National Clinical Guideline Centre

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Pneumonia

Diagnosis and management of community- and hospital-acquired pneumonia in adults

Clinical guideline 191

Methods, evidence and recommendations

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Appendices A-P are in separate files.

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1 Introduction

Pneumonia is a common condition with significant morbidity and mortality and is therefore important to patients, the population and the NHS.

Who should read this guidance?

Appropriate pneumonia management is of relevance to a wide range of medical disciplines. Respiratory infection is a common reason for presentation to a GP with community-acquired pneumonia (CAP) being diagnosed and managed in 5 –12% of cases of lower respiratory tract infection (LRTI). Most will be managed by the GP, but 22 –42% of cases will be referred to hospital and others will present directly to the Accident & Emergency (A&E) department. Between 1.2 and 10% of patients admitted with CAP will require management in the intensive care unit (ITU).

In hospital, A & E, acute, general, respiratory, elderly care, intensive care and infectious disease physicians, as well as microbiologists, biochemists and nurses may all be involved in managing CAP. Pneumonia that arises in patients already admitted to hospital for another reason has a point prevalence of around 1% in UK hospitals. It can present to any hospital specialist providing inpatient care.

Aims of the guidance

The microbial causes of pneumonia vary according to its origin and the immune constitution of the patient. Pneumonia is classified into community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP) and pneumonia in the immunocompromised. The guideline development process is guided by its scope - published after stakeholder consultation. This guideline does not cover all aspects of pneumonia, but focuses on areas of uncertainty or variable practice and those considered of greatest clinical importance. Best practice guidance on the diagnosis and management of CAP and HAP is offered, based on systematic analysis of clinical and economic evidence with the aim of reducing mortality and morbidity from pneumonia and maximising resources.

Definitions and diagnosis

The diagnosis of pneumonia is based on assessment of symptoms and clinical signs, which usually include cough, fever and difficulty breathing. However these features may be absent (for example in the elderly). When present, these features can overlap with other infective and non-infective conditions of the respiratory tract and so a precise diagnosis may be difficult to make. As a consequence a number of connected and poorly defined terms are often used in place of pneumonia. These include ‘chest infection’, ‘lower respiratory tract infection’ and ‘bronchitis’. Because of the lack of specificity of the above features, different practitioners may use different terms for the same condition. Please see section 3.1 for definitions of terms used commonly in this guideline.

Precise diagnosis is important for antibiotic stewardship. Pneumonia is nearly always caused by bacteria and should be treated with antibiotics. Most other acute respiratory conditions are not bacterial and antibiotic therapy should usually be avoided. Guidance on acute respiratory tract infections that are likely to be self-limiting is available in NICE CG69. However, there is a group of patients who have LRTIs in the community and in whom pneumonia is not suspected, but who may indeed have pneumonia requiring antibiotic therapy. No NICE guidance was available for managing such situations and hence diagnostic and severity assessment questions pertaining to LRTI have been included in this guidance.

The accepted ‘gold standard’ for the diagnosis of pneumonia is new shadowing on the chest X-ray (CXR) of a patient with the above clinical features. This is an imperfect ‘benchmark’ because of lack of

CXR availability outside hospitals and variable X-ray quality and interpretation in hospital. It is also accepted that in the community a diagnosis of pneumonia may be made on clinical grounds alone. This guideline assumes that a definitive diagnosis of pneumonia has been made if patients have presented to hospital (and therefore have access to CXR) or if a primary care clinician suspects pneumonia (a clinical diagnosis of pneumonia as opposed to an ill-defined respiratory illness). It is the intention of the GDG that recommendations from this guideline should not be inappropriately applied to the other conditions mentioned above. To this end, in as much as the scope allows, the guideline considers what evidence is available to help practitioners improve diagnostic certainty when CXR confirmation is difficult.

Patient-centred care

Patients and healthcare professionals have rights and responsibilities as set out in the NHS Constitution for England – all NICE guidance is written to reflect these. Treatment and care should take into account individual needs and preferences. Patients should have the opportunity to make informed decisions about their care and treatment, in partnership with their healthcare professionals. Healthcare professionals should follow the Department of Health's advice on consent. If someone does not have capacity to make decisions, healthcare professionals should follow the code of practice that accompanies the Mental Capacity Act and the supplementary code of practice on deprivation of liberty safeguards. In Wales, healthcare professionals should follow advice on consent from the Welsh Government.

NICE has produced guidance on the components of good patient experience in adult NHS services. All healthcare professionals should follow the recommendations in Patient experience in adult NHS services.

2 Foreword

This guideline is expected to be relevant to the management of most (~80%) patients with community-acquired pneumonia (CAP) or hospital-acquired pneumonia (HAP). The clinical heterogeneity of the population and disease processes means that management outside of the guideline recommendations will be appropriate in some circumstances.

Challenges of developing this guidance

In dealing with HAP the guideline development group faced a difficulty with respect to 2 specific subgroups known as ventilator-associated pneumonia (VAP) and healthcare-associated pneumonia (HCAP). VAP is the most common type of HAP occurring in those intubated on the intensive care unit (ITU) to assist ventilation. There is a large research literature on VAP and nearly all that is known about HAP is based on these studies, while HAP occurring on the general ward has received little research input. For this reason the scope defined that the guideline should not deal with VAP.

HCAP is a relatively recently-proposed subgroup of patients with pneumonia. It groups together patients with pneumonia developing in hospital and nursing homes, together with those who have received recent intravenous antibiotic therapy, chemotherapy, or wound care within the past 30 days of the current infection; and those who have attended a hospital or haemodialysis clinic. The intention is to group together those at high risk of pneumonia caused by antibiotic-resistant bacteria and for whom different empirical antibiotic therapy might be appropriate. While studies in North America and Asia support this grouping, recent studies in Europe have found microbial causes in this group to be similar to HAP and CAP and this terminology has not been generally adopted in the UK. For this reason HCAP has not been addressed in the guideline.

Guideline structure

The following chapter defines various terms in order to facilitate accurate interpretation and implementation of the recommendations generated by the GDG.

It also aims to help readers with different perspectives and interests navigate the document and access the material most relevant to them.

3 Navigating this guideline

3.1 Terms used

Clinical diagnosis of community-acquired pneumonia

Diagnosis based on symptoms and signs of lower respiratory tract infection in a patient who, in the opinion of the GP and in the absence of a chest X-ray, is likely to have community-acquired pneumonia. This might be because of the presence of focal chest signs, illness severity or other features.

Community-acquired pneumonia

Pneumonia that is acquired outside hospital. Pneumonia that develops in a nursing home resident would be included in this definition. When managed in hospital the diagnosis is usually confirmed by chest X-ray.

Dual antibiotic therapy

Treatment with 2 different antibiotics at the same time.

Hospital-acquired pneumonia

Pneumonia that develops 48 hours or more after hospital admission and that was not incubating at hospital admission. When managed in hospital the diagnosis is usually confirmed by chest X-ray. For the purpose of this guideline, pneumonia that develops in hospital after intubation (ventilator-associated pneumonia) is excluded from this definition.

Lower respiratory tract infection

An acute illness (present for 21 days or less), usually with cough as the main symptom, and with at least 1 other lower respiratory tract symptom (fever, sputum production, breathlessness, wheeze or chest discomfort or pain) and no alternative explanation (such as sinusitis or asthma). Pneumonia, acute bronchitis and exacerbation of chronic obstructive airways disease are included within this definition.

Mortality risk

The percentage likelihood of death occurring in a patient in the next 30 days.

Pneumonia (X-ray confirmed)

Diagnosis based on symptoms and signs of an acute lower respiratory tract infection and confirmed by a chest X-ray showing new shadowing that is not due to any other cause (such as pulmonary oedema or infarction).

Severity assessment

A judgement by the managing clinician as to the likelihood of adverse outcomes in a patient. This is based on a combination of clinical understanding and knowledge in addition to a mortality risk score. The difference between categories of severity and mortality risk can be important. Typically the mortality risk score will match the severity assessment. However, there may be situations where the mortality score does not accurately predict mortality risk and clinical judgement is needed. An

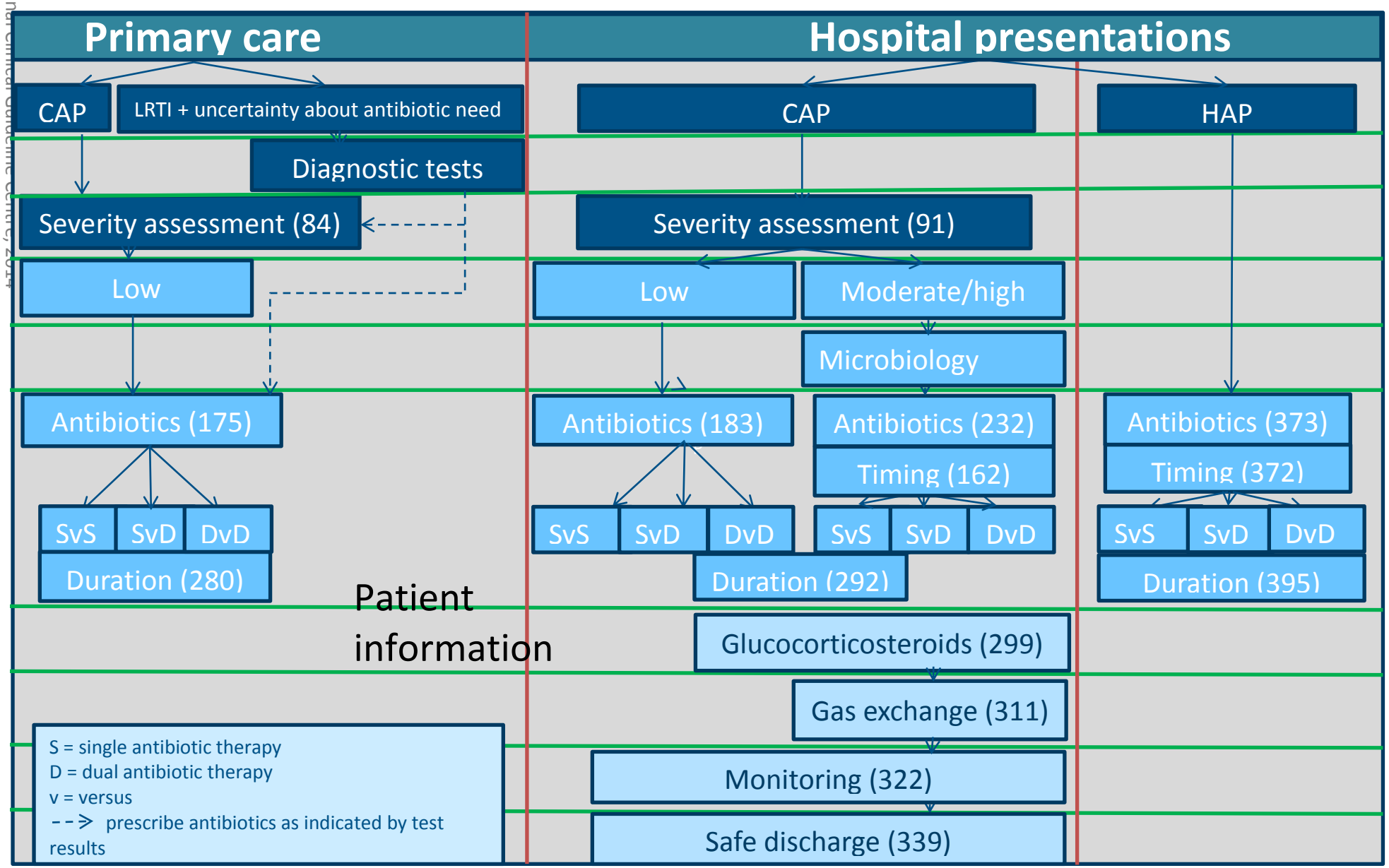
example might be a patient with a low mortality risk score who has an unusually low oxygen level, who would be considered to have a severe illness.

3.2 Finding information relevant to you

Consideration was given to developing guidance pertaining to different places of care such as the community, general ward and ITU. However it was felt by the GDG that use of an objective severity assessment tool and severity-based recommendations following a care pathway would be more clinically appropriate. Reasons for this include the transition of patients from primary to hospital-based care, sometimes including ITU, variable availability of interventions, the delivery of different interventions in facilities with the same name (for example ITU) and the development of treatments (for example non-invasive ventilation) and units (for example High Dependency Units) that do not fit easily into this classification.

Click on the hyperlinks or note the page numbers in brackets that indicate where information can be found.

Figure 1: Pneumonia guideline map (brackets are page numbers and are hyperlinked to the relevant section)



4 Development of the guideline

4.1 What is a NICE clinical guideline?

NICE clinical guidelines are recommendations for the care of individuals in specific clinical conditions or circumstances within the NHS – from prevention and self-care through primary and secondary care to more specialised services. We base our clinical guidelines on the best available research evidence, with the aim of improving the quality of health care. We use predetermined and systematic methods to identify and evaluate the evidence relating to specific review questions.

NICE clinical guidelines can:

- provide recommendations for the treatment and care of people by health professionals
- be used to develop standards to assess the clinical practice of individual health professionals
- be used in the education and training of health professionals
- help patients to make informed decisions
- improve communication between patient and health professional.

While guidelines assist the practice of healthcare professionals, they do not replace their knowledge and skills.

We produce our guidelines using the following steps:

- Guideline topic is referred to NICE from the Department of Health.
- Stakeholders register an interest in the guideline and are consulted throughout the development process.
- The scope is prepared by the National Clinical Guideline Centre (NCGC).
- The NCGC establishes a guideline development group.
- A draft guideline is produced after the group assesses the available evidence and makes recommendations.
- There is a consultation on the draft guideline.
- The final guideline is produced.

The NCGC and NICE produce a number of versions of this guideline:

- the 'full guideline' contains all the recommendations, together with details of the methods used and the underpinning evidence
- the 'NICE guideline' lists the recommendations
- 'information for the public' is written using suitable language for people without specialist medical knowledge
- NICE Pathways brings together all connected NICE guidance.

This version is the full version. The other versions can be downloaded from NICE at www.nice.org.uk.

4.2 Remit

NICE received the remit for this guideline from the Department of Health. They commissioned the NCGC to produce the guideline.

The remit for this guideline is: to develop a clinical guideline on pneumonia (including community-acquired pneumonia).

4.3 Who developed this guideline?

A multidisciplinary Guideline Development Group (GDG) comprising health professionals and researchers as well as a lay member developed this guideline (see the list of Guideline Development Group members and the acknowledgements).

The National Institute for Health and Care Excellence (NICE) funds the National Clinical Guideline Centre (NCGC) and thus supported the development of this guideline. The GDG was convened by the NCGC and chaired by Professor Mark Woodhead in accordance with guidance from NICE.

The group met every 4-6 weeks during the development of the guideline. At the start of the guideline development process all GDG members declared interests including consultancies, fee-paid work, share-holdings, fellowships and support from the healthcare industry. At all subsequent GDG meetings, members declared arising conflicts of interest.

Members were either required to withdraw completely or for part of the discussion if their declared interest made it appropriate. The details of declared interests and the actions taken are shown in Appendix B:.

Staff from the NCGC provided methodological support and guidance for the development process. The team working on the guideline included a project manager, systematic reviewers, health economists and information scientists. They undertook systematic searches of the literature, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate and drafted the guideline in collaboration with the GDG.

4.4 What this guideline covers

Groups that will be covered

- Adults (18 and older) with a suspected or confirmed diagnosis of CAP.
- Adults with a suspected or confirmed diagnosis of HAP.
- No patient subgroups have been identified as needing specific consideration.

Key clinical issues that will be covered

- Diagnostic investigations, including C-reactive protein and procalcitonin.
- Microbiological investigations, including sputum and blood culture, and urinary antigens.
- Severity assessment tools to guide referral, admission to hospital and admission to intensive care units.
- Pharmacological interventions:
  - antibiotic treatment:
    - when to start
    - which antibiotic or combination of antibiotics
    - duration
  - glucocorticosteroid treatment.

Note that guideline recommendations will normally fall within licensed indications; exceptionally, and only if clearly supported by evidence, use outside a licensed indication may be recommended. The guideline will assume that prescribers will use a drug's summary of product characteristics to inform decisions made with individual patients.

- Gas exchange management:
  - continuous positive airway pressure

  - non-invasive ventilation.
- Monitoring response, including:
  - C-reactive protein
  - procalcitonin.
- Criteria for safe discharge.
- Patient information such as information on self-care and self-medication, condition-specific information, support and communication needs of patients (and carers and families as appropriate).

For further details please refer to the scope in **Appendix A:** and review questions in section 5.1.

4.5 What this guideline does not cover

Groups that will not be covered

- People younger than 18 years.
- Patients who acquire pneumonia while intubated (ventilator-associated pneumonia) and/or on the intensive care unit.
- Patients who are immunocompromised (have a primary immune deficiency or secondary immune deficiency related to HIV infection, or drug or systemic disease-induced immunosuppression).
- Patients in whom pneumonia is an expected terminal event.
- Pneumonia complicating bronchiectasis.

Clinical issues that will not be covered

- Management of specific identified pathogens (including tuberculosis and viruses).
- Pneumonia associated with clinically significant bronchiectasis, including cystic fibrosis.
- Prevention strategies, including vaccination or lifestyle advice.
- Management strategies:
  - complementary and alternative treatments
  - statins
  - granulocyte-colony stimulating factor
  - nebulised saline
  - fluids
  - nutrition
  - physiotherapy
  - palliative care.
- Management of complications.
- Follow-up after hospital discharge, including investigations.

4.6 Relationships between the guideline and other NICE guidance

Related NICE Interventional procedures guidance:

- Extracorporeal membrane carbon dioxide removal. NICE interventional procedure 428 (2012).
- Extracorporeal membrane oxygenation for severe acute respiratory failure in adults. NICE interventional procedure guidance 391 (2011).

Related NICE Clinical guidelines:

- Infection. NICE clinical guideline 139 (2012).
- Patient experience in adult NHS services. NICE clinical guideline 138 (2012).
- Medicines adherence. NICE clinical guideline 76 (2009).
- Respiratory tract infections – antibiotic prescribing. NICE clinical guideline 69 (2008).
- Feverish illness in children. NICE clinical guideline 47 (2007).

Related NICE Public health guidance:

- Healthcare-associated infections quality improvement guide. NICE advice (2011).
- Technical patient safety solutions for ventilator associated pneumonia. NICE patient safety guidance 2 (2008).

Related NICE guidance currently in development:

- Drug allergy: the diagnosis and management of drug allergy in adults and children. NICE clinical guideline. Publication expected 2014.

5 Methods

This chapter sets out in detail the methods used to review the evidence and to generate the recommendations that are presented in subsequent chapters. This guidance was developed in accordance with the methods outlined in the NICE guidelines manual 2012[143].

5.1 Developing the review questions and outcomes

Review questions were developed in a PICO framework (patient, intervention, comparison and outcome) for intervention reviews, in a framework of population, index tests, reference standard and target condition for reviews of diagnostic test accuracy and using population, presence or absence of risk or protective factors under investigation (for example prognostic factors) and outcomes for prognostic reviews.

This use of a framework guided the literature searching process, critical appraisal and synthesis of evidence and facilitated the development of recommendations by the Guideline Development Group (GDG). The review questions were drafted by the NCGC technical team and refined and validated by the GDG. The questions were based on the key clinical areas identified in the scope (**Appendix A:**).

A total of 17 review questions were identified.

Full literature searches, critical appraisals and evidence reviews were completed for all the specified review questions.

Table 1: Review questions

Chapter	Type of review	Review questions	Outcomes
6.2	Prognostic	1. In adults with lower respiratory tract infection in the community, what is the clinical value and cost effectiveness of testing C-reactive protein, procalcitonin or performing a chest X-ray over clinical assessment to inform antibiotic prescribing decisions and need for hospital admission?	• Hospital admission. • Antibiotic treatment. • Mortality. • Re-consultation. • Health-related quality-of-life. • Resolution of symptoms/treatment failure (opposite direction).
8	Prognostic	2. In adults presenting with lower respiratory tract infection or suspected community-acquired pneumonia in the community, what is the most accurate and cost-effective severity assessment tool to identify patients whose outcome will be improved by referral to hospital?	• Mortality. • Hospital admission. • Health-related quality-of-life. • Test practicality.
8	Prognostic	3. In adults with community-acquired pneumonia (presenting to Accident & Emergency) what is the most accurate and cost-effective severity assessment tool to stratify patients at first	• Mortality (as an indicator of when hospital or ITU admission is required). • Hospital admission. • Assessment for ITU admission (ITU admission, need for invasive

Chapter	Type of review	Review questions	Outcomes
		presentation according to who would benefit from a) hospital admission? b) ITU assessment?	ventilation or vasopressor support as surrogates). • Test practicality.
8	Prognostic	4. In adults with hospital-acquired pneumonia what is the most accurate and cost-effective severity assessment tool to stratify patients at first presentation according to who would benefit from ITU assessment?	• Mortality. • Assessment for ITU admission (ITU admission, need for invasive ventilation or vasopressor support as surrogates). • Test practicality.
9	Diagnostic	5. In adults with community-acquired pneumonia or hospital-acquired pneumonia in a hospital setting, what microbiological test or combination of tests at presentation (including urinary pneumococcal and urinary legionella antigen, blood culture and sputum culture) is most likely to be clinically and cost effective?	• Change in antibiotic prescription/treatment. • Length of stay. • Hospital re-admission. • Mortality (< 60 days). • Clinical cure. • Failure to respond to treatment (measured as clinical failure, clinical relapse or clinical instability). • Health-related quality-of-life (30- or 90-days). • Withdrawal due to adverse events. • Complications (composite of empyema, effusion, abscess, metastatic infection, superinfection, MODS).
10.1	Interventional	6. In adults with suspected community-acquired pneumonia is earlier rather than later antibiotic administration more clinically and cost effective?	• Mortality (at 30 days). • Hospital admission. • Length of hospital stay. • Clinical cure (success or improvement, clinical stability [opposite direction] as surrogates). • Health-related quality-of-life (measured by CAP, EQ5D or SF-36). • Hospital re-admission. • *C. difficile*-associated diarrhoea. • Withdrawal due to treatment-related adverse events. • Complications (composite of empyema, effusion, abscess, metastatic infection, superinfection,

Chapter	Type of review	Review questions	Outcomes
			MODS).
18.1	Interventional	7. In adults with hospital-acquired pneumonia is earlier rather than later antibiotic administration more clinically and cost effective?	• Mortality (at 30 days). • Hospital admission. • Length of hospital stay. • Clinical cure (success or improvement, clinical stability [opposite direction] as surrogates). • Health-related quality-of-life (measured by CAP, EQ5D or SF-36). • Hospital re-admission. • *C. difficile*-associated diarrhoea. • Withdrawal due to treatment-related adverse events. • Complications (composite of empyema, effusion, abscess, metastatic infection, superinfection, MODS)..
10.3	Interventional	8. In adults with community-acquired pneumonia what is the most clinically- and cost-effective empirical antibiotic choice?	• Mortality (at30 days) • Hospital admission (including ITU admission). • Length of hospital stay. • Clinical cure (success or improvement, or maintaining clinical cure as surrogates). • Health-related quality-of-life (measured by CAP, EQ5D or SF-36). • *C. difficile*-associated diarrhoea. • Withdrawal due to treatment-related adverse events. • Complications (composite of empyema, effusion, abscess, metastatic infection, superinfection, MODS).
18.3	Interventional	9. In adults with hospital-acquired pneumonia what is the most clinically- and cost-effective empirical antibiotic choice?	• Mortality (at 30 days). • Hospital re-admission. • Length of hospital stay. • Clinical cure (success or improvement as surrogates). • Health-related quality-of-life.

Chapter	Type of review	Review questions	Outcomes
			• *C. difficile*-associated diarrhoea. • Withdrawal due to treatment-related adverse events. • Complications (composite of empyema, effusion, abscess, metastatic infection, superinfection, MODS).
10.12	Interventional	10. In adults with community-acquired pneumonia what is the clinical and cost effectiveness of short- compared with longer-course antibiotics?	• Mortality (at any point in time) • Relapse rate. • Hospital admission. • Length of hospital stay. • Clinical cure (success or improvement as surrogates). • Health-related quality-of-life (measured by CAP, EQ5D or SF-36). • Hospital re-admission. • *C. difficile*-associated diarrhoea. • Withdrawal due to treatment-related adverse events. • Complications (composite of empyema, effusion, abscess, metastatic infection, superinfection, MODS). • Hospital re-admission.
18.9	Interventional	11. In adults with hospital-acquired pneumonia what is the clinical and cost effectiveness of short- compared with longer-course antibiotics?	• Mortality (at any point in time). • Relapse rate. • Hospital re-admission. • Length of hospital stay. • Clinical cure (success or improvement as surrogates). • *C. difficile*-associated diarrhoea. • Withdrawal due to treatment-related adverse events. • Complications (composite of empyema, effusion, abscess, metastatic infection, superinfection, MODS).

