NICE National Institute for Health and Care Excellence

Evidence review: identifying those patients with RTIs who are likely to be at risk of developing complications

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Introduction

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

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

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

- For sore throat/acute pharyngitis/acute tonsillitis:
  - quinsy, cellulitis/impetigo, acute AOM, contralateral AOM, acute rhinosinusitis
- For acute otitis media:
  - mastoiditis, deafness, contralateral AOM
- For acute cough/acute bronchitis:
  - pneumonia
- For acute rhinosinusitis and common cold:
  - frontal abscess.

Overview

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

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

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

Acute sore throat/acute pharyngitis/acute tonsillitis

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

prevalence of quinsy within the study period was 96 cases per 100,000 patients with sore throat (per annum between 1995 and 1997).

Outcome 1: development of quinsy after initial uncomplicated sore throat

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

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

Further analysis was also carried out based on different diagnoses of sore throat, such as tonsillitis and sore throat/pharyngitis (adjusted for age, sex, smoking status, lung disease at patient level and clustering at practice level). The interval between diagnosis of a sore throat and development of quinsy was a median of 2 days (interquartile range 1 to 6 days) for tonsillitis, and 3 days (interquartile range 2 to 5 days) for sore throat/pharyngitis. Results from this further analysis showed that prescription of antibiotics after recording a diagnosis of a sore throat generally did not seem to reduce the risk of developing quinsy (antibiotic given after all diagnoses [adjusted OR = 1.2, 95% CI 0.7 to 1.8]; antibiotics given after tonsillitis [adjusted OR = 0.6, 95% CI 0.3 to 1.3]; antibiotics given after sore throat/pharyngitis [adjusted OR = 1.2, 95% CI 0.7-2.2]). However, considerable caution is needed in estimating the effect of antibiotics in this study owing to confounding by indication in routine databases (individuals with more severe illness are more likely to be given antibiotics than individuals with less severe illness).

Evidence statements

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

Evidence to recommendations

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

Acute cough/acute bronchitis

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

Survey of General Practice (Bont 2007). The aim of this study was to identify and validate a prediction rule for complications of LRTIs in elderly primary care patients.

Outcome 1: complications and hospital admission before cough resolution

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

In the derivation study (Hay 2004), multivariate analysis showed that only the presence of a chest sign (OR = 2.78, 95% CI 1.04 to 7.35, p = 0.048) and the presence of fever (OR = 4.65, 95% CI 1.63 to 13.3, p = 0.007) were significant independent predictors of complications and hospital admission before cough resolution in pre-school children. Further logistic regression also showed that lack of fever and chest signs was a good predictor for ruling out complications in children with cough, with a likelihood ratio (LHR) of 0.56 (95% CI 0.35 to 0.91). Fever only or both fever and chest sign LHR = 3.54 (95% CI 1.62 to 7.68) and only fever and chest sign LHR = 5.39 (95% CI 0.95 to 30.6) were found to be good predictors for complications in children with cough. However, the discriminatory ability of this particular prediction model was weak, with an area under receiver operating characteristic (ROC) below 0.70 (ROC = 0.68). A further validation study by Hay (2007) of the earlier derivation study (Hay 2004) was also identified. In the further validation study, however, chest sign and fever were not found to be significant predictors of complications and hospital admission in children with cough. Instead, chest sign and fever were found to be protective against complications and hospital admission (post-test probability: neither fever nor chest sign = 13.7 [95% CI 7.5 to 22.3]; chest sign only = 13.8 [95% CI 3.9 to 32.0]; fever only = 9.1 [95% CI 0.0 to 41.0]; both fever and chest sign = 0.0 [95% CI 0.0 to 37.0]). A completely different

set of variables were found to be significant independent predictors of complications and hospital admission: age (OR = 0.95, 95% CI 0.90 to 0.99, p = 0.03); deprivation (OR = 0.79, 95% CI 0.64 to 0.97, p = 0.02); number of GP visits in previous year (OR = 1.14, 95% CI 1.02 to 1.27, p = 0.02). The authors commented that the contradictory findings from the validation study compared with the derivation study could be a result of spectrum bias (that is, sociodemographic differences, possible reduced levels of circulating influenza-like illness between the derivation and validation cohorts) and confounding by indication (that is, clinicians' antibiotic prescriptions tended to be targeted at children with chest signs or fever). Thus, the evidence provided by these two studies needs cautious interpretation.

