing and/or no prescribing as strategies for managing acute sore throat												
Quality assessment								**Summary of findings**				
Outcome	No. of studies	Design	Limitations	Inconsistency	Directness	Sparse data	Other considerations	Intervention	Control	Relative risk	NNT	Quality
Usage of antibiotics [L]	1	RCT	No serious	No important	No uncertainty	No	No/1+[e]/No/No	No AB 23/174 (13%)	Immediate 210/211 (99%)	0.13 (0.09, 0.19)	1.16 (1.09, 1.23)	High
Usage of antibiotics [L]	1	RCT	No serious	No important	No uncertainty	No	No/1+[e]/No/No	Delayed 55/176 (31%)	Immediate 210/211 (99%)	0.31 (0.25, 0.39)	1.47 (1.33, 1.63)	High
Usage of antibiotics [L]	1	RCT	No serious	No important	No uncertainty	No	No/1+[e]/No/No	No AB 23/174 (13%)	Delayed 55/176 (31%)	0.42 (0.27, 0.65)	5.5 (3.84, 11.1)	High
Outcome	No. of studies	Design	Limitations	Inconsistency	Directness	Sparse data	Other considerations	Kruskal–Wallis, χ^2				Quality
Resolution of symptoms by 3 days[a] [L]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	No AB = 35%; immediate = 37%; delayed = 30% χ^2 = 2.50, p = 0.28				High
Outcome	No. of studies	Design	Limitations	Inconsistency	Directness	Sparse data	Other considerations	Intervention	Control	Relative risk	NNT	Quality
Sore throat[c] (severity) [P]	1	RCT	No serious	No important	Uncertainty[f]	Imprecise or sparse data[j]	No/No/No/No	Mean score, Student t-test Delayed = 1.6, Immediate = 1.3, p = 0.006				Moderate
Sore throat[d] (duration) [L]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	Median (IQR), Kruskal–Wallis, χ^2 Delayed = 5 (3–7), no AB = 5 (3–7), immediate = 4 (3–6) χ^2 = 1.9, p = 0.39				High
Outcome	No. of studies	Design	Limitations	Inconsistency	Directness	Sparse data	Other considerations	Intervention	Control	Relative risk	NNT	Quality
Diarrhoea [L]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	Delayed 23/179 (13%)	Immediate 23/215 (11%)	1.02 (0.69, 2.06)	50 (25, 112.5)	High
Diarrhoea [L]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	No AB 16/186 (9%)	Immediate 23/215 (11%)	0.80 (0.43, 1.47)	50 (14.28, 133.3)	High
Diarrhoea [L]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	No AB 16/186 (9%)	Delayed 23/179 (13%)	0.66 (0.36, 1.22)	25 (10, 100)	High
Outcome	No. of studies	Design	Limitations	Inconsistency	Directness	Sparse data	Other considerations	Intervention	Control	Relative risk	NNT	Quality
Reconsultation with sore throat (in 1 month) [L]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	Delayed 12/238 (5%)	Immediate 22/246 (9%)	0.56 (0.28, 1.11)	25.6 (12.1, 100.0)	High

Reconsultation with sore throat (in 1 month) [L]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	No AB 22/232 (9%)	Immediate 22/246 (9%)	1.06 (0.60, 1.86)	200 (23.8, 218.8)	High
Reconsultation with sore throat (in 1 month) [L]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	No AB 22/232 (9%)	Delayed 12/238 (5%)	1.88 (0.95, 3.71)	22.7 (11.3, 1428.0)	High
Outcome	No. of studies	Design	Limitations	Inconsistency	Directness	Sparse data	Other considerations	Intervention	Control	Relative risk	NNT	Quality
Reconsultation with sore throat (in 12 months) [L]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	Delayed 50/169 (30%)	Immediate 90/148 (61%)	0.48 (0.37, 0.63)		High
Reconsultation with sore throat (in 12 months) [L]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	No AB 70/149 (47%)	Immediate 90/148 (61%)	0.77 (0.62, 0.95)		High
Reconsultation with sore throat (in 12 months) [L]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	No AB 70/149 (47%)	Delayed 50/169 (30%)	1.58 (1.19, 2.11)		High
Outcome	No. of studies	Design	Limitations	Inconsistency	Directness	Sparse data	Other considerations	Intervention	Control	Relative risk	NNT	Quality
Belief AB are effective [L]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	Delayed 99/165 (60%)	Immediate 181/207 (87%)	0.68 (0.59, 0.78)	3.7 (2.85, 5.55)	High
Belief AB are effective [L]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	No AB 95/173 (55%)	Immediate 181/207 (87%)	0.62 (0.54, 0.72)	3.12 (2.43, 4.16)	High
Belief AB are effective [L]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	No AB 95/173 (55%)	Delayed 99/165 (60%)	0.91 (0.76, 1.09)	20 (6.66, 120.0)	High
Outcome	No. of studies	Design	Limitations	Inconsistency	Directness	Sparse data	Other considerations	Intervention	Control	Relative risk	NNT	Quality
Patient satisfaction[k] [L]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	Delayed 165/177 (93%)	Immediate 202/211 (96%)	0.97 (0.92, 1.02)	50 (16.6, 200)	High
Patient satisfaction[k] [L]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	No AB 166/184 (90%)	Immediate 202/211 (96%)	0.94 (0.89, 0.99)	20 (11.11, 100.0)	High
Patient satisfaction[k] [L]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	No AB 166/184 (90%)	Delayed 165/177 (93%)	0.96 (0.90, 1.02)	50 (14.28, 150.0)	High

[a] Symptoms included sore throat, cough, headache, unwell and fever
[c] The presence and severity of symptom from checklist scale 1–3 (day 3)
[d] Median (interquartile range) duration of symptom (days) after 3 days
[c & d] Data were not pooled due to different methods of measurements
[e] Strong association

[f] Population were all culture positive and placebo tablets were used as control. All these do not reflect the actual primary care consultation
[h&I] Data were not pooled due to big difference in follow-up period
[j] Relatively small sample
[k] Satisfaction with consultation (scoring 'very' or 'moderate')
L = Little et al. (1997)
P = Pichichero et al. (1987)
G = Gerber et al. (1990)

GRADE profile – outcomes

The effectiveness of delayed antibiotic prescribing and/or no prescribing as strategies for managing common cold												
Quality assessment								Summary of findings				
Outcome	No. of studies	Design	Limitations	Inconsistency	Directness	Sparse data	Other considerations	Intervention[a]	Control[b]	Relative risk	NNT	Quality
Usage of antibiotics	1	RCT	No serious	No important	No uncertainty	Imprecise or sparse data[c]	No/No/No/No	Delayed 27/62 (43%)	Immediate 54/61 (89%)	0.49 (0.36, 0.66)	2.27 (1.69, 3.33)	Moderate
Temperature (^{o}C) – day 3	1	RCT	No serious	No important	No uncertainty	Imprecise or sparse data[d]	No/No/No/No	Mean score (^{o}C) Delayed = 36.7, immediate = 36.9 **Analysis of comparison not provided*				Moderate
Symptom scores[e] (day 3)	1	RCT	No serious	No important	No uncertainty	Imprecise or sparse data[d]	No/No/No/No	Mean score Delayed = 5.4, immediate = 5.1 **Analysis of comparison not provided*				Moderate
Belief AB are effective	1	RCT	No serious	No important	No uncertainty	Imprecise or sparse data[c]	No/No/No/No	Delayed 51/67 (76%)	Immediate 47/62 (76%)	1.00 (0.82, 1.21)	322 (7.14, 340.4)	Moderate
Patient satisfaction[f] (day 3)	1	RCT	No serious	No important	No uncertainty	Imprecise or sparse data[c]	No/No/No/No	Delayed 64/67 (96%)	Immediate 58/62 (94%)	1.02 (0.93, 1.10)	100 (20, 111.1)	Moderate