Chapter	Type of review	Review questions	Outcomes
11	Interventional	12. In adults with community-acquired pneumonia or hospital-acquired pneumonia requiring management in hospital, what is the clinical and cost effectiveness of initial glucocorticosteroid treatment in addition to antibiotic treatment compared with antibiotic treatment alone?	• Mortality (at 30 days). • Length of hospital stay. • Need for ventilatory or ionotropic support. • Clinical cure (success or improvement as surrogates).. • Health-related quality-of-life (measured by CAP, EQ5D or SF-36). • Hyperglycaemia (end of follow-up). • Withdrawal due to treatment-related adverse events. • Complications (composite of empyema, effusion, abscess, metastatic infection, superinfection, MODS).
12	Interventional	13. In adults with community-acquired pneumonia or hospital-acquired pneumonia managed in hospital, what is the clinical and cost effectiveness of non-invasive ventilation compared with continuous positive airways pressure or usual care?	• Mortality (at 30 days).Need for intubation/invasive ventilation (tracheostomy or oral endotracheal tube). • Length of hospital (or ITU) stay. • Clinical cure (success or improvement as surrogates). • Health-related quality-of-life (measured by CAP, EQ5D or SF-36). • Duration of ventilatory assistance. • Complications (composite of empyema, effusion, abscess, metastatic infection, superinfection, MODS).
12	Interventional	14. In adults with community-acquired pneumonia or hospital-acquired pneumonia managed in hospital, what is the clinical and cost effectiveness of non-invasive ventilation, continuous positive airways pressure or usual care compared with elective intubation?	• Mortality (at 30 days). • Length of hospital (or ITU) stay. • Ventilator-free days. • Clinical cure (success or improvement as surrogates). • Health-related quality-of-life (measured by CAP, EQ5D or SF-36). • Duration of ventilatory assistance. • Complications (composite

Chapter	Type of review	Review questions	Outcomes
			of empyema, effusion, abscess, metastatic infection, superinfection, MODS).
13	Prognostic	15. In adults with community-acquired pneumonia or hospital-acquired pneumonia managed in hospital, what is the clinical and cost effectiveness of C-reactive protein or procalcitonin monitoring in addition to clinical observation in helping to determine when to stop or change treatment and when to discharge?	• Mortality. • Clinical cure. • Treatment failure. • Inappropriate use of antibiotics. • Duration of treatment. • ITU admission or need for invasive ventilation/ionotropic support. • Hospital re-admission (30 days). • Length of hospital stay. • Health-related quality-of-life (up to 30 days). • Complications (including relapse at 30 days).
14	Prognostic	16. What is the prognostic value, clinical and cost effectiveness of various factors for assessing whether it is safe to discharge adults with community-acquired pneumonia or hospital-acquired pneumonia requiring management in hospital?	• Mortality (30 days). • Hospital re-admission. • Health-related quality-of-life. • Activities of daily living. • Complications (composite of empyema, effusion, abscess, metastatic infection, superinfection, MODS).
15	Qualitative	17. What advice should be given to adults about what symptoms and duration of symptoms can be expected following treatment for community-acquired or hospital-acquired pneumonia, and when should patients be advised to consult or re-consult a GP?	• Proportion with specific symptoms and time to resolution of these symptoms at specific time points after diagnosis. • Alteration or additional course of antibiotics after discharge from hospital or initial primary care consultation. • Re-consultation (pneumonia related). • Change in quality-of-life (including symptom domains). • Return to usual activities or activities of daily living.

5.2 Searching for evidence

5.2.1 Clinical literature search

Systematic literature searches were undertaken to identify all published clinical evidence relevant to the review questions. Searches were undertaken according to the parameters stipulated within The guidelines manual 2012.[143]

Databases were searched using relevant medical subject headings, free-text terms and study type filters where appropriate. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to retrieve articles published in English. All searches were conducted in Medline, Embase, and The Cochrane Library. All searches were updated on 17 March 2014. Any studies added to the databases after this date (even those published prior to this date) were not included unless specifically stated in the text.

Search strategies were quality assured by cross checking reference lists of highly relevant papers, analysing search strategies in other systematic reviews and asking the GDG members to highlight any additional studies. The questions, the study types applied, the databases searched and the years covered can be found in Appendix F:.

The titles and abstracts of records retrieved by the searches were sifted for relevance, with potentially significant publications obtained in full text. These were assessed against the inclusion criteria.

During the scoping stage, a search was conducted for guidelines and reports on websites of organisations relevant to the topic. Searching for grey literature or unpublished literature was not undertaken. Searches for electronic, ahead of print or “online early” publications are not routinely undertaken. All references suggested by stakeholders at the scoping consultation were considered.

5.2.2 Health economic literature search

Systematic literature searches were also undertaken to identify health economic evidence within published literature relevant to the review questions. The evidence was identified by conducting a broad search relating to pneumonia in the NHS Economic Evaluation Database (NHS EED), the Health Economic Evaluations Database (HEED) and Health Technology Assessment (HTA) databases with no date restrictions. Additionally, the search was run on Medline and Embase using a specific economic filter, from 2011 to ensure recent publications that had not yet been indexed by the economic databases were identified. This was supplemented by additional searches that looked for economic papers specifically relating to gas exchange management as this was an area identified for original economic modelling. Studies published in languages other than English were not reviewed. Where possible, searches were restricted to articles published in English.

The search strategies for the health economics literature search are included in Appendix F:. All searches were updated on 17 March 2014. No papers published after this date were considered.

5.3 Evidence of effectiveness

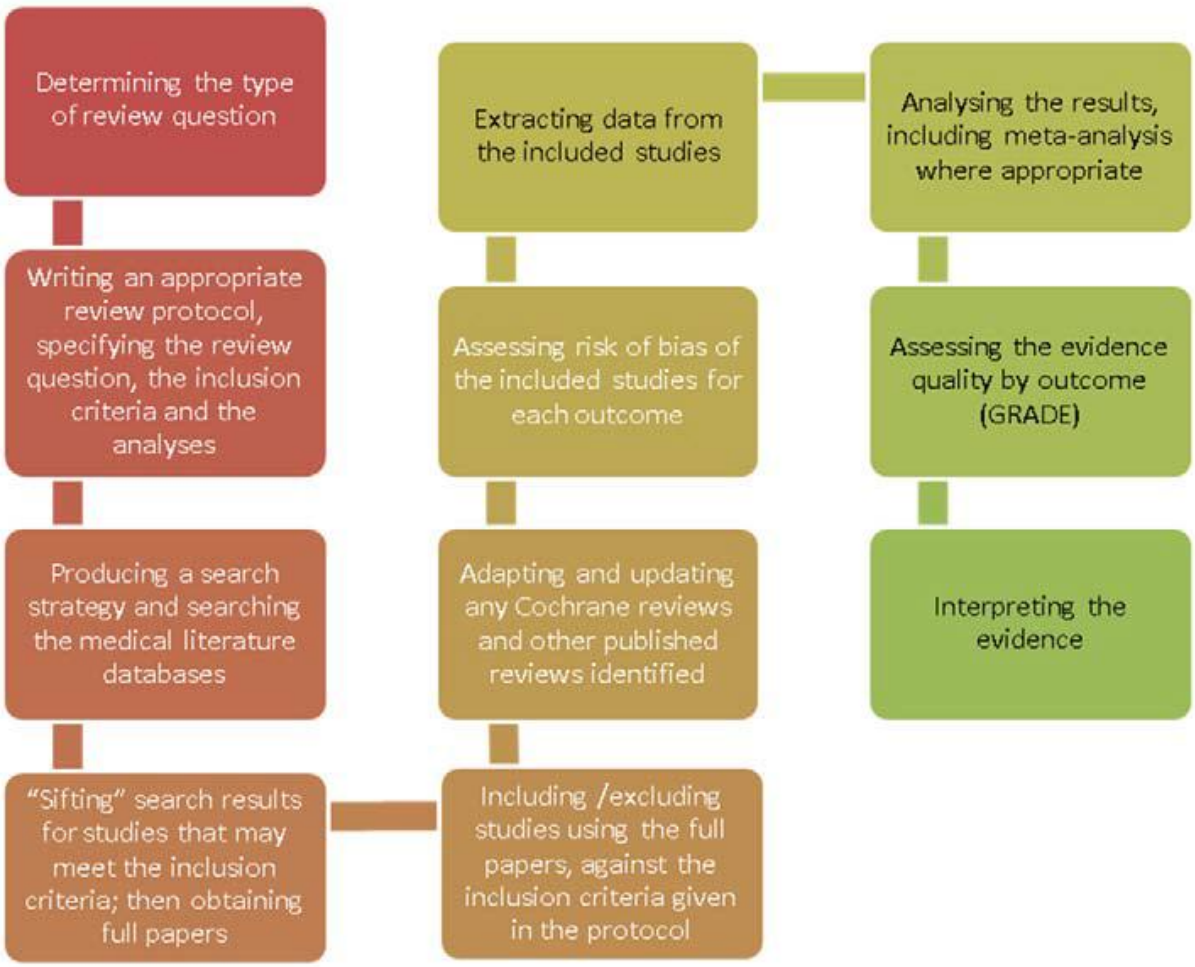
The evidence was reviewed following the steps shown schematically in Figure 2:

- Potentially relevant studies were identified for each review question from the relevant search results by reviewing titles and abstracts. Full papers were then obtained.
- Full papers were reviewed against pre-specified inclusion and exclusion criteria to identify studies that addressed the review question in the appropriate population and reported on outcomes of interest (review protocols are included in Appendix C:).

- Relevant studies were critically appraised using the appropriate checklist as specified in the guidelines manual 2012.[143] for diagnostic questions the QUADAS-2 checklist was followed.[195]
- Key information was extracted on the study's methods, PICO factors and results. These were presented in summary tables in each chapter and evidence tables (in Appendix G:).
- Summaries of evidence were generated by outcome and were presented in GDG meetings:
  - Randomised studies: data were meta-analysed where appropriate and reported in GRADE profiles (for intervention reviews).
  - Observational studies: data were presented as a range of values or meta-analysed (where appropriate) in GRADE profiles and usually this was organised by outcomes. When observational studies with multivariate analyses were included, these were presented separately as the confounding factors in the analyses were often not the same across studies. When comparative observational studies presented frequency data along with results from a multivariate analysis, the adjusted estimate of relative effect size (adjusted OR or RR) was presented along with the absolute effect size (which was calculated based on the frequencies of 2 groups).
  - Diagnostic studies were presented as measures of diagnostic test accuracy (sensitivity, specificity, positive and negative predictive value, area under the curve). A meta-analysis could not be conducted due to heterogeneity of included studies.
  - Prognostic studies: data were presented as a range of values, usually in terms of the relative effect as reported by the authors. For the severity assessment review, meta-analysis was conducted to calculate the absolute effect measure when the data were available. However, for the presentation of relative effect, it was decided to include the risk ratio (RR) of the median study with the range of RRs of all included studies in order to capture a more representative distribution of relative effects of all available evidence.
  - Qualitative studies: the themes of the studies were organised in a modified version of a GRADE profile, where possible, along with quality assessment otherwise presented in a narrative form.

80% of all data extracted was quality assured by a second reviewer. 50% of the GRADE quality assessment was quality assured by a second reviewer to minimise any potential risk of reviewer bias or error.

Figure 2: Step-by-step process of review of evidence in the guideline



5.3.1 Inclusion and exclusion criteria

The inclusion and exclusion of studies was based on the review protocols, which can be found in Appendix C:. Excluded studies by review question (with the reasons for their exclusion) are listed in Appendix J:. The GDG was consulted about any uncertainty regarding inclusion or exclusion.

Population

The guideline population was defined to be adults diagnosed with pneumonia (hospital- or community-acquired).

For some review questions (such as assessing the prognostic role of CRP, PCT and CXR to inform antibiotic prescribing), the review population also included the general population of lower respiratory tract infection.

Regarding population characteristics, the following inclusion criteria were applied:

- Studies with mixed LRTI populations were included if results were stratified for CAP or if patients with CAP made up more than 75% of the sample.
- Studies with mixed CAP and nursing home pneumonia populations were included if patients with CAP made up more than 75% of the sample.
- Place of management was used as a surrogate for severity assessment and each study was assessed for directness of population. Patients with CAP managed outside hospital or as

outpatients were considered to have low-severity CAP. Patients with CAP managed in hospital/ITU were considered to have high-severity CAP.

- Studies in which more than 50% of the patient population was assessed as having low-severity CAP based on severity assessment tools were reviewed within the low-severity CAP stratum even if patients were all managed in hospital.
- Studies in which the population was sub-grouped into suspected (for example, pneumococcal and non-pneumococcal) pneumonia origin were included as long as treatment was not delayed to determine aetiology.
- Adequate definition of HAP to clarify occurrence at least 48 hours after hospital admission.

5.3.2 Methods of combining clinical studies

5.3.2.1 Data synthesis for intervention reviews

Where possible, meta-analyses were conducted to combine the results of studies for each review question using Cochrane Review Manager (RevMan5) software. Fixed-effects (Mantel-Haenszel) techniques were used to calculate risk ratios (relative risk) for the binary outcomes such as mortality and ITU admission.

For the continuous outcomes, measures of central tendency (mean) and variation (standard deviation) were required for meta-analysis. Data for continuous outcomes such as length of hospital stay and duration of antibiotic therapy were analysed using an inverse variance method for pooling weighted mean differences and, where the studies had different scales, standardised mean differences were used. A generic inverse variance option in RevMan5 was used if any studies reported solely the summary statistics and 95% confidence interval (95% CI) or standard error; this included any hazard ratios reported. However, in cases where standard deviations were not reported per intervention group, the standard error (SE) for the mean difference was calculated from other reported statistics (p values or 95% CIs) if available; meta-analysis was then undertaken for the mean difference and SE using the generic inverse variance method in RevMan5. When the only evidence was based on studies that summarised results by presenting medians (and interquartile ranges), or only p values were given, this information was assessed in terms of the study's sample size and was included in the GRADE tables without calculating the relative or absolute effects or as a narrative summary. Consequently, aspects of quality assessment such as imprecision of effect could not be assessed for evidence of this type and this has been recorded in the footnotes of the GRADE tables. When more than 2 studies reported a continuous outcome, the presentation of mean (SD) per comparison group was taken by averaging the means of included studies.

Where reported, time-to-event data were presented as a hazard ratio or results from a Cox hazard proportion model were given as a result from a multivariate analysis.

Stratified analyses were predefined for some review questions at the protocol stage when the GDG identified that these strata to be different in terms of clinical characteristics and the interventions were expected to have a different effect on low-, intermediate- and high-risk groups for CAP.

Statistical heterogeneity was assessed by visually examining the forest plots, and by considering the chi-squared test for significance at $p < 0.1$ or an I-squared inconsistency statistic (with an I-squared value of more than 50% indicating considerable heterogeneity). If the heterogeneity still remained, a random-effects (DerSimonian and Laird) model was employed to provide a more conservative estimate of the effect. Where considerable heterogeneity was present, we set out to perform predefined subgroup analyses based on the following factors:

- intravenous and oral administration
- standard duration of treatment compared with no standard duration (for most antibiotics the standard duration is 7 days

- predominant disease aetiology (including resistance profiles)
- CAP in primary care with CXR-confirmed diagnosis or clinical assessment alone.

For interpretation of the binary outcome results, differences in the absolute event rate were calculated using the GRADEpro software, for the median event rate across the control arms of the individual studies in the meta-analysis. Absolute risk differences were presented in the GRADE profiles and in clinical summary of findings tables, for discussion with the GDG.

When the only results presented in the studies were in relation to multivariate analysis (adjusted RR, OR or HR), forest plots were not produced and the estimate of absolute effect size could not be calculated.

Network meta-analyses (NMA) for assessing the relative efficacy of antibiotic therapies for either CAP or HAP were not performed. The aim of an NMA is to include all relevant evidence in order both to answer questions on the clinical effectiveness of interventions when no direct comparison is available and to give a ranking of treatments in terms of efficacy. The decision not to conduct a NMA was mutually agreed by the technical team and the GDG considering the following:

- heterogeneity of the patient groups in the different studies
- many of the included trials were old and as such fluctuations in epidemiology of pathogens and resistance profiles are subject to change
- the non-representative nature of the patients in most of the studies (particularly the age difference when compared with those with pneumonia in the UK population)
- different definitions of outcomes (such as clinical cure)
- the mixture of non-inferiority and superiority studies
- the majority of evidence was of low to very low quality.

The GDG agreed that they would not have any confidence in the results of an NMA. In addition, no RCT data was found for one comparison of the most commonly prescribed antibiotic therapies for pneumonia in UK clinical practice (beta-lactam compared with a beta-lactam and macrolide), thus limiting the applicability of findings from a NMA which would include only RCTs.

Data synthesis for prognostic factor reviews

Odds ratios (ORs), risk ratios (RRs) or hazard ratios (HRs), with their 95% confidence intervals (95% CIs) for the effect of the pre-specified prognostic factors were extracted from the papers. Although the protocol was set up to look first at RCTs (of mainly test and treat study design), prospective cohort studies with the appropriate study population were also considered to be high-quality evidence to answer these questions. Prospective cohort studies were preferred if they reported multivariate analyses, including key confounders as identified by the GDG at the protocol stage for a specific outcome. The GDG considered that age, comorbidities (with more emphasis on previous heart, lung and liver disease) and malignancies could skew the predictive ability of the investigated tools to assess mainly mortality and ITU admission for patients with CAP. If the severity tools took these confounders into consideration in their scoring, then univariate analysis was still considered valid to address this question.

For the severity assessment review in which we assessed the role of several severity assessment tools to categorize patients into risk groups related to the likelihood of experiencing outcomes (most importantly mortality and ITU admission), we used 2 approaches to summarize the evidence:

- Summary of discriminatory analysis; a receiver operator characteristics (ROC) curve using the performance criteria for each severity assessment tool, and the area under these curves (AUC). The AUCs were approximated for some tools, such as the revised American Thoracic Society score (rATS), which were scored as binary outcomes. The results of the largest observational studies were highlighted.

- Data were summarised in GRADE tables for the studies that tested the same tools. Frequencies were summarised across all studies per risk group for the same tool. Given the heterogeneity of observational studies, we presented the relative risk ratio (RR) of the median study and the range of RRs of all included studies. However, the absolute effect was derived from the pooled estimate of effect size (from meta-analysis). This was decided in order to make the best use of all the included studies to inform decision-making.

5.3.2.2 Data synthesis for diagnostic test accuracy review

For diagnostic test accuracy studies, the following outcomes were reported: sensitivity, specificity, positive predictive value, negative predictive value, and area under the curve (AUC; 0.9-1: excellent, 0.8-0.9: good, 0.7-0.8: fair, 0.60-0.70: poor, < 0.5: fail). Heterogeneity is represented on a ROC curve by vertical displacements around the ROC curve, and this was examined in subgroup analyses when possible.

5.3.2.3 Data synthesis for qualitative review

For the qualitative review in the guideline, results were presented in 2 ways:

- A modified version of the GRADE table was used by summarising the information on the included studies in relation to themes around the outcomes in the review. NICE checklists on assessing qualitative studies were used to assess the quality assessment of individual studies.
- Results were reported narratively either by individual study or by summarising the range of values as reported across similar studies.

5.3.3 Type of studies

Randomised trials, non-randomised trials, and observational studies (including diagnostic or prognostic studies) were included in the evidence reviews as appropriate.

Conference abstracts were not automatically excluded from the review but were initially assessed against the inclusion criteria and included only if no other published full paper was available for a particular review question.

Literature reviews, posters, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

For most intervention reviews in this guideline, parallel randomised controlled trials (RCTs) were included because they are considered the most robust study design for unbiased estimation of intervention effects. Crossover RCTs were not appropriate for any of the interventional questions as they were designed to test the relative efficacy of antibiotics and the carry over effect of cross over trials would be a bias in the estimate of these effects.

If the GDG believed RCT data were not appropriate or there was limited evidence from RCTs, well-conducted non-randomised comparative studies were included. Please refer to Appendix C: for full details on the study design of studies selected for each review question. For example the GDG noticed that it was unlikely that there was randomised evidence for the comparison of beta lactam with beta-lactam plus a macrolide, so observational studies with multivariate analyses were also considered for this (most commonly prescribed) comparison only.

For diagnostic reviews, cross-sectional and retrospective studies were included. For prognostic reviews, prospective and retrospective cohort studies were included. Case-control or case series studies were not included for any review question.

Type of analysis

Estimates of effect from individual studies were based on available case analysis (ACA): that is, analysing only data that were available for participants at the end of follow-up, without making any imputations for missing data. The GDG recorded several potential reasons for people with pneumonia dropping out before trial completion:

- adverse effects (including deaths)
- withdrawal of consent
- investigator's discretion
- loss to follow-up (e.g. moving house, second opinions from clinicians not in the study).

The ACA method was used rather than an intention-to-treat with imputation analysis (ITT), in order to avoid making assumptions about the participants for whom outcome data was not available, and furthermore assuming that those with missing outcome data had the same event rate as those who continued. In addition, ITT analysis tends to bias the results towards no difference, and therefore the effect may be smaller than in reality. Using ACA, we avoided incorrectly weighting studies in meta-analysis by using a denominator that does not reflect the true sample size with outcome data available. If there was a differential missing data rate between the 2 arms in a study that was greater than 10%, a sensitivity analysis was performed to determine whether the size and direction of effect would be changed by using an ITT or ACA analysis and whether there was an impact on the meta-analysis. If this were the case, a footnote in the GRADE tables was added to describe the dependence on these assumptions. However, the majority of trials included in the review of evidence for this guideline had less than 10% differential missing outcome data.

When the studies reported only ITT results (through imputation), and the number of events was larger than the number of completers in the trial (ACA), we used the ITT analysis (we used the proportion of events from the ITT numbers to derive the number of events for the final sample size of completers).

5.3.4 Appraising the quality of evidence by outcomes

The evidence for outcomes from the included RCTs and, where appropriate, observational studies was evaluated and presented using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group (http://www.gradeworkinggroup.org/). The software developed by the GRADE working group (GRADEpro) was used to assess the quality of each outcome, taking into account individual study quality factors and the meta-analysis results. The 'Clinical/Economic evidence profile' table includes details of the quality assessment and pooled outcome data, where appropriate, an absolute measure of intervention effect and the summary of quality of evidence for that outcome. In this table, the columns for intervention and control indicate summary measures and measures of dispersion (such as mean and standard deviation or median and range) for continuous outcomes and frequency of events (n/N: the sum across studies of the number of patients with events divided by sum of the number of completers) for binary outcomes. Reporting or publication bias was only taken into consideration in the quality assessment and included in the 'Clinical evidence profile' table if it was apparent.

The evidence for each outcome was examined separately for the quality elements listed and defined in Table 2. Each element was graded using the quality levels listed in Table 3**.**

The main criteria considered in the rating of these elements are discussed below. Footnotes were used to describe reasons for grading a quality element as having serious or very serious limitations. The ratings for each component were summed to obtain an overall assessment for each outcome (Table 4).

The GRADE toolbox is currently designed only for randomised trials and observational studies but we adapted the quality assessment elements and outcome presentation for diagnostic accuracy and prognostic studies subject to data availability.

Table 2: Description of quality elements in GRADE for intervention studies

Quality element	Description
Risk of bias (study limitations)	Limitations in the study design and implementation may bias the estimates of the treatment effect. High risk of bias for the majority of the evidence decreases confidence in the estimate of the effect.
Inconsistency	Inconsistency refers to an unexplained heterogeneity of results.
Indirectness	Indirectness refers to differences in study population, intervention, comparator and outcomes between the available evidence and the review question, or recommendation made, such that the effect estimate is changed.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of the effect. Imprecision results if the confidence interval includes the clinically important threshold.
Publication bias	Publication bias is a systematic underestimate or an overestimate of the underlying beneficial or harmful effect due to the selective publication of studies.

Table 3: Levels of quality elements in GRADE

Level	Description
None	There are no serious issues with the evidence.
Serious	The issues are serious enough to downgrade the outcome evidence by one level.
Very serious	The issues are serious enough to downgrade the outcome evidence by two levels.

Table 4: Overall quality of outcome evidence in GRADE

Level	Description
High	Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low	Any estimate of effect is very uncertain.

5.3.5 Grading the quality of clinical evidence

After results were pooled, the overall quality of evidence for each outcome was considered. The following procedure was adopted when using GRADE:

1. A quality rating was assigned, based on the study design. RCTs start High, observational studies as Low, and uncontrolled case series as Low or Very low, with the exception of prognostic studies for which observational studies are initially rated as High quality.
2. The rating was then downgraded for the specified criteria: risk of bias (study limitations), inconsistency, indirectness, imprecision and publication bias. These criteria are detailed below. Evidence from observational studies (which had not previously been downgraded) was upgraded if there was: a large magnitude of effect, a dose-response gradient, and if all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results showed no effect. Each quality element considered to have 'serious' or 'very serious' risk of bias was rated down by 1 or 2 points respectively.
3. The downgraded/upgraded ratings were then summed and the overall quality rating was revised. For example, all RCTs started as High and the overall quality became Moderate, Low or Very low if 1, 2 or 3 points were deducted respectively.
4. The reasons or criteria used for downgrading were specified in the footnotes.

The details of the criteria used for each of the main quality elements are discussed further in the following sections (5.3.6 to 5.3.9).

5.3.6 Risk of bias

Bias can be defined as anything that causes a consistent deviation from the truth. Bias can be perceived as a systematic error, for example, if a study was carried out several times and there was a consistently wrong answer, the results would be inaccurate.

The risk of bias for a given study and outcome is associated with the risk of over- or underestimation of the true effect.

The risks of bias are listed in Table 5.

A study with a poor methodological design does not automatically imply high risk of bias; the bias is considered individually for each outcome and it is assessed whether this poor design will impact on the estimation of the intervention effect.

Table 5: Risk of bias in randomised controlled trials

Risk of bias	Explanation
Allocation concealment	Those enrolling patients are aware of the group to which the next enrolled patient will be allocated (this is a major problem in "pseudo" or "quasi" randomised trials with allocation by for example, day of week, birth date, chart number).
Lack of blinding	Patient, caregivers, those recording outcomes, those adjudicating outcomes, or data analysts are aware of the arm to which patients are allocated. As mortality is the most critical outcome for this guideline and its effect is not biased by lack of blinding, unblinded studies were not automatically downgraded for this outcome.
Incomplete accounting of patients and outcome events	Missing data not accounted for and failure of the trialists to adhere to the intention to treat principle when indicated.
Selective outcome reporting	Reporting of some outcomes and not others on the basis of the results.
Other risks of bias	For example: • stopping early for benefit observed in randomised trials, in particular in the absence of adequate stopping rules • use of unvalidated patient-reported outcomes • recruitment bias in cluster randomised trials.

