

NICE clinical guideline 69 – Antibiotic prescribing – respiratory tract infections

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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
<ul style="list-style-type: none"> • 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 <ul style="list-style-type: none"> - 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) 	<ul style="list-style-type: none"> • 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
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- #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
- *metaRegister* of Controlled Trials – *mRCT*

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 scarletiform 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 contralateral)).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.

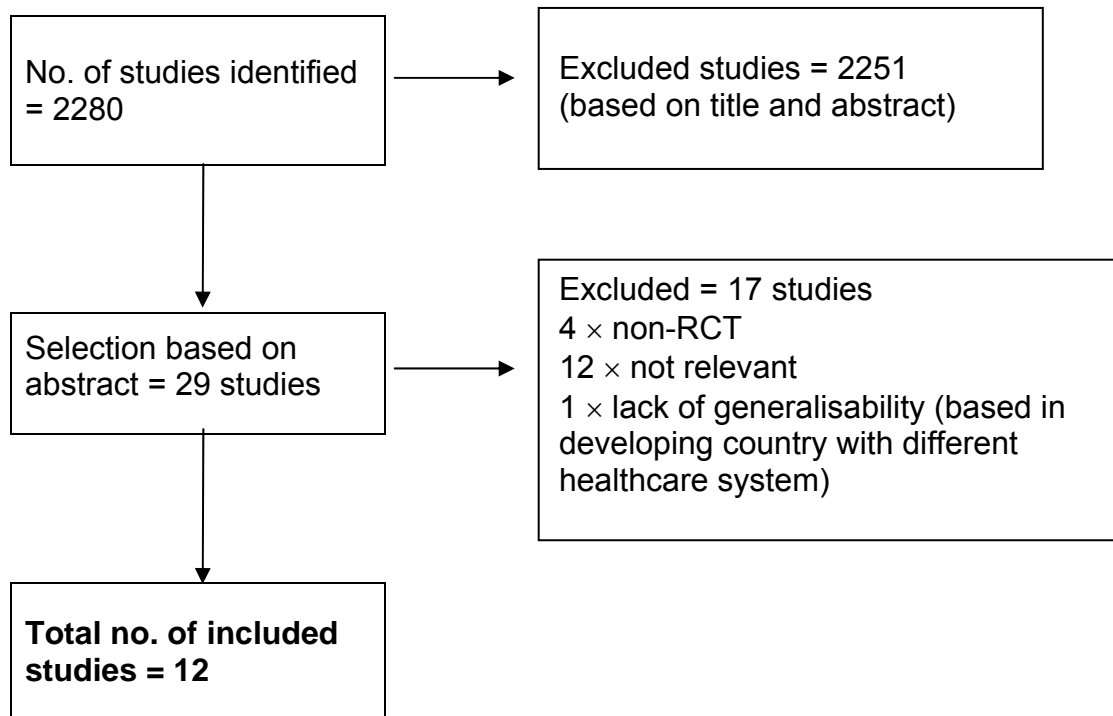
20. (hui or hui1 or hui2 or hui3).tw.
21. disutili\$.tw.
22. rosser.tw.
23. quality of wellbeing.tw.
24. quality of well-being.tw.
25. qwb.tw.
26. willingness to pay.tw.
27. standard gamble\$.tw.
28. time trade off.tw.
29. time tradeoff.tw.
30. tto.tw.
31. or/1-30

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 <i>(inclusion/exclusion criteria)</i>	<p>Intervention studies comparing the effectiveness of delayed and/or no antibiotic prescribing strategies with immediate prescribing strategy in primary care settings. Conditions included are:</p> <ul style="list-style-type: none"> • acute otitis media • acute cough/bronchitis • acute sore throat • acute sinusitis • common cold. <p>As well as the clinical effectiveness, the modes of delivery of delayed and no prescribing strategies were also explored and include:</p> <ul style="list-style-type: none"> • 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). <p>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.</p> <p>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.</p>

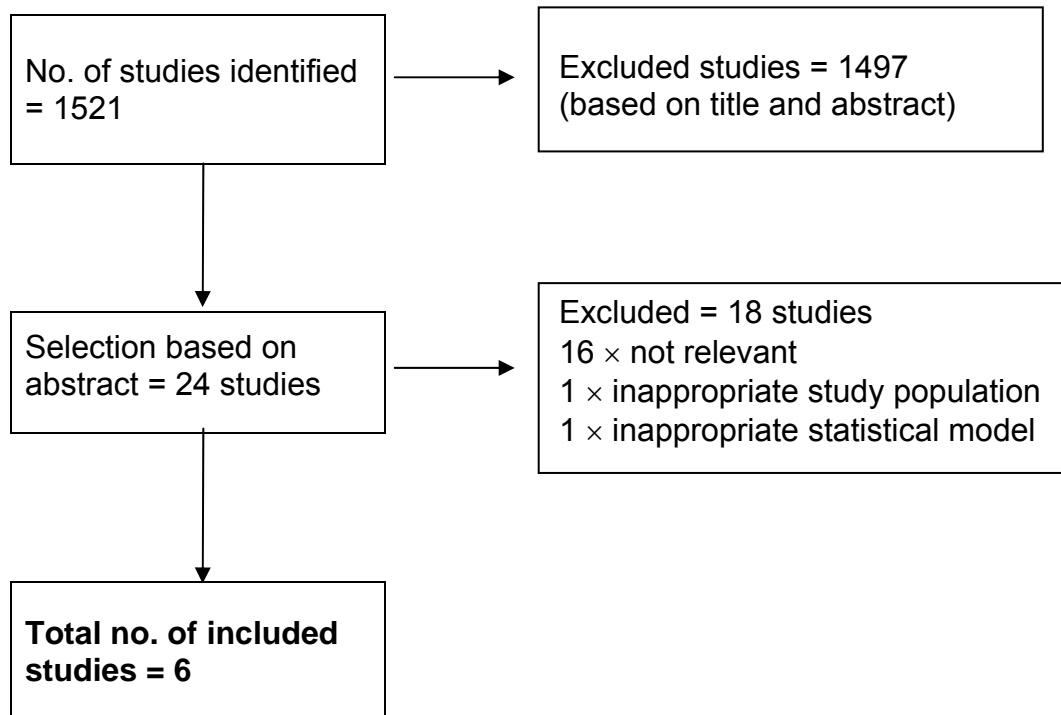
Flow chart 1 Volume of evidence for chapter 1



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	<ul style="list-style-type: none"> • Prospective/retrospective cohort studies and case-control studies were included. • Uncontrolled studies, including case series of those with complications, were excluded.
Population	<p>All adults and children in primary care settings excluding:</p> <ul style="list-style-type: none"> • children aged under 3 months • individuals with defined comorbidities • those not presenting in primary care and first contact (emergency department) settings.
Contents of papers <i>(inclusion/exclusion criteria)</i>	<p>Studies that explore clinical symptoms, signs and/or prediction rule models that predict serious complications in those presenting with:</p> <ul style="list-style-type: none"> • acute otitis media • acute cough/bronchitis • acute sore throat • acute sinusitis • common cold. <p>Complications were explored for:</p> <ul style="list-style-type: none"> • 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). <p>Studies that specifically looked at derivation or validation of diagnostic tools/assessments for the above complications were excluded.</p>