[a] Delayed antibiotics
[b] Immediate antibiotics
[c] Relatively small sample
[d] Relatively small sample and limited data provided
[e] One point scored for each of 15 symptoms (dry cough, night cough, sneezing, sore throat, pain on inspiration, pain when coughing, hoarse voice, headache, staying home from work or unable to do normal daily tasks, unwell, diarrhoea, vomiting, nausea without vomiting, runny nose, blocked nose)
[f] Patient satisfaction with the consultation measured on 'very or moderately satisfied'

GRADE profile – outcomes

The use of specific information leaflet or structured explanation in antibiotic management strategies for RTIS												
Quality assessment								Summary of findings				
Outcome	No. of studies	Design	Limitations	Inconsistency	Directness	Sparse data	Other considerations	Intervention	Control	Relative risk	NNT	Quality
Usage of antibiotics (next 2 weeks) [M2]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	Delayed (leaflet) 49/104 (47%)	Delayed (no leaflet) 63/101 (62%)	0.76 (0.59, 0.97)	6.66 (3.57, 100.0)	High
Usage of antibiotics (next 2 weeks) [M2]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	Delayed (leaflet) 49/104 (47%)	Immediate (no leaflet) 44/46 (96%)	0.49 (0.39, 0.60)	2.08 (1.69, 2.70)	High
Usage of antibiotics (at 1 week) [P]	1	RCT	No serious	No important	Uncertainty[a]	Imprecise or sparse data[b]	No/1+[c]/No/No	Delayed (struc expla) 18/44 (41%)	Delayed (no struc expla) 32/37 (86%)	0.47 (0.32, 0.68)	2.22 (1.58, 3.70)	Moderate
Usage of antibiotics (at 3 weeks) [L]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	Leaflet[d] 160/281 (57%)	No Leaflet[d] 159/291 (55%)	1.04 (0.90, 1.20)	50 (20, 110.0)	High
Outcome	No. of studies	Design	Limitations	Inconsistency	Directness	Sparse data	Other considerations	Intervention	Control	Relative risk	NNT	Quality
Reconsultation (within 4 weeks) [M2]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	Delayed (leaflet) 11/104 (11%)	Delayed (no leaflet) 14/105 (13%)	0.79 (0.37, 1.66)	50 (9.09, 116.6)	High
Reconsultation (within 4 weeks) [M1]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	No AB (leaflet) 15/136 (11%)	No AB (no leaflet) 26/147 (18%)	0.62 (0.34, 1.12)	16.6 (7.14, 100.0)	High
Reconsultation (within 4 weeks) [M1]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	Immediate (leaflet) 60/369 (16%)	Immediate (no leaflet) 81/354 (23%)	0.71 (0.52, 0.95)	16.6 (9.09, 100.0)	High

[a] Setting was two primary care clinics belonging to HMO-Clalit Health services (CHS) in the southern district of Israel, possible issue on generalisability
[b] Relatively small sample
[c] Strong association
[d] Leaflet factor: both leaflet and no leaflet included all three groups = delayed, no AB and immediate AB

L = Little et al. (2005)
M1 = Macfarlane et al. (1997)
M2 = Macfarlane et al. (2002)
P = Pshetizky et al. (2003)

6.4.5 – Draft prognostic checklist

Methodology checklist: DRAFT prognostic studies

Study identification *Include author, title, reference, year of publication*				
Guideline topic		**Key question no:**		
Checklist completed by:				
SECTION 1: INTERNAL VALIDITY				
In a well-conducted study:		**In this study this criterion is:** ***(Circle one option for each question)***		
1.1	The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results	Yes	No	Unclear
1.2	Loss to follow-up (from sample to study population) is unrelated to key characteristics (i.e. the study data adequately represent the sample), sufficient to limit potential bias	Yes	No	Unclear
1.3	The prognostic factor of interest is adequately measured in study participants to sufficiently limit bias	Yes	No	Unclear
1.4	The outcome of interest is adequately measured in study participants to sufficiently limit bias	Yes	No	Unclear
1.5	Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes	No	Unclear
1.6	The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results	Yes	No	Unclear

SECTION 2: OVERALL ASSESSMENT OF THE STUDY		
2.1	How well was the study done to minimise bias? *Code ++, + or –*	
2.2	If coded as + or – what is the likely direction in which bias might affect the study results?	

6.5 Appendix 5 – Health economic evidence

6.5.1 Aims

A simple economic evaluation was undertaken to estimate the cost effectiveness of a delayed prescribing strategy versus immediate or no prescribing strategies for the management of sore throat.

6.5.2 Method

The economic evaluation consisted of a decision tree analysis incorporating the care pathway for managing patients with sore throat. This was based on an open randomised trial by Little et al. (1997). The trial was conducted in the UK within primary care, and so provides a relevant setting on which to base the economic model. The trial investigated three prescribing strategies for sore throat. Patients aged 4 years and over were randomised to three groups: prescription for antibiotics, no prescription and prescription for antibiotics if symptoms were not starting to settle after 3 days. The decision tree model was developed using the software package TreeAge Pro 2008 (TreeAge Software, Inc.).

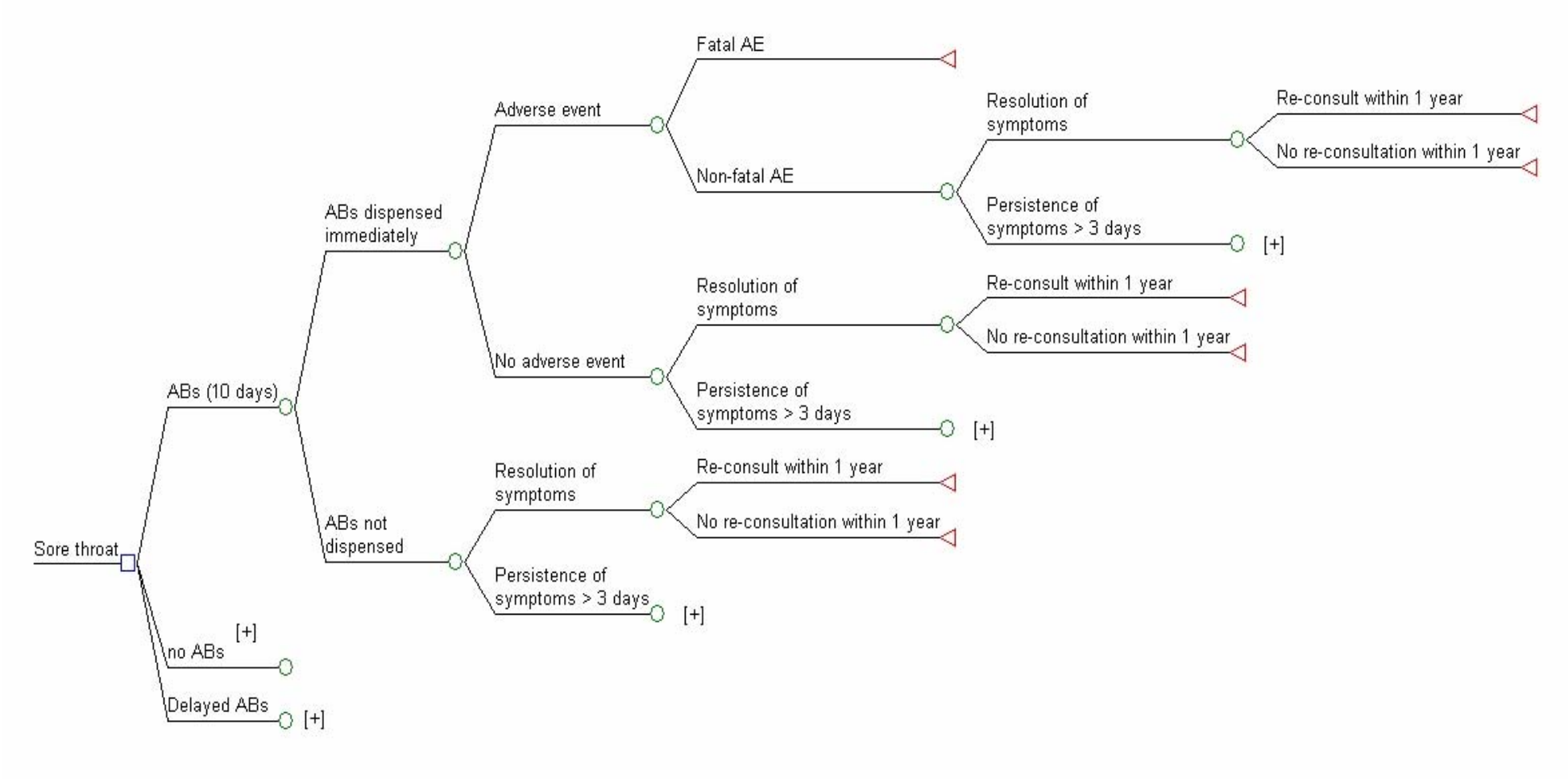
In the model, patients were assigned to one of the following strategies as in Little et al. (1997).