5.3.6.1 Diagnostic studies

For diagnostic accuracy studies, the Quality Assessment of Diagnostic Accuracy Studies version 2 (QUADAS-2) checklist was used (see Appendix F in The guidelines manual[143]). Risk of bias and applicability in primary diagnostic accuracy studies in QUADAS-2 consists of 4 domains (see Figure 3):

- patient selection
- index test
- reference standard
- flow and timing.

Figure 3: Summary of QUADAS-2 checklist

DOMAIN	PATIENT SELECTION	INDEX TEST	REFERENCE STANDARD	FLOW AND TIMING
Description	Describe methods of patient selection: Describe included patients (prior testing, presentation, intended use of index test and setting)	Describe the index test and how it was conducted and interpreted	Describe the reference standard and how it was conducted and interpreted	Describe any patients who did not receive the index test(s) and/or reference standard or who were excluded from the 2x2 table (refer to flow diagram): Describe the time interval and any interventions between index test(s) and reference standard
Signalling questions (yes/no/unclear)	Was a consecutive or random sample of patients enrolled?	Were the index test results interpreted without knowledge of the results of the reference standard?	Is the reference standard likely to correctly classify the target condition?	Was there an appropriate interval between index test(s) and reference standard?
	Was a case-control design avoided?	If a threshold was used, was it pre-specified?	Were the reference standard results interpreted without knowledge of the results of the index test?	Did all patients receive a reference standard?
	Did the study avoid inappropriate exclusions?			Did all patients receive the same reference standard?
				Were all patients included in the analysis?
Risk of bias: High/low/unclear	Could the selection of patients have introduced bias?	Could the conduct or interpretation of the index test have introduced bias?	Could the reference standard, its conduct, or its interpretation have introduced bias?	Could the patient flow have introduced bias?
Concerns regarding applicability: High/low/unclear	Are there concerns that the included patients do not match the review question?	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Are there concerns that the target condition as defined by the reference standard does not match the review question?	

Source: QUADAS-2 website, University of Bristol[195]

Optional domain, multiple test accuracy is applicable when a single study examined more than 1 diagnostic test (head-to-head comparison between 2 or more index tests reported within the same study). This optional domain contains 3 questions relating to risk of bias:

- Did all patients undergo all index tests or were the index tests appropriately randomised amongst the patients?
- Were index tests conducted within a short time interval?
- Are index test results unaffected when undertaken together on the same patient?

5.3.6.2 Prognostic studies

For prognostic studies, quality was assessed using the checklist for prognostic studies (Appendix I in The guidelines manual[143]). The quality rating (Low, High, Unclear) was derived by assessing the risk of bias across 6 domains: selection bias, attrition bias, prognostic factor bias, outcome measurement bias, control for confounders and appropriate statistical analysis, with the last 4 domains being assessed for each outcome. More details about the quality assessment for prognostic studies are shown below:

- The study sample represents the population of interest with regard to key characteristics (CAP or HAP).
- Missing data are unrelated to key characteristics, sufficient to limit potential bias – reasons for missing data are adequately described.
- The prognostic factor of interest is adequately measured in study participants.
- The outcome of interest is adequately measured in study participants.
- Important potential confounders are accounted for appropriately.
- The statistical analysis is appropriate for the design of the study, limiting potential for the presentation of invalid results.

5.3.7 Inconsistency

Inconsistency refers to an unexplained heterogeneity of results. When estimates of the treatment effect across studies differ widely (that is when there is heterogeneity or variability in results), this suggests true differences in underlying treatment effect.

Heterogeneity in meta-analyses was examined and sensitivity and subgroup analyses performed as pre-specified in the protocols (Appendix C:).

When heterogeneity existed (chi-squared $p < 0.1$, I-squared inconsistency statistic of > 50% or evidence from examining forest plots), but no plausible explanation was found (for example duration of intervention or different follow-up periods) the quality of evidence was downgraded by 1 or 2 levels, depending on the extent of uncertainty to the results contributed by the inconsistency in the results. In addition to the I-squared and chi-squared values, the decision for downgrading was also dependent on factors such as whether the intervention is associated with benefit in all other outcomes or whether the uncertainty about the magnitude of benefit (or harm) of the outcome showing heterogeneity would influence the overall judgment about net benefit or harm (across all outcomes).

When outcomes are derived from a single trial, inconsistency is not an issue for downgrading the quality of evidence. However, “no inconsistency” is nevertheless used to describe this quality assessment in the GRADE tables.

5.3.8 Indirectness

Directness refers to the extent to which the populations, intervention, comparisons and outcome measures are similar to those defined in the inclusion criteria for the reviews. Indirectness is important when these differences are expected to contribute to a difference in effect size, or may affect the balance of harms and benefits considered for an intervention.

The GDG noted the following common sources of important indirectness in the mixed populations included in studies reviewed within the guideline:

- excluding or limiting to the elderly
- including patients with nursing home acquired pneumonia
- hospital patients without chest x-ray confirmation of diagnosis
- pathogen proportions not representative of UK spectrum.

The GDG agreed that although the following circumstances could, in principle, be considered indirect evidence, it was unlikely that effect estimates would be affected. It was therefore agreed that this evidence would not to be downgraded for indirectness:

- including young people aged 12 to 18 years (population can be extrapolated)
- excluding those not eligible for penicillin treatment
- including a proportion with ‘prior antibiotic treatment’ when we are interested in empirical therapy (a proportion in practice will have received prior antibiotic therapy)
- including CXR-confirmed cure in the definition of outcome of clinical cure.

5.3.9 Imprecision

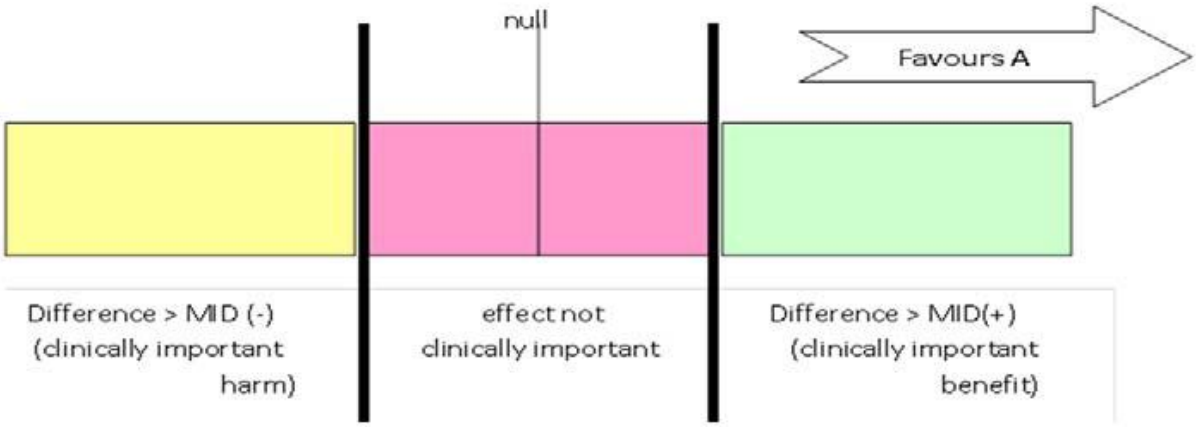
Imprecision in guidelines concerns whether the uncertainty (confidence interval) around the effect estimate means that it is not clear whether there is a clinically important difference between interventions or not. Therefore, imprecision differs from the other aspects of evidence quality in that it is not really concerned with whether the point estimate is accurate or correct (has internal or

external validity) instead it is concerned with the uncertainty about what the point estimate is. This uncertainty is reflected in the width of the confidence interval.

The 95% confidence interval (95% CI) is defined as the range of values that contain the population value with 95% probability. The larger the trial, the smaller the 95% CI and the more certain the effect estimate.

Imprecision in the evidence reviews was assessed by considering whether the width of the 95% CI of the effect estimate was relevant to decision-making, considering each outcome in isolation. Figure 4 considers a positive outcome for the comparison of treatment A versus B. Three decision-making zones can be identified, bound by the thresholds for clinical importance (minimal important difference – MID) for benefit and for harm. The MID for harm for a positive outcome means the threshold at which drug A is less effective than drug B by an amount that is clinically important to patients (favours B).

Figure 4: Illustration of precise and imprecise outcomes based on the confidence interval of outcomes in a forest plot



When the confidence interval of the effect estimate is wholly contained in one of the 3 zones (for example, clinically important benefit), we are not uncertain about the size and direction of effect (whether there is a clinically important benefit, or the effect is not clinically important, or there is a clinically important harm), so there is no imprecision.

When a wide confidence interval lies partly in each of 2 zones, it is uncertain in which zone the true value of effect estimate lies, and therefore there is uncertainty over which decision to make (based on this outcome alone). The confidence interval is consistent with 2 decisions and so this is considered to be imprecise in the GRADE analysis and the evidence is downgraded by 1 level ('serious imprecision').

If the confidence interval of the effect estimate crosses into 3 zones, this is considered to be very imprecise evidence because the confidence interval is consistent with 3 clinical decisions and there is a considerable lack of confidence in the results. The evidence is therefore downgraded by 2 levels in the GRADE analysis ('very serious imprecision').

Implicitly, assessing whether the confidence interval is in, or partially in, a clinically important zone, requires the GDG to estimate an MID or to say whether they would make different decisions for the 2 confidence limits.

The GDG considered it clinically acceptable to use the GRADE default MID to assess imprecision: a 25% relative risk reduction or relative risk increase was used, which corresponds to clinically important thresholds for a risk ratio of 0.75 and 1.25 respectively. This default MID was used for all

the dichotomous outcomes in the interventions evidence reviews. For continuous outcomes, an MID was calculated by adding or subtracting 0.5 standard deviations.

5.3.10 Assessing clinical importance

The GDG assessed the evidence by outcome in order to determine if there was, or potentially was, a clinically important benefit, a clinically important harm or no clinically important difference between interventions. To facilitate this, binary outcomes were converted into absolute risk differences (ARDs) using GRADEpro software: the median control group risk across studies was used to calculate the ARD and its 95% CI from the pooled risk ratio.

The assessment of benefit, harm, or no benefit or harm was based on the point estimate of absolute effect for intervention studies which was standardised across the reviews.

This assessment was carried out by the GDG for each critical outcome, and an evidence summary table was produced to compile the GDG's assessments of clinical importance per outcome, alongside the evidence quality and the uncertainty in the effect estimate (imprecision).

5.3.11 Evidence statements

Evidence statements are summary statements that are presented after the GRADE profiles, summarising the key features of the clinical evidence presented. The wording of the evidence statements reflects the certainty or uncertainty in the estimate of effect. The evidence statements are presented by comparison (for intervention reviews) or by outcome and encompass the following key features of the evidence:

- the number of studies and the number of participants for a particular outcome
- a brief description of the participants
- an indication of the direction of effect (if one treatment is beneficial or harmful compared with the other, or whether there is no difference between the 2 tested treatments)
- a description of the overall quality of evidence (GRADE overall quality).

5.4 Evidence of cost effectiveness

The GDG is required to make decisions based on the best available evidence of both clinical and cost effectiveness. Guideline recommendations should be based on the expected costs of the different options in relation to their expected health benefits (that is, their 'cost effectiveness') rather than the total implementation cost.[143] Thus, if the evidence suggests that a strategy provides significant health benefits at an acceptable cost per patient treated, it should be recommended even if it would be expensive to implement across the whole population.

Evidence on cost effectiveness related to the key clinical issues being addressed in the guideline was sought.

- A systematic review of the published economic literature was undertaken.
- New cost-effectiveness analysis was conducted in priority areas.

5.4.1 Literature review

The health economist:

- identified potentially relevant studies for each review question from the economic search results by reviewing titles and abstracts. Full papers were then obtained
- reviewed full papers against pre-specified inclusion/exclusion criteria to identify relevant studies (see below for details)

- critically appraised relevant studies using the economic evaluations checklist as specified in the guidelines manual[143]
- extracted key information about study methods and results into evidence tables (included in Appendix H:)
- generated summaries of the evidence in NICE economic evidence profiles (included in the relevant chapter for each review question) – see below for details.

5.4.1.1 Inclusion and exclusion criteria

Full economic evaluations (studies comparing costs and health consequences of alternative courses of action: cost–utility, cost-effectiveness, cost-benefit and cost-consequence analyses) and comparative costing studies that addressed the review question in the relevant population were considered potentially includable as economic evidence.

Studies were excluded that only reported cost per hospital (not per patient), or only reported average cost effectiveness without disaggregated costs and effects. Literature reviews, abstracts, posters, reviews, letters, editorials, comment articles, unpublished studies and studies not in English were excluded.

Remaining studies were prioritised for inclusion based on their relative applicability to the development of this guideline and the study limitations. For example, if a high quality, directly applicable UK analysis was available, then other less relevant studies may not have been included. Where exclusions occurred on this basis, this is noted in the relevant section.

For more details about the assessment of applicability and methodological quality see the economic evaluation checklist (Appendix G of the guidelines manual,[143] and the health economics review protocol in **Appendix C:**).

When no relevant economic studies were found from the economic literature review, relevant UK NHS unit costs related to the compared interventions were presented to the GDG to inform the possible economic implications of the recommendations.

5.4.1.2 NICE economic evidence profiles

The NICE economic evidence profile has been used to summarise cost and cost-effectiveness estimates. The economic evidence profile shows, for each economic study, an assessment of applicability and methodological quality for each economic evaluation, with footnotes indicating the reasons for the assessment. These assessments were made by the health economist using the economic evaluation checklist from The guidelines manual.[143]. It also shows the incremental costs, incremental effects (for example, quality-adjusted life years [QALYs]) and the incremental cost-effectiveness ratio for the base-case analysis in the evaluation, as well as information about the assessment of uncertainty in the analysis. See Table 6 for more details.

If a non-UK study was included in the profile, the results were converted into pounds sterling using the appropriate purchasing power parity.[155]

Table 6: Content of NICE economic evidence profile

Item	Description
Study	First author name, reference, date of study publication and country perspective.
Applicability	An assessment of applicability of the study to the clinical guideline, the current NHS situation and NICE decision-making[(a)]: • Directly applicable – the study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness. • Partially applicable – the study fails to meet one or more applicability criteria and this could change the conclusions about cost effectiveness. • Not applicable – the study fails to meet one or more applicability criteria and this is likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review.
Limitations	An assessment of methodological quality of the study[(a)]: • Minor limitations – the study meets all quality criteria, or fails to meet one or more quality criteria, but this is unlikely to change the conclusions about cost effectiveness. • Potentially serious limitations – the study fails to meet one or more quality criteria, and this could change the conclusion about cost effectiveness. • Very serious limitations – the study fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies would usually be excluded from the review.
Other comments	Particular issues that should be considered when interpreting the study.
Incremental cost	The mean cost associated with one strategy minus the mean cost of a comparator strategy.
Incremental effects	The mean QALYs (or other selected measure of health outcome) associated with one strategy minus the mean QALYs of a comparator strategy.
Cost effectiveness	Incremental cost-effectiveness ratio (ICER): the incremental cost divided by the incremental effects.
Uncertainty	A summary of the extent of uncertainty about the ICER reflecting the results of deterministic or probabilistic sensitivity analyses, or stochastic analyses of trial data, as appropriate.

(a) Applicability and limitations were assessed using the economic evaluation checklist from the guidelines manual.[143]

5.4.2 Undertaking new health-economic analysis

As well as reviewing the published economic literature for each review question, as described above, new economic analysis was undertaken by the health economist in selected areas. Priority areas for new health economic analysis were agreed by the GDG after formation of the review questions and consideration of the available health economic evidence.

The GDG identified microbiological tests as the highest priority area for original economic modelling. Due to the likely considerable variation in clinical practice, differences in costs, and potential impact on quality- of-life there is uncertainty over the cost effectiveness of different microbiological tests alone or in combination.

The following general principles were adhered to in developing the cost-effectiveness analysis.

- Methods were consistent with the NICE reference case.[144]
- The GDG was involved in the design of the model, selection of inputs and interpretation of the results.

- Model inputs were based on the systematic review of the clinical literature supplemented with other published data sources where possible.
- When published data was not available GDG expert opinion was used to populate the model.
- Model inputs and assumptions were reported fully and transparently.
- The results were subject to sensitivity analysis and limitations were discussed.
- The model was peer-reviewed by another health economist at the NCGC.

Full methods for the cost-effectiveness analysis for microbiological tests are described in Appendix L:.

5.4.3 Cost-effectiveness criteria

NICE's report 'Social value judgements: principles for the development of NICE guidance' sets out the principles that GDGs should consider when judging whether an intervention offers good value for money.[142] In general, an intervention was considered to be cost effective if either of the following criteria applied (given that the estimate was considered plausible).

a. The intervention dominated other relevant strategies (that is, it was both less costly in terms of resource use and more clinically effective compared with all the other relevant alternative strategies), or
b. The intervention cost less than £20,000 per QALY gained compared with the next best strategy.

If the GDG recommended an intervention that was estimated to cost more than £20,000 per QALY gained, or did not recommend one that was estimated to cost less than £20,000 per QALY gained, the reasons for this decision are discussed explicitly in the 'Recommendations and link to evidence' section of the relevant chapter with reference to issues regarding the plausibility of the estimate or to the factors set out in 'Social value judgements: principles for the development of NICE guidance' guidance'.[142]

If a study reported the cost per life year gained but not QALYs, the cost per QALY gained was estimated by multiplying by an appropriate utility estimate to aid interpretation. The estimated cost per QALY gained is reported in the economic evidence profile with a footnote detailing the life-years gained and the utility value used. When QALYs or life years gained are not used in the analysis, results are difficult to interpret unless one strategy dominates the others with respect to every relevant health outcome and cost.

5.4.4 In the absence of economic evidence

When no relevant published studies were found, and a new analysis was not prioritised, the GDG made a qualitative judgement about cost effectiveness by considering expected differences in resource use between options and relevant UK NHS unit costs alongside the results of the clinical review of effectiveness evidence.

5.5 Developing recommendations

Over the course of the guideline development process, the GDG was presented with:

- Evidence tables of the clinical and economic evidence reviewed from the literature. All evidence tables are in **Appendix G:** and Appendix H:.
- Summary of clinical and economic evidence and quality (as presented in chapters **Error! eference source not found.** to 19].)
- Forest plots and summary ROC curves (Appendix I:).
- A description of the methods and results of the cost-effectiveness analysis undertaken for the guideline (Appendix L:).

Recommendations were drafted on the basis of the GDG interpretation of the available evidence, taking into account the balance of benefits, harms and costs between different courses of action. This was either done formally in an economic model, or informally. Firstly, the net benefit over harm (clinical effectiveness) was considered, focusing on the critical outcomes. When this was done informally, the GDG took into account the clinical benefits and harms when one intervention was compared with another. The assessment of net benefit was moderated by the importance placed on the outcomes (the GDG's values and preferences), and the confidence the GDG had in the evidence (evidence quality). Secondly, it was assessed whether the net benefit justified any differences in costs.

When clinical and economic evidence was of poor quality, conflicting or absent, the GDG drafted recommendations based on their expert opinion. The considerations for making consensus-based recommendations include the balance between potential harms and benefits, the economic costs or implications compared with the economic benefits, current practices, recommendations made in other relevant guidelines, patient preferences and equality issues. The consensus recommendations were agreed through discussions in the GDG, and through methods of consensus [via a web-based questionnaire]. Formal methods of consensus were not used. The GDG also considered whether the uncertainty was sufficient to justify delaying making a recommendation to await further research, taking into account the potential harm of failing to make a clear recommendation (See section 5.5.1 below).

The wording of recommendations was agreed by the GDG and focused on the following factors:

- The actions health professionals need to take.
- The information readers need to know.
- The strength of the recommendation (for example the word 'offer' was used for strong recommendations and 'consider' for weak recommendations).
- The involvement of patients (and their carers if needed) in decisions on treatment and care.
- Consistency with NICE's standard advice on recommendations about drugs, waiting times and ineffective interventions.

The main considerations specific to each recommendation are outlined in the 'Recommendations and link to evidence' sections within each chapter.

5.5.1 Research recommendations

When areas were identified for which good evidence was lacking, the GDG considered making recommendations for future research. Decisions about inclusion were based on factors such as:

- the importance to patients or the population
- national priorities
- potential impact on the NHS and future NICE guidance
- ethical and technical feasibility.

5.5.2 Validation process

This guidance is subject to a 6-week public consultation and feedback as part of the quality assurance and peer review of the document. All comments received from registered stakeholders are responded to in turn and posted on the NICE website when the pre-publication check of the full guideline occurs.

5.5.3 Updating the guideline

Following publication, and in accordance with the NICE guidelines manual, NICE will undertake a review of whether the evidence base has progressed significantly to alter the guideline recommendations and warrant an update.

5.5.4 Disclaimer

Health care providers need to use clinical judgement, knowledge and expertise when deciding whether it is appropriate to apply guidelines. The recommendations cited here are a guide and may not be appropriate for use in all situations. The decision to adopt any of the recommendations cited here must be made by practitioners in light of individual patient circumstances, the wishes of the patient, clinical expertise and resources.

The National Clinical Guideline Centre disclaims any responsibility for damages arising out of the use or non-use of these guidelines and the literature used in support of these guidelines.

5.5.5 Funding

The National Clinical Guideline Centre was commissioned by the National Institute for Health and Care Excellence to undertake the work on this guideline.

6 Guideline summary

6.1 Key priorities for implementation

From the full set of recommendations, the GDG selected 6 key priorities for implementation. The criteria used for selecting these recommendations are listed in detail in The guidelines manual.[143] The reasons that each of these recommendations was chosen are shown in the table linking the evidence to the recommendation in the relevant chapter.

Presentation with lower respiratory tract infection

1. For people presenting with symptoms of lower respiratory tract infection in primary care, consider a point of care C-reactive protein test if after clinical assessment a diagnosis of pneumonia has not been made and it is not clear whether antibiotics should be prescribed. Use the results of the C-reactive protein test to guide antibiotic prescribing in people without a clinical diagnosis of pneumonia as follows:
   - Do not routinely offer antibiotic therapy if the C-reactive protein concentration is less than 20 mg/litre.
   - Consider a delayed antibiotic prescription (a prescription for use at a later date if symptoms worsen) if the C-reactive protein concentration is between 20 mg/litre and 100 mg/litre.
   - Offer antibiotic therapy if the C-reactive protein concentration is greater than 100 mg/litre.

Community-acquired pneumonia

Microbiological tests

8. For patients with moderate- or high-severity community-acquired pneumonia:
   - take blood and sputum cultures **and**
   - consider pneumococcal and legionella urinary antigen tests.

Timely diagnosis and treatment

9. Put in place processes to allow diagnosis (including X-rays) and treatment of community-acquired pneumonia within 4 hours of presentation to hospital.

Antibiotic therapy

Low-severity community-acquired pneumonia

11. Offer a 5-day course of a single antibiotic to patients with low-severity community-acquired pneumonia.

15. Do not routinely offer patients with low-severity community-acquired pneumonia:
    - a fluoroquinolone
    - dual antibiotic therapy.

Patient information

23. Explain to patients with community-acquired pneumonia that after starting treatment their symptoms should steadily improve, although the rate of improvement will vary with the severity of the pneumonia, and most people can expect that by:

    - 1 week: fever should have resolved
    - 4 weeks: chest pain and sputum production should have substantially reduced
    - 6 weeks: cough and breathlessness should have substantially reduced
    - 3 months: most symptoms should have resolved but fatigue may still be present
    - 6 months: most people will feel back to normal.

6.2 Full list of recommendations

Presentation with lower respiratory tract infection

1. For people presenting with symptoms of lower respiratory tract infection in primary care, consider a point of care C-reactive protein test if after clinical assessment a diagnosis of pneumonia has not been made and it is not clear whether antibiotics should be prescribed. Use the results of the C-reactive protein test to guide antibiotic prescribing in people without a clinical diagnosis of pneumonia as follows:
   - Do not routinely offer antibiotic therapy if the C-reactive protein concentration is less than 20 mg/litre.
   - Consider a delayed antibiotic prescription (a prescription for use at a later date if symptoms worsen) if the C-reactive protein concentration is between 20 mg/litre and 100 mg/litre.
   - Offer antibiotic therapy if the C-reactive protein concentration is greater than 100 mg/litre.

Community-acquired pneumonia

Severity assessment in primary care

2. When a clinical diagnosis of community-acquired pneumonia is made in primary care, determine whether patients are at low, intermediate or high risk of death using the CRB65 score (see box 1[a]).

Box 1: CRB65 score for mortality risk assessment in primary care[a]

CRB65 score is calculated by giving 1 point for each of the following prognostic features:

- confusion (abbreviated Mental Test score 8 or less, or new disorientation in person, place or time)[b]
- raised respiratory rate (30 breaths per minute or more)
- low blood pressure (diastolic 60 mmHg or less, or systolic less than 90 mmHg)
- age 65 years or more.

Patients are stratified for risk of death as follows:

- 0: low risk (less than 1% mortality risk)
- 1 or 2: intermediate risk (1-10% mortality risk)
- 3 or 4: high risk (more than 10% mortality risk).

3. Use clinical judgement in conjunction with the CRB65 score to inform decisions about whether patients need hospital assessment as follows:
   - consider home-based care for patients with a CRB65 score of 0
   - consider hospital assessment for all other patients, particularly those with a CRB65 score of 2 or more.

[a] Lim WS, van der Eerden MM, Laing R, et al. (2003) Defining community-acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax 58: 377–82.
[b] For guidance on delirium, see the NICE guideline on delirium.