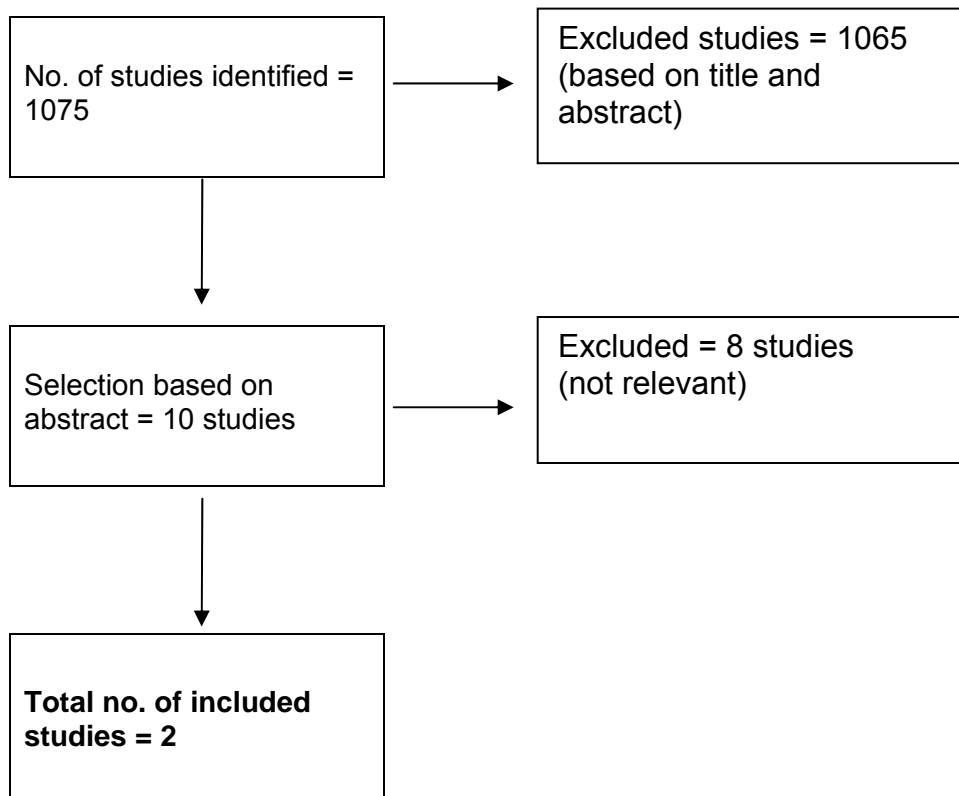
Flow chart 2 Volume of evidence for chapter 2



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

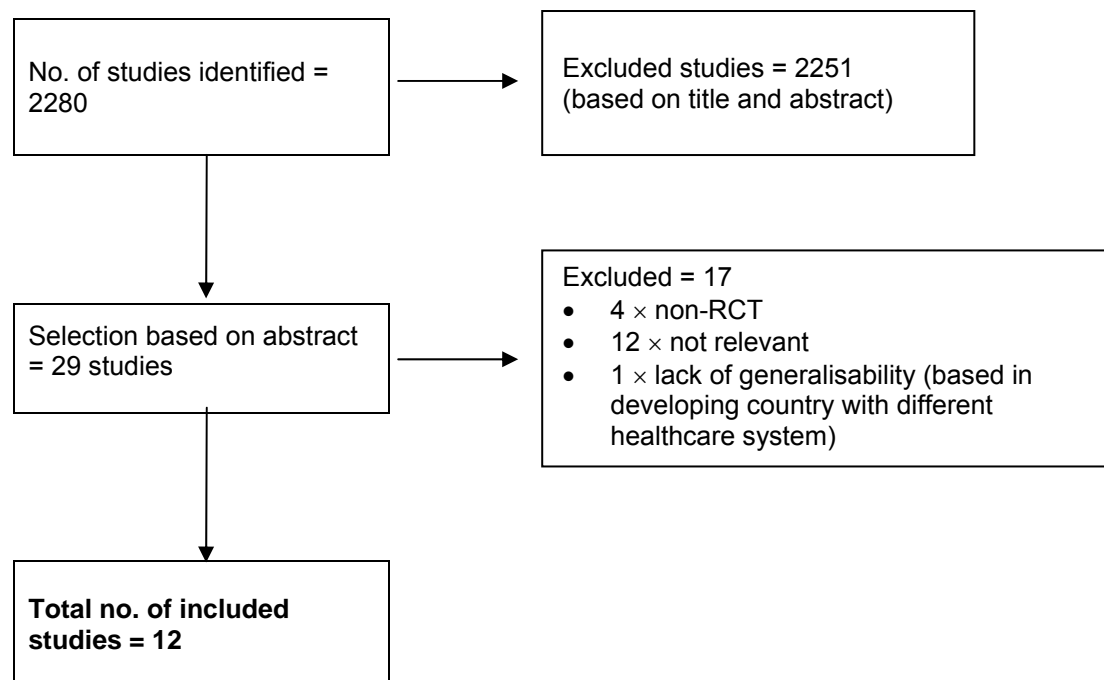
Language	English
Status	Published papers (full papers only)
Study design	Qualitative study and questionnaire survey
Population	<p>All adults and children/parents in primary care and first contact (emergency department) settings consulting with the RTIs defined in the scope excluding:</p> <ul style="list-style-type: none"> • parents of children aged under 3 months • individuals with specific comorbidities (e.g. asthma, COPD). <p>Evidence from population subgroups (e.g. BME) who may have differing preferences than the population included in the antibiotic management trials will be sought.</p>
Contents of papers <i>(inclusion/exclusion criteria)</i>	<p>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:</p> <ul style="list-style-type: none"> • acute otitis media • acute cough/bronchitis • acute sore throat • acute sinusitis • common cold. <p>Studies that specifically explored differing preferences of subgroups (e.g. BME) on antibiotic management strategies were included.</p> <p>Studies that reported general attitudes or expectations regarding antibiotic use were excluded.</p>

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>(I Group)</i> Male = 57% Median age = 3.6 Mean temp at triage = 37.1 <i>(C Group)</i> 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> <ul style="list-style-type: none"> 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> <ul style="list-style-type: none"> 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 <i>*Analysis adjusted for race/ethnicity, insurance status, baseline symptoms</i>	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> Otagia Fever Diarrhoea Vomiting Unscheduled visits <u>2) 11–14 days</u> Otagia 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

						<p><u>3) 30–40 days</u> Unscheduled visits</p> <p>Further analysis within the intervention group (AB filled vs. AB not filled)</p> <p>Willingness to withhold AB for future episodes of AOM</p> <p><u>4–6 days</u> Otolgia</p> <p>Fever</p> <p>Diarrhoea</p> <p>Vomiting</p>	<p>I = 22%, C = 21%, p = 0.85</p> <p><u>4–6 days</u> AB filled = 28% AB not filled = 63%, p < 0.001</p> <p><u>11–14 days</u> AB filled = 31% AB not filled = 65%, p < 0.001</p> <p><u>40 days</u> AB filled = 26% AB not filled = 66%, p < 0.001</p> <p>RR = 1.62 (95% CI: 1.26–2.03), p < 0.001</p> <p>RR = 2.95 (95% CI: 1.75–4.99), p < 0.001</p> <p>RR = 2.46 (95% CI: 0.73–8.29), p = 0.13</p> <p>RR = 3.28 (95% CI: 1.19–9.04), p = 0.01</p>
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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>(I Group)</i> Mean prior duration of illness (days) = 1.46 Aged > 3 = 57% Perforated ear drum = 7% Bulging ear drum = 47% Red ear drum = 82% <i>(C Group)</i> 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> <ul style="list-style-type: none"> 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> <ul style="list-style-type: none"> 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> <i>*Daily diary of presence of symptoms</i> 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