- Strategy 1: immediate prescription for antibiotics.
- Strategy 2: no antibiotic prescription.
- Strategy 3: delayed antibiotics (patients were given a prescription that they could collect if symptoms were not starting to settle within 3 days).

A diagrammatic representation of the tree is given in figure 1. If patients had persistent symptoms for more than 3 days in the model, they then followed the pathway shown in figure 2. All the strategies in the tree follow the same pathway, although the probabilities of prescription uptake, complications, reconsultation and relapse within 1 year vary according to each strategy. Therefore, even though not all of the branches are fully expanded in the diagrams below, the decision pathways are duplicated across the alternative strategies.

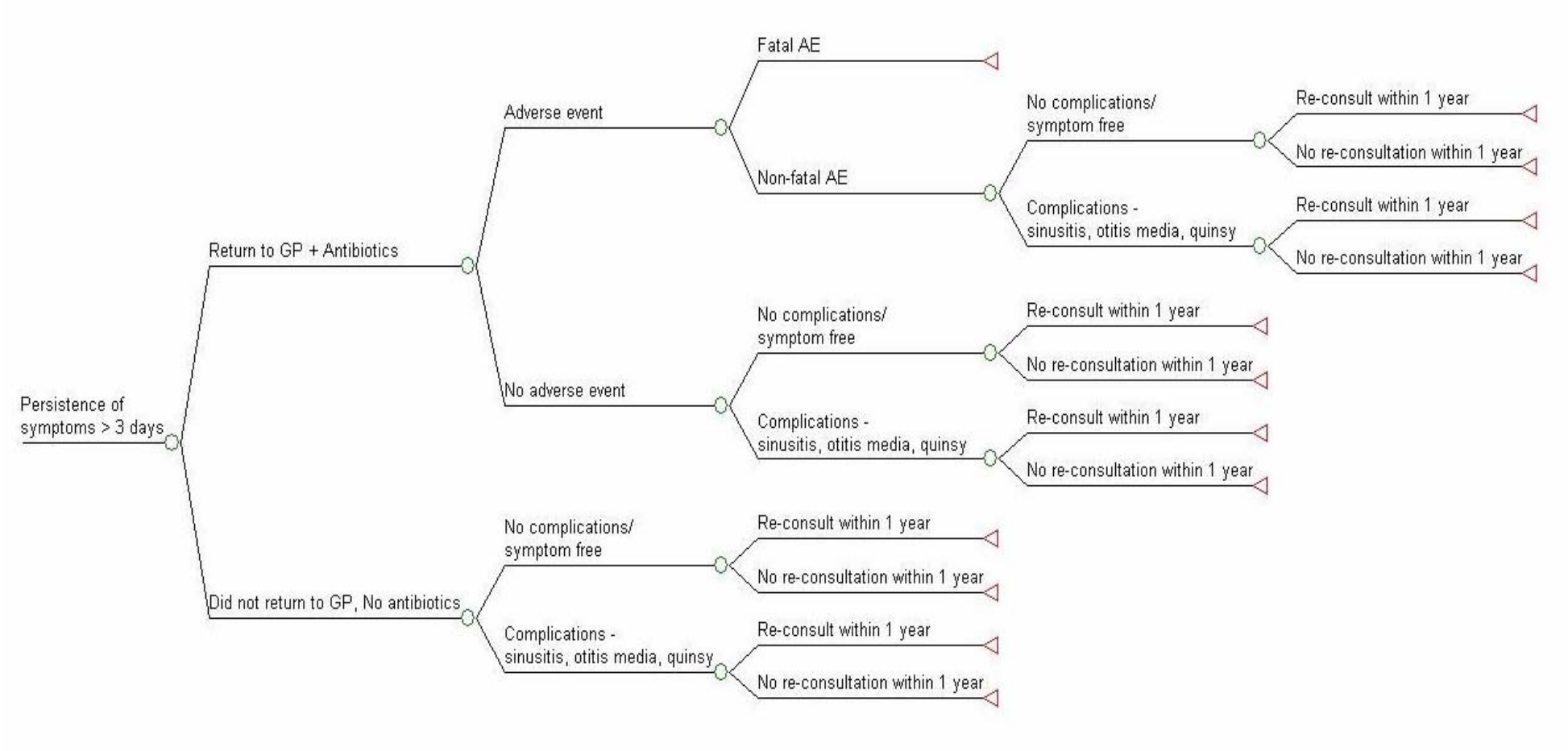
The model provides an estimate of costs in the base case and of costs and health outcomes in terms of quality-adjusted life years (QALYs) in subsequent analyses. The analysis adopts a 1-year time horizon to reflect the acute nature of sore throat. Simple one-way and multiway deterministic sensitivity analyses were used to explore the contribution of individual parameters to overall uncertainty in the cost-effectiveness estimates. While probabilistic sensitivity analysis has powerful attractions, not least in terms of providing a more accurate estimation of expected costs and benefits in non-linear models, it was considered unnecessary in this instance given the structure of the model and the nature of the data used to populate it. Probabilistic sensitivity analysis was unlikely to significantly alter the results of the analysis or provide any further information to inform decision-making.

Figure 1 Diagrammatic representation of the decision tree



ABs – antibiotics, AE – adverse event

Figure 2 Diagrammatic representation of the decision sub tree



AE – adverse event

6.5.3 Probabilities and treatment effects

Table 6.1 sets out the probabilities and other individual parameter estimates used in the model.

6.5.3.1 Probability of receiving antibiotics

At first consultation in the Little et al. (1997) study, patients were assigned to one of each of the arms described above. However, due to the pragmatic and open nature of the study, some patients in the no antibiotics arm received antibiotics at the first consultation. According to Little et al. (1997), at first consultation, 99% of patients given a prescription for antibiotics used their prescription in the immediate antibiotics arm, 13% of patients in the no antibiotics arm were given and subsequently used a prescription for antibiotics and 31% of patients in the delayed arm who were given a prescription used their prescription for antibiotics. In the trial, patients were analysed by intention to treat. The economic model assumes in the base case that all outcomes follow the protocol of no patients receiving antibiotics in the no antibiotics arm and all patients receiving antibiotics in the immediate antibiotics arm. This may underestimate the costs of antibiotics and subsequent adverse events, particularly in the no antibiotics strategy and slightly overestimate the costs in the immediate antibiotics arm. The proportion of people using their prescription in the delayed strategy was assumed to be 31% as reported in the trial. The percentage of patients using their prescription of antibiotics from the trial for each of the strategies was tested in sensitivity analysis.

6.5.3.2 Resolution of symptoms

The probability that patients' symptoms will persist for more than 3 days is taken from Little et al. (1997). This is a particularly important variable in the model as it acts as a proxy for the effectiveness of antibiotics. The paper reports the resolution of symptoms within 3 days as 37%, 35% and 30% for immediate antibiotics, no antibiotics and delayed antibiotics, respectively. The differences were not statistically significant ($p = 0.28$) between the groups.