Severity assessment in hospital

4. When a diagnosis of community-acquired pneumonia is made at presentation to hospital, determine whether patients are at low, intermediate or high risk of death using the CURB65 score (see box 2)[c]

> **Box 2: CURB65 score for mortality risk assessment in hospital[c]**
> CURB65 score is calculated by giving 1 point for each of the following prognostic features:
> • confusion (abbreviated Mental Test score 8 or less, or new disorientation in person, place or time)[d]
> • raised blood urea nitrogen (over 7 mmol/litre)
> • raised respiratory rate (30 breaths per minute or more)
> • low blood pressure (diastolic 60 mmHg or less, or systolic less than 90 mmHg)
> • age 65 years or more.
>
> Patients are stratified for risk of death as follows:
> • 0 or 1: low risk (less than 3% mortality risk)
> • 2: intermediate risk (3-15% mortality risk)
> • 3 to 5: high risk (more than 15% mortality risk).

5. Use clinical judgement in conjunction with the CURB65 score to guide the management of community-acquired pneumonia, as follows:
   - consider home-based care for patients with a CURB65 score of 0 or 1
   - consider hospital-based care for patients with a CURB65 score of 2 or more
   - consider intensive care assessment for patients with a CURB65 score of 3 or more.
6. Stratify patients presenting with community-acquired pneumonia into those with low-, moderate- or high-severity disease. The grade of severity will usually correspond to the risk of death.

Microbiological tests

7. Do not routinely offer microbiological tests to patients with low-severity community-acquired pneumonia.
8. For patients with moderate- or high-severity community-acquired pneumonia:
   - take blood and sputum cultures and
   - consider pneumococcal and legionella urinary antigen tests.

Timely diagnosis and treatment

9. Put in place processes to allow diagnosis (including X-rays) and treatment of community-acquired pneumonia within 4 hours of presentation to hospital.
10. Offer antibiotic therapy as soon as possible after diagnosis, and certainly within 4 hours to all patients with community-acquired pneumonia who are admitted to hospital.

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[c] Lim WS, van der Eerden MM, Laing R, et al. (2003) Defining community-acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax 58: 377–82

[d] For guidance on delirium, see the NICE guideline on delirium.

Antibiotic therapy

Low-severity community-acquired pneumonia

11. Offer a 5-day course of a single antibiotic to patients with low-severity community-acquired pneumonia.
12. Consider amoxicillin in preference to a macrolide or a tetracycline for patients with low-severity community-acquired pneumonia. Consider a macrolide or a tetracycline for patients who are allergic to penicillin.
13. Consider extending the course of the antibiotic for longer than 5 days as a possible management strategy for patients with low-severity community-acquired pneumonia whose symptoms do not improve as expected after 3 days.
14. Explain to patients with low-severity community-acquired pneumonia treated in the community, and when appropriate their families and carers, that they should seek further medical advice if their symptoms do not begin to improve within 3 days of starting the antibiotic, or earlier if their symptoms are worsening.
15. Do not routinely offer patients with low-severity community-acquired pneumonia:
    - a fluoroquinolone
    - dual antibiotic therapy.

Moderate- and high-severity community-acquired pneumonia

16. Consider a 7- to 10-day course of antibiotic therapy for patients with moderate- or high-severity community-acquired pneumonia.
17. Consider dual antibiotic therapy with amoxicillin and a macrolide for patients with moderate-severity community-acquired pneumonia.
18. Consider dual antibiotic therapy with a beta-lactamase stable beta-lactam[e] and a macrolide for patients with high-severity community-acquired pneumonia.

Glucocorticosteroid treatment

19. Do not routinely offer a glucocorticosteroid to patients with community-acquired pneumonia unless they have other conditions for which glucocorticosteroid treatment is indicated.

Monitoring in hospital

20. Consider measuring a baseline C-reactive protein concentration in patients with community-acquired pneumonia on admission to hospital, and repeat the test if clinical progress is uncertain after 48 to 72 hours.

Safe discharge from hospital

21. Do not routinely discharge patients with community-acquired pneumonia if in the past 24 hours they have had 2 or more of the following findings:
    - temperature higher than 37.5°C
    - respiratory rate 24 breaths per minute or more

[e] Available beta-lactamase stable beta-lactams include: co-amoxiclav, cefotaxime, ceftaroline fosamil, ceftriaxone, cefuroxime and piperacillin-tazobactam.

- heart rate over 100 beats per minute.
- systolic blood pressure 90 mmHg or less
- oxygen saturation under 90% on room air
- abnormal mental status
- inability to eat without assistance.

22. Consider delaying discharge for patients with community-acquired pneumonia if their temperature is higher than 37.5°C.

Patient information

23. Explain to patients with community-acquired pneumonia that after starting treatment their symptoms should steadily improve, although the rate of improvement will vary with the severity of the pneumonia, and most people can expect that by:
    - 1 week: fever should have resolved
    - 4 weeks: chest pain and sputum production should have substantially reduced
    - 6 weeks: cough and breathlessness should have substantially reduced
    - 3 months: most symptoms should have resolved but fatigue may still be present
    - 6 months: most people will feel back to normal.
24. Advise patients with community-acquired pneumonia to consult their healthcare professional if they feel that their condition is deteriorating or not improving as expected.

Hospital-acquired pneumonia

Antibiotic therapy

25. Offer antibiotic therapy as soon as possible after diagnosis, and certainly within 4 hours, to patients with hospital-acquired pneumonia.
26. Choose antibiotic therapy in accordance with local hospital policy (which should take into account knowledge of local microbial pathogens) and clinical circumstances for patients with hospital-acquired pneumonia.
27. Consider a 5- to 10-day course of antibiotic therapy for patients with hospital-acquired pneumonia.

6.3 Key research recommendations

1. In moderate- to high-severity community-acquired pneumonia does using legionella and pneumococcal urinary antigen testing in addition to other routine tests improve outcomes?
2. What is the clinical effectiveness of continuous positive pressure ventilation compared with usual care in patients with community-acquired pneumonia and type I respiratory failure without a history of chronic obstructive pulmonary disease?
3. In patients hospitalised with moderate- to high-severity community-acquired pneumonia, does using C-reactive protein monitoring in addition to clinical observation to guide antibiotic duration safely reduce the total duration of antibiotic therapy compared with a fixed empirical antibiotic course?
4. Can rapid microbiological diagnosis of hospital-acquired pneumonia reduce use of extended-spectrum antibiotic therapy, without adversely affecting outcomes?

7 Diagnostic tests

Adults with lower respiratory tract infection (LRTI) who see their GP present a spectrum of disease severity or aetiology that needs different approaches to management. At one extreme, a severely-ill patient with community-acquired pneumonia (CAP) will need antibiotic therapy and immediate hospital referral, at the other, a patient with mild symptoms requires reassurance, and perhaps symptomatic medications, only. The causes may range from severe and progressive bacterial infection to mild and self-limiting viral infections. It is generally accepted that patients with the former will benefit from antibiotic therapy, but patients with the latter may not derive benefit and may be harmed (due to side effects) by such treatment. The clinical symptoms and signs (for example, those classically associated with pneumonia) available to GPs are not sensitive discriminators of these different patient descriptions and so research has been conducted to examine whether diagnostic accuracy and clinical management can be improved by the use of simple investigations including chest X-ray (CXR) and blood tests.

The CXR has been the tool used by convention to confirm or refute a pneumonia diagnosis in hospital. While it is available to and used by GPs, it is not available in GP surgeries and CXR reporting to the GP may be delayed, limiting its clinical usefulness in primary care.

Other tests have been developed to detect molecules in the blood that are purportedly only present at high levels in the presence of inflammation and particularly bacterial infection. The most widely evaluated are C-reactive protein (CRP) and more recently procalcitonin (PCT). When performed in the conventional laboratory these have similar limitations of access and turn-around time to those of CXR, but they have now been developed as point-of-care tests potentially providing rapid results in general practice.

Such tests will cause inconvenience and discomfort to patients and there is an associated cost so an assessment of the balance between benefit and harm is important.

This section examines whether or not these tests have an added prognostic value in primary care presentations of LRTI and whether or not antibiotic therapy or hospital admission is indicated.

7.1 Review question: In adults with lower respiratory tract infection in the community, what is the clinical value and cost effectiveness of testing C-reactive protein, procalcitonin or performing a chest X-ray over clinical assessment to inform antibiotic prescribing decisions and need for hospital admission?

For full details see review protocol in Appendix C:.

The question was not asked for hospital-acquired pneumonia.

7.2 Clinical evidence

We searched for systematic reviews of randomised controlled trials (RCTs) and RCTs investigating the value of C-reactive protein (CRP), procalcitonin (PCT) or chest x-ray (CXR) in addition to clinical judgement compared with standard care, or with each other, in guiding antibiotic therapy and hospital admission in adults presenting with LRTI in the community. Randomised trials (RCTs) comparing these strategies were included in preference to observational studies.

This review question aimed to test the predictive ability of CRP, PCT or CXR over clinical assessment to inform patient management. Although these tests are called "diagnostic tests" this question did not look at the diagnostic accuracy of these tests to confirm pneumonia.

Eleven studies were included in the review:

- Three RCTs reported in 4 papers[36-38,122] comparing CRP with usual care
- One systematic review (SR) of 14 RCTs reported in 2 papers[175,177], including a Cochrane review comparing PCT with usual care. Individual RCTs in this systematic review were checked for additional outcomes not reported in the SR but included in our review protocol. One RCT[50] included in this systematic review provided such additional outcomes and these are presented separately in the GRADE tables below.

  This SR was assessed by the GDG as only partially applicable to this review question for the following reasons:

  - Population: included all acute respiratory tract infections, from unspecified upper respiratory tract infections to confirmed CAP, VAP or COPD.
  - Intervention: included both initial and follow-up measurements, which may have influenced management and hence outcomes.
  - Setting: the setting inclusion criteria were more inclusive than those specified in the protocol for this review question. More specifically, all settings (primary care, emergency department and intensive care unit) were included. Results are presented for the overall population but also for the pre-specified setting subgroup analysis when available.

  However, it was included in this review (although results were interpreted with caution) given its gold standard type of analysis (IPD meta-analysis) and because it pre-specified clinical setting and acute respiratory infection (ARI) diagnosis subgroup analysis.
- As no randomised data were found directly comparing PCT with CRP, an indirect comparison was performed using RCTs with comparable populations from the comparisons of CRP and PCT with standard care. Three studies were used for this indirect comparison (2 studies reported in 3 publications for CRP[36-38] and 1 study reported in 2 publications for PCT[29,30] [see Cochrane review[177] for study details]. As the only common outcome from these RCTs was antibiotic treatment (at consultation), the GDG also considered observational studies comparing CRP and PCT directly in the same cohort of patients. This resulted in the inclusion of 2 additional studies reported in 3 publications[95,96,199] which assessed the diagnostic accuracy of PCT and CRP for detecting pneumonia from an undifferentiated LRTI population in the community.
- No relevant clinical studies were identified either for the comparison of CXR with usual care or to test the value of any of the prognostic markers in guiding the decision for hospital admission (all were designed to investigate antibiotic guidance even though this outcome was reported as an indication of potential harm in some studies).
- Surrogates were used to describe some of the outcomes set up in the protocol:
  - initiation of antibiotic therapy was presented as a surrogate of antibiotic treatment
  - patient-reported feelings of recovery, days of restricted activities and the opposite of treatment failure were all considered surrogates of resolution of symptoms
  - any information related to quality-of-life outcomes was recorded in GRADE tables; 1 study included the patient enablement score whereas another study did not specify the score employed.

Evidence from these studies is summarised in the clinical GRADE evidence profiles below (Table 8, Table 9, Table 10 and Table 11). See also the study selection flow chart in Appendix D: forest plots in Appendix I:, study evidence tables in Appendix G: and exclusion list in Appendix J:.

In the last update search, a Cochrane review on the role of biomarkers as point-of-care tests to guide prescription of antibiotic therapy in patients with acute respiratory infections in primary care was

identified at the pre-publication stage (Aabenhus* et al, pre-publication). The preliminary results were shared confidentially by the authors with this GDG. This Cochrane review identified randomised evidence only for the role of CRP and included 3 additional studies that were excluded from this review for the following reasons; 1 study was unpublished (Andreeva 2014),[7] 1 study was published only in Norwegian (Melbye 1995)[132] and 1 study included children (Diederichsen 2000).[63] The direction of results reported in this draft Cochrane review are similar to that of our evidence review; however, as the review was unpublished at the time of writing, the data is not included in the evidence review below.

* Data now published in full as Aabenhus R, Jensen JUS, Jørgensen KJ, Hróbjartsson A, Bjerrum L. Biomarkers as point-of-care tests to guide prescription of antibiotics in patients with acute respiratory infections in primary care. Cochrane Database of Systematic Reviews 2014; Issue 11:CD010130. DOI: 10.1002/14651858.CD010130.pub2

Table 7: Summary of studies included in the review

Study	Prognostic factor/intervention N randomised	Control/N randomised	Population and setting	Number of patients	Outcomes	Comments
Randomised data						
Cals 2010[37]	CRP point of care tests to assist prescribing in addition to clinical assessment. Prescribing recommendations: < 20 mg/l: no antibiotics > 100 mg/l: immediate antibiotics 20 to 99 mg/l: delayed prescription. N = 56	Management strategy (immediate, delayed, or no antibiotics) based on clinical assessment alone. N = 51	• LRTI or rhinosinusitis – results stratified (only LRTI results included in this analysis) • Primary care	258 (107 with LRTI)	• antibiotic treatment • mortality • hospital admission • QoL (patient enablement score as surrogate) • resolution of symptoms (feeling recovered as surrogate)	• Physicians allowed to deviate from the proposed CRP-based prescribing. • Unblinded. • Not powered to detect differences in LRTI subgroup.
Cals 2007 & 2009[36,38]	CRP point-of-care test (with or without enhanced communication skills training) to complement clinical findings and help in deciding on diagnosis and treatment. No instructions on what to prescribe. N = 227	Clinical assessment alone (with or without enhanced communication skills training). N = 204	• LRTI • Primary care	431	• antibiotic treatment • hospital admission • QoL (patient enablement score as surrogate) • mortality • re-consultation	• Cluster randomised. • No clear prescribing protocol for CRP arm. • Unblinded.
Little 2013[122]	CRP point-of-care test training (with or without enhanced communication skills training) to help in deciding on diagnosis and treatment Guidance for using CRP to guide antibiotics prescribing: < 20 mg/l: withhold antibiotics	Clinical assessment alone (with or without enhanced communication skills training) N = 2040 (1170 and 870 with and without	• LRTI (79.1%) and URTI (20.9%) • Primary care	4264	• antibiotic treatment • time to resolution of symptoms • hospital admission • mortality	• Cluster randomised. • Unblinded. • 64.2% in 'CRP' group and 4.6% in 'no CRP' group actually received the test. • Training was

Study	Prognostic factor/intervention N randomised	Control/N randomised	Population and setting	Number of patients	Outcomes	Comments
	≥ 100 mg/l: prescribe antibiotics 21 to 50 mg/l: withhold antibiotics in most cases 51 to 99 mg/l: withhold antibiotics in most cases but consider delayed prescription in some. N = 2224 (1162 and 1062 with and without communication training, respectively)	communication training, respectively)				internet-based. • Multivariate analysis adjusted for baseline antibiotic prescribing rate, clustering by physician and practice, and potential confounders related to clinical severity such as age, smoking, sex, major cardiovascular or respiratory comorbidity, baseline symptoms, blood pressure, physician's rating of severity, and duration of cough.
Schuetz 2012[175,177]	PCT-guided antibiotics Similar PCT algorithms used among included studies. Variability: • Single PCT measurement on admission to guide initiation of antibiotics or repeated measurements for guiding the duration of treatment. • Thresholds for recommending antibiotic treatment differed. N = 2085	Clinical assessment alone N = 2126	• Initial suspicion of ARI ○ 3 studies LRTI (n = 2820) ○ 3 studies CAP (n = 585) ○ 1 study VAP (n = 101) ○ 4 studies sepsis or bacterial infection (n = 497) ○ 1 study COPD (n = 208) • All settings ○ 2 in primary care (n = 1008) ○ 7 in ED/hospital (n = 2605) ○ 5 in ITU (n = 598)	14 trials, 4211 participants	• mortality • resolution of symptoms (days with restricted activities as surrogate) • antibiotic treatment	• Physicians were allowed to deviate from the proposed PCT-based prescribing. • Multivariate hierarchical model adjusted for age and diagnosis and trial as a random-effect.

Study	Prognostic factor/intervention N randomised	Control/N randomised	Population and setting	Number of patients	Outcomes	Comments
Christ-Crain 2004[50].	PCT-guided antibiotics (all treatment decisions ultimately at the discretion of the physician). N = 124 Advice for using PCT to guide antibiotics prescribing: • ≤ 0.1 µg/l: antibiotics strongly discouraged • 0.1 to 0.25 µg/l: antibiotics discouraged • 0.25 to 0.5 µg/l: antibiotics advised • ≥ 0.5 µg/l: antibiotics strongly recommended.	No PCT N = 119	• Suspected LRTI • Emergency department	243	• quality-of-life (score unknown) • hospital admission	• Unclear adherence to PCT algorithm
Briel 2008[29,30]	PCT-guided antibiotics N = 232 Algorithm used: • PCT < 0.1 µg/l: a bacterial infection was considered highly unlikely and the use of antibiotics was discouraged. • PCT > 0.25 µg/l: a bacterial infection was considered likely and the use of antibiotics was recommended. • PCT of 0.1 to 0.25 µg/l: a bacterial infection was considered unlikely and the use	No PCT N = 226	• Patients with upper or lower ARIs • Primary care (53 primary care centres in Switzerland)	458	• antibiotic treatment	• Open-label trial. • 85% adherence to PCT algorithm.

Study	Prognostic factor/intervention N randomised	Control/N randomised	Population and setting	Number of patients	Outcomes	Comments
	of antibiotics was not recommended. When antibiotics were withheld from patients, a second PCT measurement was mandatory within 6 to 24 hours for safety reasons. The use of antibiotics was recommended if this second measurement was > 0.25 µg/l or if PCT levels had increased from the first measurement by more than 50% and the patient showed no clinical improvement. All patients given antibiotics based on PCT were reassessed after 3 days. Discontinuation of antibiotic treatment was then recommended in patients with a PCT ≤ 0.25 µg/l					
Observational data – diagnostic test accuracy studies of PCT and CRP						
Holm 2007[95,96]	CRP and PCT (both measured by venous blood tests in lab not at point-of-care); also assessed symptoms and signs alone. Various thresholds assessed.	Chest X-ray	• LRTI (GP diagnosis) • Primary care	364	• AUC, PPV, NPV, sensitivity and specificity for predicting CXR pneumonia or bacterial aetiology • AUC for predicting hospitalisation	• High proportion of those registered did not attend for assessment.

Study	Prognostic factor/intervention N randomised	Control/N randomised	Population and setting	Number of patients	Outcomes	Comments
van Vugt 2013[199]	CRP and PCT (both measured by venous blood tests in lab not at point of care)	Chest X-ray	• LRTI (GP diagnosis) • Primary care	2820	• AUC for predicting CXR pneumonia • NPV and PPV for CRP only	• CXR could have been delayed 5 days or more after initial consultation.

Table 8: Clinical evidence profile: CRP compared with standard care for adults with lower respiratory tract infection in primary care

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CRP	Standard care	Relative (95% CI)	Absolute	Quality
Antibiotic treatment (initial prescription) [Cals 2007/2009, Cals 2010]											
2	randomised trials	no serious	no serious	no serious	serious[2]	none	93/283 (32.8%)	134/255 (52.5%)	RR 0.61 (0.5 to 0.75)	203 fewer per 1000 (from 130 fewer to 260 fewer)	Moderate
Antibiotic treatment (follow-up 28 days) [Cals 2007/2009, Cals 2010, Little 2013]											
3	randomised trials	no serious	serious[1]	no serious	serious[2]	none	862/2507 (34.4%)	1 133/2295 (49.4%)	RR 0.69 (0.6 to 0.8)	153 fewer per 1000 (from 99 fewer to 197 fewer)	Low
Mortality (follow-up 28 days) [Cals 2007/2009, Cals 2010, Little 2013]											
3	randomised trials	no serious	no serious	no serious	serious[3]	none	0/2507 (0%)	0/2295 (0%)	-	-	Moderate
Hospital admission [Cals 2007/2009, Cals 2010, Little 2013]											
3	randomised trials	no serious	no serious	no serious	serious[2]	none	22/2507 (0.88%)	8/2298 (0.35%)	AOR 2.91 (0.96 to 8.82)[8]	7 more per 1000 (from 0 fewer to 26 more)	Moderate
Resolution of symptoms [Little 2013]											
1	randomised trial	serious[4]	no serious	no serious	no serious	none	-	-	HR 0.93 (0.84 to 1.03)	-	Moderate
Resolution of symptoms (feeling recovered as a surrogate) (follow-up 7 days) [Cals 2010]											

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CRP	Standard care	Relative (95% CI)	Absolute	Quality
1	randomised trial	serious[4]	no serious	no serious	very serious[5]	none	12/51 (23.5%)	9/49 (18.4%)	RR 1.28 (0.59 to 2.77)	52 more per 1000 (from 75 fewer to 326 more)	Very Low
Quality-of-life (patient enablement score) (max 12 points) (Better indicated by lower values) [Cals 2007/2009, Cals 2010]											
2	randomised trials	serious[4]	serious[6]	serious[9]	no serious	none	2.73 (2.6)	2.85 (2.4)	-	MD 0.14 lower (0.76 lower to 0.47 higher)	Very low
Re-consultation (follow-up 28 days) [Cals 2007/2009]											
1	randomised trial	Serious[7]	no serious	no serious	serious[2]	none	79/227 (34.8%)	62/204 (30.4%)	RR 1.15 (0.87 to 1.51)	46 more per 1000 (from 40 fewer to 155 more)	Very Low

[1] *I^2 = 63%*
[2] *95% CI crosses one default MID*
[3] *No events recorded*
[4] *Unblinded and patient-reported subjective outcome*
[5] *95% CI crosses both default MIDs*
[6] *Two studies show opposite directions of effect (I^2 = 61%)*
[7] *Unclear allocation concealment*
[8] *OR adjusted for baseline antibiotic prescribing rate, clustering by physician and practice, and potential confounders related to clinical severity such as age, smoking, sex, major cardiovascular or respiratory comorbidity, baseline symptoms, blood pressure, physician's rating of severity, and duration of cough. Absolute effect calculated from frequencies.*
[9] *One study also included patients with rhinosinusitis in this analysis, in addition to LRTI in patients*

Table 9: Clinical evidence profile: PCT compared with standard care for adults with lower respiratory tract infection in the community

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCT	Control	Relative (95% CI)	Absolute	Quality
Antibiotic treatment (initiation of antibiotic therapy as a surrogate) (follow-up 2 weeks to 2 months) [Schuetz 2012]											
14	randomised trials; IPD meta-analysis	no serious	no serious	serious[1]	no serious	none	1341/2085 (64.3%)	1778/2126 (83.6%)	AOR 0.24 (0.2 to 0.29)[9]	286 fewer per 1000 (from 239 fewer to 331 fewer)	Moderate
Antibiotic treatment (initiation of antibiotic therapy as a surrogate) - primary care (follow-up 1 month) [Schuetz 2012]											
2	randomised trials; IPD meta-analysis	no serious	no serious	serious[2]	no serious	none	116/507 (22.9%)	316/501 (63.1%)	AOR 0.1 (0.07 to 0.14)[9]	485 fewer per 1000 (from 438 fewer to 524 fewer)	Moderate
Antibiotic treatment (initiation of antibiotic therapy as a surrogate) - ED (follow-up 2 to 6 weeks) [Schuetz 2012]											
7	randomised trials; IPD meta-analysis	no serious	no serious	serious[3]	no serious	none	939/1291 (72.7%)	1151/1314 (87.6%)	AOR 0.34 (0.28 to 0.41)[9]	170 fewer per 1000 (from 133 fewer to 212 fewer)	Moderate
Mortality (follow-up 2 weeks to 2 months) [Schuetz 2012]											
14	randomised trials; IPD meta-analysis	no serious	no serious	serious[1]	serious[4]	none	118/2085 (5.7%)	134/2126 (6.3%)	AOR 0.94 (0.71 to 1.24)[10]	4 fewer per 1000 (from 17 fewer to 14 more)	Low
Mortality - Primary care (follow-up 1 month) [Schuetz 2012]											
2	randomised trials; IPD meta-analysis	no serious	no serious inconsistency	serious[2]	very serious[5]	none	0/507 (0%)	1/501 (0.2%)	OR 0.33 (0.01 to 8.09)	1 fewer per 1000 (from 2 fewer to 14 more)	Very low
Mortality - ED (follow-up 2 to 6 weeks) [Schuetz 2012]											
7	randomised	no	no	serious[3]	very	none	61/1291	59/1314	AOR 1.03	1 more per 1000	Very