	<i>interaction between treatment and age</i>	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		<u>Adverse events:</u> 1) Rash 2) Diarrhoea <u>Other outcomes:</u> 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: $\chi^2 = 0.1$, $p = 0.74$ Immediate = 25/135 Delayed = 14/150 Diff: $\chi^2 = 5.2$, $p = 0.02$ Immediate = 19/135 Delayed = 45/150 Diff: $\chi^2 = 10.3$, $p < 0.01$ Immediate = 100/131 Delayed = 64/140 Diff: $\chi^2 = 19.3$, $p < 0.01$ Immediate = 123/135 Delayed = 115/150 Diff: $\chi^2 = 10.8$, $p < 0.01$ Immediate = 109/132 Delayed = 92/147 Diff: $\chi^2 = 13.81$, $p < 0.01$
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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>(I Group)</i> 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% <i>(C Group)</i> 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> <ul style="list-style-type: none"> • 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)

	<i>*No statistical differences</i>					<i>sadness, restlessness, poor appetite, limitation in activity, attending school or day care (7-point scale, from not present to extreme problem)</i> <i>Failure: returned to doctor (day 0–12) with acute ear symptoms</i> <i>Recurrence: returned to doctor (day 13–30) with acute ear symptoms</i> <i>Cure: without a failure or recurrence episode before the day 30 visit were considered cured</i>	
<p>Chief findings/comments:</p> <ul style="list-style-type: none"> • A well conducted single-blinded RCT with detailed information. • Study found that delayed strategy reduced AB consumption but not on other outcomes. <p><u>Methodology/potential confounder/bias:</u></p> <ul style="list-style-type: none"> • Did not investigate diverse events. <p><u>Generalisability:</u></p> <ul style="list-style-type: none"> • 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) (I Group)</u> 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> <ul style="list-style-type: none"> 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> <ul style="list-style-type: none"> 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, $p = 0.04$

Chief findings/comments:

- 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
<p>ID: 425</p> <p>Level of evidence: (1+)</p> <p>Study type: open RCT</p> <p>Authors: Little et al. (2005)</p>	<p>Patients aged 3 years or older with uncomplicated acute lower respiratory tract infection (≤ 21 days) who presented in primary care</p> <p><u>A 2 × 3 factorial design:</u> Factor 1 = info leaflet, no leaflet Factor 2 = AB strategies (immediate AB, delayed AB, no AB)</p> <p><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</p> <p><u>At baseline (based on N = 807):</u> Children = 17% Adults = 66% Older patients = 17%</p> <p><u>Leaflet</u> Mean age = 39 Prior duration of cough (mean days) = 9.6 Mean temperature = 36.6</p> <p><u>No leaflet</u> Mean age = 38 Prior duration of cough (mean days) = 9.5</p>	<p><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)</p> <p><u>Exclusions:</u></p> <ul style="list-style-type: none"> • 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) <p><u>Study period:</u> 18/08/98–30/07/03</p>	<p><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</p> <p><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))</p> <p><u>Mode of delivery:</u></p> <ul style="list-style-type: none"> • 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) 	<p><u>(Factor 2)</u> No AB prescription (as control)</p> <p><u>(Factor 1)</u> No information leaflet (as control)</p> <p><u>Mode of delivery:</u></p> <ul style="list-style-type: none"> • 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	<p><u>Daily symptom diary:</u> <u>Primary outcomes (1):</u> (No AB as control) – controlling effect of leaflet</p> <p><u>1) Delayed AB vs. no AB</u> Duration of cough – day (until very little problem)</p> <p>Duration of moderately bad cough – day</p> <p>Severity of symptoms (point scale 0–6)</p> <p><u>2) Immediate AB vs. no AB</u> Duration of cough – day (until very little problem)</p> <p>Duration of moderately bad cough – day</p> <p>Severity of symptoms (point scale 0–6)</p> <p><u>Adjusted severity of symptoms – point scale 0–6 on 6 symptoms (adjusted baseline variables):</u></p> <p>1) Delayed AB vs. no AB</p> <p>2) Immediate AB vs. no AB</p> <p>3) Leaflet vs. no leaflet</p>	<p>Mean diff = 0.75 (95% CI: –0.37 to 1.88), p = 0.19</p> <p>Mean diff = 0.13 (95% CI: –1.70 to 2.00), p = 0.89</p> <p>Mean diff = 0.06 (95% CI: –0.15 to 0.27), p = 0.56</p> <p>Mean diff = 0.11 (95% CI: –1.01 to 1.24), p = 0.19</p> <p>Mean diff = 0.52 (95% CI: –1.30 to 2.40), p = 0.19</p> <p>Mean diff = -0.10 (95% CI: –0.31 to 0.11), p = 0.11</p> <p>Adj mean diff = –0.02, p = 0.86</p> <p>Adj mean diff = –0.07, p = 0.49</p> <p>Adj mean diff = –0.05, p = 0.58</p>

	<p>Mean temperature = 36.7</p> <p><u>No AB</u> Mean age = 39 Prior duration of cough (mean days) = 9.9 Mean temperature = 36.7</p> <p><u>Delayed AB</u> Mean age = 38 Prior duration of cough (mean days) = 9.4 Mean temperature = 36.6</p> <p><u>Immediate AB</u> Mean age = 40 Prior duration of cough (mean days) = 9.4 Mean temperature = 36.6</p> <p><i>*No significant differences at baseline comparisons</i></p>	<p><u>Settings:</u> 37 physicians in primary settings in the region of southwest England</p>	<p><u>Analgesics:</u> Advice to take an analgesic</p>	<p><u>Analgesics:</u> Advice to take an analgesic</p>		<p><u>Adverse events (Diarrhoea):</u> 1) Delayed AB vs. no AB</p> <p>2) Immediate AB vs. no AB</p> <p><u>Primary outcomes (2):</u> (No leaflet as control) – controlling effect of AB strategies</p> <p>Duration of cough (until very little problem)</p> <p>Duration of moderately bad cough</p> <p>Severity of symptoms</p> <p><u>Questionnaire outcomes:</u> 1) AB strategies Used AB</p> <p>Believed in AB</p> <p>Very satisfied</p> <p>2) Info leaflet: Used AB</p>	<p>OR = 1.17 (95% CI: 0.67–2.03), p = 0.58</p> <p>OR = 1.22 (95% CI: 0.70–2.12), p = 0.48</p> <p>Mean diff = 0.26 (95% CI: –0.66 to 1.18), p = 0.58</p> <p>Mean diff = 0.20 (95% CI: –0.16 to 2.00), p = 0.83</p> <p>Mean diff = -0.03 (95% CI: –0.20 to 0.15), p = 0.77</p> <p>No AB (16%), delayed AB (20%), immediate AB (96%), p < 0.01</p> <p>No AB (47%), Delayed AB (40%), Immediate AB (75%), P < 0.01</p> <p>No AB (72%), delayed AB (77%), immediate AB (86%), p = 0.05</p> <p>No leaflet (57%), leaflet provided (55%) p = 0.58</p>
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						<p>Believed in AB</p> <p>Very satisfied</p> <p><u>Re-attendance within 1 month</u> (No AB as control) 1) Delayed AB</p> <p>2) Immediate AB</p> <p>(No leaflet as control) Leaflet provided</p>	<p>No leaflet (56%), leaflet provided (54%) $p = 0.73$</p> <p>No leaflet (76%), leaflet provided (78%) $p = 0.24$</p> <p>Incidence rate ratio estimate = 0.65 (95% CI: 0.40–1.04), $p = 0.08$</p> <p>Incidence rate ratio estimate = 0.55 (95% CI: 0.33–0.91), $p = 0.02$</p> <p>Incidence rate ratio estimate = 1.63 (95% CI: 1.07–2.49), $p = 0.02$</p>
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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> <i>(I1 Group – no AB)</i> Age > 12 years = 73% Male = 35% Duration > 3 days before seeing doctor = 40% Tonsillitis or pharyngitis = 85% Initial temp >37.5°C = 19% <i>(I2 Group – delayed AB)</i> Age > 12 years = 75% Male = 37% Duration > 3 days before seeing doctor = 41% Tonsillitis or pharyngitis = 83% Initial temp >37.5°C = 24% <i>(C Group)</i> 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> <ul style="list-style-type: none"> 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> <ul style="list-style-type: none"> 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