Outcome 2: 30-day hospitalisation or death

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

Table 10 Significant predictors and scoring system

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

Predictors after initial diagnosis	Regression coefficient	Score
Use of antibiotics in previous month	0.615	2

The scoring system was separated into three risk groups: low risk (score ≤ 2), medium risk (score 3–5) and high risk (score ≥ 7). The discriminatory abilities of this prediction scoring system in the derivation cohort were:

- low risk – sensitivity = 0.82, specificity = 0.52, percentage of risk of endpoint 3.2%;
- medium risk – sensitivity/specificity = not reported, percentage of risk of endpoint = 9.9%;
- high risk – sensitivity = 0.35, specificity = 0.92, percentage of risk of endpoint = 30.9%, with good discriminatory power (area under ROC = 0.75 [95% CI 0.72 to 0.78]).

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

Evidence statements

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

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

- suspected or diagnosed pneumonia at the presence of consultation
- history of:
  - congestive heart failure
  - diabetes

  - COPD or exacerbation of COPD
- 80 years or older
- present use of oral glucocorticoids
- hospitalisation in previous year
- use of antibiotics in previous month.

Evidence to recommendations

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

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

Acute otitis media (AOM)

Two good quality studies were included as the basis of recommendations. One was a prospective cohort study (Damoiseaux et al. 2006) on long-term prognosis of AOM in infancy (6 months to 24 months) with a prediction model for complication (recurrent AOM). The setting of this study was family practices in the Netherlands. The other study was a follow-up secondary analysis study of an RCT cohort (Little et al. 2006). This was a UK primary care-based study looking for clinical predictors of complications (recurrent AOM and hearing impairment) from AOM in children (6 months to 10 years). No studies were identified regarding the complication mastoiditis. Based on Hospital Episode Statistics (2006–07) there were 952 finished consultant episodes of mastoiditis and in relation to GP-registered populations (GP Registered Populations 2007), there were 50,542,505 registered patients in England. These constituted a crude rate of 144 cases of mastoiditis per 1,000,000 patients per annum, indicating that mastoiditis is a rare complication. A large Dutch cohort study also showed that mastoiditis is likely to be very rare when using a 72-hour wait-and-see policy before prescribing antibiotics (van Buchem et al. 1985).

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

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

Table 11 Significant predictors and scoring system

Predictors after initial diagnosis	Regression coefficient	Score (baseline starts from -9)
Male	0.60	6
Passive smoking	-0.76	-8
Winter season	0.86	9
Persistent symptoms	0.82	8

The scoring system was then separated into three cut-off points: below -8, below -1 and below 5. The discriminatory abilities of this prediction scoring system were:

- below -8 – sensitivity = 93%, specificity = 23%, positive predictive value (PPV) = 54%, negative predictive value (NPV) = 77%);
- below -1 – sensitivity = 72%, specificity = 56%, PPV = 62%, NPV = 67%;
- below 5 – sensitivity = 51%, specificity = 76%, PPV = 68%, NPV = 61%.

The discriminatory power of the model was weak, with an area under ROC of 0.69 (95% CI 0.62 to 0.76), and this particular model was not validated in different primary care populations.

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

Little (2006) also investigated predictors of functional hearing impairment following initial AOM in children in their study. Functional hearing impairment in this study was

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

Evidence statements

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

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

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

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

Evidence to recommendations

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

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

Acute rhinosinusitis

No studies were identified for acute rhinosinusitis.

Evidence statement

No evidence was identified for acute rhinosinusitis.