When patients had unresolved symptoms, they could return to the GP and receive a further prescription for antibiotics. As a simplifying assumption in the model, all patients returning to the GP as a result of unresolved symptoms

received further antibiotics. However, not all patients would return to their GP due to unresolved symptoms, and because these data are unavailable from Little et al. (1997), an assumption was made. The GDG felt it appropriate to use the number of patients who had returned to their GP and received antibiotics within 1 month (data were available from Little et al. 1997). Even though the timeframe of the illness is much shorter than 1 month, these data are a more realistic assumption of the number of patients who would return to their GP and receive a prescription for further antibiotics following unresolved symptoms. Raw data were requested from the authors during the clinical review and the data for re-attendance within 1 month was 9% for immediate antibiotic prescribing and no antibiotic strategies, and 5% for delayed antibiotics. These differences were not statistically significant between the groups (p = 0.145, chi square test).

6.5.3.3 Probability of developing complications

Complications as a result of delayed prescribing of antibiotics for sore throat are considered to include sinusitis, otitis media, quinsy and rheumatic fever and glomerulonephritis. Rheumatic fever and glomerulonephritis have the potential to be very serious and costly, but these complications are very rare. Evidence from the Cochrane review on sore throat (Del Mar et al. 2006) shows no cases of rheumatic fever in the studies it reports from the year 1975 onwards. This is supported by Davey (1994), who reports that there have been no cases of acute rheumatic fever seen in the UK for more than 20 years. Therefore only suppurative complications of sore throat are considered in the model. The treatment of sinusitis and otitis media was antibiotics (amoxicillin). The treatment for quinsy included a hospital stay and these costs are considered in the model. Resolution of symptoms and the probability of complications act as a proxy for the effectiveness of antibiotics and are therefore important variables to consider within the model.

The probability of developing complications was derived from Del Mar et al. (2006). This Cochrane review explored the probability of developing various complications of sore throat. The meta-analyses from this study provided estimates on the development of complications that could be used for the economic analysis. For each of the suppurative complications, numbers of

patients experiencing complications in the control group were used to calculate a baseline probability of complications. The relative risk (RR) of developing complications with antibiotics provided in Del Mar et al. (2006) was then used to calculate the probability of developing complications for the antibiotics group. Del Mar et al. (2006) reported the following RRs: sinusitis, RR = 0.48, 95% confidence interval (CI): 0.08–2.76; otitis media, RR = 0.30, 95% CI: 0.15–0.58; quinsy, RR = 0.15, 95% CI: 0.05–0.47. No studies were identified in the clinical review that directly examined the risk of developing the complications of interest in a delayed antibiotics strategy versus an immediate or no antibiotics prescribing strategy. However, a study by Sharland et al. (2005) demonstrated that a reduction in antibiotic prescribing in children was not associated with an increase in admissions to hospital for quinsy or rheumatic fever. Using this evidence for the base case we have used the same rate of complications for both the delayed and immediate antibiotics strategies. This assumption was tested in sensitivity analysis.

The baseline probability of experiencing a complication was calculated using patient numbers from Del Mar et al. (2006). In each analysis from Del Mar et al. (2006), the number of patients experiencing each complication in the control group was divided by the overall number of patients in the control group. To calculate the probability of experiencing complications with antibiotics, the relative risks from Del Mar et al. (2006) were applied to the probability of experiencing complications with no adverse events. The probabilities for each complication were then summed to provide an estimate of the overall probability of experiencing any of the complications taken into account in either the no antibiotics or immediate antibiotics strategies. This calculation assumes that the complications are mutually exclusive, meaning that it is assumed that only one complication can be experienced at any one time. This is a recognised limitation of the model. An example calculation is provided below.

Example calculation for complication – otitis media (data from Del Mar et al. 2006)

28 out of 1435 patients experienced otitis media as a complication of sore

throat in the control arms of the studies in the meta-analysis.

Baseline probability of otitis media in no antibiotic strategy

= 28/1435

= 0.0195

Relative risk of experiencing otitis media if antibiotics are given

= 0.30

Probability of experiencing otitis media in antibiotic strategy

= 0.0195 * 0.30

= 0.0059

The probability of experiencing otitis media is added to the probabilities of experiencing sinusitis and quinsy to provide an overall probability of complications for each of the strategies in the model.

By calculating the probability of complications in this way, the individual baseline risk of complication or the RR of each of the complications (and therefore the probability of complications for immediate and delayed prescribing strategies) can be varied in sensitivity analysis.

Given the limitations in data and the importance of this variable, the probabilities of developing complications were examined in sensitivity analysis.

Table 6.1 Summary of model parameters, values and sources

Parameter – probabilities	Base case	Lower	Upper	Source/comment
Antibiotics used				
Antibiotics dispensed/used after prescription given antibiotics arm	1	–	0.99	Assumption. Little et al. (1997) reported that some patients did not have their antibiotics dispensed or use their antibiotics in the immediate antibiotics arm (1%). This was tested in sensitivity analysis
Antibiotics dispensed/used after prescription given delayed antibiotics arm	0.31	–	–	Little et al. (1997)
Antibiotics dispensed/used after prescription given no antibiotics arm	0	0.13	–	Assumption. Little et al. (1997) reported that some patients in the no antibiotics arm of the trial received antibiotics. Sensitivity analysis was conducted using the figure reported in Little et al. (1997) for those who received antibiotics in the no antibiotics arm (13%)
Resolution of symptoms – probabilities				
Resolution of symptoms in the antibiotics strategy	0.37	0	1	Little et al. (1997)
Resolution of symptoms in the delayed antibiotics strategy	0.3	0	1	Little et al. (1997)
Resolution of symptoms in the no antibiotics strategy	0.35	0	1	Little et al. (1997)
Return to GP and receive antibiotics when symptoms haven't resolved in the antibiotics strategy	0.09	0	1	Reconsultation rates from Little et al. (1997)
Return to GP and receive antibiotics when symptoms haven't resolved in the no antibiotics strategy	0.09	0	1	Reconsultation rates from Little et al. (1997)
Return to GP and receive antibiotics when symptoms haven't resolved in the delayed antibiotics strategy	0.05	0	1	Reconsultation rates from Little et al. (1997)
Complications – probabilities				
Develop otitis media with no antibiotics	0.0195	–	–	Taken from Del Mar et al. (2006). Calculated simply by taking the number of

				patients experiencing otitis media with no antibiotics over the total number of patients in the control arms
Develop sinusitis with no antibiotics	0.0048	–	–	Taken from Del Mar et al. (2006). Calculated simply by taking the number of patients experiencing sinusitis with no antibiotics over the total number of patients in the control arms
Develop quinsy with no antibiotics	0.0231	0.002	0.200	Taken from Del Mar et al. (2006). Calculated simply by taking the number of patients experiencing quinsy with no antibiotics over the total number of patients in the control arms
Overall probability of developing complications with no antibiotics	0.0474	–	–	Calculated from Del Mar et al. (2006). The probabilities of having each complication were added to give an overall probability of complication. This assumes each complication is mutually exclusive
Overall probability of developing complications with antibiotics	0.0116	–	–	Calculated from Del Mar et al. (2006). This was calculated as an overall probability of developing complications (otitis media, sinusitis or quinsy). The probability of developing each complication was multiplied by the relative risk of complications taken from Del Mar et al. (2006) and added together. This assumes each complication is mutually exclusive
Overall probability of developing complications with delayed antibiotics	0.0116	0.0474	0.0116	Assumed to be the same as 'immediate antibiotics' in the base case. Varied in sensitivity analysis between the probability of complications when no antibiotics are given and the probability of complications when antibiotics are given
Adverse reactions – probabilities				
Allergic reaction (anaphylaxis) to penicillin	0.0005	0.00025	0.001	BNF, September 2007 (Number 54)
Death due to anaphylactic shock	0.1	0.05	0.2	Taken from Neuner et al. (2003)
Adverse events to switched antibiotics	0	–	–	Assumption. Adverse reactions to the antibiotics used when patients had to switch from penicillin were considered very rare and unlikely to impact on costs according to the GDG. Therefore, to reduce complexity in the model, this was set to zero in the base case
Death due to an adverse reaction caused by switched antibiotics	0	–	–	Assumed to be zero in the base case

Reconsulation – probabilities				
Reconsultation in the antibiotics strategy within a year	0.38	0	1	Little et al. (1997)
Reconsultation in the delayed antibiotics strategy within a year	0.23	0	1	Little et al. (1997)
Reconsultation in the no antibiotics strategy within a year	0.32	0	1	Little et al. (1997)

6.5.3.4 Adverse consequences of antibiotics

The BNF states that anaphylactic reactions occur in less than 0.05% of treated patients (September 2007, No. 54). This figure was consequently used in the model to represent the probability that anaphylaxis will occur as a result of an adverse event due to penicillin. Following anaphylaxis due to penicillin, Neuner et al. (2003) used a probability of death of 0.1. We used this as the assumed base case probability of death following anaphylaxis in the model.