	<p>seeing doctor = 34% Tonsillitis or pharyngitis = 84% Initial temp >37.5°C = 25%</p> <p><i>*No significant differences at baseline comparisons</i></p>	<p>network expressing an interest in ENT research</p>				<p><u>No. of (%) with event:</u></p> <p>1) Diarrhoea</p> <p>2) Stomach ache</p> <p>3) Vomiting</p> <p>4) Rash</p> <p><u>Satisfaction, belief and intention of patients (scoring 'very' or 'moderate'):</u></p> <p>1) Satisfaction with consultation</p> <p>2) GP dealt with worries</p> <p>3) Likely to consult in future (sore throat)</p> <p>4) AB are effective</p>	<p>(0-4), $\chi^2 = 4.0$, p = 0.13</p> <p>Immediate = 23/215 (11%), no AB = 16/186 (9%), delayed = 23/179 (13%) $\chi^2 = 1.7$, p = 0.43</p> <p>Immediate = 66/215 (31%), no AB = 52/186 (28%), delayed = 48/179 (27%) $\chi^2 = 0.9$, p = 0.62</p> <p>Immediate = 18/215 (8%), no AB = 22/186 (12%), delayed = 15/179 (8%) $\chi^2 = 1.7$, p = 0.42</p> <p>Immediate = 14/215 (7%), no AB = 21/186 (12%), delayed = 11/179 (6%) $\chi^2 = 4.0$, p = 0.61</p> <p>Immediate = 202/211 (96%), no AB = 166/184 (90%), delayed = 165/177 (93%) $\chi^2 = 4.7$, p = 0.09</p> <p>Immediate = 201/211 (95%), no AB = 165/184 (90%), delayed = 164/177 (93%) $\chi^2 = 4.5$, p = 0.1</p> <p>Immediate = 148/187 (79%), no AB = 87/162 (54%), delayed = 92/162 (57%) $\chi^2 = 27.0$, p = 0.001</p> <p>Immediate = 181/207 (87%), no AB = 95/173 (55%), delayed = 99/165 (60%) $\chi^2 = 55.0$, p = 0.001</p>
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						<p><u>Legitimation of illness:</u></p> <p>1) Work or school</p> <p>2) Family or friends</p> <p>Subgroup analyses for duration of sore throat (in days):</p> <p><u>Selected subgroups (median and IQR):</u></p> <p>i) Enlarged cervical glands (n = 309)</p> <p>ii) Pharyngitis (n = 374)</p> <p>iii) Age under 12 (n = 149)</p> <p>iv) Dysphagia (n = 395)</p> <p>v) Temperature >37.5°C (n = 285)</p> <p>vi) Tonsillitis</p> <p>vii) Purulent exudate</p>	<p>Immediate = 128/209 (61%), no AB = 117/184 (64%), delayed = 96/177 (54%) $\chi^2 = 3.56$, p = 0.17</p> <p>Immediate = 75/210 (36%), no AB = 69/183 (38%), delayed = 67/176 (38%) $\chi^2 = 0.27$, p = 0.9</p> <p>Immediate = 4(3–7), no AB = 4(3–6), delayed = 5(3–6), $\chi^2 = 0.67$, p = 0.7</p> <p>Immediate = 5(3–7), no AB = 5(3–7), delayed = 5(3–7), $\chi^2 = 0.05$, p = 0.98</p> <p>Immediate = 3(2–5), no AB = 4(2–6), delayed = 4(3–5), $\chi^2 = 4.5$, p = 0.11</p> <p>Immediate = 5(3–6), no AB = 5(3–7), delayed = 5(3–7), $\chi^2 = 5.5$, p = 0.06</p> <p>Immediate = 4(2–5), no AB = 3(2–5), delayed = 5(4–7), $\chi^2 = 10.0$, p = 0.01</p> <p>Immediate = 4(3–6), no AB = 4(3–6), delayed = 5(4–7), $\chi^2 = 2.7$, p = 0.25</p> <p>Immediate = 4(3–6), no AB = 4(3–6), delayed =</p>
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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: <ul style="list-style-type: none"> 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> <ul style="list-style-type: none"> 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
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Chief findings/comments:

- 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.

Methodology/potential confounder/bias:

- 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.

Generalisability:

- 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>(I Group)</i> 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% <i>(C Group)</i> 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> <ul style="list-style-type: none"> 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

Chief findings/comments:

- 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.

Methodology/potential confounder/bias:

- 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>(I Group)</i> 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%) <i>(C Group)</i> 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): <ul style="list-style-type: none"> • Presence of acute inflammation of the nasal or pharyngeal mucosa in the absence of other specifically defined respiratory infection <u>Exclusions:</u> <ul style="list-style-type: none"> • 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> <ul style="list-style-type: none"> • 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 (°C) 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 0.2°C 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	C = 58/62 (94%), I = 64/67 (96%), p = 0.71
						3) likely to see doctors for next common cold	C = 40/62 (65%), I = 49/67 (73%), p = 0.343
						4) AB are effective	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> <ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> 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: <ul style="list-style-type: none"> 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> <ul style="list-style-type: none"> Prescription was given at consultation Standard verbal reassurance/information (based on a prompt card) <i>*Delayed or immediate based on clinical decision made without additional guidance or investigations.</i>	1) Delayed prescribing (no leaflet) 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)

	<p>Clear = 79% General signs = 17% Focal signs = 4%</p> <p><i>*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</i></p>		<p><u>Analgesics:</u> Not reported</p>	<p><u>Analgesics:</u> Not reported</p>			
<p>Chief findings/comments:</p> <ul style="list-style-type: none"> • 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. <p><u>Methodology/potential confounder/bias:</u></p> <ul style="list-style-type: none"> • Methods of delay, i.e. no. of days not clear and not as a controlled variable. <p><u>Generalisability:</u> UK GP practices, generalisable to UK population.</p>							