Evidence to recommendations

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

However, the GDG acknowledged that intraorbital and intracranial complications are serious complications of acute rhinosinusitis. Hence, the GDG came to the consensus conclusion that immediate antibiotic prescription and/or further

appropriate investigation and management should be offered to adults and children who appear unwell and with symptoms and signs suggestive of intraorbital and intracranial complications.

Common cold

No studies were identified for common cold.

Evidence statement

No evidence was identified for common cold.

Evidence to recommendation

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

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Williams Jr JW, Aguilar C, Cornell J et al. (2003) Antibiotics for acute maxillary sinusitis. Cochrane Database of Systematic Reviews, Issue 2. Art. No.: CD000243. DOI: 10.1002/14651858.CD000243.

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Literature searches

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?’.

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

1. "signs and symptoms"/
2. ((sign or signs) adj5 symptom$).tw.
3. risk factors/
4. factor$.tw.
5. predict$.tw.
6. or/1-5
7. Ambulatory Care/

8. Family Practice/
9. Physicians, Family/
10. Primary Health Care/
11. Emergency Service, Hospital/
12. Community Health Services/
13. Outpatient Clinics, Hospital/
14. ((general or family) adj (practice$ or practitioner$ or physician$ or doctor$)).tw.
15. GP$.tw.
16. (primary adj2 care).tw.
17. primary healthcare.tw.
18. (ambulatory adj2 care).tw.
19. ((walk-in or walk in) adj2 centre$).tw.
20. (accident and emergency).tw.
21. (emergency adj2 department$).tw.
22. (community health adj2 (care or service$)).tw.
23. ((outpatient or hospital) adj2 clinic$).tw.
24. or/7-23
25. Pharyngitis/
26. exp Tonsillitis/
27. exp Laryngitis/
28. pharyngitis.tw.
29. tonsillitis.tw.
30. laryngitis.tw.
31. (sore$ adj3 throat$).tw.
32. (throat$ adj3 infect$).tw.
33. or/25-32
34. Rheumatic Fever/
35. Glomerulonephritis/
36. Otitis Media/
37. Sinusitis/
38. Peritonsillar Abscess/
39. Impetigo/
40. Cellulitis/
41. (rheumatic adj2 fever$).tw.
42. glomerulonephritis.tw.
43. (otitis adj2 media).tw.
44. sinusitis.tw.
45. (peritonsillar adj2 abscess$).tw.
46. quinsy.tw.
47. impetigo.tw.
48. cellulitis.tw.
49. poor outcome$.tw.
50. complication$.tw.
51. Co.fs
52. Rheumatic Heart Disease/
53. (rheumatic adj2 carditis).tw.
54. Scarlet Fever/
55. (scarlet fever or scarletiniform rash$ or scarlatina).tw.
56. Tonsillectomy/
57. tonsillectom$.tw.

58. (illness$ adj3 duration$).tw.
59. Prognosis/
60. prognosis.tw.
61. or/34-60
62. 6 and 24 and 33 and 61
63. Earache/
64. Otitis Media/
65. earache$.tw.
66. (ear$ adj3 (ache$ or infect$ or inflamm$)).tw.
67. (otitis adj2 media$).tw.
68. otalgia.tw.
69. or/63-68
70. Mastoiditis/
71. Intracranial Thrombosis/
72. Brain Abscess/
73. Otitis Media, Suppurative/
74. Deafness/
75. exp Sinus Thrombosis, Intracranial/
76. Epidural Abscess/
77. Tympanic Membrane Perforation/
78. mastoiditis.tw.
79. ((cerebral or intracranial or brain) adj2 (thrombosis or thrombus)).tw.
80. ((cerebral or brain) adj2 abscess$).tw.
81. (sinus adj2 (thrombosis or thrombus or thrombophlebitis)).tw.
82. ((epidural or subperiosteal or cerebellar or sundural) adj2 abscess$).tw.
83. (otitis adj2 media adj2 (suppurative or purulent$ or contralateral or contra-lateral)).tw.
84. deafness.tw.
85. (hearing adj2 (loss or impair$)).tw.
86. poor outcome$.tw.
87. complication$.tw.
88. (illness$ adj3 duration$).tw.
89. Prognosis/
90. prognosis.tw.
91. Co.fs.
92. ((tympanic membrane or eardrum) adj2 (perforat$ or rupture$)).tw.
93. or/70-92
94. 6 and 24 and 69 and 93
95. Cough/
96. exp Bronchitis/
97. cough$.tw.
98. bronchit$.tw.
99. bronchiolit$.tw.
100. or/95-99
101. Pneumonia/
102. exp Empyema/
103. pneumonia.tw.
104. empyema.tw.
105. pyothorax.tw.
106. poor outcome$.tw.