For other antibiotics considered in the present analysis, the base case estimate also assumes a zero risk of anaphylaxis and death due to anaphylaxis. In terms of non-fatal allergic reactions, these are not considered in the base case. This is mainly because milder reactions were not considered as serious or costly as anaphylaxis. However, the potential costs of mild reactions are taken into account in sensitivity analysis. A proportion of patients who have to switch antibiotics due to mild reactions when they are first prescribed antibiotics is considered in sensitivity analysis to assess the effect of the extra costs that may be incurred in terms of a further course of antibiotics. This proportion of patients will incur the cost of two courses of antibiotics – the original course and the cost of the course they have had to switch to.

6.5.3.5 Reconsultation

The probability of returning to the GP with a new episode of sore throat within a year for each of the three strategies was available from another study by Little et al. (1997) on re-attendance and complications.

6.5.3.6 Health-related quality of life weights

Evidence on utility weights in sore throat and in RTIs in general was poor. Hence in the base case analysis for this economic model only costs were taken into consideration. Neuner et al. (2003) reported that a utility value of 0.95 was applied to patients with pharyngitis in their model. Neuner et al. (2003) presented the QALDs lost due to various health states. Aside from the utility for pharyngitis, all other utilities were derived from two older studies (Hillner and Centor 1987; Herman 1984). Therefore, in the present analysis, assumptions were made regarding the disutility of an adverse reaction to antibiotics (anaphylaxis) and the most serious complication examined in the

model, quinsy (see table 6.2). Utility estimates were assigned as fixed values within the model. Due to the poor evidence on utilities for sore throat, extensive sensitivity analyses were carried out to examine the effect of utilities on the model. Although the values selected are extreme, no clinically acceptable ranges could be applied due to an absence of data to inform such ranges. This sensitivity analysis aimed to assess the impact of health-related quality of life on expected results over the widest range of utility values possible (0 to 1).

Table 6.2 Utility weights used in the model

Health state	Estimate	Lower	Upper	Time spent in state	Source / comment
No sore throat	1	0	1	–	Base case assumption
Sore throat	0.95	0	1	5 days	Based on the utility for pharyngitis taken from Neuner et al. (2003). Number of days taken from Little et al. (1997) (average number of days with symptoms)
Adverse events to antibiotics (anaphylaxis)	0.5	0	1	1 day	Base case assumption. Number of days taken from estimated length of stay for anaphylactic shock ('National schedule of reference costs 2006–7')
Complications	0.5	0	1	2 days	Base case assumption. Number of days taken from estimated length of stay for quinsy ('National schedule of reference costs 2006–7')

6.5.3.7 Costs

Costs were considered from the perspective of the NHS and Personal Social Services and for the year 2006–7. The unit costs of health services were obtained whenever possible from standard national sources. Table 6.3 summarises the unit cost and resource use estimates considered in the model.

Data for the acquisition cost of antibiotics was primarily sourced from the Drug Tariff (accessed February 2008, http://www.ppa.org.uk/edt/February_2008/mindex.htm). Prices were not sourced from the BNF as some of the antibiotic acquisition costs have changed since the publication of the most recently available version (September 2007, No. 54). The prices of drugs used in the model were not expected to influence the overall results and the price changes from 2007 to 2008 were very small. Therefore although the cost year is 2006-7 for the

overall analysis, it was considered appropriate to use the most up to date drug acquisition costs available. The overall cost of antibiotic treatment will differ for children as the dose and (in some cases) the method of administration will be different compared with adults. Both the costs for the adult population and the child population have been taken from the Drugs Tariff. In the base case, any patient that required a switch of antibiotics in the model (due to unresolved symptoms or mild adverse events in sensitivity analysis) was assumed to switch to erythromycin. Amoxicillin was the assumed treatment for patients experiencing otitis media or sinusitis as complications in the base case.

The cost for a GP consultation was taken from 'Unit costs of health and social care', Personal Social Services Research Unit (PSSRU), 2007. This document provides a cost of an average consultation lasting for about 12 minutes and a cost of a consultation on a per minute basis. The GDG considered that a consultation for sore throat would take only 8 minutes and therefore the cost of a GP consultation for sore throat was estimated to be £23.20.

Data for hospitalisation costs were primarily sourced from the National Schedule of Reference Costs 2006-7 for NHS trusts. The diagnosis codes were obtained for quinsy and anaphylaxis (J36.X and T88.6, respectively), and these codes were subsequently mapped to the relevant HRG codes (using the HRGv4 code to group, The Casemix Service, March 2007). The average cost cited within the 'Schedule for quinsy' (HRG CZ22Y) was available for adults of 19 years or over. Each diagnosis code may have more than one HRG code which relate to various subgroups of patients. The reference costs give a specific cost for children admitted with quinsy in a separate HRG code (PA33A and PA33B which are for patients less than or equal to 18 years for intermediate upper respiratory tract disorders with and without complications). This cost (£647, without complications) was used to cost for children. The length of stay is the same; only the overall cost differs between children and adults for quinsy. Cost of complications was calculated as a weighted average of the number of people who were expected to experience otitis media, sinusitis or quinsy. The average cost cited in the

schedule for anaphylaxis for adults was £374. As for quinsy, there was a separate specific code available for children. This code (PA50Z) was used in the analysis of a child population and was slightly more than for an adult at £548.

No discounting of costs and health outcomes was applied due to the short time frame of the analysis.

Table 6.3 Unit cost estimates used in the model

Cost	Estimate	Range	Source / comment
Antibiotics (per course – adults)			
Penicillin V	£9.66	Fixed	Drugs Tariff, February 2008
Erythromycin	£9.49	Fixed	Drugs Tariff, February 2008
Clarithromycin	£3.67	Fixed	Drugs Tariff, February 2008
Amoxicillin	£1.99	Fixed	Drugs Tariff, February 2008
Antibiotics (per course – children)			
Penicillin V	£2.60	Fixed	Drugs Tariff, February 2008
Erythromycin	£5.56	Fixed	Drugs Tariff, February 2008
Clarithromycin	£11.16	Fixed	Drugs Tariff, February 2008
Amoxicillin	£2.38	Fixed	Drugs Tariff, February 2008
Secondary care and outpatient costs			
GP consultation, £2.90 per min	£23.20	Lower: £21 Upper: £50	PSSRU 2007 assumption of an 8-minute consultation (GDG consensus) including direct care staff costs and with qualification costs
Hospitalisation cost for peritonsillar abscess (quinsy) for adults	£790	Lower: £364 Upper: £862	Non-elective costs. 'National schedule of reference costs 2006–7' using HRG code CZ22Y – Intermediate head, neck and ear disorders 19 years and over without CC. 2-day average length of stay
Hospitalisation cost for peritonsillar abscess (quinsy) for children	£647	Fixed	Non-elective costs. 'National schedule of reference costs 2006–7' using HRG code PA33B – Intermediate upper respiratory tract disorders without CC
Hospitalisation cost for anaphylaxis for adults	£374	Lower: £265 Upper: £573	Non-elective costs. 'National schedule of reference costs 2006–7' using HRG code WA16Y – Shock and anaphylaxis without CC. 1 day average length of stay
Hospitalisation cost for anaphylaxis for children	£548	Fixed	Non-elective costs. 'National schedule of reference costs 2006–7' using HRG code PA50Z – Ingestion poisoning or allergies

6.5.4 Results

6.5.4.1 Base case

Adult population cost model

In the base case only the expected costs of the three antibiotic management strategies were determined. These costs are shown in table 6.4 below. The lowest cost option in the base case analysis is delayed antibiotics. The immediate antibiotics strategy is approximately three times the cost of the delayed and no antibiotics strategies. This is due to the cost of antibiotics and adverse events due to antibiotics not experienced in the other strategies.