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 <u>No. of participants (completed trial):</u> Total = 81 I = 44 C = 37 <i>*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'</i>	<u>Inclusions:</u> Children aged 3 months to 4 years diagnosed with AOM (high fever [$>38^{\circ}\text{C}$], purulent ear discharge, opacity or bulging of the eardrum) <u>Exclusions:</u> Children exhibiting a toxic child appearance, a temperature of $\geq 39.5^{\circ}\text{C}$, extreme restlessness/irritability or vomiting, or where there was uncertainty of the diagnosis <u>Study period:</u> The winter of 1998–1999 <u>Settings:</u> 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: <ul style="list-style-type: none"> Natural history of AOM Possible complications from AOM Advice on the use of analgesics <u>Mode of delivery:</u> Prescription was given at consultation <u>Analgesics:</u> Parents were recommended in cases of high fever or severe pain to administer paracetamol prescribed according to the child's weight	Delayed prescribing <u>without</u> 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) <u>Mode of delivery:</u> Prescription was given at consultation <u>Analgesics:</u> No advice on analgesics	1 week after the consultation	Parents administration of AB <u>Day of AB administration:</u> 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: (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: <ul style="list-style-type: none"> 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 	1) No antibiotic without information leaflet 2) Immediate antibiotic without information leaflet Mode of delivery: N/A Analgesics: 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%)

Chief findings/comments:

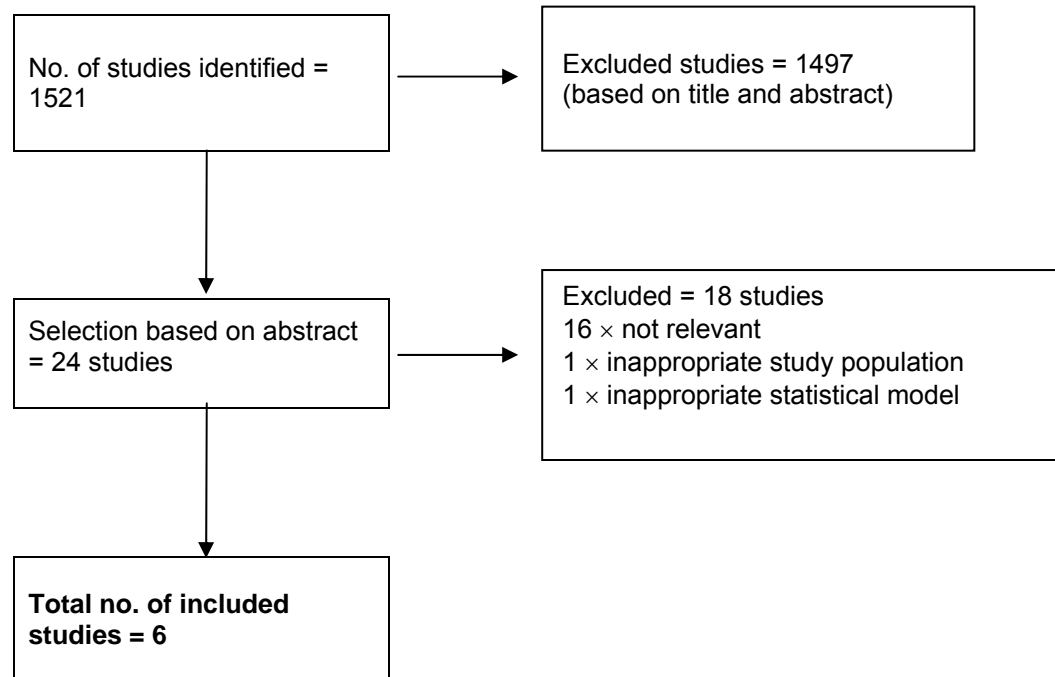
- The findings suggested that informing patients about the natural history of acute lower respiratory tract symptoms is an effective strategy for reducing the need for patients to return for a second consultation.

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)	<p><u>Study group:</u> Cases of quinsy following initial uncomplicated sore throat = 192</p> <p><i>*total cases of quinsy = 606</i></p> <p><u>Control group:</u> Cases of sore throat without quinsy = 198124</p> <p><u>Study period:</u> 1995 – 1997</p> <p><u>Setting:</u> UK-wide primary care data from the General Practice Research database (GPRD)</p>	<p><u>Inclusion (study group):</u> 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</p> <p><u>Characteristics of cases:</u> (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%</p> <p>(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%</p>	<p>Prevalence of quinsy = 15.8 per 1000 patients with sore throat, per annum</p> <p><u>Clinical variables:</u> Age, sex, smoking status, type of diagnosis, exposure to AB, lung disease</p> <p><u>Outcome of interest:</u> The development of quinsy after initial uncomplicated sore throat</p> <p><i>*Note:</i> <i>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)</i></p>	Use of 30 days of sore throat record	<p><u>After logistic regression:</u></p> <p>Age (21–40 years old)</p> <p>Smoking</p> <p>Male</p> <p><i>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)</i></p> <p>AB given after all events</p> <p>AB given after 'tonsillitis'</p> <p>AB given after 'sore throat/pharyngitis'</p> <p><i>*There was similar level of AB exposure in quinsy cases (88.0%) and controls (84.7%).</i></p> <p><i>*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</i></p>	<p>Adj OR = 3.4 (95%CI: 2.1–5.5)</p> <p>Adj OR = 2.5 (95%CI: 1.8–3.5)</p> <p>Adj OR = 1.6 (95%CI: 1.1–2.2)</p> <p>No. of cases = 169 Adj OR = 1.2 (95%CI: 0.7–1.8)</p> <p>No. of cases = 81 Adj OR = 0.6 (95%CI: 0.3–1.3)</p> <p>No. of cases = 88 Adj OR = 1.2 (95%CI: 0.7–2.2)</p>

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) <i>*Area under ROC = 0.68</i> 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)

Additional comments:

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 <i>*Note:</i> <i>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</i> <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)

Additional comments:

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)	<p><u>Study group 1 (derivation cohort):</u> Total no. of patients = 1693 (3166 episodes)</p> <p><u>Study group 2 (Validation cohort):</u> Total no. of patients = 2465 episodes of LRTIs</p> <p><u>Study period:</u> Jan 1997 to Feb 2003</p> <p><u>Setting: (Derivation cohort)</u> Patient data stored in the database of the Utrecht GP research network in the Netherlands (35 GPs)</p> <p><u>(Validation cohort)</u> Data of patients from the 2nd Dutch National Survey of General Practice in 2001, included 163 GPs in 85 practices</p>	<p><u>Inclusion (derivation cohort):</u> Patients aged ≥65 years visiting the general practitioner with LRTIS. LRTIS defined as episodes of pneumonia, acute bronchitis and COPD</p> <p><u>Exclusion (derivation cohort):</u> 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</p> <p><u>Inclusion (validation cohort):</u> Patients aged ≥65 years visiting the general practitioner with episodes of pneumonia and acute bronchitis</p> <p><u>Study group: (Derivation cohort):</u> Acute bronchitis = 1120 episodes Exacerbation of COPD = 1523 episodes Pneumonia = 523</p> <p>30-day hospitalization or death = 274 Death = 76 Mean age = 75.5 Male = 45% With 1 or more comorbid conditions = 85%</p> <p><u>(Validation cohort):</u> Acute bronchitis = 1736 episodes Pneumonia = 729 30-day hospitalization or death = 178 Death = 59</p>	<p><u>Clinical predictive variables:</u> 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</p> <p><u>After logistic regression: Diagnosis (score):</u> Acute bronchitis (0) Exacerbation of COPD (2) Pneumonia (4) Age: 65–79 (0) ≥80 (2)</p> <p>Congestive heart failure (1) Diabetes (2) Using oral glucocorticoids (3)</p> <p><u>Hospitalisation in previous year:</u> 0 (0) 1 (2) ≥2 (3)</p> <p>use of AB in previous month (2)</p> <p><u>Management:</u> Separate into low (score ≤2), medium (score 3–5) and high risk (score ≥7) group</p> <p><u>Outcome of interest:</u> 30-day hospitalization or death</p>	N/A Retrospective study of databases	<p><u>Predictive model (predicting 30-day hospitalisation or death):</u></p> <p><u>Derivation study:</u> Low risk (score ≤2)</p> <p>Medium risk (score 3–5)</p> <p>High risk (score ≥7)</p> <p><u>Validation study:</u> Low risk (score ≤2)</p> <p>Medium risk (score 3–5)</p> <p>High risk (score ≥7)</p>	<p>Sensitivity = 0.82, specificity = 0.52 % of risk of end point = 3.2%</p> <p>Sensitivity/specificity = not reported % of risk of end point = 9.9%</p> <p>Sensitivity = 0.35, specificity = 0.92 % of risk of end point = 30.9%</p> <p>Area under ROC = 0.75 (95%CI: 0.72–0.78)</p> <p>Sensitivity = 0.42, specificity = 0.81 % of risk of end point = 5.3%</p> <p>Sensitivity/specificity = not reported % of risk of end point = 14.5%</p> <p>Sensitivity = 0.06, specificity = 0.98 % of risk of end point = 22.0%</p> <p>Area under ROC = 0.74 (95%CI: 0.71–0.78)</p>

<u>Additional comments:</u> 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)

Additional comments:

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)

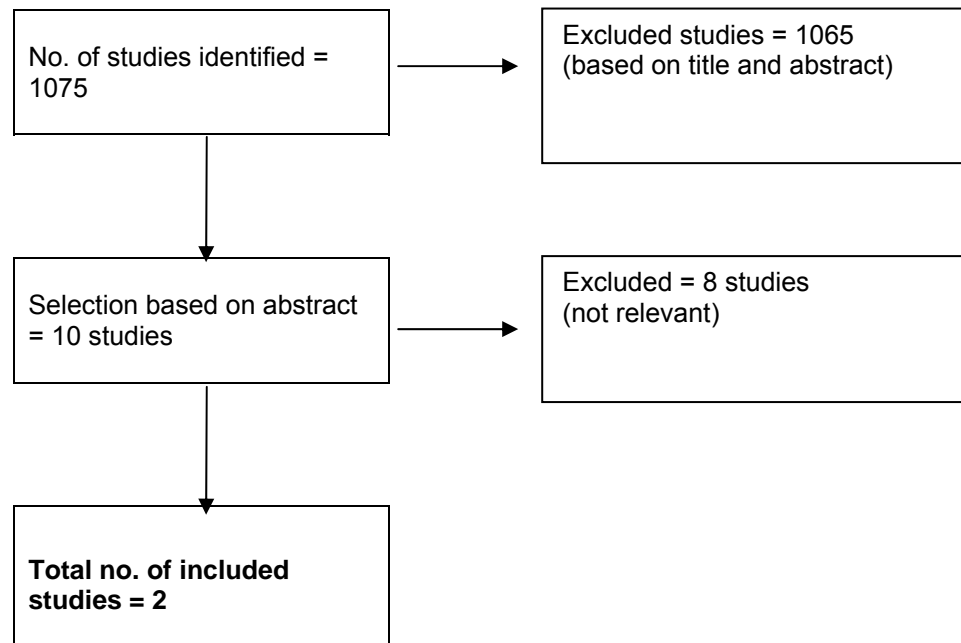
Study type	No. of patients	Patient characteristics	Prognostic/diagnostic factor(s)	Follow-up	Outcome measures	Results
<p>ID: 3105</p> <p>Level: (+)</p> <p>Follow-up secondary analysis of RCT cohort</p> <p>Author: Little et al. (2006)</p>	<p><u>Study group:</u> Total no. of patients (completed follow-up) = 219</p> <p><u>Study period:</u> Not stated</p> <p><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</p>	<p><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</p> <p><u>Exclusion:</u> Otosopic 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</p> <p><u>Study group (based on 315 patients):</u> Under AB treatment = 151 Under delayed treatment = 164</p> <p><i>(AB group)</i> Mean prior duration of illness (days) = 1.46 Aged > 3 = 57% Perforated ear drum = 7% Bulging ear drum = 47% Red ear drum = 82%</p> <p><i>(Delayed group)</i> Mean prior duration of illness (days) = 1.48 Aged > 3 = 62% Perforated ear drum = 9% Bulging ear drum = 46% Red ear drum = 78%</p>	<p><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</p> <p><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)</p>	<p>3 months and 1 year</p>	<p><u>After logistic regression, the significant independent predictors (out of 10 variables) were:</u></p> <p><u>1) Episodes of earache (after 3 months)</u> ear discharge bulging drum</p> <p><u>2) Episodes of earache (after 1 year)</u> past history – previous episodes of otitis media</p> <p><u>3) Poor score (9 or more) on child function (after 3 months)</u> past history – previous episodes of otitis media</p> <p><u>4) Poor score (9 or more) on child function (after 1 year)</u> past history – previous episodes of otitis media</p> <p><u>Prescribing strategies:</u> <i>The delayed prescribing strategy did not significantly increase risk of:</i></p> <p>Earache (after 3 months)</p> <p>Earache (after 1 year)</p> <p>Poor score on function (after 3 months)</p> <p>Poor score on function (after 1 year)</p>	<p>LHR = 7.04, p = 0.004 LHR = 5.50, p = 0.019</p> <p>LHR = 8.04, p = 0.005</p> <p>LHR = 4.95, p = 0.026</p> <p>LHR = 4.56, p = 0.033</p> <p>OR = 0.89 (95%CI: 0.48–1.65)</p> <p>OR = 1.03 (95%CI: 0.60–1.78)</p> <p>OR = 1.37 (95%CI: 0.72–2.60)</p> <p>OR = 1.16 (95%CI: 0.61–2.23)</p>

Additional comments:

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
<p>ID: 3995</p> <p>Level of evidence: (3)</p> <p>Survey questionnaire</p> <p>Edwards et al. (2003)</p>	<p>Total no. of patients/parents responded = 256 (68.4% response rate)</p> <p><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</p> <p><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</p> <p><u>Period:</u> Feb to Oct 2000.</p>	<p><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</p> <p>In order to provide a degree of standardisation, the patients received a leaflet briefly detailing the rationale of the technique and relevant instructions</p>	<p><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.</p> <p><u>Patient expectations during consultation:</u> (those took AB: n = 136, those didn't take AB: n = 120)</p> <p><u>Antibiotic prescription:</u> Those took AB = 89 (66.4%); those didn't take AB = 78 (66.1%), p = 1.00</p> <p><u>Other prescription:</u> Those took AB = 13 (9.7%); those didn't take AB = 11 (9.3%), p = 1.00</p> <p><u>Advice:</u> Those took AB = 43 (32.1%); those didn't take AB = 53 (44.5%), p = 0.05</p> <p><u>Tests or referral:</u> Those took AB = 2 (1.5%); those didn't take AB = 3 (2.5%), p = 0.67</p> <p><u>Sick note:</u> Those took AB = 5 (3.7%); those didn't take AB = 7 (5.9%), p = 1.00</p> <p><u>No expectations:</u> Those took AB = 25 (18.7%); those didn't take AB = 19 (16.0%), p = 0.57</p> <p><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</p>

			<p>the antibiotics they were prescribed, while the remaining responders claimed that they only took some of them.</p> <p><u>Satisfaction:</u> 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</p>
<p><u>Additional comments:</u> No comparisons between immediate, delayed and no prescribing strategy.</p>			

Back-up antibiotic prescriptions for common respiratory symptoms

Study type	Patient population, setting and period	Methodology	Outcomes
<p>ID: 4604</p> <p>Level of evidence: (3)</p> <p>Survey questionnaire</p> <p>Couchman et al. (2000)</p>	<p>Total no. of patients/parents = 947 Those prescribed delayed AB and responded = 255 (89.2% response rate).</p> <p><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</p> <p><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</p> <p><u>Period:</u> January and April 1999</p>	<p><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</p> <p>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</p>	<p><u>From the 947 enrolled patients:</u></p> <ul style="list-style-type: none"> • No AB = 441 (46.6%) • Delayed AB = 286 (30.2%) • Immediate AB = 220 (23.2%) <p>The overall delayed AB fill rate = 50.2% <i>*Fill rates did not differ significantly by patient characteristics or their self-reported satisfaction with the care received</i></p> <p>Patients' self-reported satisfaction with delayed AB = 96.1%</p>

Additional comments:
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 ^d	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+ ¹ /No/No	<u>Delayed</u> 120/382 (31%)	<u>Immediate</u> 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	<u>Delayed</u> 130/282 (46%)	<u>Immediate</u> 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	<u>Delayed</u> 150	<u>Immediate</u> 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	<u>Delayed</u> 150	<u>Immediate</u> 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+ ¹ /No/No	<u>Delayed</u> 24/282 (9%)	<u>Immediate</u> 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	<u>Delayed</u>	<u>Immediate</u>	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	<u>Delayed</u> 115/150 (77%)	<u>Immediate</u> 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	<u>Delayed</u> 100	<u>Immediate</u> 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				Quality
Outcome	No. of studies	Design	Limitations	Inconsistency	Directness	Sparse data	Other considerations	Intervention ^b	Control ^c	Relative risk	NNT	
Pick up of antibiotic prescription ^a [D]	1	RCT	No serious	No important	No uncertainty	No	No/1+ ^d /No/No	<u>Delayed</u> 43/95 (45%)	<u>Immediate</u> 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	<u>Delayed</u> 39/197 (20%)	<u>Immediate</u> 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	<u>No AB</u> 29/182 (16%)	<u>Immediate</u> 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	<u>No AB</u> 29/182	<u>Delayed</u> 39/197	0.80 (0.52, 1.24)	33.33 (9.09, 33.33)	High

Outcome	No. of studies	Design	Limitations	Inconsistency	Directness	Sparse data	Other considerations	(16%) Intervention	(20%) 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	<i>Log-rank [Mantel-Haenszel] test (result not reported), with p value > 0.4</i>		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

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	(40%) <u>No AB</u> 61/131 (47%)	(75%) <u>Immediate</u> 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	(40%) <u>No AB</u> 61/131 (47%)	(40%) <u>Delayed</u> 57/141 (40%)	1.15 (0.87, 1.51)	16.6 (5.88, 20.0)	High
Patient satisfaction ⁱ [D]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	<u>Delayed</u> 40/73 (54%)	<u>Immediate</u> 55/75 (73%)	0.74 (0.58, 0.95)	5.55 (3.03, 33.33)	High
Patient satisfaction ⁱ [L]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	<u>Delayed</u> 147/190 (77%)	<u>Immediate</u> 166/194 (86%)	0.90 (0.82, 0.99)	12.5 (6.66, 100.0)	High
Patient satisfaction ⁱ [L]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	<u>No AB</u> 130/181 (72%)	<u>Immediate</u> 166/194 (86%)	0.83 (0.75, 0.93)	7.69 (4.76, 20.0)	High
Patient satisfaction ⁱ [L]	1	RCT	No serious	No important	No uncertainty	No	No/No/No/No	<u>No AB</u> 130/181 (72%)	<u>Delayed</u> 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% $\chi^2 = 2.50$, $p = 0.28$				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) $\chi^2 = 1.9$, $p = 0.39$				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	<u>Delayed</u> 27/62 (43%)	<u>Immediate</u> 54/61 (89%)	0.49 (0.36, 0.66)	2.27 (1.69, 3.33)	Moderate
Temperature (°C) – day 3	1	RCT	No serious	No important	No uncertainty	Imprecise or sparse data ^d	No/No/No/No	Mean score (°C) Delayed = 36.7, immediate = 36.9 <i>*Analysis of comparison not provided</i>			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 <i>*Analysis of comparison not provided</i>			Moderate	
Belief AB are effective	1	RCT	No serious	No important	No uncertainty	Imprecise or sparse data ^c	No/No/No/No	<u>Delayed</u> 51/67 (76%)	<u>Immediate</u> 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	<u>Delayed</u> 64/67 (96%)	<u>Immediate</u> 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 <i>Include author, title, reference, year of publication</i>				
Guideline topic		Key question no:		
Checklist completed by:				
SECTION 1: INTERNAL VALIDITY				
In a well-conducted study:		In this study this criterion is: <i>(Circle one option for each question)</i>		
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? <i>Code ++, + or –</i>
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.).