107. complication$.tw.
108. Co.fs.
109. (illness$ adj3 duration$).tw.
110. Prognosis/
111. prognosis.tw.
112. or/101-111
113. 6 and 24 and 100 and 112
114. exp Sinusitis/
115. sinusit$.tw.
116. or/114-115
117. Brain Abscess/
118. ((cerebral or brain) adj2 abscess$).tw.
119. ((epidural or subperiosteal or cerebellar or sundural) adj2 abscess$).tw.
120. poor outcome$.tw.
121. complication$.tw.
122. Co.fs.
123. (illness$ adj3 duration$).tw.
124. Prognosis/
125. prognosis.tw.
126. or/117-125
127. 6 and 24 and 116 and 126
128. Common Cold/
129. Rhinitis/ and Sinusitis/
130. cold$.tw.
131. coryza$.tw.
132. rhinosinusit$.tw.
133. or/128-132
134. Otitis Media with Effusion/
135. Eustachian Tube/
136. (otitis adj2 media adj2 (effusion or serous or secretory)).tw.
137. (eustachian tube adj (dysfunction or inflamm$)).tw.
138. poor outcome$.tw.
139. complication$.tw.
140. Co.fs.
141. (illness$ adj3 duration$).tw.
142. Prognosis/
143. prognosis.tw.
144. or/134-143
145. 6 and 24 and 133 and 144
146. animals/
147. humans/
148. 146 not (146 and 147)
149. 62 not 148
150. 94 not 148
151. 113 not 148
152. 127 not 148
153. 145 not 148

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.

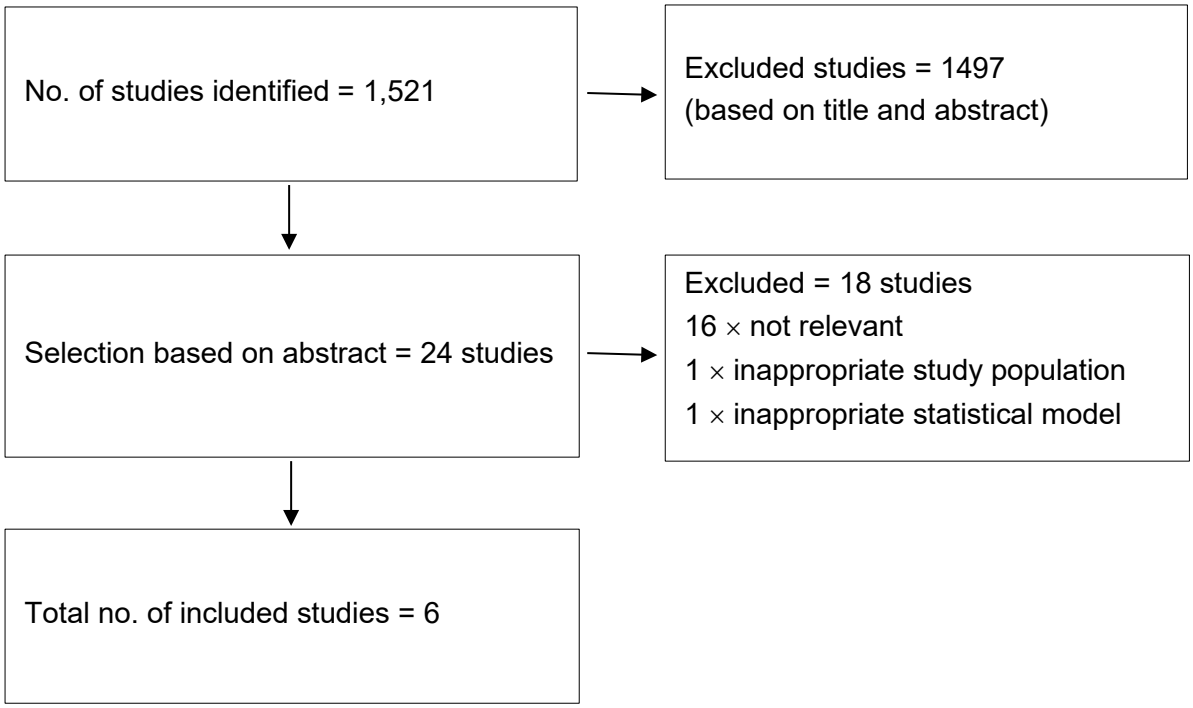
1. "Quality of Life"/
2. quality of life.tw.
3. "Value of Life"/
4. Quality-Adjusted Life Years/
5. quality adjusted life.tw.
6. (qaly$ or qald$ or qale$ or qtime$).tw.
7. disability adjusted life.tw.
8. daly$.tw.
9. Health Status Indicators/
10. (sf36 or sf 36 or short form 36 or shortform 36 or sf 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