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCT	Control	Relative (95% CI)	Absolute	Quality
	trials; IPD meta-analysis	serious	serious		serious[5]		(4.7%)	(4.5%)	(0.7 to 1.52)[11]	(from 13 fewer to 22 more)	low
Hospital admission - ED (follow-up 10 to 14 days) [Christ-Crain 2004]											
1	randomised trial	no serious	no serious	no serious	serious[4]	none	101/124 (81.5%)	88/119 (73.9%)	RR 1.1 (0.96 to 1.26)	74 more per 1000 (from 30 fewer to 192 more)	Moderate
Resolution of symptoms (days with restricted activities)(follow-up 14 days) - Primary care (follow-up 1 month; Better indicated by lower values) [Schuetz 2012]											
2	randomised trials; IPD meta-analysis	serious[6]	no serious	serious[2]	no serious	none	9 (6 to 14)	9 (5 to 14)	-	Median 0.05 higher (0.46 lower to 0.56 higher)	Low
Non-resolution of symptoms - Treatment failure (follow-up 2 weeks to 2 months) [Schuetz 2012]											
14	randomised trials; IPD meta-analysis	no serious	no serious	serious[1]	serious[4]	none	398/2085 (19.1%)	466/2126 (21.9%)	AOR 0.82 (0.69 to 0.97)[11]	32 fewer per 1000 (from 5 fewer to 57 fewer)	Low
Resolution of symptoms - Treatment failure as surrogate - Primary care (follow-up 1 month) [Schuetz 2012]											
2	randomised trials; IPD meta-analysis	no serious	no serious	serious[2, 8]	serious[4]	none	159/507 (31.4%)	164/501 (32.7%)	AOR 0.95 (0.73 to 1.24)[11]	11 fewer per 1000 (from 65 fewer to 49 more)	Low
Resolution of symptoms - Treatment failure as surrogate- ED (follow-up 2 to 6 weeks) [Schuetz 2012]											
7	randomised trials; IPD meta-analysis	no serious	no serious	serious[3, 8]	serious[4]	none	182/1291 (14.1%)	228/1314 (17.4%)	AOR 0.76 (0.61 to 0.95)[11]	36 fewer per 1000 (from 7 fewer to 60 fewer)	Low
Quality-of-life - Final score - ED (follow-up 10 to 14 days; Better indicated by lower values) [Christ-Crain 2004]											
1	randomised	serious[7]	no	no	no	none	21.9	22.9	-	MD 1 lower (4.75	Modera

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCT	Control	Relative (95% CI)	Absolute	Quality
	trial		serious	serious	serious		(14.7)	(15.1)		lower to 2.75 higher)	te
Re-consultation											
0	no evidence available										

[1] *Includes data from different settings (Primary care, ED and ITU) and different diagnoses (unspecified LRTI, URTI, confirmed CAP and other diagnoses) - however, this is accounted for in the analysis. Includes different PCT algorithms (variability in thresholds and frequency of testing)*
[2] *Included all ARIs (not just LRTI) and PCT not conducted as a point of care test*
[3] *Includes different PCT algorithms (variability in thresholds and frequency of testing)*
[4] *95% CI crosses 1 default MID*
[5] *95% CI crosses both default MIDs*
[6] *Unclear blinding (risk of performance bias)*
[7] *Quality-of-life scale not defined*
[8] *Treatment failure is a surrogate of resolution of symptoms*
[9] *Multivariate hierarchical model was adjusted for age and diagnosis and trial as a random-effect. Absolute effect calculated from frequencies*
[10] *Analyses with individual patient data from all trials and added interaction terms (e.g. low adherence x procalcitonin group) in the regression model to test for effect modification. Absolute effect calculated from frequencies*
[11] *Multivariate hierarchical regression with outcome of interest as dependent variable, procalcitonin group; age and ARI diagnosis as independent variables; and trial as a random-effects. Absolute effect calculated from frequencies*

Table 10: Clinical evidence profile: Indirect comparison of CRP and PCT for adults with lower respiratory tract infection in the community

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CRP	PCT	Relative (95% CI)	Absolute	Quality
Antibiotic treatment (at index consultation) [Cals 2007/2009, Cals 2010, Briel 2008]											
3	randomised trials	no serious risk of bias	no serious	serious[1]	no serious	none	91/283 (32.2%)	43/114 (37.7%)	RR 1.61 (1.45 to 1.78)	230 more per 1000 (from 170 more to 294 more)	Moderate
Mortality											
0	no evidence available										
Hospital admission											
0	no evidence available										
Resolution of symptoms											
0	no evidence available										
Quality-of-life											
0	no evidence available										
Re-consultation											
0	no										

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CRP	PCT	Relative (95% CI)	Absolute	Quality
	evidence available										

[1] *Based on a calculated indirect comparison using data from trials of PCT and CRP compared with usual care*

Table 11: Observational studies comparing the diagnostic accuracy of PCT with CRP for adults with lower respiratory tract infection in the community

Test	No of studies	n	Risk of bias	Inconsistency	Indirectness	Imprecision	Area Under Curve (95% CI)	Quality
Radiographic pneumonia [Holm 2007, Van Vugt 2013]								
C-reactive protein	2	3184	serious[1]	no serious	serious[2]	N/A	0.78 (0.74 to 0.82) 0.79*	Low
Procalcitonin	2	3184	serious[1]	no serious	serious[2]	N/A	0.71 (0.67 to 0.76) 0.73*	Low
Symptoms and signs alone	1	2820	serious[3]	no serious	no serious indirectness	N/A	0.70 (0.65 to 0.75)	Moderate
Bacterial aetiology [Holm 2007]								
C-reactive protein	1	364	serious[4]	no serious	serious[2]	N/A	0.63*	Low
Procalcitonin	1	364	serious[4]	no serious	serious[2]	N/A	0.61*	Low
Hospitalisation [Holm 2007]								
C-reactive protein	1	364	serious[4]	no serious	serious[2]	N/A	0.75*	Low
Procalcitonin	1	364	serious[4]	no serious	serious[2]	N/A	0.76*	Low

[1] *One study had 15% with data missing for either reference standard or index test and in 1 study only 53% of those recruited attended for assessment*
[2] *Point-of care test not used*
[3] *10% with data missing for reference standard*
[4] *Only 53% of those recruited attended for assessment*

*No data were given by the authors on the values of 95% confidence interval.

7.3 Economic evidence

Published literature

Two economic evaluations relating to this review question were identified.[35,154] One economic evaluation[154] was a cost–utility analysis which compared CRP with clinical judgement. In this analysis CRP was cost effective compared with clinical judgement with an ICER of £7,364 per QALY gained. However, in this analysis hospital admissions in the CRP group were fewer than in the control group, while our clinical review showed the opposite direction of effect. Given this inconsistency and the setting where this study was conducted (Sweden and Norway), we performed our own cost analysis to include an increase in hospital admissions as was suggested by the clinical review, and combine it with the increase in QALYs estimate (0.0012) provided by the study by Oppong. The new NCGC analysis is summarised in the economic evidence profile below and described in the tables below.

Both economic evaluations identified were excluded due to a combination of limited applicability and methodological limitations or the availability of more applicable evidence.[35,154] These are reported in Appendix K:, with reasons for exclusion given.

See also the economic article selection flow diagram in **Appendix E:**.

In our analysis, to estimate the difference in cost between CRP and clinical judgement alone (usual care), we considered the resources reported in the clinical studies included in our clinical review. The cost calculations are described in detail in the table below.

Table 12: Resource use and cost of interventions

	Number of patients using the resource[a] (n)	Total number of patients[a] (N)	Unit cost of resource[c]	Total cost for the cohort (C) = n *[d]	Cost per patients = C/N
Antibiotic use					
CRP	91	283	£1.30[b]	£118	£0.42
Usual care	134	255		£174	£0.68
Hospital admission					
CRP	22	2507	£715[c]	£15,726	£6.27
Usual care	8	2298		£5,718	£2.49
Re-consultation					
CRP	79	227	£43[d]	£3,397	£14.96
Usual care	62	204		£2,666	£13.07
Cost of test including equipment					
CRP			£13.50[e]		£13.50
Usual care			£0		£0
Total cost					
CRP					£35.16
Usual care					£16.24

(a) Based on the clinical review (see Table 8)
(b) Cost of amoxicillin (500mg, 15 tab) – from MIMS[1]
(c) Pooled average of DZ22C HRG code 'Unspecified Acute Lower Respiratory Infection without complications' from NHS Reference Costs[60]
(d) PSSRU 2012 GP Consultation - 11.7 minutes[57]
(e) Personal communication and GDG expert opinion. The range was £12 to £15 for each test and we used the mean value in this analysis.

Using the cost of the 2 strategies as obtained above, we combined these data with the incremental QALYs provided in the study by Oppong. The ICER calculation is described in the table below.

Table 13: Incremental cost-effectiveness analysis of CRP compared with usual care

Strategy	Cost per patient	Incremental cost	Incremental QALY	ICER
Usual Care	£16.24	-		
CRP	£35.16	£18.92	0.0012	£15,763

Table 14: Economic evidence profile point-of-care CRP compared with clinical assessment alone

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty
NCGC Analysis	Directly applicable[a]	Minor limitations	The incremental cost was calculated using the resource use based on the studies included in the clinical review (see 7.2), and UK costs were attached. Incremental QALYs were taken from Oppong et al[154].	£18.92[b]	0.0012 QALYs[c]	£15,763 per QALY gained	Providing point-of-care CRP tests cost less than £15.13, they are cost-effective at a 20K per QALY threshold.

(a) Analysis performed from a UK NHS and PSS perspective
(b) Cost components included CRP tests (including staff time and equipment costs) GP consultation, antibiotics, hospital admission and consultation. 2012 UK pounds
(c) QALYs constructed using weekly EQ-5D questionnaires until the end of 28 days estimated through a regression analysis in Oppong et al[154]

Unit costs

No economic evaluations were identified for either PCT or CXR. Relevant unit costs are provided below to aid consideration of cost effectiveness. The figures provided below include the cost of the staff time to perform the test together with the cost of the equipment.

Table 15: Cost of diagnostic tests

Test	Cost	Source
Point-of-care PCT	£25 to £35	GDG estimate
Point-of-care CRP	£12 to £15	GDG estimate
X-ray	£25	NHS Tariff 2013 to 2014[62]

7.4 Evidence statements

7.4.1 Clinical

7.4.1.1 Comparison of CRP with usual care

- Moderate quality evidence from an analysis of over 500 patients participating in 2 RCTs indicated that using CRP to assist antibiotic prescribing decisions at index consultation for people presenting in primary care with LRTI can reduce antibiotic treatment.
- Low quality evidence from an analysis of over 4500 patients participating in 3 RCTs indicated that antibiotic prescribing at 28 days of follow-up in the group using CRP may be substantially reduced compared with those receiving usual care.
- No significant differences were found between the CRP and usual care groups for the outcomes of mortality, re-consultation, symptom resolution and quality-of-life.
- Moderate quality of evidence from 3 trials showed that no difference was found in hospital admission between patients who received CRP and those who received usual care.

7.4.1.2 Comparison of PCT with usual care

- Moderate quality data from a systematic review of more than 4000 patients showed that using PCT to assist antibiotic prescribing (and subsequent management) decisions for people presenting with ARI in any setting may reduce initiation of antibiotic therapy. Moderate to very low quality evidence from this systematic review showed no clinically important difference in mortality, resolution of symptoms or quality-of-life outcomes between the PCT and usual care groups. Subgroup analysis on the type of setting (primary care or emergency department) showed the same direction of results as the whole population.
- Moderate quality evidence from 1 randomised study of over 200 patients in an emergency department setting suggested that the rate of hospital admission was higher in the PCT group compared with the usual care group.

7.4.1.3 CRP compared with PCT

- Results of an indirect comparison based on 3 randomised studies suggested that antibiotic prescriptions may be reduced more by using PCT than using CRP.
- Low quality evidence from the 2 diagnostic accuracy studies comparing the ability of CRP and PCT to predict pneumonia or hospitalisation suggested that CRP may be more accurate for predicting cases with CXR-confirmed pneumonia than PCT. No difference was found between CRP and PCT for diagnosing the bacterial cause of pneumonia or predicting hospitalisation.

7.4.2 Economic

- One cost–utility analysis found that point-of-care CRP testing was cost effective compared with clinical assessment alone (ICER: £15,763 per QALY gained). This analysis was assessed as directly applicable with minor limitations.
- No relevant economic evaluations were identified that compared PCT or CXR with clinical judgement.

7.5 Recommendations and link to evidence

Table 16: Linking evidence to recommendations – CRP and PCT for guiding antibiotic prescribing decisions

Recommendations	**1. For people presenting with symptoms of lower respiratory tract infection in primary care, consider a point of care C-reactive protein test if after clinical assessment a diagnosis of pneumonia has not been made and it is not clear whether antibiotics should be prescribed. Use the results of the C-reactive protein test to guide antibiotic prescribing in people without a clinical diagnosis of pneumonia as follows:** **• Do not routinely offer antibiotic therapy if the C-reactive protein concentration is less than 20 mg/litre.** **• Consider a delayed antibiotic prescription (a prescription for use at a later date if symptoms worsen) if the C-reactive protein concentration is between 20 mg/litre and 100 mg/litre.** **• Offer antibiotic therapy if the C-reactive protein concentration is greater than 100 mg/litre.**
Relative values of different outcomes	The GDG considered antibiotic prescription rates, mortality, hospital admission rates and quality-of-life the most important outcomes for this question. Antibiotic prescription rates were felt to be the most directly relevant outcome, with other outcomes likely to represent downstream effects from this.
Trade-off between clinical benefits and harms	Three RCTs examining the addition of CRP testing to usual care to guide antibiotic prescription in patients presenting to primary care with LRTI were considered. These showed a significant reduction in antibiotic prescription rates in the CRP group compared with usual care both at the index consultation and within 28 days. There was a trend towards more hospital admissions in the CRP compared with the usual care group although the difference in terms of absolute effect was small. In addition, the reasons for admission were not stated in every case, and the GDG could not be sure that all admissions were appropriate. There was also a trend towards higher re-consultation rates in the CRP group compared with usual care. In contrast, there was no clinically important difference in resolution of symptoms, feeling recovered at 7 days, or mean patient enablement score. No deaths were reported in either group. One systematic review examining the addition of PCT testing to usual care to guide antibiotic prescription was considered. This included a wider spectrum of conditions (upper and lower respiratory tract infections, with some studies excluding patients with suspected pneumonia) and settings (not exclusively primary care) than the CRP studies. There was a significant reduction in antibiotic prescription rates across all settings. Mortality rates were low with only small absolute differences between the PCT and usual care groups. Hospital admission was only reported in the Emergency Department setting, where there was a suggestion that admission rates may be higher in the PCT group. There was no important difference in median days with restricted activities or final quality-of-life scores. There were fewer cases of treatment failure in the PCT group overall, though this effect was small in the

	subgroup of patients presenting to primary care. No RCTs directly comparing CRP to PCT to guide antibiotic prescription were available. An indirect comparison of 2 studies using CRP and 1 using PCT suggested a greater reduction in antibiotic use at index consultation for PCT. However, the extremely high rate of antibiotic prescription in the control group for the PCT study compared with the CRP studies meant that the GDG could not generalise from these results. The area under receiver-operated curves (AUROC) was reported for CRP, PCT and clinical judgement alone for predicting consolidation on CXR for patients with LRTI presenting to primary care. In 1 study the AUROC was 0.70 for clinical judgement alone, 0.71 when PCT was added, and 0.78 when CRP was added to clinical judgement, suggesting that CRP had a stronger correlation with consolidation on CXR than PCT or clinical judgement alone. When determining the 3 CRP concentration cut-points, the GDG balanced the benefits of antibiotic therapy in the minority of patients with pneumonia against the harms of unnecessary antibiotic prescription for those who do not have pneumonia. The GDG considered a 'no antibiotic' strategy appropriate for those with a CRP concentration of less than 20 mg/l since this was the numerically largest group and the frequency of CXR-confirmed pneumonia was lowest in this group. The GDG considered the 'offer an antibiotic' strategy to be appropriate for those with a CRP concentration higher than 100 mg/l because of the small patient numbers and the high frequency of CXR-confirmed pneumonia in this group. The GDG noted that there appears to be a gradation of pneumonia risk in the intermediate-risk group with a CRP concentration between 20 and 100 mg/l. The majority of patients in this group had CRP concentrations lower than 50 mg/l with a low risk of CXR-confirmed pneumonia and the GDG agreed that in this situation a 'delayed antibiotic' prescription strategy was appropriate. The group whose CRP concentrations were between 50 and 100 mg/l were smaller in number but with a slightly higher risk of having CXR-confirmed pneumonia so the GDG agreed that it would be reasonable for a GP to have a lower threshold for prescribing antibiotic therapy in this group or arranging for a clinical review (despite classifying them in the intermediate group where a delayed antibiotic prescription would be the usual action). However, the GDG was also concerned that a recommendation featuring 4 groups and 4 different courses of action was too complicated and more likely to fail to be implemented than a strategy with fewer options. No suitable studies examining the additional benefit of performing a CXR to guide antibiotic prescription or admission in patients with LRTI presenting to primary care were identified, and no studies examining the benefit of CRP or PCT testing to guide hospital admission in such patients were available.
Trade-off between net health benefits and resource use	One cost-utility analysis found that point-of-care CRP is cost effective compared with clinical judgement alone with an ICER of £7,364 per QALY gained.[154] However this study was partially applicable as it was conducted in Norway and Sweden; furthermore in this analysis hospital admissions in the CRP group were fewer than in the control group, while our clinical review showed the opposite direction of effect. For this reason we calculated the incremental cost of CRP compared with clinical judgement based on the resource use identified in our clinical review, and we combined the incremental cost calculated by the NCGC with the incremental QALY estimated in the study by Oppong et al[154] to obtain an ICER. This ICER was £15,763 per QALY, still below the £20,000 per QALY threshold for cost effectiveness. The GDG concluded that CRP was likely to be cost effective. No economic studies were found on PCT and CXR and an original analysis was

	deemed unnecessary as some conclusions on the cost effectiveness of PCT could be drawn on the basis of the clinical evidence and unit costs alone. Studies included in our clinical review showed that CRP has a higher area under the ROC curve than PCT suggesting CRP detects pneumonia more accurately. An indirect comparison showed a larger reduction in antibiotic prescribing from PCT. However, the GDG were distrusting of this figure due to the extremely high rates of antibiotic prescribing in that study compared with usual UK practice – therefore the absolute reduction could be lower in UK practice. It is also unknown whether antibiotics were appropriately or inappropriately not prescribed. In addition, hospital admission increased with both CRP and PCT (neither of these was statistically significant). It is unknown if these were appropriate admissions to hospital and the emergency department data for PCT is indirect. Furthermore, CRP is considerably cheaper than PCT (£12 to £15 compared with £25 to £35) when considering the cost of tests alone. Given all these cost components, CRP was considered to be cheaper than PCT and more clinically useful. The GDG expressed concerns around CXR due to practical constraints as there is the need to send patients to A & E to get an X-ray. There is uncertainty over firstly, how many patients attend for an X-ray and secondly, when the X-ray would get reviewed. This can encourage the prescription of antibiotics that are not needed as this is cheaper and gets to those that need it without waiting.
Quality of evidence	The evidence on CRP testing was of variable quality, ranging from high to very low quality by GRADE criteria. For antibiotic prescription rate at index consultation, which the GDG considered one of the most important outcomes, evidence was of high quality. The systematic review examining PCT testing used individual patient data, though the data output varied from moderate to very low quality by GRADE criteria. This was partly due to the evidence being indirect; however, as few studies with direct evidence were available and sensitivity analyses around setting and diagnosis were performed, it was agreed that the indirect evidence could still be informative. The evidence regarding diagnostic test accuracy was of moderate to low quality by GRADE criteria. This was examined as supplementary information to help discriminate the relative value of PCT and CRP as both seemed potentially worthwhile based on the separate RCT data. One economic evaluation was considered to have minor limitations; even though it used observational data it was felt the result would not change. The other had potentially serious limitations due to explicit exclusion of QALYs and the potential over-estimation of the ICER through the outcome considered.
Other considerations	The GDG felt that PCT testing appeared to offer little additional benefit over clinical assessment alone in the identification of the subgroup of patients with LRTI in the community who have pneumonia. This suggests that PCT testing is unlikely to result in a higher number of appropriate antibiotic prescriptions in patients with pneumonia. However, there did appear to be a significant reduction in antibiotic prescription rates overall with PCT testing, suggesting that the benefit of PCT testing lies in fostering an appropriate restriction of antibiotics in patients with respiratory tract infections without pneumonia. This is likely to be due to the doctor and patient having increased confidence in the management strategy. CRP testing also appeared to afford a benefit in terms of appropriate control of antibiotic prescriptions. However, the GDG considered that CRP testing had several advantages over PCT testing: it shows better correlation with consolidation on chest

x-ray, which may lead to an increase in appropriate antibiotic prescriptions in patients with pneumonia; the current cost is lower; and healthcare professionals in the UK are familiar with CRP due to its widespread use as a laboratory test, which could result in less training being needed for its implementation as a point-of-care test. The trend towards a possible increase in hospital admissions was noted by the GDG, the studies did not clearly suggest whether these admissions were appropriate or not and should be an area for future monitoring or research.

Whilst the evidence supported the use of point-of-care testing in this setting, the GDG acknowledged that point-of-care testing for CRP or PCT is not widely used in the UK at present, and that the introduction of their use would represent a significant change in practice. As such, there would be significant costs associated with training, implementation and subsequent quality assurance of equipment. Whilst the studies examining point-of-care testing included large numbers of patients, the "real-life" experience of these tests outside the trial setting is limited, and it is unclear whether the benefits would translate as well across all practices and individual prescribers. In particular, the rate of antibiotic prescribing varies widely between different practitioners, hence the reduction in overall antibiotic use (the main benefit of point-of-care testing) would also vary accordingly. The other area of uncertainty relates to the apparent increase in hospital admissions and re-consultation rates associated with point-of-care testing. The studies were not able to demonstrate whether this increase in healthcare utilisation was appropriate (with sick patients flagged up correctly, reducing overall harm) or inappropriate (with increased anxiety and healthcare utilisation in patients who would have had a good outcome without point-of-care testing). With large-scale implementation of point-of-care testing, these differences could have significant financial implications which could potentially outweigh the benefits of reduced antibiotic prescribing. As such, the GDG felt that the recommendation should be to "consider" the use of these tests, rather than a stronger recommendation to "offer" them.

The GDG discussed whether patient groups in whom CRP does not rise substantially with serious infections (such as elderly patients or those with cirrhotic liver disease) could be at risk of not receiving appropriate antibiotic therapy following point-of-care CRP testing. It was agreed that the threshold for prescribing antibiotic therapy following clinical assessment alone would be lower for these patients, and if antibiotic therapy is thought to be indicated following clinical assessment alone, with comorbidity and other factors taken into consideration, then CRP testing would not be necessary anyway. It was concluded that this risk was low, and that a specific recommendation for these groups was not required.

The GDG considered whether a laboratory CRP test with rapid turnaround could be an alternative management strategy in primary care rather than point-of-care testing. One of the advantages of point-of-care testing is the immediate availability of the result, allowing the result and its implications to be discussed during the consultation. It was noted that this interaction with the patient is likely to play a major part in the appropriate reduction of antibiotic prescription rates, whereas laboratory testing would usually give a result within hours, with implications being relayed to the patient by telephone or a second face-to-face consultation. It is not clear whether the laboratory-based strategy would result in as large a reduction in antibiotic prescription rates. The GDG agreed that this strategy may be suitable in some circumstances, but concluded that they could not make a specific recommendation for it.

Several studies considered as part of this question also showed a significant reduction in antibiotic prescription rates with additional communication skills training over usual care. In some cases, this reduction was of a similar magnitude to that seen with point-of-care testing. The GDG did not feel that it could make a

	recommendation specifically for additional communication skills training for several reasons. Firstly, this was not a topic specifically addressed by the guideline, so the GDG could not be sure that all the relevant evidence regarding this subject had been collated. Secondly, it was unknown whether communication skills training would have a sustained effect, with re-training becoming necessary after a period of time, whereas point-of-care testing is a relatively fixed intervention whose effects should not diminish with time. Finally, no cost-effectiveness analysis on additional communication skills training was available. Nevertheless, the GDG wished to emphasise the importance of communication skills, and that the doctor-patient interaction is likely to have a large effect on appropriate antibiotic use in this setting. The GDG wished to emphasise that the CRP test should be considered only when there is doubt about the need for antibiotics after a clinical assessment (i.e. NOT those patients with a clear clinical diagnosis of pneumonia, and who should receive a single antibiotic as soon as possible, and NOT those with a clinical diagnosis of a self-limiting illness, who would not need antibiotic therapy). **Key priority for implementation** The GDG agreed that point-of-care CRP testing in primary care would require a significant focus on key infrastructural and clinical requirements for high-quality care.

8 Severity assessment tools

Since prevention of the patient's death is the ultimate goal of care, tools have been devised to predict risk of death. Levels of risk can then be interpreted to determine the level of care required. In patients with community-acquired pneumonia (CAP) or hospital-acquired pneumonia (HAP), the clinical spectrum of illness severity is wide. At one extreme, patients may have mild illness that can be managed at home with appropriate antibiotic therapy. At the other extreme, patients with severe illness may be helped by hospital admission and even intensive care unit (ITU) support including a variety of different medical interventions.

When patients first present for medical attention in the community, to Accident & Emergency, or in hospital, an important aspect of management is to determine who will and will not need these different aspects of care. Historically this has been done using clinical acumen, but efforts to improve the accuracy of severity assessment have led to the development of a variety of objective severity assessment tools or scores. The purpose of this section is to identify whether there is evidence to recommend that particular severity assessment tools may aid clinicians in determining which patients will benefit from hospital admission or ITU support.

The following table summarises the criteria of the most common severity assessment tools selected for this purpose.