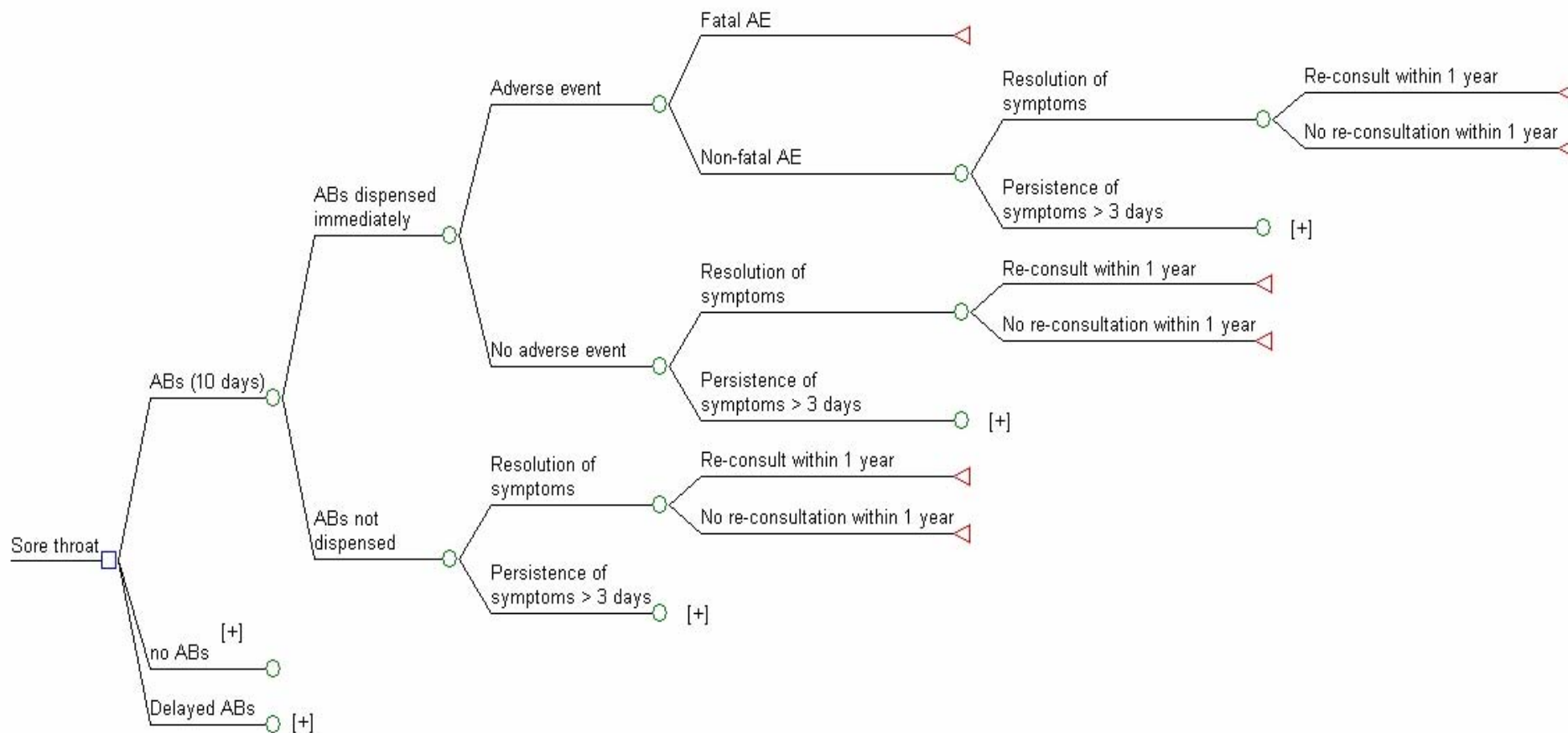
In the model, patients were assigned to one of the following strategies as in Little et al. (1997).

- 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.

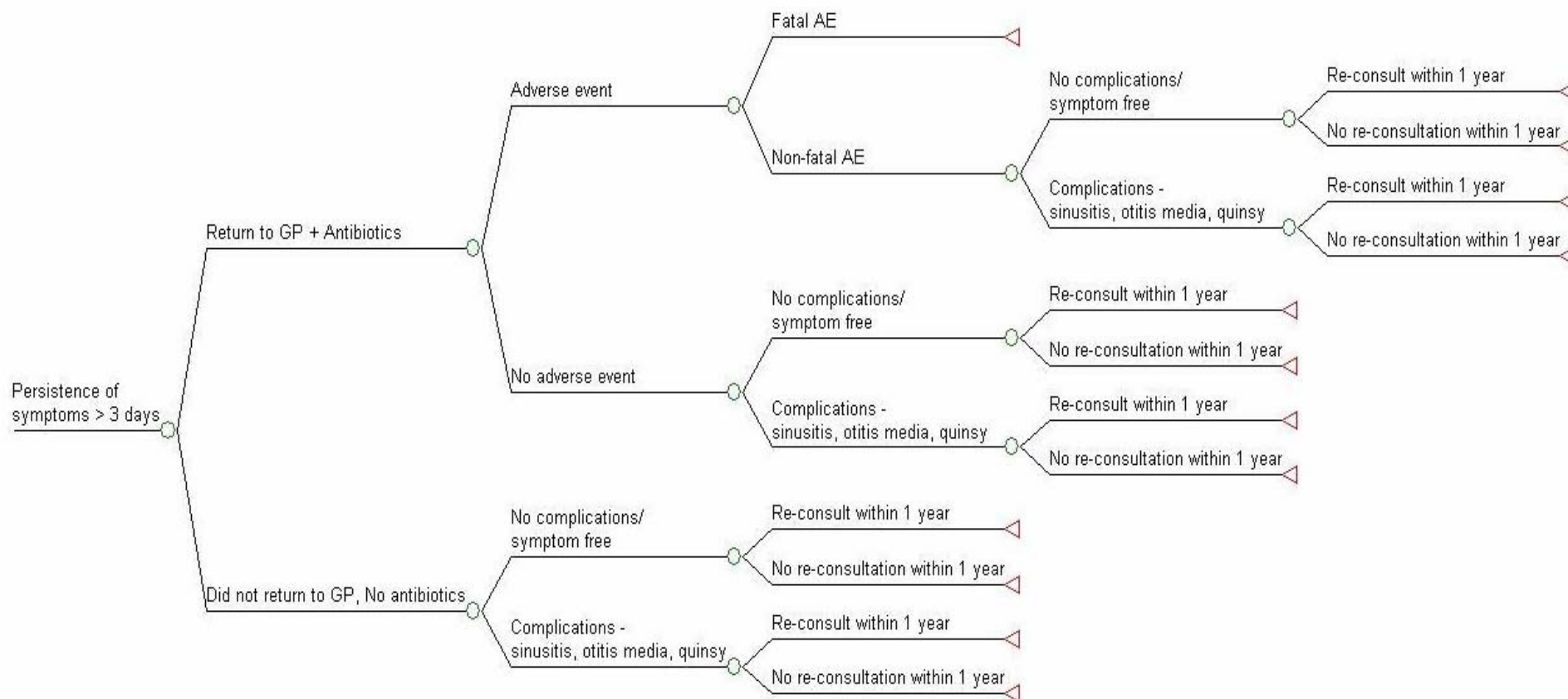
The model provides an estimate of costs in the base case and of costs and health outcomes in terms of quality-adjusted life years (QALYs) in subsequent analyses. The analysis adopts a 1-year time horizon to reflect the acute nature of sore throat. Simple one-way and multiway deterministic sensitivity 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

Reconsultation – 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 NICE clinical guideline 69 – Respiratory tract infections – antibiotic prescribing (Appendices) 99 of 119

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
<i>Antibiotics (per course – adults)</i>			
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
<i>Antibiotics (per course – children)</i>			
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
<i>Secondary care and outpatient costs</i>			
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. <i>Annals of Family Medicine</i> 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 <table border="1"> <thead> <tr> <th>Pathway</th> <th>QALDs lost</th> </tr> </thead> <tbody> <tr> <td>Resolution with observation</td> <td>1.6590</td> </tr> <tr> <td>Clinical failure</td> <td>3.3981</td> </tr> </tbody> </table>	Pathway	QALDs lost	Resolution with observation	1.6590	Clinical failure	3.3981
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
	Mastoiditis	0.11	0.11	0.06
	Other costs*	130.61	144.42	143.63
	Total	132.40	146.00	155.30
	*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.			