Inclusion and exclusion criteria and evidence tables

Inclusion and exclusion criteria

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

Studies included and excluded



Evidence tables

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)	<u>Study group:</u> Cases of quinsy following initial uncomplicated sore throat = 192 *total cases of quinsy = 606 <u>Control group:</u> Cases of sore throat without quinsy = 198124 <u>Study period:</u> 1995 – 1997 <u>Setting:</u> UK-wide primary care data from the General Practice Research database (GPRD)	<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 <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% (Control events) Male = 38.0% Median age (IQR) = 23 (12–38) Smoker = 18.4% Tonsillitis = 22.0% Sore throat/pharyngitis = 78.0% Exposure to AB = 84.7%	Prevalence of quinsy = 15.8 per 1000 patients with sore throat, per annum <u>Clinical variables:</u> Age, sex, smoking status, type of diagnosis, exposure to AB, lung disease <u>Outcome of interest:</u> The development of quinsy after initial uncomplicated sore throat <u>*Note:</u> Logistic regression adjusted for confounding factors at patient level (chronic diseases, comorbidities, recent prescriptions for immunosuppressive drugs) and at practice level (practice deprivation index, tonsillitis, RTIs for which AB were prescribed)	Use of 30 days of sore throat record	<u>After logistic regression:</u> Age (21–40 years old) Smoking Male <u>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)</u> AB given after all events AB given after ‘tonsillitis’ AB given after ‘sore throat/pharyngitis’ *There was similar level of AB exposure in quinsy cases (88.0%) and controls (84.7%). *The interval between diagnosis of a sore throat and development of quinsy was a	 Adj OR = 3.4 (95%CI: 2.1–5.5) Adj OR = 2.5 (95%CI: 1.8–3.5) Adj OR = 1.6 (95%CI: 1.1–2.2) No. of cases = 169 Adj OR = 1.2 (95%CI: 0.7–1.8) No. of cases = 81 Adj OR = 0.6 (95%CI: 0.3–1.3) No. of cases = 88 Adj OR = 1.2 (95%CI: 0.7–2.2)

Study type	No. of patients	Patient characteristics	Prognostic/diagnostic factor(s)	Follow-up	Outcome measures	Results
					median of 2 days (IQR = 1–6) for tonsillitis, and 3 days (IQR = 2–5) for sore throat/pharyngitis	

Additional comments:

The majority of cases of quinsy seem to arise without the patient having presented previously with any warning symptoms.