Table 17: Description of the severity assessment tools included in the review

Severity assessment tools	Developed to predict what?	Number of criteria	Types of criteria (scoring points)	Scoring system
PSI	Mortality	20	**Demographics** 1. Age 2. Sex 3. Nursing home resident **Co-morbidities** 4. Neoplastic disease 5. Liver disease 6. Congestive heart failure 7. Cerebrovascular disease 8. Renal disease **Examination findings** 9. Altered mental status 10. Respiratory rate ≥ 30 per minute 11. Systolic blood pressure < 90 mmHg 12. Temperature < 35°C or ≥ 40°C 13. Pulse ≥ 125 beats per minute **Laboratory findings** 14. pH < 7.35 (do ABG only if hypoxic) 15. Blood urea level ≥ 10.7 mmol/L 16. Sodium < 130 mEq/L 17. Glucose ≥ 13.9 mmol/L 18. Haematocrit < 0.30 19. PaO_2 < 60 mmHg or oxygen saturation < 90% 20. Pleural effusion	• I to V (low risk ≤ 2, intermediate risk = 3, high risk ≥ IV)
CURB65	Mortality	5	1) confusion (Abbreviated Mental test score	• 0 to 5 (low

Severity assessment tools	Developed to predict what?	Number of criteria	Types of criteria (scoring points)	Scoring system
			≤ 8 or new disorientation in person, place, or time) 2) raised blood urea nitrogen (> 7 mmol/L) 3) raised respiratory rate (≥ 30/min) 4) low blood pressure (diastolic ≤ 60 mmHg or systolic < 90 mmHg) 5) age ≥ 65 years	risk ≤ 1, intermediate = 2, high ≥ 3)
CRB65	Mortality	4	1) confusion 2) raised respiratory rate (≥ 30 per min) 3) low blood pressure (diastolic ≤ 60 mmHg or systolic < 90 mmHg) 4) age ≥ 65 years	• 0 to 4 (low risk = 0, intermediate = 1 or 2, high ≥ 3)
CURB	Mortality	4	1) confusion 2) raised blood urea nitrogen (> 7mmol/L) 3) raised respiratory rate (≥ 30 per min) 4) low blood pressure (diastolic ≤ 60 mmHg or systolic < 90 mmHg)	• 0 to 4 (low risk ≤ 1, intermediate = 2, high ≥ 3)
IDSA/ATS	ITU admission	2 major 9 minor	Major criteria: invasive ventilation, septic shock Minor criteria: 1) raised respiratory rate (≥ 30 per min) 2) PaO_2/FiO_2 ratio ≤ 250 3) multilobar radiographic shadowing 4) confusion or disorientation 5) uraemia (BUN ≥ 20 mg/dL) 6) leukopenia (< 4000 WBCs/mm^3) 7) thrombocytopenia (< 100,000 platelets/mm^3) 8) Hypothermia (temperature < 36°C) 9) Hypotension requiring resuscitation	• 0 to 9 (low risk ≤ 2 minor criteria, high risk: 1 major or ≥ 3 minor)
ATS 2001	ITU admission	2 major 3 minor	Major criteria: invasive ventilation, septic shock Minor criteria: 1) low systolic blood pressure ≤ 90 mmHg 2) multilobar disease 3) PaO_2/FiO_2 ratio ≤ 250	• 0 to 3 (low risk < 2 minor criteria, high risk: 1 major or ≥ 2 minor)
SMART-COP	Need for intensive respiratory and/or vasopressor support	8	1. low systolic blood pressure < 90 mmHg 2. multilobar CXR involvement 3. albumin level < 35 g/l 4. raised respiratory rate (≥ 30 per min) 5. tachycardia ≥ 125 beats per min 6. confusion (new onset) 7. low oxygen 8. pH < 7.35	• 0 to 8 (low risk ≤ 2, intermediate risk 3 to 4, high risk 5 to 6, very high risk ≥ 7)

[1] *Low blood pressure and raised respiratory rate were the criteria common across all severity assessment tools.*

8.1 Review question: In adults presenting with a lower respiratory tract infection or suspected community-acquired pneumonia in the community, what is the most accurate and cost-effective severity assessment tool to identify patients whose outcome will be improved by referral to hospital?

For full details see review protocol in Appendix C:.

For details of the question pertaining to hospital-acquired pneumonia, please see section 8.11.

8.2 Clinical evidence

We searched for systematic reviews, randomised (RCTs) and non-randomised comparative (non-RCT) studies or external validation studies to compare severity assessment tools for patients with lower respiratory tract infection (LRTI) or suspected pneumonia. Two studies were included in this review.[22,80]

The study by Francis et al.[80] was a prospective observational study in 14 primary care networks across 13 European countries where clinicians recorded symptoms on presentation and management. They assessed the role of CRB65 to predict mortality and hospitalisation in patients who presented with acute or worsened cough as the main or dominant symptom or clinical presentation that suggested a LRTI. However, only 12.6% of patients from the cohort had complete data for CRB65, which might have introduced a high risk of bias. Duration of illness was less than 28 days, and the median duration of symptoms was 5 days. The average age of the sample was 49.3 years, and 71.4% of the patients received antibiotic therapy. For these reasons, quality of evidence from this study was assessed as low. None of the patients in this study died so results were presented only for the outcome of hospitalisation from a multivariate analysis adjusted for antibiotic prescription (Table 18).

Table 18: Results from the multivariate analysis for hospitalisation of patients with lower respiratory tract infection (N = 339)

	AOR (95% CI)
CRB65 ≥ 1	3.12 (0.16 to 60.24)
Antibiotic prescription (confounder)	2.26 (0.21 to 24.54)
Interaction	0.64 (0.02 to 18.41)

See also the study selection flow chart in Appendix D:, forest plots in Appendix I:, study evidence tables in Appendix G: and exclusion list in Appendix J:.

The study by Bont[22] was a prospective validation study in elderly patients (≥ 65 years) with chest X-ray-confirmed or suspected CAP presenting to primary care in The Netherlands. CRB65 was assessed for its ability to predict mortality in this population, compared with the original derivation cohort of patients hospitalised with CAP. The comparison of the test characteristics of CRB65 in primary care patients with hospital patients needs to be interpreted with caution, as mortality rates are lower in primary care. Furthermore, the patient cohort in the Bont study was aged 65 years and older whereas in the Lim cohort all ages were included, therefore the applicability of the study is limited (low quality evidence).

Results are presented in Table 19 and Table 20.

Table 19: Prevalence of 30-day mortality by CRB65 scoring in the derivation and external validation studies

CRB65 score	30-day mortality % - derivation cohort (hospital patients, n = 932)	30-day mortality % - validation cohort (elderly primary care patients, n = 314)
0	2/212 (0.9)	0
1	18/344 (5.2)	2/230 (0.9)
2	30/251 (11.8)	5/61 (8.2)
3	36/111 (32.4)	4/23 (28.4)
4	3/14 (21.4)	0

None of the patients in the primary care cohort had CRB65 scores of 0 or 4, and mortality was low across all severity levels compared with hospitalised patients in the derivation cohort.

Table 20: Comparison of the test characteristics of CRB65 ≥ 2 to predict 30-day mortality between the derivation and validation studies

Test characteristics	Derivation cohort (hospital patients, n = 718)*	Validation cohort (elderly primary care patients, n = 314)
Sensitivity (%)	76.8	82.2
Specificity (%)	64.3	75.2
PPV (%)	18.6	10.7
NPV (%)	96.3	99.1

**The study has not reported the reason why the number of patients in the derivation cohort (n = 718) in this analysis is lower than the number of patients (n = 932) given in Table 19 for 30-day mortality.*

A CRB65 cut-off score of 2 or higher showed slightly higher accuracy at predicting mortality in the validation study compared with the derivation cohort.

8.3 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow diagram in Appendix E:.

Economic considerations

Severity assessment tools may be used by clinicians to guide hospital admission or ITU assessment according to the severity of illness. If accurate they will also be cost effective as they will ensure the most appropriate care is provided to patients and the resources are therefore used appropriately. However, if patients are admitted to hospital or ITU unnecessarily due to the inaccuracy of a severity assessment tool, there are potentially important cost implications. The cost of hospital admission and ITU admission are represented in the tables below to aid consideration of cost effectiveness.

Table 21: Cost of hospital admission for pneumonia

Currency code	Currency description	Average unit cost	Lower quartile unit cost	Upper quartile unit cost	Av. LOS (days)
Non-elective long stay (including excess bed days)					
DZ11A	Lobar, Atypical or Viral Pneumonia, with Major CC	£2,784	£2,198	£3,154	9.05
DZ11B	Lobar, Atypical or Viral Pneumonia, with Intermediate CC	£2,079	£1,667	£2,329	6.57
DZ11C	Lobar, Atypical or Viral Pneumonia, without CC	£1,360	£1,095	£1,531	3.91
Non-elective short stay					
DZ11A	Lobar, Atypical or Viral Pneumonia, with Major CC	£494	£332	£540	-
DZ11B	Lobar, Atypical or Viral Pneumonia, with Intermediate CC	£452	£327	£484	-
DZ11C	Lobar, Atypical or Viral Pneumonia, without CC	£427	£305	£474	-

(a) NHS Reference Costs 2011-2012[61]

Table 22: Cost of hospital admission for lower respiratory tract infection

Currency code	Currency description	FCEs	Average unit cost	Lower quartile unit cost	Upper quartile unit cost	Av. LOS (days)
Non-elective long stay (including excess bed days)						
DZ22A	Unspecified Acute Lower Respiratory Infection with Major CC	28,987	£2,462	£1,978	£2,780	8.12
DZ22B	Unspecified Acute Lower Respiratory Infection with Intermediate CC	21,248	£1,881	£1,499	£2,105	5.86
DZ22C	Unspecified Acute Lower Respiratory Infection without CC	2,826	£1,367	£1,068	£1,547	3.96
Non-elective short stay						
DZ22A	Unspecified Acute Lower Respiratory Infection with Major CC	17,845	£464	£325	£514	-
DZ22B	Unspecified Acute Lower Respiratory Infection with Intermediate CC	21,382	£429	£314	£471	-
DZ22C	Unspecified Acute Lower Respiratory Infection without CC	8,523	£412	£288	£448	-

(a) NHS Reference Costs 2011-2012.[61]

Table 23: Cost of ITU

Currency code	Currency description	Bed days	National average unit cost	Lower quartile unit cost	Upper quartile unit cost	Critical care periods
XC01Z	Adult Critical Care, 6 or more Organs Supported	7,811	£1,796	£1,351	£2,201	2,479
XC02Z	Adult Critical Care, 5 Organs Supported	39,122	£1,745	£1,436	£1,939	6,265
XC03Z	Adult Critical Care, 4 Organs Supported	159,159	£1,586	£1,366	£1,781	26,448
XC04Z	Adult Critical Care, 3 Organs Supported	290,494	£1,401	£1,180	£1,569	58,085
XC05Z	Adult Critical Care, 2 Organs Supported	341,695	£1,223	£1,010	£1,395	93,060
XC06Z	Adult Critical Care, 1 Organ Supported	436,367	£868	£666	£998	156,930
XC07Z	Adult Critical Care, 0 Organs Supported	41,347	£631	£403	£749	17,292

8.4 Evidence statements

8.4.1 Clinical

- Low-quality evidence from 1 external validation study for patients with LRTI over 65 years old showed that CRB65 may discriminate risk of mortality in a primary care setting although no events were found for patients with CRB65 score 0 and 4 which restricts the applicability of its findings.
- The outcome of hospitalisation for patients with LRTI presented in a primary care setting was not found to be accurately predicted by the CRB65 tool. This was shown by low quality evidence from a multicentre European observational study.

8.4.2 Economic

- No relevant economic evaluations were identified.

8.5 Recommendations and link to evidence

Table 24: Linking evidence to recommendations – severity assessment tools in primary care

Recommendations	**2. When a clinical diagnosis of community-acquired pneumonia is made in primary care, determine whether patients are at low, intermediate or high risk of death using the CRB65 score (see box 1[a]).** **Box 1: CRB65 score for mortality risk assessment in primary care[a]** CRB65 score is calculated by giving 1 point for each of the following prognostic features: • confusion (abbreviated Mental Test score 8 or less, or new disorientation in person, place or time)[b] • raised respiratory rate (30 breaths per minute or more) • low blood pressure (diastolic 60 mmHg or less, or systolic less than 90 mmHg) • age 65 years or more. Patients are stratified for risk of death as follows: • 0: low risk (less than 1% mortality risk) • 1 or 2: intermediate risk (1-10% mortality risk) • 3 or 4: high risk (more than 10% mortality risk). **3. Use clinical judgement in conjunction with the CRB65 score to inform decisions about whether patients need hospital assessment as follows:** • **consider home-based care for patients with a CRB65 score of 0** • **consider hospital assessment for all other patients, particularly those with a CRB65 score of 2 or more.** *(a) Lim WS, van der Eerden MM, Laing R, et al.(2003) Defining community-acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax58: 377–82* *(b) For guidance on delirium, see the NICE guideline on delirium.*
Relative values of different outcomes	The GDG considered the ability of a severity assessment tool to predict mortality the most important outcome, but also took into account the ease-of-use of the tools. Evidence that use of a tool could influence management (such as appropriate

	hospital admission) was also considered an important outcome.
Trade-off between clinical benefits and harms	CRB65 was the only severity assessment tool with suitable available evidence. Mortality was recorded in both observational studies included in the review of evidence. No deaths were reported in the first study that examined the use of CRB65 in patients with LRTI across 13 European countries. Hospitalisation was recorded and no difference was found between the patients with CRB65 score 1 or more, or less than 1 after adjusting for the effect of antibiotic prescription. Mortality was recorded in the second study that examined the use of CRB65 in patients over the age of 65 with suspected or chest X-ray confirmed CAP. An increased risk of death was found with increasing CRB65 scores between 1 and 3 (no patients had a CRB65 score of 0 (all patients were aged 65 years or more) or 4).
Trade-off between net health benefits and resource use	No economic studies were available on severity assessment tools. The cost effectiveness of a tool depends on the cost of the assessment and the accuracy of the tool, together with the downstream benefits and costs (for example health gain from correct admission compared with health detriment from non-admission, cost of admissions, cost of further care needed after required admission was missed). If the information needed for the risk tool can be gathered in the normal care pathway, there will not be any additional cost in undertaking the risk assessment; however staff time still may be involved in interpreting and explaining this risk assessment to patients. CRB65 is based on easily-available clinical parameters alone, thus not associated with a meaningful increase in costs and therefore the GDG considered it likely to be cost effective if it is clinically effective.
Quality of evidence	Evidence on the use of CRB65 in LRTI consisted of 1 validation study conducted across 13 European countries. Although some patients with LRTI may have pneumonia on further investigation, most will not; the study results are therefore not directly applicable to suspected CAP. Moreover, results were reported for only 12.6% of the original sample, limiting the usefulness of the results as a basis for a recommendation in patients with LRTI. Evidence on CRB65 in suspected CAP was limited to a single validation study conducted in the Netherlands. The study only included patients over the age of 65, which limits its applicability to the whole population.
Other considerations	The GDG agreed that there was insufficient evidence on which to base a recommendation for the use of CRB65 in LRTI. As evidence for the use of CRB65 in suspected CAP was also limited, the GDG discussed whether a recommendation for its use should be made. Although the GDG acknowledged that there was only 1 study of CRB65 in suspected pneumonia in the community, they were cognisant of the 7 studies of the same tool in patients admitted to hospital (section 8.7.1) and that the results concurred. It was therefore concluded that the evidence did support the ability of CRB65 to stratify patients by risk of death, and therefore its use was felt likely to be beneficial in informing management decisions. Whilst the GDG agreed that a CRB65 of 0 was associated with a low risk of death, and a score of ≥ 2 was clearly associated with a higher risk of death, a CRB65 score of 1 appeared to be less informative. A CRB65 score of 1 in patients over 65 presenting to primary care (who score 1 based on age alone) had a low risk of death in 1 study,

	whilst a CRB65 of 1 in all ages was associated with a higher risk of death in the CRB65 derivation study. The GDG therefore noted the uncertainty regarding the risk of death in patients of all ages with a CRB65 score of 1 presenting to primary care, which is likely to include some patients suitable for management at home, and others who would benefit from referral for hospital assessment. The GDG did not feel that there was sufficient evidence to make an age-specific recommendation for patients over the age of 65, notwithstanding the inclusion of age in the CRB65 scoring system. The GDG concluded that a recommendation to consider the need for hospital assessment in patients with a CRB65 score of 1 was appropriate, while emphasising the importance of hospital assessment in those with a CRB65 score of ≥ 2, whose risk of death is more plainly evident.

8.6 Review question: In adults with community-acquired pneumonia (presenting to Accident & Emergency) what is the most accurate and cost-effective severity assessment tool to stratify patients at first presentation according to who would benefit from

a) hospital admission?

b) ITU assessment?

For full details see review protocol in Appendix C:.

8.7 Clinical Evidence

We searched for systematic reviews, randomised (RCTs) and non-randomised comparative (non-RCTs) studies investigating the predictive ability of severity assessment tools (in patients assessed at hospital presentation) to determine which patients would benefit from hospital admission or ITU assessment and/or intensive respiratory or vasopressor support.

We selected for inclusion only studies that reported either or both:

- Discriminatory analysis; a receiver operator characteristics (ROC) curve using the performance criteria for each severity assessment tool, and the area under these curves (AUC). The AUCs were approximated for some tools, such as the revised American Thoracic Society score (rATS), which were scored as binary outcomes.
- Multivariate analysis adjusted for any of the pre-specified confounders in the protocol of this review question. The GDG considered that age, comorbidities (with more emphasis on previous heart, lung and liver disease) and malignancies could skew the predictive ability of the investigated tools to assess mortality and need for ITU assessment in patients with CAP. Therefore, these factors were considered as important confounders when the severity tools did not already incorporate them as 1 of their criteria. If the severity tools did take these confounders into consideration in their scoring, then univariate analysis was still considered valid in addressing this question.

We did not consider derivation studies or non-comparative validation studies (either internal or external) that only assessed the performance of 1 tool within the study cohort as the derivation tools will necessarily perform well in the derivation cohort (by definition) and thus the comparison is biased. Therefore, only comparative validation studies that assessed and compared the performance of more than 1 tool within the same study cohort were included.

No RCTs were found comparing the prognostic scoring systems as guides to further management such as hospital or ITU admission and/or intensive respiratory or vasopressor support. Therefore, these tools were reviewed in non-RCTs in order to estimate their ability to predict mortality and/or ITU admission in patients with CAP.

Non-RCT prognostic studies are prone to publication bias. Studies of larger sample size which are less prone to bias were given higher importance than studies of smaller sample sizes.

Forty-seven studies were included in the review; 19 studies compared the PSI with CURB65, CURB or CRB65, 10 studies compared the PSI, CURB65 with modified ATS criteria and the ATS/IDSA, 3 studies compared CURB65 and CRB65, 1 study compared PSI, CURB65 with SMART-COP, 15 studies included other tools that could not be grouped together.

Evidence from these is summarised in the clinical evidence profiles in Appendix G:. See also the study selection flow chart in **Appendix D:**, forest plots in **Appendix I:** and exclusion list in **Appendix J:**.

The results are presented by comparisons of severity assessment tools. Within each comparison, outcomes of mortality and ITU admission are reported separately. When more than 2 studies reported results for the most critical outcome in this review (mortality) (using the same utilities (for example RRs or AUCs), this information is presented in a table with a summary of their point estimates.

When studies provided mortality or ITU admission rates stratified by risk group, the risk ratios (RRs) and the corresponding absolute effects were then summarised in GRADE tables. The GDG noted that it would be relevant for decision-making if the comparisons of risk groups within each tool were made in 2 ways:

- by comparing high- with low-risk groups (as defined by the authors) and
- by comparing 3 levels of risk (low, intermediate and high risk).

The scoring of risk groups in each tool was as defined in the derivation and validation studies.

Although the protocol specified that sensitivity, specificity, positive and negative predictive values would be included as supplementary information if necessary, it was decided that the most robust type of analysis for the prognostic nature of this review was the available discriminatory and multivariate analyses with the corresponding meta-analysis (where appropriate). It was thus deemed unnecessary to include this supplementary information.

Table 25: Summary of studies included in this review

Study	Setting	Study design	Population		N (analysed)	Outcomes (prevalence %)	Type of results[b]
			Age (years)	High-risk (%)			
PSI compared with CURB65, CURB, CRB65							
Varshochi 2013[200]	Iran	Prospective	Mean age 64	68%	134	• in-hospital mortality (26.1%)	Frequencies, AUC
Luque 2012[125]	Spain	Prospective	Mean age 73	74.9%	152	• 30-day mortality (11.8%)	Frequencies, AUC
Aujesky 2005A[10]	USA	Prospective	55% > 65	32%	3181	• 30-day mortality (4.6%)	Frequencies, AUC
Ananda-Rajah 2008[6]	Australia	Retrospective	Mean 72	75.3%/ 9.3% nursing homes	390	• 30-day mortality (15.4%) • ITU admission (10.5%)	Frequencies, AUC
Tejera 2007[190]	Spain	Prospective	Median 73	75.2%	226	• mortality during admission (12.4%)	AUC, Narrative summary of multivariate analysis

Study	Setting	Study design	Population		N (analysed)	Outcomes (prevalence %)	Type of results[b]
			Age (years)	High-risk (%)			
Abishegan aden 2012[2]	Singapore	Retrospective	Mean 76.7	52.1%	1052	• 30-day mortality (17.2%)	ORs, AUC
Man 2007[126]	Hong Kong	Prospective	Mean 72	52.7%/ 24.3% nursing homes	1016	• 30-day mortality (8.6%) • ITU admission (4%)	Frequencies, AUC
Lee 2013[113]	Korea	Retrospective secondary analysis	Mean 70.1	54.9%	744	• 30-day mortality (13.4%)	ORs, AUC
Alavi-Moghaddam 2013[4]	Iran	Prospective	Mean 68	90%	200	• mortality during hospital stay (18%) • ITU admission (15%)	Frequencies, AUC
Ochoa-Gondar 2011[149]	Spain	Prospective population based	Mean 77.4	62.5%	590	• 30-day mortality (13.6%)	Frequencies, AUC
Capelastegui 2006[39]	Spain	Retrospective	Mean 61.8	35.6%	1776	• 30-day mortality (6.7%) • mechanical ventilation (1%)	Frequencies, AUC
Menendez 2009[135]	Spain	Prospective	Mean 67.3	52.3%	453	• 30-day mortality (7.9%)	Frequencies, AUC
Chen 2010[48]	Taiwan	Prospective	Mean 68	12.5%	987	• 30-day mortality (6.8%)	AUC
Bello 2012[19]	Spain	Prospective	Median age 73	60.9%	228	• 30-day mortality (5.8%)	AUC
Chang 2013[47]	New Zealand	Prospective	Median age 69	50.7%	453	• 30-day mortality (5.7%)	Frequencies
Schuetz 2011A, 2010A[176,17]	Switzerland	Prospective	Median age 73	51.1%	925	• 30-day mortality (5.4%)	Frequencies, AUC

Study	Setting	Study design	Population		N (analysed)	Outcomes (prevalence %)	Type of results[b]
			Age (years)	High-risk (%)			
[8]							
Dwyer 2011[66]	Sweden	Retrospective	Mean age: Survivors- 60.6 Non-survivors – 70.3	49.0%	375	• mortaliy (9%)	Frequencies
Kim 2013[106]	Korea	Prospective	Age < 50 years: 20.5%	35.5%	883	• mortality • ITU admission	Frequencies
CURB65 compared with CRB65							
Chalmers 2008[43]	UK	Prospective	Mean age 66	35.6%	1007	• 30-day mortality (9.6%)	AUC
Zuberi 2008[210]	Pakistan	Prospective	Mean age 60.4		137	• 30-day mortality (13.1%)	AUC, ORs
Bauer 2006[17]	Germany	Prospective	Mean age Outpatients: 53 Inpatients: 66		2184	• 30-day mortality (4.3%)	AUC
PSI compared with CURB65, CURB, CRB65 compared with modified ATS criteria							
Buising 2006[34]	Australia	Prospective	Median: 74	66.8%	392	• in-hospital mortality (9.4%) • ITU admission (6.6%)	AUC
Valencia 2007[196]	Spain	Prospective	Mean age: 79	All patients with PSI-V	457	• hospital mortality (23%) • ITU admission (20%)	PPV, NPV
Angus 2002[8]	USA and Canada	Prospective	NR	50%	1339	• 30-day mortality: Non-ITU (6.9%), ITU	AUC, RRs

Study	Setting	Study design	Population		N (analysed)	Outcomes (prevalence %)	Type of results[b]
			Age (years)	High-risk (%)			
						(15.3%) • ITU admission (12.7%)	
Ewig 2004[71]	Spain	Prospective	Mean age 67.8	44.1%	489	• in-hospital mortality (8%) • ITU admission (19%)	AUC
Feldman 2009[73]	Multi-country	Secondary analysis of a prospective study	NR	49.5%	739	• 14-day mortality (14.3%)	AUC
Spindler 2006[188]	Sweden	Prospective (plus retrospective analysis of 28 patients)	Mean age 57.1	46.5%	114	• mortality (11.4%)	AUC
PSI and CURB65, CURB, CRB65 compared with IDSA/ATS (major, minor criteria)							
Liapikou 2009[117]	Spain	Prospective	Mean age: • ITU patients: 64 • Non-ITU patient: 67			• in-hospital mortality (5.2%) • ITU admission (11.2%)	Unadjusted RRs
Phua 2009 (only minor criteria)[160]	Singapore	Retrospective			1242	• in-hospital mortality (14.7%)	AUC, Adjusted RRs
Guo 2012 (only minor criteria)[89]	China	Retrospective	Mean age 47.5	CURB65 ≥ 3: 1.2%	1230	• in-hospital mortality (1.3%)	Frequencies
Kontou 2009[109]	USA	Retrospective			158	• in-hospital mortality (12.7%) • ITU admission (19.6%)	Adjusted RRs
PSI and CURB65 compared with SMART-COP							
Chalmers	UK	Prospecti	Media		335	• IRVS (9.9%)	AUC