Table 6.4 Base case analysis

Antibiotic strategy	Expected costs (£)
Immediate antibiotics	45.50
No antibiotics	16.00
Delayed antibiotics	14.00

Inclusion of utilities – adult model

When utilities were included in the model the results showed that there are only very small QALY differences between the strategies. This is due to the short timeframe of the analysis and the relative mild severity of sore throat. The results of the QALY analysis is shown in table 6.5 below.

Table 6.5 QALY model – incremental cost-effectiveness ratios

Antibiotic strategy	Costs per person	QALYs per person	Incremental cost-effectiveness ratio (versus delayed antibiotics)
Delayed antibiotics	14.00	0.99924	–
No antibiotics	16.00	0.99923	Dominated*
Immediate antibiotics	45.50	0.99925	£3,628,772 per QALY

*No antibiotics are more costly and less effective than delayed antibiotics

Child population model

The GDG recommended that children should be considered separately in the model. This is because the cost of antibiotics and the complication rates for sore throat in children may be different in this patient population. Although the

review carried out by Del Mar et al. (2006) included children in the population of the review, the authors found that there was not enough data to make specific conclusions about the use of antibiotics in children. The GDG considered that children are more likely to experience otitis media as a complication of sore throat whereas adults were more likely to experience quinsy as a complication, therefore the consequences of complications in the child population are likely to be lower. The cost of antibiotics for children is also lower than for adults in most cases. A second analysis with costs of antibiotics specific to children and a lower cost of complications and adverse events was carried out. The baseline probability of otitis media was increased by 50% and the baseline probability of quinsy was decreased by 50% and the costs of antibiotics were altered to reflect a scenario that may represent a child population with sore throat. This was achieved by taking the probability of experiencing complications from Del Mar et al. (2006) used in the base case and increasing the probability of experiencing otitis media to 0.0293 from 0.0195 and decreasing the probability of experiencing quinsy from 0.0231 to 0.0116.

The expected costs of each strategy are shown in table 6.6 below.

Table 6.6 Base case analysis – child population

Antibiotic strategy	Expected costs (£)
Immediate antibiotics	37.20
No antibiotics	9.20
Delayed antibiotics	8.70

When utilities are taken into consideration very small QALY differences were realised and the overall cost per QALY of moving from a delayed to an immediate antibiotics strategy was £5,180,871 per QALY (table 6.7).

Table 6.7 QALY model – incremental cost-effectiveness ratios – child population

Antibiotic strategy	Costs per person	QALYs per person	Incremental cost-effectiveness ratio (versus delayed antibiotics)
Delayed antibiotics	£8.70	0.99924	
No antibiotics	£9.20	0.99924	Dominated*
Immediate antibiotics	£37.20	0.99924	£5,180,871 per QALY

*No antibiotics are more costly and less effective than delayed antibiotics

6.5.5 Sensitivity analysis

A number of sensitivity analyses were undertaken. All the analyses described below are based on the adult population model with utilities included.

6.5.5.1 Utilities

Due to paucity of evidence on utilities in sore throat, a sensitivity analysis was carried out to assess their effect. An analysis was undertaken varying all utility estimates as a set between their upper and lower estimates. When keeping all other parameters as per the base case, varying the utility of sore throat, no sore throat, adverse events and complications, did not significantly alter the results. This is likely to be due to the short duration of sore throat, adverse events and complications and the small differences realised between the strategies. The utility of complications makes the biggest difference to the result. As the utility of developing complications increases, the immediate antibiotics strategy becomes even less cost effective, and in fact is eventually dominated by the other strategies (it is more expensive and produces fewer QALYs compared with the alternative options). If the utility of complications is very low then the incremental cost-effectiveness ratio (ICER) of the immediate antibiotics strategy decreases, producing an ICER of £636,279 per QALY when the utility is zero.

6.5.5.2 Probability of receiving antibiotics

An analysis was carried out on the effect of varying the probability of receiving antibiotics in the model. In the base case analysis it was assumed that no patients received antibiotics in the no antibiotics arm and all patients received antibiotics in the immediate antibiotics arm. In Little et al. (2007) some patients reported antibiotic use in the no antibiotics strategy and not all patients reported antibiotic use in the immediate antibiotics arm. To test the base case assumption we ran the model with the percentage of patients who reported antibiotic use in each of the strategies. Antibiotic use was reported in 99% of patients in the immediate antibiotics group, 13% of patients in the no antibiotics group and 31% in the delayed antibiotics group. This analysis did not substantially affect the results. The incremental cost effectiveness of moving from a delayed strategy to an immediate prescribing strategy

increased slightly from £3,628,772 to £3,643,748 due to slight decreases in both costs and utilities in the immediate antibiotics arm.

6.5.5.3 Costs

A one-way sensitivity analysis was performed on three cost parameters in the model. Costs that varied in one-way sensitivity analyses were the cost of a GP consultation, the cost of a hospitalisation for quinsy and the cost of hospitalisation for anaphylaxis (table 6.8). Although these costs were obtained from reliable published sources, sensitivity analysis was carried out to account for any additional cost in the treatment of anaphylaxis or quinsy that had not previously been taken into consideration. Sensitivity analysis was performed to assess how the cost of a GP visit influences the model results due to the uncertainty surrounding the length of a consultation for sore throat.

As the cost of a GP consultation is increased, the cost of each of the arms is increased. The cost of the immediate antibiotics arm increases most. If the cost of a GP consultation is increased to £34 (the cost of a 12-minute consultation), the cost of the immediate antibiotics arm increases so that this strategy costs £61.00 per person. This increases the ICER of immediate antibiotics compared with delayed antibiotics to £5,132,000 per QALY. Due to the high numbers of patients in the immediate antibiotics strategy who have a GP consultation, the costs in this strategy increase at a greater rate than the costs in the other strategies and therefore the immediate antibiotics strategy becomes even less cost effective when the GP consultation cost is increased. As the cost of treating quinsy is increased, the cost of each of the strategies is increased. The expected costs of the immediate antibiotics strategy increases at a lower rate than the other strategies due to there being fewer complications associated with this strategy. Therefore, the immediate antibiotics strategy becomes relatively more cost effective; however, it still does not fall within accepted cost-effectiveness thresholds. Varying the cost of hospitalisation for anaphylaxis does not have a substantial effect on the model as the number of patients experiencing anaphylaxis is very low.

Table 6.8 Sensitivity analysis on costs. All other parameters are at their base case values

Parameter	Value	Overall expected cost of strategy		
		Delayed ABs	No ABs	Immediate ABs
Cost of GP consultation	Lower – £21	13	16	42
	Upper – £50	20	21	84
Cost of hospitalisation for quinsy	Lower – 364	9	10	45
	Upper – 862	14	17	46
Cost of hospitalisation for anaphylaxis	Lower – 265	14	16	45
	Upper – 573	14	16	46

6.5.5.4 Complications

Sensitivity analysis was carried out on the rate of complications due to the lack of data on the rate of complications if a delayed strategy is adopted. Complications in the model were calculated using a baseline probability of complications with no antibiotics and applying relative risks to estimate the probability of experiencing complications when antibiotics are given. The same relative risks were used to determine the probability of experiencing complications in the delayed antibiotic strategy. This assumption was varied in sensitivity analysis by varying the relative risks and therefore the probability of experiencing complications in the delayed antibiotics strategy. As expected, increasing the probability of experiencing complications in the delayed strategy increased the costs in this strategy and slightly decreased the QALYs. The overall direction of the results did not change, although the ICER of changing from a delayed to an immediate prescribing strategy decreased from £3,628,772 to £1,691,158 per QALY. This remains well outside accepted thresholds of cost effectiveness.