Prescription of AB after recording a diagnosis of a sore throat generally does not seem to reduce the risk of developing quinsy, although there is a suggestion that when doctors use the term ‘tonsillitis’, AB may have protective effect BUT the results are not statistically significant.

The use of retrospective data, and there are some missing data (i.e. on smoking), and data were not collected on compliance with AB prescriptions (i.e. patients might not be taking the course as prescribed).

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

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

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)	Study group: Total no. of patients = 164 Where follow-up completed = 154 Study period: Oct 2004 to May 2005. Setting: 13 general practices in Bristol and Tayside, UK	Inclusion: 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 Study group: Median age, month (IQR) = 24 (12–37) Male = 54% Prescribed = 24% Reconsulted = 23% Recorded as having complication = 12%	Clinical predictive variables: The use of a validated symptom diary Socio-demographic factors Outcome of interest: Complications: 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 Hospital admission before cough resolution: 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	Multivariate model (independent predictors): Age Deprivation No. of GP visits in previous year *Note: Chest sign and fever that were found as a significant model of prediction in the derivation study were not significant predictors in this validation study Post-test probability: 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)	Study group 1 (derivation cohort): Total no. of patients = 1693 (3166 episodes) Study group 2 (Validation cohort): Total no. of patients = 2465 episodes of LRTIs Study period: Jan 1997 to Feb 2003 Setting: (Derivation cohort) Patient data stored in the database of the Utrecht GP research network in the Netherlands (35 GPs) (Validation cohort) Data of patients from the 2nd Dutch National Survey of General Practice in 2001, included 163 GPs in 85 practices	Inclusion (derivation cohort): Patients aged ≥65 years visiting the general practitioner with LRTIS. LRTIS defined as episodes of pneumonia, acute bronchitis and COPD Exclusion (derivation cohort): Patients who were treated with AB for another RTI within the previous 3 weeks, if at the moment of presentation, the patient was known to have lung cancer, a haematological malignancy or an infection with HIV, used immunosuppressive medication or was hospitalised during the 2 weeks preceding the diagnosis Inclusion (validation cohort): Patients aged ≥65 years visiting the general practitioner with episodes of pneumonia and acute bronchitis Study group: (Derivation cohort): Acute bronchitis = 1120 episodes Exacerbation of COPD = 1523 episodes Pneumonia = 523 30-day hospitalisation or death = 274 Death = 76 Mean age = 75.5 Male = 45% With 1 or more comorbid conditions = 85% (Validation cohort): Acute bronchitis = 1736 episodes Pneumonia = 729	Clinical predictive variables: Increasing age, hospitalisation in the 12 months prior to diagnosis, heart failure, use of insulin, use of oral glucocorticoids, use of AB in the month prior to diagnosis, type of diagnosis After logistic regression: Diagnosis (score): Acute bronchitis (0) Exacerbation of COPD (2) Pneumonia (4) Age: 65–79 (0) ≥80 (2) Congestive heart failure (1) Diabetes (2) Using oral glucocorticoids (3) Hospitalisation in previous year: 0 (0) 1 (2) ≥2 (3) use of AB in previous month (2) Management: Separate into low (score ≤2), medium (score 3–5) and high risk (score ≥7) group Outcome of interest:	N/A Retrospective study of databases	Predictive model (predicting 30-day hospitalisation or death): Derivation study: Low risk (score ≤2) Medium risk (score 3–5) High risk (score ≥7) Validation study: Low risk (score ≤2) Medium risk (score 3–5) High risk (score ≥7)	Sensitivity = 0.82, specificity = 0.52 % of risk of end point = 3.2% Sensitivity/specificity = not reported % of risk of end point = 9.9% Sensitivity = 0.35, specificity = 0.92 % of risk of end point = 30.9% Area under ROC = 0.75 (95%CI: 0.72–0.78) Sensitivity = 0.42, specificity = 0.81 % of risk of end point = 5.3% Sensitivity/specificity = not reported % of risk of end point = 14.5% Sensitivity = 0.06, specificity = 0.98 % of risk of end point = 22.0% Area under ROC = 0.74 (95%CI: 0.71–0.78)

Study type	No. of patients	Patient characteristics	Prognostic/diagnostic factor(s)	Follow-up	Outcome measures	Results
		30-day hospitalisation or death = 178 Death = 59	30-day hospitalisation or death			

Additional comments:

Retrospective study of databases, both derivation and validation.