Study	Setting	Study design	Population		N (analysed)	Outcomes (prevalence %)	Type of results[b]
			Age (years)	High-risk (%)			
2008B[45]		ve	n age 36			• 30-day mortality (1.5%)	
Other tools							
Fukuyama 2011 (SCAP, PSI, A-DROP, CURB65, IDSA/ATS, SMART-COP)[83]	Japan	Prospective	Median age 76		505	• in-hospital mortality (6.5%) • ITU admission (6.3)	PPV, NPV
Barlow 2007(CURB65, CRB65, SIRS, SEWS)[13]	UK	Retrospective	Median age 74	CURB65 ≥ 3: 38%	218	• 30-day mortality (3%) • ITU admission (19%)	AUC, Frequencies
Shindo 2008A (A-DROP, CURB65)[180]	Japan	Retrospective	Mean age 75		329	• 30-day mortality (9.4%) • ITU admission (14.6%)	AUC, Frequencies
Brown 2009 (IDSA/ATS 2007, SMART-COP, CURB65)[31]	USA	Retrospective	Mean age 56.2	Mean score CURB65 : 1.1 points	2413	• 30-day mortality (3.7%)	AUC
Kohno 2013 (A-DROP, PSI)[108]	Japan	Prospective	Mean age 76.3		482	• 28-day mortality (12.3%) • ITU admission (8.7%)	AUC
Kasamatsu 2012 (CURB65, PSI, A-DROP)[105]	Japan	Prospective	Mean age 67.9	56.47%	170	• 30-day mortality (11.8%)	AUC
Salluh 2008 (CURB65, APACHE-II, SOFA)[173]	Brazil	Prospective	Median age 71		72	• in-hospital mortality (16.7%)	AUC

Study	Setting	Study design	Population		N (analysed)	Outcomes (prevalence %)	Type of results[b]
			Age (years)	High-risk (%)			
Jeong 2011 (APACHE-II, PSI, CURB65)[101]	Korea	Retrospective	Mean age: Survivors 67.58 Non-survivors 77.03	50.80%	502	• 30-day mortality (12.2%)	AUC
Xiao 2013 (APACHE-II, PSI, CURB65)[206]	China	Retrospective	Mean age: 75 years (SD 8)	33.3% with 1 major or 2 minor criteria (a)	240	• 28-day mortality (35%) • need for mechanical ventilation (32.9%)	AUC
Belkhouja 2012 (SOFA, CURB65, PSI)[18]	Tunisia	Retrospective	Mean age 49.5	54.5%	132	• ITU mortality (23%)	ORs
Yang 2012 (PSI, CURB65, Sepsis score)[207]	China	Retrospective	Mean age 61.1		675	• 30-day mortality (10.5%)	AUC, Frequencies
Chalmers 2008B (PSI ≥ IV SMART-COP > 2, CURB65 ≥ 3)[45]	UK	Prospective	Median age 36		335	• need for mechanical ventilation or inotropic support (9.9%)	AUC
Robins-Browne 2012 (PSI ≥ IV SMART-COP ≥ 3 CORB ≥ 2)[167]	Australia	Prospective	Mean age 50	21.2%	367	• intensive respiratory or vasopressor support • mortality	AUC, frequencies
Ribeiro 2013[162] (PSI,	Portugal	Retrospective	Mean age 58.7	8.4%	142	• mortality (1.4%)	AUC, Frequenci

Study	Setting	Study design	Population		N (analysed)	Outcomes (prevalence %)	Type of results[b]
			Age (years)	High-risk (%)			
CURB65, SCAP, SMART-COP)			years (SD 16.9)			• ITU admission (15.5%) • mechanical ventilation (7%) • vasopressor support (7%)	es
Chalmers 2011 (IDSA/ATS minor criteria, PSI, CURB65, CRB65, SMART-COP, SCAP)[46]	UK	Prospective	Median 63	PSI mean 3 (1.52)	1062	• 30-day mortality (4.5%) • ITU admission (7.6%) • mechanical ventilation or vasopressor support (6.6%)	AUC

(a) Major criteria: pH < 7.30 and systolic blood pressure < 90 mmHg), minor criteria: age > 80 years old, respiratory rate ≥ 30 breaths/min, blood urea nitrogen > 30 mg/dL, $PaO_2/FiO_2 \leq 250$, Multilobar/bilateral infiltrates and altered mental status)

(b) Type of results refers to the main findings used for the final presentation of analysis (frequencies, ORs or RRs and AUCs). When studies did not present any of these results but presented only sensitivity, specificity, positive and negative predictive value then this information is presented in this column

8.7.1 PSI, CURB65, CRB65 or CURB

19 studies were included in the evidence review for the comparison of PSI compared with CURB65, CRB65 or CURB.

All included studies reported the outcome of mortality in their results. The majority of studies for this comparison assessed the role of these tools to predict mortality using a discriminatory analysis (AUCs). Four studies (Capelastegui 2006[39], Chalmers 2008[43], Zuberi 2008[210], Bauer 2006[17]) compared CURB65 only with CRB65 or CURB. (See Table 26 and Table 27.)

None of the included studies accounted for confounders.

Table 26: Summary of discriminatory analysis (AUCs) for PSI compared with CURB65, CRB65 or CURB for the prediction of mortality

	Summary (range) of point estimates of AUCs	Included studies	Quality of included studies	Notes [1]
PSI	0.71 to 0.89	16	Moderate to low quality	Aujesky 2005A: 0.81 (0.78 to 0.84)
CURB65	0.67 to 0.87	18	Moderate to low quality	Aujesky 2005A: 0.76 (0.73 to 0.80)
CURB	0.73 to 0.80	2	Moderate to low quality	Aujesky 2005A: 0.73 (0.68 to 0.76)

	Summary (range) of point estimates of AUCs	Included studies	Quality of included studies	Notes [1]
CRB65	0.69 to 0.86	8	Moderate to low quality	Capelastegui 2006: 0.86 (0.84 to 0.89)

[1] *Results from the largest study*

Table 27: Results of multivariate analyses for the prediction of mortality*

	ORs/RRs from multivariate analysis (95% CI)	Included studies	Quality of included studies	Notes
PSI IV PSI V CURB65 = 5	OR 4.76 (1.01 to 22.53) OR 7.10 (1.42 to 35.42) OR 37.02 (2.49 to 550.32)	1 Lee 2013	Low quality	Model was adjusted by quartile of red cell distribution width, haematocrit, mean corpuscular haemoglobin, albumin, cholesterol, prothrombin time.
CURB65 ≥ 3	RR 3.3 (1.2 to 9)	1 Tejera 2007	Very low quality	Multivariate model included age, dehydration, subjective nutritional score, hand grip, Glasgow coma score, severity of sepsis, PSI, TNFα, IL-6, Strem-1 and IGF-1.

**Only the factors that remained significant in the multivariate models are presented in this table*

Only 1 study (Schuetz 2011A[176]) reported the AUC for the prediction of ITU admission; both PSI and CURB65 had low AUCs for predicting this outcome (AUC for PSI: 0.65 (0.59 to 0.71), for CURB65: 0.64 (0.58 to 0.70)).

None of the studies which compared only CURB65 with CRB65 reported information on ITU admission.

Table 28: Clinical evidence profile: PSI to predict mortality and ITU admission

Quality assessment						No of patients			Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	High-risk PSI	Intermediate-risk PSI	Low-risk PSI	Relative Risk of median study (range of RRs of studies)	Absolute (from pooled effect size)	Quality
Mortality [Kim 2013, Schuetz 2010A, Ananda-Rajah 2008, Abisheganaden 2012, Alavi-Moghaddam 2013, Ochdagondar 2011, Lee 2013, Chen 2010, Man 2007, Luque 2012, Chang 2013, Aujesky 2005A, Varshochi 2013, Tejera 2007, Dwyer 2011, Menendez 2009]											
16	cohort studies	serious[1]	no serious	serious[2]	no serious	911/5810 (15.7%)		126/5979 (2.1%)*	RR 7.69[3] (2.53 to 41.29)	134 more per 1000 (from 107 more to 167 more)	Low
					serious[4]		103/2573 (4%)	23/3406 (0.7%)	RR 3.16[5] (0.93 to 31.15)	23 more per 1000 (from 13 more to 39 more)	Very low
					serious[4]	911/5801 (15.7%)	103/2573 (4%)		RR 4.18[6] (1.02 to 24.30	105 more per 1000 (from 79 more to 136 more)	Very low
ITU admission [Man 2007, Ananda-Rajah 2008, Kim 2013]											
3	cohort studies	serious[7]	no serious	serious[8]	no serious	122/1144 (10.7%)		42/1163 (3.6%)	RR 2.39[9] (1.33 to 4.49)	84 more per 1000 (from 49 more to 135 more)	Low

[1] *4 out of 11 included studies were retrospective. 1 study did not specify if the included patients were consecutive and unselected*
[2] *Most of the studies have included nursing home patients (< 25%)*
[3] *Source: Aujesky 2005A study*
[4] *Confidence interval crosses 1 DEFAULT MID.*
[5] *Source: Abisheganaden 2012*
[6] *Source: Luque 2012*
[7] *One study was retrospective.*
[8] *24.7% of the sample in 1 study was nursing home patients.*
[9] *Source: Ananda-Rajah 2008*

**Includes the intermediate-risk group*

Table 29: Clinical evidence profile: CURB65 to predict mortality and ITU admission

Quality assessment						No of patients			Effect		Quality
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	High-risk CURB65	Intermediate-risk CURB65	Low-risk CURB65	Relative Risk of median study (range of RRs of studies)	Absolute (from pooled effect size)	
Mortality [Kim 2013, Schuetz 2010A, Ananda-Rajah 2008, Abisheganaden 2012, Alavi-Moghaddam 2013, Ochdagondar 2011, Lee 2013, Chen 2010, Man 2007, Luque 2012, Chang 2013, Aujesky 2005A, Varshochi 2013, Tejera 2007, Dwyer 2011, Menendez 2009, Zuberi 2008, Capelastegui 2006]											
18	cohort studies	serious[1]	no serious	serious[2]	no serious	600/2785 (21.5%)		563/10937 (5.1%)*	RR 3.73[5] (2.11 to 10.34)	132 more per 1000 (from 113 more to 152 more)	Low
					very serious[3]		377/3752 (10%)	186/6937 (2.7%)	RR 2.84[6] (0.42 to 33.12)	61 more per 1000 (from 47 more to 76 more)	Very low
					serious[4]	600/2785 (21.5%)	377/3752 (10%)		RR 2.32[7] (1.23 to 8.38)	109 more per 1000 (from 88 more to 134 more)	Very low
ITU admission [Man 2007, Ananda-Rajah 2008, Kim 2013]											
3	cohort studies	serious[8]	no serious	serious[9]	no serious	52/523 (9.9%)		92/1784 (5.2%)	RR 2.05[10] (1.28 to 2.50)	63 more per 1000 (from 24 more to 117 more)	Low

[1] *5 studies were retrospective, 4 studies recruited not consecutive patients*
[2] *Some studies have included nursing home patients (< 25%)*
[3] *Confidence interval crosses both default MIDs*
[4] *Confidence interval crosses 1 default MID*
[5] *Source: Chen 2010*
[6] *Source: Abisheganaden 2012*
[7] *Source: Ochdagondar 2011*
[8] *One study was retrospective*
[9] *24.7% of the sample in 1 study was nursing home patients*
[10] *Source: Man 2007*

**Includes the intermediate-risk group*

Table 30: Clinical evidence profile: CURB to predict mortality

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High - risk CURB	Low-risk CURB	Mean Relative Risk (95% CI)	Absolute (from pooled effect size)	Quality
30-day mortality [Aujesky 2005A, Bauer 2006]											
2	cohort studies	serious[1]	no serious	serious[2]	no serious	reduced effect for RR >> 1 or RR << 1[3]	111/808 (13.7%)	101/3716 (2.7%)	RR 5.12 (3.94 to 6.66)	107 more per 1000 (from 76 more to 147 more)	Low

[1] *One study did not specify if the patients were selected consecutively*
[2] *One study included both outpatients and hospital patients*
[3] *Analysis was not adjusted for confounders*

Table 31: Clinical evidence profile: CRB65 to predict mortality

Quality assessment						No of patients			Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	High-risk CRB65	Intermediate-risk CRB65	Low-risk CRB65	Relative Risk of median study (range of RRs of studies)	Absolute (from pooled effect size)	Quality
30-day mortality (Man 2007, Ochdagondar 2011, Zuberi 2008, Bauer 2006, Capelastegui 2006, Menendez 2009, Dwyer 2011)											
7	cohort studies	serious[1]	no serious	serious[2]	no serious	132/385 (34.3%)		311/5289 (5.9%)*	RR 5.47[3] (3.61 to 9.20)	303 more per 1000 (from 243 more to 375 more)	Low
					no serious		304/3952 (7.7%)	7/1437 (0.5%)	RR 4.46[4](2.16 to 122)	58 more per 1000 (from 28 more to 116 more)	Low
					no serious	132/385 (34.3%)	304/3952 (7.7%)		RR 4.43[5](3.34 to 6.32)	260 more per 1000 (from 206 more to 325 more	Low

[1] *2 studies were retrospective and 3 studies did not include consecutive patients*
[2] *2 studies included mixed populations of outpatients and hospital patients*
[3] *Source: Dwyer 2011*
[4] *Source: Menendez 2009*
[5] *Source: Bauer 2006*

**Includes the intermediate-risk group*

8.7.2 PSI, CURB65 compared with American Thoracic Society (ATS) 2001 criteria

Six non-RCTs (Buising 2006[34], Ewig 2004[71], Feldman 2009[73], Spindler 2006[188], Valencia 2007[196], Angus 2002[8]) were identified for this comparison.

The GDG considered that the modified ATS 2001 criteria were less relevant for this review question as they combined both minor and major criteria (which required a prior severity assessment process) to predict mortality.

8.7.2.1 Prediction of mortality

All included studies except 1 (Valencia 2007[196]) assessed the role of these tools to predict mortality using a discriminatory analysis (AUCs). Only 1 study (Angus 2002[8]) gave the relative risk (RR) of high-risk compared with low-risk groups as defined by each tool. The Modified ATS criteria showed less discriminatory ability to predict mortality (as depicted by lower AUC) compared with PSI and CURB65.

Table 32: Summary of discriminatory analysis (AUCs) for PSI, CURB65 and CURB, compared with modified ATS criteria (2001) in prediction of mortality

	Summary (range) of point estimates of AUCs	Included studies	Quality of included studies	Notes[1,2]
PSI	0.72 to 0.85	4	Low to very low quality	• Buising 2006 used a threshold of PSI ≥ IV • Angus 2002: 0.75 (0.71 to 0.77)[2]
CURB65	0.74 to 0.84	3	Low to very low quality	• Buising 2006 used a threshold of CURB65 ≥ 3 • Feldman 2009:0.74[2]
Modified ATS	0.63 to 0.83	4	Low to very low quality	• Angus 2002: 0.63 (0.57 to 0.69)[2]
CURB	0.82	1	Low quality	• Buising 2006 used a threshold of CURB ≥ 2

[1] *Ewig 2004 and Valencia 2006 did not provide AUCs of tools for the prediction of mortality*
[2] *Results from the largest study*

Table 33: Results from univariate or multivariate analysis comparing the ability of PSI, original and modified ATS criteria (2001) to predict 30-day mortality

	Included studies	RRs (95% CI)	Quality[1]
PSI ≥ 4	Angus 2002	16.8 (6.8 to 41.8)	Low quality
Modified ATS	Angus 2002	1.3 (0.9 to 2.1)	Low quality
Original ATS	Angus 2002	2.6 (1.5 to 4.5)	Low quality

[1] *Analysis was not adjusted for confounders.*

8.7.2.2 Prediction of ITU admission

Results from the multivariate analysis showed that patients with a higher number of modified ATS criteria may have a higher chance of being admitted to ITU compared with those assessed as high risk by PSI and ATS. However this analysis was not adjusted for confounders and its interpretation needs caution.

Table 34: Summary of discriminatory analysis (AUCs) for PSI, CURB65 and CURB compared with modified ATS criteria (2001) in predicting ITU admission

	Summary (range) of point estimates of AUCs	Included studies	Quality of included studies	Notes
PSI	0.60 to 0.69	2	Low to very low quality	• Buising 2006 used a threshold of PSI ≥ IV • Angus 2002: 0.6 (0.56 to 0.65)[1]
CURB65	0.66	1	Low quality	• Buising 2006 used a threshold of CURB65 ≥ 3
Modified ATS	0.68 to 0.90	2	Low to very low quality	• Ewig 2004[71] and Valencia 2007[196] did not provide AUC results for the Modified ATS tool • Angus 2002: 0.68 (0.64 to 0.73)[1]
CURB	0.73 to 0.76	2	Low to very low quality	• Buising 2006 [34] used a threshold of CURB ≥ 2

[1] *Results from the largest study*

Table 35: Results from multivariate analysis PSI compared with modified ATS criteria (2001) in predicting ITU admission

	Included studies	RRs (95% CI)	Quality[1]
PSI ≥ 4	Angus 2002	2.7 (1.9 to 3.9)	Low quality
Modified ATS	Angus 2002	4.9 (3.4 to 7.1)	Low quality
Original ATS	Angus 2002	3.0 (2.0 to 4.5)	Low quality

[1] *Analysis was not adjusted for confounders*

8.7.3 PSI, CURB65 compared with IDSA/ATS

Four studies were identified for this comparison; 2 (Phua 2009[160], Guo 2012[89]) focused only on the IDSA/ATS minor criteria whereas the other 2 (Kontou 2009[109], Liapikou 2009[117]) included both major and minor criteria of IDSA/ATS.

8.7.3.1 Prediction of mortality

Table 36: Summary of discriminatory analysis (AUCs) for PSI, CURB65 compared with IDSA/ATS in predicting mortality

	Summary of point estimates of AUCs (95% CI)	Included studies	Quality of included studies	Notes
PSI	0.86 (0.83 to 0.88)	1	Very low quality (retrospective)	Kontou 2009[109] did not provide AUC data
CURB65	0.82 (0.78 to 0.85)	1	Very low quality (retrospective)	Kontou 2009 did not provide AUC data
IDSA/ATS (minor criteria)	0.88 (0.86 to 0.91)	1	Very low quality (retrospective)	Kontou 2009 did not provide AUC data

Table 37: Results from multivariate analysis comparing the PSI, CURB65 with IDSA/ATS in predicting mortality

	RRs or ORs (95% CI)	Included studies	Quality of included studies	Notes
PSI ≥ III ≥ IV V	 RR 81.46 (11.46 to 579.23)[1] RR 25.06 (11.87 to 52.91)[2] RR 7.87 (5.95 to 10.42)[3]	Phua 2009	Very low quality (retrospective)	
CURB65 ≥ 1 ≥ 2 ≥ 3 ≥ 4 5	 RR 15.57 (5.45 to 38.91) RR 8.86 (5.65 to 13.91) RR 5.20 (3.98 to 6.79) RR 5.12 (4.03 to 6.50) RR 7.19 (6.26 to 8.27)	Phua 2009	Very low quality (retrospective)	Adjusted by delay to ITU transfer
Mean score CURB65	OR 3.76 (1.31 to 10.82)	Kontou 2009		Adjusted by mechanical ventilation
IDSA/ATS (minor criteria) ≥ 1 ≥ 2 ≥ 3 ≥ 4 ≥ 5	 RR 23.17 (7.45 to 72.03) RR 25.71 (12.77 to 51.75) RR 12.11 (8.53 to 17.20) RR 6.46 (5.08 to 8.20) RR 6.49 (5.24 to 8.04)	Phua 2009	Very low quality (retrospective)	Adjusted by delay to ITU transfer

	RRs or ORs (95% CI)	Included studies	Quality of included studies	Notes
≥ 6 7	RR 7.54 (6.53 to 8.70) RR 6.85 (5.99 to 7.84)			
IDSA/ATS (≥ 1 major and ≥ 3 minor) (high-severity CAP)	6.8 (4.6 to 10.1)	Liapikou 2009	Low quality	

[1] *PSI ≥ III was compared with PSI < II*
[2] *PSI ≥ IV was compared with PSI < II*
[3] *PSI ≥ V as compared with PSI < II*

Table 38: Clinical evidence profile: CURB65 to predict mortality compared with IDSA/ATS tool (minor criteria)

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High-risk CURB65 (≥ 3)	Low- to intermediate-risk CURB65 (< 3)	Relative (95% CI)	Absolute	Quality
Mortality [Guo 2012]											
1	cohort study	serious[1]	no serious	no serious	no serious	reduced effect for RR >> 1 or RR << 1[2]	4/14 (28.6%)	12/1216 (0.99%)	28.95 (10.64 to 78.82)	277 more per 1000 (from 260 more to 283 more)	Moderate

[1] *Retrospective study*
[2] *Results were not controlled for confounders*

Table 39: Clinical evidence profile: IDSA/ATS (minor criteria) to predict mortality

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	High-risk IDSA/ATS (≥ 3 minor criteria)	Low-risk IDSA/ATS (< 3 minor criteria)	Relative (95% CI)	Absolute	Quality
Mortality [Guo 2012]											
1	cohort study	serious[1]	no serious	no serious	serious[2]	reduced effect for RR >> 1 or RR << 1[3]	2/54 (3.7%)	10/1176 (0.85%)	4.36 (0.98 to 19.39)	29 more per 1000 (from 1 fewer to35 more)	Low

[1] *Retrospective study*
[2] *The CI was consistent with both a clinically important effect and no clinically important effect*
[3] *Results were not controlled for confounders*

8.7.3.2 Prediction of ITU admission

Only 1 study (Liapikou 2009[117]) reported isolated results for the role of severe IDSA/ATS criteria (≥ 1 of 2 major criteria and ≥ 3 out of 9 minor criteria) in predicting ITU mortality (RR 17.5 [12.8 to 23.9]). However, no comparative data were given for this outcome for the other tools (PSI, CURB) included in the analysis.

8.7.4 PSI and CURB65 compared with SMART-COP

One prospective study at low risk of bias (Chalmers 2008B[45]) was identified. This study compared the ability of SMART-COP with PSI and CURB65 to predict the need for intensive vasopressor and/or respiratory support (IVRS). SMART-COP defined patients as high risk if 3 or more criteria were present.

The following table presents a summary of the discriminatory analysis for the role of SMART-COP compared with PSI and CURB65.

Table 40: Discriminatory analysis of high-risk groups of SMART-COP compared with PSI and CURB65 in predicting IVRS

High-risk groups	Included studies	AUC (95% CI)
PSI ≥ IV	Chalmers 2008B	0.80 (0.75 to 0.84)
CURB65 ≥ 3	Chalmers 2008B	0.81 (0.76 to 0.86)
SMART-COP ≥ 3	Chalmers 2008B	0.87 (0.83 to 0.91)

[1] *Chalmers 2008B study included a young population (median age 36 [28 to 43])*

8.7.5 Other tools

13 studies included different severity assessment tools and compared their ability to predict mortality and/or ITU admission. The following table presents the studies by severity assessment tools when discriminatory analysis (using the AUC) or multivariate analysis was reported.

Table 41: Summary of characteristics and discriminatory analysis of studies comparing other severity assessment tools

Studies[1]	Severity assessment tools	Outcomes	AUC (95% CI)[2]/multivariate analysis	Quality
Barlow 2007	• CURB65 • CRB65 • SIRS • SEWS	30-day mortality	0.79 (0.72 to 0.86) 0.75 (0.67 to 0.83) 0.70 (0.59 to 0.81) 0.61 (0.49 to 0.72)	High risk of bias (retrospective study).
Shindo 2008A	• A-DROP • CURB65	30-day mortality	0.846 (0.790 to 0.903) 0.835 (0.763 to 0.908	High risk of bias (retrospective study with mixed population, 24.3% were nursing home patients).
Kohno 2013	• A-DROP • PSI	28-day mortality	0.67 (0.59 to 0.75) 0.63 (0.56 to 0.71)	Unclear risk of bias (prospective study with mixed population

Studies[1]	Severity assessment tools	Outcomes	AUC (95% CI)[2]/multivariate analysis	Quality
				(HCAP).
Kasamatsu 2012	• A-DROP • CURB65 • PSI	• 30-day mortality	0.88 (0.82 to 0.94) 0.88 (0.82 to 0.94) 0.89 (0.85 to 0.94)	Moderate risk of bias (prospective study of patients with moderate- to high severity CAP).
Salluh 2008	• CURB65 • APACHE-II • SOFA	• hospital mortality	0.71 (0.57 to 0.86) 0.71 (0.56 to 0.86) 0.62 (0.41 to 0.84)	Moderate risk of bias (prospective single centre study of patients with high-severity CAP).
Jeong 2011	• PSI • CURB65 • APACHE-II	• 30-day mortality	0.79 (0.74 to 0.85) 0.76 (0.70 to 0.82) 0.85 (0.80 to 0.89)	High risk of bias (retrospective study).
Xiao 2013	• PSI • CURB65 • APACHE-II	• 28-day mortality • need for mechanical ventilation	PSI: 0.87 (0.82 to 0.92) CURB65: 0.81 (0.75 to 0.87) APACHE II: 0.86 (0.80 to 0.92) PSI: 0.86 (0.81 to 0.91) CURB65: 0.79 (0.73 to 0.86) APACHE II: 0.83 (0.77 to 0.86)	High risk of bias (retrospective study of older people [> 65 years old]).
Belkhouja 2012	• SOFA • CURB65 • PSI	• ITU mortality	Independent factors in the multivariate analysis: • need for mechanical ventilation at ITU admission • SOFA ≥ 4 (OR 3.1 (1.56 to 6.13) • serum creatinine ≥ 102 µmol/l	High risk of bias (retrospective study of patients with high-severity CAP).
Yang 2012	• PSI • CURB65 • Sepsis score	30-day mortality	0.94 0.91 0.89	High risk of bias (retrospective study).
Chalmers 2008	• PSI ≥ IV • SMART-COP > 2 • CURB65 ≥ 3	• need for mechanical ventilation or inotropic support	0.80 (0.75 to 0.84) 0.87 (0.83 to 0.91) 0.81 (0.76 to 0.86)	Low risk of bias (prospective study, not clear if consecutive patients were

Studies[1]	Severity assessment tools	Outcomes	AUC (95% CI)[2]/multivariate analysis	Quality
				enrolled).
Robinson-Browne 2012	• PSI ≥ IV • SMART-COP ≥ 3 • CORB ≥ 2	• intensive respiratory or vasopressor support	0.76 (0.68 to 0.85) 0.89 (0.86 to 0.93) 0.69 (0.60 to 0.78)	Moderate risk of bias (prospective singe centre study).
Brown 2009	• IDSA/ATS 2007 • SMART-COP • CURB65	• mortality	0.88 (0.85 to 0.90) 0.83 (0.80 to 0.86) 0.76 (0.73 to 0.80)	High risk of bias (retrospective study of patients with high-severity CAP).
Ribeiro 2013	• PSI ≥ III • CURB65 > 1 • SCAP > 10 • SMART-COP > 2	• mortality	0.96 0.96 0.95 0.88	High risk of bias (retrospective study of patients with low-risk CAP who were mainly admitted to hospital).
	• PSI ≥ III • CURB65 > 1 • SCAP > 10 • SMART-COP > 2	• ITU admission	0.62 0.70 0.85 0.85	
	• PSI ≥ III • CURB65 > 1 • SCAP > 10 • SMART-COP > 2	• need for mechanical ventilation	0.62 0.66 0.88 0.81	
	• PSI ≥ III • CURB65 > 1 • SCAP > 10 • SMART-COP > 2	• need for vasopressor support	0.59 0.72 0.83 0.82	
Chalmers 2011	• IDSA/ATS minor criteria • PSI • CURB65 • CRB65 • SMART-COP • SCAP • 2001 ATS minor criteria	• 30-day mortality	0.78 (0.74 - 0.82) 0.81 (0.78 to 0.85) 0.74 (0.70 to 0.78) 0.73 (0.68 to 0.77) 0.79 (0.75 to 0.83) 0.74 (0.70 to 0.78) 0.68 (0.63 to 0.72)	Moderate risk of bias (prospective study of patients without IDSA/ATS major criteria for ITU admission).
	• IDSA/ATS minor criteria • PSI • CURB65 • CRB65 • SMART-COP • SCAP • 2001 ATS minor criteria	• ITU admission	0.85 (0.82 to 0.88) 0.74 (0.71 to 0.77) 0.74 (0.71 to 0.78) 0.73 (0.69 to 0.76) 0.85 (0.83 to 0.88) 0.75 (0.72 to 0.78) 0.70 (0.67 to 0.73)	
	• IDSA/ATS minor criteria	• mechanical ventilation or vasopressor	0.85 (0.82 to 0.88)	

Studies[1]	Severity assessment tools	Outcomes	AUC (95% CI)[2]/multivariate analysis	Quality
	• PSI • CURB65 • CRB65 • SMART-COP • SCAP • 2001 ATS minor criteria	support	0.73 (0.70 to 0.77) 0.73 (0.70 to 0.77) 0.71 (0.67 to 0.75) 0.83 (0.80 to 0.86) 0.75 (0.71 to 0.78) 0.69 (0.65 to 0.72)	

[1] *Fukuyama 2011 study was not included in the table as its results were only related to diagnostic accuracy of tools (sensitivity, specificity, positive and negative predictive value)*
[2] *AUCs results are presented for each tool for all outcomes with the order of 30-day mortality, ITU admission, mechanical ventilation or vasopressor support*

8.8 Economic evidence

Published literature

No relevant economic evaluations were identified.