A one-way sensitivity analysis was carried out on the baseline risk of developing quinsy, that is, on the probability of complications with no antibiotics. Only the probability of quinsy was varied as it is the most serious and costly complication considered. When we examined the baseline probability of developing quinsy (base case = 0.0231, range tested: 0.002–0.2) the direction of results is as expected, and the results also show that as the probability increases, the ICER for going from a delayed to an immediate prescribing strategy decreases and eventually the immediate antibiotics strategy dominates the others. This occurs when the baseline probability is

approximately 0.135, approximately six times the baseline value. The baseline probability of developing quinsy must be approximately 0.127 for the immediate antibiotics strategy to achieve an ICER of £20,000. It is important to note that the relative risks are not affected in this analysis and are therefore the same as the base case.

6.5.5.5 Resolution of symptoms

The probability of symptoms resolving in each of the strategies was varied from zero to one in three separate sensitivity analyses. When the probability of symptoms resolving with antibiotics equals zero, the immediate antibiotic strategy is dominated by the delayed strategy. When the probability of resolution of symptoms is one, the ICER of changing from a delayed to an immediate prescribing strategy is £977,500 per QALY. This variable acts as a proxy for the effectiveness of antibiotics in each of the strategies and therefore this result shows that as the effectiveness of immediate antibiotics increases, the immediate antibiotics strategy becomes relatively more cost effective. In this analysis, the ICER becomes lower than the base case but it is still outside of accepted cost-effectiveness thresholds. This is due to symptoms continuing to resolve in the other strategies and the remaining high cost of the immediate antibiotics strategy.

Varying the probability of symptoms resolving with delayed antibiotics does not change the direction of the results; the delayed antibiotics strategy is always the most cost effective. As the probability of symptoms resolving with no antibiotics increases, the immediate antibiotics strategy becomes dominated by the delayed and no antibiotic strategies.

6.5.5.6 Multiway sensitivity analysis

A two-way sensitivity analysis was carried out to assess the impact on model results of varying the underlying baseline risk of complications and the probability of symptoms resolving following a prescription of antibiotics. This was carried out by varying both the probability of symptoms resolving with immediate antibiotics and the baseline probability of developing quinsy. This analysis was carried out on the base case model (adult population and utilities included), and thus the complication rate was the same in both the immediate and delayed strategies. This is due to absence of data on the effect of

delayed strategies of antibiotic prescription and is a noted limitation of the analysis.

Table 6.9 shows the incremental cost effectiveness of moving from a delayed strategy to an immediate antibiotics strategy. The shaded area shows where the ICER for the immediate strategy is £30,000 per QALY gained and when the immediate antibiotics strategy becomes the dominant strategy compared with the delayed antibiotics strategy. When all three strategies are considered, at probabilities of developing quinsy of 0.002 or less, the no antibiotics strategy dominates both the delayed and immediate strategies.

Table 6.9 Two-way sensitivity analysis on resolution of symptoms with antibiotics (base case = 0.37) and probability of developing quinsy with no antibiotics (base case = 0.0231)

Probability of resolution of symptoms with antibiotics	Probability of developing quinsy										
	0.002	0.022	0.042	0.061	0.081	0.101	0.121	0.141	0.160	0.180	0.200
0.25	delayed*	8,770,051	1,255,289	553,187	289,061	150,527	65,212	7391	immediate**	immediate	immediate
0.3	delayed	6,129,389	1,134,924	510,060	265,514	135,082	54,000	immediate	immediate	immediate	immediate
0.35	delayed	4,692,249	1,032,948	471,517	244,027	120,831	43,582	immediate	immediate	immediate	immediate
0.4	delayed	3,788,547	945,445	436,864	224,340	107,639	33,878	immediate	immediate	immediate	immediate
0.45	delayed	3,167,772	869,539	405,540	206,235	95,394	24,815	immediate	immediate	immediate	immediate
0.5	delayed	2,715,041	803,067	377,088	189,531	83,996	16,333	immediate	immediate	immediate	immediate
0.55	delayed	2,370,255	744,373	351,130	174,070	73,361	8,377	immediate	immediate	immediate	immediate
0.6	delayed	2,098,919	692,168	327,351	159,718	63,414	900	immediate	immediate	immediate	immediate
0.65	delayed	1,879,823	645,432	305,489	146,361	54,091	immediate	immediate	immediate	immediate	immediate
0.7	delayed	1,699,204	603,348	285,320	133,897	45,335	immediate	immediate	immediate	immediate	immediate
0.75	delayed	1,547,745	565,255	266,655	122,242	37,096	immediate	immediate	immediate	immediate	immediate

Figures indicate ICERs for immediate antibiotics compared with delayed antibiotics in £ per QALY gained.

*delayed = delayed dominates

**immediate = immediate dominates

Noting that the base case probability of resolution of symptoms with antibiotics was 0.37 (37%) and the probability of developing quinsy was 0.0231 (2.31%), the results show that when symptom resolution at 3 days following antibiotic prescription is approximately 25%, the baseline probability for developing quinsy has to be greater than 0.14 (14%) for immediate antibiotic prescribing to become the optimal strategy. When symptom resolution at 3 days following antibiotic prescription is between 30 and 60%, the baseline probability for developing quinsy has to be greater than 0.12 (12%) for immediate antibiotic prescribing to become the optimal strategy. When symptom resolution at 3 days following antibiotic prescription is between 60 and 75%, the baseline probability for developing quinsy has to be greater than 0.10 (10%) for immediate antibiotic prescribing to become the optimal strategy. This shows that as the probability of resolving symptoms and the probability of developing quinsy increases, immediate prescribing becomes relatively more cost effective. Even at high probabilities of symptoms resolving, patients must have a five-fold increase in baseline risk of developing quinsy for the immediate antibiotics strategy to become considered cost effective.

Overall, the combined effect of varying the probability of resolution of symptoms with antibiotics and the probability of developing quinsy shows that there may be evidence for considering immediate antibiotics for those at increased risk of developing complications and in whom antibiotics may be more effective. It is however important to note that this analysis does not take into account changes in relative risks of complications between the delayed and immediate strategies

6.5.5.7 Other sensitivity analyses

Probability of anaphylaxis and death due to anaphylaxis

As the probability of anaphylaxis and death due to anaphylaxis are increased, the expected costs of the immediate strategy rise and there is also a corresponding reduction in the expected QALYs. The immediate antibiotics strategy is eventually dominated by the other two options when the probability of anaphylaxis approaches 0.0006. The immediate antibiotics strategy is eventually dominated by the other two options when the probability of death due to anaphylaxis approaches 0.14.

Mild adverse events

The costs of mild adverse events are taken into account in the model. A proportion of patients will incur the cost of two courses of antibiotics as they have had to switch antibiotics. The proportion of patients switching was varied between 0 and 50% in the sensitivity analysis to determine the impact of this parameter on model results. Increasing the number of patients who require a switch of antibiotics increases the costs in the model, particularly of the immediate antibiotics strategy. This does not result in a change in the direction of the result and makes the immediate antibiotics strategy even less cost effective.

Probability of reconsultation following unresolved symptoms

This parameter assumes that patients who reconsult due to unresolved symptoms will all receive further antibiotics. As the probability of reconsultation due to unresolved symptoms increases in the delayed and no antibiotics strategies, these strategies become the most cost-effective options with slightly lower costs and higher benefits than in the base case. As the probability of resolution of symptoms in the no antibiotic strategy approaches one, this strategy dominates the others as it is the least expensive and most effective.

It has not been possible to separate out the number of patients who return for a consultation following unresolved symptoms who subsequently receive

further antibiotics and who do not subsequently receive antibiotics due to lack of data. Although this is a known limitation of the model, in line with the other results in sensitivity analysis, it is not expected that this would make a substantial difference to the overall direction of the results.

Reconsultation within the year

As expected, increasing the consultation rate within a year for each of the strategies individually decreases the cost effectiveness of the strategy in which the variable is being altered. The overall direction of results remains unchanged.