Validation study did not include COPD.

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

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

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
ID: 3105 Level: (+) Follow-up secondary analysis of RCT cohort Author: Little et al. (2006)	Study group: Total no. of patients (completed follow-up) = 219 Study period: Not stated Setting: 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	Inclusion: 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 Exclusion: 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 Study group (based on 315 patients): Under AB treatment = 151 Under delayed treatment = 164 (AB group) Mean prior duration of illness (days) = 1.46 Aged > 3 = 57% Perforated ear drum = 7% Bulging ear drum = 47% Red ear drum = 82% (Delayed group) Mean prior duration of illness (days) = 1.48 Aged > 3 = 62% Perforated ear drum = 9% Bulging ear drum = 46% Red ear drum = 78%	Clinical predictive variables: High temperature on day 1 (>37.5°C), vomiting, ear discharge, bulging drum, previous episodes of RTIs, family/social factors Outcome of interest: Episodes of earache and poor score on child function (9 or more, based on 14 descriptions of how hearing impairment with chronic secretory otitis media presents)	3 months and 1 year	After logistic regression, the significant independent predictors (out of 10 variables) were: 1) Episodes of earache (after 3 months) ear discharge bulging drum 2) Episodes of earache (after 1 year) past history – previous episodes of otitis media 3) Poor score (9 or more) on child function (after 3 months) past history – previous episodes of otitis media 4) Poor score (9 or more) on child function (after 1 year) past history – previous episodes of otitis media Prescribing strategies: The delayed prescribing strategy did not significantly increase risk of: Earache (after 3 months) Earache (after 1 year) Poor score on function (after 3 months)	 LHR =7.04, p = 0.004 LHR = 5.50, p = 0.019 LHR = 8.04, p = 0.005 LHR = 4.95, p = 0.026 LHR = 4.56, p = 0.033 OR = 0.89 (95%CI: 0.48–1.65) OR = 1.03 (95%CI: 0.60–1.78) OR = 1.37 (95%CI: 0.72–2.60) OR = 1.16 (95%CI: 0.61–2.23)

Study type	No. of patients	Patient characteristics	Prognostic/diagnostic factor(s)	Follow-up	Outcome measures	Results
					Poor score on function (after 1 year)	

Additional comments:

This is a secondary analysis that requires cautious interpretation.

No area under ROC for discriminatory ability.

Methodology checklist: prognostic studies

Methodology checklist

Study identification Include author, title, reference, year of publication	
Guideline topic	
Key question no:	
Checklist completed by:	

Methodology checklist section 1: internal validity

In a well-conducted study:	**In this study this criterion is:** (Circle one option for each question)
1.1 The study sample represents the population of interest on key characteristics, sufficient to limit potential bias to the results	Yes / No / Unclear
1.2 Loss to follow-up (from sample to study population) is unrelated to key characteristics (i.e. the study data adequately represent the sample), sufficient to limit potential bias	Yes / No / Unclear
1.3 The prognostic factor of interest is adequately measured in study participants to sufficiently limit bias	Yes / No / Unclear
1.4 The outcome of interest is adequately measured in study participants to sufficiently limit bias	Yes / No / Unclear
1.5 Important potential confounders are appropriately accounted for, limiting potential bias with respect to the prognostic factor of interest	Yes / No / Unclear
1.6 The statistical analysis is appropriate for the design of the study, limiting potential for presentation of invalid results	Yes / No / Unclear

Methodology checklist section 2: overall assessment of the study

2.1 How well was the study done to minimise bias? Code ++, + or –	

2.2 If coded as + or – what is the likely direction in which bias might affect the study results?	