6.5.6 Discussion

6.5.6.1 Evidence limitations

In general, poor evidence on the effectiveness of antibiotics and the rate of complications in the delayed antibiotic prescribing strategy hinder the validity of the results of this evaluation. Even with extensive deterministic sensitivity analysis the model shows that immediate prescribing will always be the most expensive strategy (if it assumed that there are clinically insignificant differences between alternative strategies in terms of resolution of symptoms, and complications are comparatively rare). Given that the effectiveness of antibiotic use in terms of resolution of symptoms and complications is unclear, it would be cost saving to move to a delayed antibiotic prescribing strategy and reassess those effectiveness parameters when further data become available.

6.5.6.2 Antimicrobial resistance

An aspect that has not been taken into consideration in this model is the impact of antimicrobial resistance. The addition of such an outcome in the analysis is likely to make the immediate antibiotic prescribing strategy even less desirable compared with delayed prescribing or no prescribing of antibiotics at all.

6.5.6.3 Adult and child populations

The GDG recommended that children should be considered separately in the economic analysis. This is because the cost of antibiotics and the complication rates for sore throat may be different in this patient population. The GDG considered that children are more likely to experience otitis media whereas adults are more likely to experience quinsy, therefore the costs of complications in the child population are likely to be lower. The cost of antibiotics for children is also lower than for adults in most cases. Altering the model to account for a child population does not affect the overall direction of the results. Therefore, similar recommendations could be made for children and adults.

6.5.6.4 Other subgroups

A subgroup analysis was carried out by means of a two-way analysis on probability of resolution of symptoms with antibiotics and probability of developing quinsy. Given that there is no evidence from the literature on the

effect on complication of delayed versus immediate antibiotics, this should be considered as an exploratory analysis. The analysis does not look at varying the effect on relative risks of complications for the strategies. Despite these limitations there is evidence that subgroups with a higher baseline risk of developing complications may benefit from an immediate prescribing strategy.

6.5.6.5 Setting

Only GP visits are taken into account in this analysis. It may be useful to look at the effect that varying prescribing rate has on different settings, such as A&E departments, walk-in centres and NHS direct.

6.5.6.6 Overall

In the base case analysis for the adult population the delayed antibiotic strategy was the least costly, followed by the no antibiotics strategy. The immediate antibiotics strategy was the most expensive strategy at approximately three times the cost of the other strategies. In the child population the cost minimisation exercise was consistent with the adult population model.

The data available on utilities in this area are scarce. This is likely to be because of the short duration of the condition and the relative mild severity of sore throat. This was the justification for conducting a cost minimisation exercise for the base case analysis then examining the effect of adding utilities. When utilities were incorporated into the model based on the available literature and a set of assumptions, the differences in QALYs between the alternative strategies were very small. This is not an unexpected result, and is arguably clinically plausible. Assigning utilities to short periods of time such as days or parts of days, as is the case in studies of short-term illnesses, is a less explored and thus less developed methodological area in the economic evaluation of health interventions. Therefore, further research in this area is important.

In one-way sensitivity analysis, none of the variables tested influenced the overall direction of the results. The delayed and no antibiotic strategies remain the least expensive. In some cases the immediate antibiotics arms becomes dominated. This is particularly the case if you remove even the smallest

disutility of complications (set the utility of complications to equal one), because the other arms become more effective if the disutility of complications is not taken into account.

In summary, the model suggests that an immediate antibiotic strategy is not cost effective under all scenarios explored in the present analysis and is dominated in some cases.

6.5.6.7 References

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6.6 Appendix 6 – Health economic evidence tables

This section provides evidence tables that summarise the data provided in the published economic evaluations identified for the purpose of this guideline. One study (Stewart and Philips 1994) was also reviewed but since the authors only considered costs, no further details are presented here.

Note: Economic evaluations that examined strategies for the diagnosis of RTI were excluded from detailed consideration since they do not consider the relevant patient population covered by this guideline.

Published economic evaluations were quality assessed using methods as described in the current 'Guidelines methods manual'.

Data extraction table for included study – delayed strategy

Primary Source	Coco A (2007) Cost-effectiveness analysis of treatment options for acute otitis media. *Annals of Family Medicine* 5: 29–38
Author	Coco
Date	2007
Type of economic evaluation	Cost utility analysis
Currency used	US dollars
Year to which costs apply	2001
Perspective used	The analysis was from a societal perspective including non-health care costs of parental work loss and transportation.
Timeframe	30 days
Comparators	Four antibiotic strategies were compared: watchful waiting, delayed prescription, 5 days of amoxicillin and 7–10 days of amoxicillin
Source(s) of effectiveness data	Effectiveness estimates for the clinical parameters were based on data from randomised clinical trials, clinical trials, a cross-national study and a pragmatic randomised control trial
Source(s) of resource use data	Published sources and authors assumptions
Source(s) of unit cost data	Costs were estimated for antibiotics, including amoxicillin, amoxicillin clavulanate and ceftriaxone (for mastoiditis only) using published average wholesale drug costs and handling costs. Resource use and costs were estimated for mastoiditis treatment, including hospitalisation, medication and outpatient costs) sourced from the Healthcare Cost and Utilization Project (HCUP). The cost of outpatient consultations was also included as an average of reimbursement from Medicaid claims for the diagnosis of AOM. Non-healthcare costs were included such as babysitting, day care, travel, parking and other expenses related to an episode of simple AOM and were calculated using published sources. Uncertainty surrounding the cost estimates was investigated in a sensitivity analysis, which enhances the generalisability of the results to other settings. The costs were appropriately adjusted for inflation and the price year was reported.
Modelling approach used	Decision tree model
Summary of effectiveness results	Quality adjusted life days (QALDs) lost – QALDs are calculated for four pathways within the model. Quality adjusted life years (QALYs) are also reported for each of the strategies **Pathway** — **QALDs lost** Resolution with observation — 1.6590 Clinical failure — 3.3981

	Resolution with amoxicillin	1.7181
	Clinical failure with amoxicillin	3.4572
	Strategy	**QALYs**
	Delayed prescription	0.99460
	Watchful waiting	0.99472
	7–10 days of amoxicillin	0.99501
	5 days of amoxicillin	0.99487

Summary of cost results

Costs, $

	Delayed prescription	**Watchful waiting**	**7–10 days of amoxicillin**	**5 days of amoxicillin**
Antibiotic	1.68	1.47	11.61	9.42
Mastoiditis	0.11	0.11	0.06	0.06
Other costs*	130.61	144.42	143.63	147.42
Total	132.40	146.00	155.30	156.90

*Other costs include non-healthcare costs, work loss costs and office consultations

Summary of cost-effectiveness results

The strategy with the highest benefit in terms of QALYs was 7–10 days of amoxicillin. This strategy had an incremental cost utility ratio (ICUR) of $55,900 per QALY compared with the least costly option which was delayed prescription. The watchful waiting strategy was extendedly dominated by the delayed strategy and the 7 to 10-day strategy and the 5-day amoxicillin strategy was dominated (more costly and less effective) by the 7 to 10-day strategy.

Sensitivity analysis

In one-way sensitivity analysis the 7 to 10-day strategy was compared with the delayed prescription strategy and the costs that had the greatest effect on the ICUR were: amoxicillin cost, non-healthcare cost, office consultation cost and work loss cost. Other variables that had the greatest effect on the ICUR were probability of clinical failure, probability of GI events, probability of non-attendance, probability of prescription redemption and the utility of a day of treatment failure. The author reported that a probabilistic sensitivity analysis had been undertaken demonstrating that 7–10 days of amoxicillin was associated with a 61% probability of the ICUR being less than $50,000 per QALY gained compared with delayed prescription.

Main conclusions

The author concluded that delayed prescription is the least costly option. Adopting such a strategy, it was argued, would lead to substantial savings for payers and would promote a decrease in the use of antibiotics for a common, primarily self-limiting RTI, potentially reducing the impact of antibiotic resistance. An important limitation of this study is that it does not consider the cost implications of antibiotic resistance. The author did not present the sensitivity analysis in full detail (no cost-effectiveness acceptability curves [CEACs] were presented). The author did not report any search methods and although parameter estimates were reported in some detail, any justification for the selection of the estimates was not provided.