One economic evaluation relating to severity assessment for CAP (presenting to Accident & Emergency) for hospital admission was identified but was excluded due to a combination of limited applicability and methodological limitations.[102] This is reported in Appendix K:, with reasons for exclusion given.

See also the economic article selection flow diagram in Appendix E:.

Economic considerations

Similarly to patients presenting to primary care, severity assessment tools may be used by clinicians for patients presenting to Accident & Emergency to guide hospital admission or need for ITU support according to the patient's severity level. If accurate they will also be cost effective as they will ensure the most appropriate care is provided to patients and the resources are therefore used appropriately. However, if patients are admitted to hospital or ITU unnecessarily due to the inaccuracy of a severity assessment tool, there are potentially important cost implications. The costs of hospital admission and ITU admission have been presented in section 8.3 to aid consideration of cost effectiveness.

8.9 Evidence statements

8.9.1 Clinical

- Low to very low quality evidence from 19 comparative non-randomised studies of over 10,000 patients with CAP presenting to hospital showed that PSI, CURB65 and CRB65 may be useful tools to accurately stratify the different risks of mortality into 3 groups (low, intermediate and high risk), but were not as good at predicting of the need for ITU admission.
- Low quality evidence from 1 non-randomised study found that SMART-COP may have some use in predicting the need for intensive respiratory and/or vasopressor support for patients with CAP presenting to hospital but there is lack of certainty for this effect.

Insufficient evidence was found to support the use of other severity assessment tools (A-DROP, APACHE II, modified ATS, ATS/IDSA, SCAP, SOFA, CORB, Sepsis score, SIRS, SEWS) for any outcomes (mortality, ITU admission or the need for intensive respiratory and/or vasopressor support) due to heterogeneity of studies included, differences in population and the tools under investigation.

8.9.2 Economic

- No relevant economic evaluations were identified.

8.10 Recommendations and link to evidence

Table 42: Linking evidence to recommendations– severity assessment tools in Accident & Emergency

Recommendations	**4. When a diagnosis of community-acquired pneumonia is made at presentation to hospital, determine whether patients are at low, intermediate or high risk of death using the CURB65 score (see box 2)[c].** **Box 2: CURB65 score for mortality risk assessment in hospital[c]** CURB65 score is calculated by giving 1 point for each of the following prognostic features: • confusion (abbreviated Mental Test score 8 or less, or new disorientation in person, place or time)[d] • raised blood urea nitrogen (over 7 mmol/litre) • raised respiratory rate (30 breaths per minute or more) • low blood pressure (diastolic 60 mmHg or less, or systolic less than 90 mmHg) • age 65 years or more. Patients are stratified for risk of death as follows: • 0 or 1: low risk (less than 3% mortality risk) • 2: intermediate risk (3-15% mortality risk) • 3 to 5: high risk (more than 15% mortality risk). **5. Use clinical judgement in conjunction with the CURB65 score to guide the management of community-acquired pneumonia, as follows:** • **consider home-based care for patients with a CURB65 score of 0 or 1** • **consider hospital-based care for patients with a CURB65 score of 2 or more** • **consider intensive care assessment for patients with a CURB65 score of 3 or more.** *(c) Lim WS, van der Eerden MM, Laing R, et al.(2003) Defining community-acquired pneumonia severity on presentation to hospital: an international derivation and validation study. Thorax58: 377–82.* *(d) For guidance on delirium, see the NICE guideline on delirium.*
Relative values of different outcomes	The GDG considered the ability of a severity assessment tool to predict mortality the most important outcome, but also took into account the ease-of-use of the tools. Evidence that use of a tool could influence management (such as appropriate hospital admission or identifying patients who would benefit from ITU assessment) was considered an important outcome, albeit one that would be influenced by additional local factors.
Trade-off between clinical benefits and harms	Most evidence was available for CURB65 and PSI. Both scores were able to accurately stratify patients into 3 groups based on different risks of death; the low-risk group was associated with less than 3% mortality, intermediate between 3% and 15%, while the high-risk group had more than 15% mortality. The results were consistent across a range of studies, which increased the confidence of the GDG in these findings. The GDG considered the simplicity of the CURB65 score to be an advantage over PSI. The CURB and CRB65 scores were compared with CURB65 and PSI. These scores were also able to stratify patients into groups based on risk of death, though there

	were fewer studies supporting these results. The GDG discussed whether the CRB65 score could allow more rapid identification of patients at low risk of death suitable for home management as it is based on clinical measures only, without any blood tests. However, the proportion of patients identified as at low risk of death is larger using the CURB65 score (using CURB65 ≤ 1) than the CRB65 score (using CRB65 = 0); a benefit which the GDG agreed outweighed the disadvantage of requiring a blood test in this setting. The ATS severe CAP criteria were compared with CURB65 and PSI. It was noted that only the minor criteria were likely to be relevant to initial decision-making in clinical practice. The ATS minor criteria were able to stratify patients based on risk of death, but the number of criteria and the complexity of some criteria (for example, calculation of the PaO_2/FiO_2 ratio) were felt to be disadvantages compared with CURB65. The SMART-COP score was compared with CURB65 and PSI. SMART-COP was designed to predict the need for intensive respiratory and/or vasopressor support (IRVS) and no mortality data were reported. The evidence suggested that the SMART-COP score may discriminate better than CURB65 or PSI those patients in need of IRVS. The GDG noted that some criteria used in SMART-COP overlapped with those used in CURB65, and the GDG favoured the simplicity of recommending a single severity assessment tool to guide both hospital admission and need for ITU assessment. It was concluded that SMART-COP was unlikely to provide a significant benefit over CURB65 when this is used in combination with clinical judgement and arterial blood gas analysis. A variety of other tools were also considered. However, limited evidence was available for each of these tools, and none appeared to have any significant advantage over those already considered.
Trade-off between net health benefits and resource use	No suitable economic studies were identified on severity assessment tools. The cost effectiveness of a severity assessment tool depends on the cost of the assessment and the accuracy of the tool, together with the downstream benefits and costs (e.g. health gain from correct admission or health detriment from non-admission, cost of admissions, cost of further care needed after missed required admission). If the information needed for the risk tool can be gathered in the normal care pathway, there will not be any additional cost in undertaking the risk assessment; however staff time still may be involved in interpreting and explaining this risk assessment to patients. The GDG considered the use of CURB65 to be simpler than most other tools (PSI, SMART-COP) and therefore CURB65 is likely to minimise staff time and costs. On the other hand, CRB65 could further reduce costs as it does not require a blood urea test. However the GDG agreed that the clinical evidence showed that the proportion of patients identified as at low risk of death is larger using the CURB65 score (using CURB65 ≤ 1) than the CRB65 score (using CRB65 = 0); this would eventually lead to less resource utilisation such as hospital and ITU admission with CURB65, which may offset the initial additional cost of blood test.
Quality of evidence	Evidence was moderate to very low quality by GRADE criteria. Prognostic cohort studies were considered by the GDG the most appropriate source of evidence to answer this review question. The main sources of bias for the included studies were the retrospective nature of their design, the inclusion of non-consecutive patients and the mixed population with nursing home patients. As non-randomised studies

	are prone to publication bias, the GDG placed more importance on the results of larger studies. The majority of included studies provided evidence for both the prevalence of outcomes by risk group and discriminatory analysis through results in AUCs. As these severity assessment tools incorporate multiple criteria, univariate analysis was still valid for the presentation of results if the tools included the most important confounding factors identified by the GDG (age, comorbidities and malignancies).
Other considerations	The GDG also took into account data from the national BTS audit of CAP (See Appendix P:) noting that a significant proportion of patients identified as being at high risk of death by virtue of their CURB65 score may not be suitable for escalation of care due to their pre-morbid level of function, comorbidities or frailty. The GDG were of the opinion that this was the reason why the scores studied were more accurate predictors of mortality than place of care (ITU). SMART COP was considered because it was the only score which was derived specifically as a potential tool to predict ventilatory support or vascular support i.e. ITU admission. In addition, occasional patients with a low score on severity assessment tools are severely unwell and require aggressive treatment including hospital admission or ITU assessment. The GDG wished to emphasise that the role of severity assessment tools is to help guide management, not to replace or overrule clinical judgement. Overall, the GDG agreed that the ability of the CURB65 score to predict mortality, in combination with its simplicity and the absence of evidence to suggest the superiority of another severity assessment tool, should lead to a recommendation for its use in this setting.

8.11 Disease severity

Severity assessment is an integral and fundamental part of pneumonia care. Many therapeutic interventions are potentially available; some are simple to enact and are associated with little harm whereas others require sophisticated technology and skills and may be associated with significant harm, especially if inappropriately applied. Risk–benefit balance is important in the employment of these interventions in patient care. Severity assessment allows selection of the most appropriate strategies for the most appropriate patients. In addition it gives the managing clinician an idea of likely prognosis which may be useful information to share with the patient and their relatives.

Traditionally clinical acumen was the basis for severity assessment. One physician's clinical acumen is not the same as another's and not surprisingly studies have found that it can be inaccurate; at different times, clinical acumen may both under and overestimate severity in individual patients.

Structured, objective scoring tools have been developed to aid clinical judgement in severity assessment. A number of such tools have been developed, most of which have been evaluated using mortality risk as the outcome.

8.11.1 The difference between severity assessment and mortality risk

It is important to realise that although mortality risk assessment is part of severity assessment, it may not always be the same as severity assessment. In most patients, illness severity will correspond to the mortality risk predicted by these tools. However no mortality risk tool is perfect and there are circumstances where the tool may be overruled by clinical judgement. Some patients with a low mortality risk score may still be severely ill. In addition, while a patient may be deemed to be severely ill by a mortality risk score, clinical judgment may indicate that it would be inappropriate to use certain interventions (for example because of prior poor functional status due to co-morbidities).

Severity assessment should be conducted using clinical acumen supplemented by mortality-risk prediction tools. The GDG wished to emphasise the importance of achieving this balance and developed a recommendation to highlight this.

8.11.2 Recommendations and link to evidence

Table 43: Linking evidence to recommendations

Recommendations	**6. Stratify patients presenting with community-acquired pneumonia into those with low-, moderate- or high-severity disease. The grade of severity will usually correspond to the risk of death.**
Relative values of different outcomes	N/A
Trade-off between clinical benefits and harms	Whilst previous pneumonia guidelines have stated the importance of using clinical judgement alongside mortality risk scores, in the experience of the GDG this message is sometimes overlooked. The GDG wished to make a clear additional recommendation highlighting that disease severity will usually, but not always, correlate with risk of death as calculated by a mortality risk score.
Trade-off between net health benefits and resource use	N/A
Quality of evidence	N/A
Other considerations	The GDG anticipates that in the majority of cases (> 80%), disease severity in CAP will correspond to mortality risk as assessed by a mortality risk score. However, in a minority of cases, management of a patient with CAP guided by mortality risk score alone could be inappropriate and could lead to harm. To give a specific example: A young patient who has previously been fit and well develops CAP. The patient is not confused, has a low serum urea level, a respiratory rate of 28/minute, and a blood pressure of 80/50 mmHg. This patient's CURB65 score is 1, indicating a low risk of death with appropriate treatment. The risk of death is low because the patient's capacity to recover from severe illness is good if they receive aggressive and appropriate intervention. However, clinical judgement may indicate that despite the low overall risk of death with treatment, this patient may have a severe illness with severe hypoxaemia or worsening hypotension, and require treatment in an ITU. In this case, management in the community with a single antibiotic which is otherwise indicated for most patients with a CURB65 score of 1 would not be appropriate and would cause harm. There is therefore a clear difference between mortality risk and disease severity in this case, and clinical judgement to identify this difference alter management accordingly (through stratification into degrees of severity) is important.

9 Microbiological tests

The various microbial causes of community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP) are each sensitive or resistant to different antibiotics. Unfortunately clinical, chest X-ray (CXR) and laboratory features do not allow accurate identification of the microbial cause in an individual patient. Empirical antibiotic therapy is usually commenced at patient presentation based on knowledge of likely pathogens. Targeting the correct antibiotic to the microbial cause in an individual patient is desirable. As clinical recovery is usual with empirical antibiotic therapy for low-severity CAP, microbiological tests are unlikely to influence management (perhaps with the exception of disease outbreaks). It is however imperative to identify when empirical antibiotic therapy should be changed in more severely ill patients because of their high mortality risk and rapid disease progression in the absence of correct treatment.

Traditional practice has been to send specimens (for example, of blood and or sputum) from each patient to the microbiology laboratory to try to identify the microbial cause in that patient and so refine the empirical antibiotic therapy. While a specific microbial cause is sometimes identified by this means, in the majority of cases no cause is found. The tests most commonly used are blood culture and sputum culture. Two new urine antigen detection tests are also available in most hospitals.

Various factors limit the clinical usefulness of these microbiological tests including sample availability (many patients do not produce sputum), sample handling (delays in reaching the laboratory can reduce yield), prior antibiotic therapy (even a single dose can result in false negative bacterial cultures), risk of false positives and delays in results reaching the managing clinician (it may take 48 hours or more for standard bacterial cultures to become positive).

All tests have an associated cost and they are likely to be most useful when they have the highest chance of guiding patient management. It would therefore be useful to know which tests, or combination of tests, are clinically and cost effective in managing moderate- or high-severity CAP, and HAP. For these reasons the GDG prioritised this question for clinical review and health economic modelling.

9.1 Review question: In adults with community-acquired pneumonia or hospital-acquired pneumonia in a hospital setting, what microbiological test or combination of tests at presentation (including urinary pneumococcal and urinary legionella antigen, blood culture and sputum culture) is most likely to be clinically and cost effective?

For full details see review protocol in Appendix C:.

No data were found for hospital-acquired pneumonia.

9.2 Clinical evidence

We searched for studies evaluating the clinical utility of performing microbiological tests for patients with CAP or HAP managed in hospital. A range of study designs were considered for inclusion in the review in the following order of preference:

- Systematic reviews (of randomised or observational studies)

- Comparative test-and-treat studies of targeted treatment followed by microbiological test results compared with empirical treatment (no test group) were sought first; randomised and non-randomised studies
- Observational studies with multivariate analyses comparing outcomes among those patients who had a microbiological test with those patients who did not have tests at point of entry.

Nine studies were included in the review: 2 RCTs[72,198], 3 non-randomised comparative studies[20,118,161] and 4 observational studies with multivariate analyses for patients with CAP.[59,112,130,194] The included study characteristics are summarised in Table 44.

No relevant studies were available for patients with HAP.

Evidence from the included studies is summarised in the clinical GRADE evidence profiles below (**Table 45**, **Table 46**, **Table 47**, **Table 48** and **Table 49**). The results of all types of studies are summarised in the GRADE tables but some outcomes are reported separately for randomised and non-randomised studies. When the studies did not indicate whether the result of a test guided a targeted treatment, this is noted in footnotes and was taken into consideration in the quality assessment of the evidence. In addition, when the timing of the tests in the studies was different (for example 24 hours prior to hospital admission or prior to start of antibiotic treatment), the outcomes across these studies are reported separately. The Uematsu study reported results by severity status for different combinations of tests compared with no test and this is also presented separately.

See also the study selection flow chart in Appendix D:, forest plots in Appendix I:, study evidence tables in Appendix G: and exclusion list in Appendix J:.

Table 44: Summary of studies included in the review

Ref	Population; study type	Comparison groups/ N	Tests used (for targeting treatment when available)	Antibiotics used empirically	Outcomes	Comments
Randomised data for community-acquired pneumonia						
Falguera 2010[72]	CAP – hospitalised	• Targeted treatment following tests N (ITT) = 88 • Empirical treatment (no tests) N (ITT) = 89	Urinary antigen tests for *S. pneumoniae* and *L. pneumophila*	Beta-lactam plus macrolide or fluoroquinolone (physician choice); 21% received fluoroquinolone.	• mortality • relapse • length of stay • hospital re-admission • withdrawal due to adverse events	• Both arms treated empirically initially and only randomised when clinically stable. • Immunosuppressed excluded. • More than 50% of patients in each group had high-severity CAP (PSI ≥ IV).
Van der Eerden 2005[198]	CAP – hospitalised	• Targeted treatment following tests N (ITT) = 152 • Empirical treatment according to ATS guidelines N (ITT) = 151	Combination of non-invasive and invasive tests including: • sputum for Gram stain and culture • *S. pneumoniae* antigen detection testing • blood culture • *L. pneumophila* serogroup 1 antigen detection • bronchoalveolar lavage (BAL) specimen and protected specimen brush (PSB) when no expectorated sputum or in case of clinical failure • thoracocentesis when pleural fluid was present • blood samples for serology (ELISA). **Directed group:** Treatment targeted at suspected	**Empirical group:** According to ATS 1993 (beta-lactam plus macrolide).	• mortality • length of stay • quality-of-life; SF36 • clinical failure; defined as no improvement or return of symptoms and signs of pneumonia	• Pathogen-directed group could have treatment directed at 'suspected' pathogen if no microbial results. • Targeting began from first treatment day (i.e. did not treat empirically first). • Invasive tests used in some cases. • Immunosuppressed excluded. • Proportion with positive test extracted to inform the economic model.

			causative agent as reported by microbiology or clinical presentation (specific criteria were used).			
Non-randomised comparative data for community-acquired pneumonia						
Benenson 2007[20]	CAP – hospitalised Retrospective database search of admissions in 2001 and 2002.	• Test N (ITT) = 684 • No test N (ITT) = 122	Blood culture.	Based on ATS 2001 guidelines supplemented by local culture-sensitivity data. The antibiotic regimen was described as narrowed (de-escalated) or broadened if changes were made based on culture results.	• mortality • change in treatment • length of stay	• Unclear why blood culture not performed in the empirical group as this test was part of recommended clinical pathway. • Of those with blood cultures (data not available for non-blood culture group), 34% had COPD, 26% CHF, and 19% had recent hospitalisation. • Immunocompromised included.
Lidman 2002[118]	CAP – hospitalised Retrospective analysis of consecutive patients admitted during 1995	• Tests N (ITT) = 482 • No tests N (ITT) = 123	Combination of non-invasive and invasive tests including: • Blood culture (n = 418) • Sputum culture (n = 182) • Serological analysis (n = 104); • Culture of pleural effusion (n = 9) • Protected brush specimens via bronchoscopy (n = 15).	Penicillin-derivative (38%), cephalosporin (36%), macrolide or doxycycline (11%), imipenem or ciprofloxacin (4%), cephalosporin + macrolide (8%) or none (3%).	• mortality • change in treatment • length of stay	• 36% were antibiotic treated on admission. • HIV-positive patients excluded.
Piso 2012[161]	CAP moderate- to high-severity (> 50% PSI IV-V)	• Test N (ITT) = 139 • No test N (ITT) = 147	Binax Now® pneumococcal antigen testing (PnAG) in addition to combination of tests including: • blood cultures	Initial antibiotic treatment: 37% co-amoxiclav or cefuroxime alone; 41% co-amoxiclav	• change in treatment (only treatment changes within 48 to 72 hours of	• High proportions with comorbidities – diabetes: 23%; coronary heart disease: 37%; chronic obstructive lung disease: 31%; renal

	N = 286 Consecutive patients - Nov 2007 - Aug 2008 all had PnAG; Sept 2008 - March 2009 - PnAG discontinued at the institution.		• sputum cultures • urinary Binax Now® Legionella antigen testing (LgAG) The control group received the tests above, except PnAG testing	/cephalosporin + macrolide; 10% cephalosporin; 1% macrolide; 11% other.	microbiological tests results were included)	insufficiency: 22%.
Observational data (with multivariate analysis) for community-acquired pneumonia						
Dedier 2001[59]	Retrospective chart review/database (cohort) CAP; moderate- to high-severity (> 70% PSI III-V)	• Blood culture within 24 hours or before antibiotic administration N (available case) = 869 • No blood culture N (available case) = 150	• Blood culture within 24 hours of hospital arrival. • Blood culture before antibiotic administration.	• Unclear	• mortality (inpatient) • length of stay (> median) • clinical instability at 48 hours	• Immunocompromised excluded. • 27% of screened patients excluded. • 49% had at least 1 chronic comorbid illness. • Multivariate analysis adjusted for: 1. Antibiotics administration ≤ 8 hours of hospital arrival 2. Blood culture ≤ 24 hours 3. Blood culture before antibiotics 4. Oxygenation measurement ≤ 24 hours 5. PSI
Lee 2011[112]	Retrospective observation (secondary analysis) of a prospective RCT.	• Blood culture before antibiotics N (available case) = 1305 • No blood culture N (available case) =	Blood culture before antibiotics.	Unclear	• mortality 30 days after presentation • length of stay • hospital re-admission	• Immunocompromised excluded. • 54% of screened patients excluded. • 39% chronic pulmonary disease.

	CAP; moderate to high-severity (> 70% PSI III-V)	757				• 16% prior antibiotics. • Multivariate analysis adjusted for: 1. PSI risk class. 2. Age. 3. Low, moderate or high intensity guideline implementation. 4. Nursing home residence. 5. Physical examination findings. 6. Lab and radiographic findings. 7. Treatments before presentation. 8. Comorbidities not contained in the PSI – cognitive impairment, history of coronary artery disease, chronic pulmonary disease, diabetes
Meehan 1997[130]	Retrospective medical record review CAP in older patients (≥ 65 years). N = 14,069	• Blood culture within 24 hours or before antibiotic administration N = not reported • No blood culture N = not reported	• Blood culture within 24 hours of hospital arrival. • Blood culture before antibiotic administration.	Unclear.	• 30-day mortality	• Limited to the older patients. • 45% of screened patients excluded. • Immunocompromised excluded. • 23% from skilled care facilities. • 58% had at least 1 comorbid illness. • Multivariate analysis adjusted for: 1. Time from hospital arrival to initial antibiotic administration. 2. Blood culture prior to initial antibiotic. 3. Blood culture within 24 hours of arrival. 4. Oxygenation assessment within 24 hours of arrival.

						5. Demographics (age, sex, nursing home residence). 6. Comorbidities (cerebrovascular disease, congestive heart failure, neoplastic disease). 7. Physical examination findings. 8. Lab/test results.
Uematsu 2014[194]	Retrospective cohort study using a multicentre claim-based inpatient database CAP	• Sputum tests, blood cultures, urine antigen tests in combination, or individually N (3 tests) = 5339 • No test N =30,744	• Sputum tests. • Blood cultures. • Urine antigen tests.	Unclear	• 30-day in-hospital mortality • length of hospital stay	• No information on antibiotic treatment. • The number of patients receiving each individual test is not reported, only the combination of tests • Limited generalisability to UK, as average length of stay in Japanese hospitals may be different to those in the UK. • HAP, HCAP, NHAP, and immunocompromised excluded. • Multivariate analysis adjusted for: 1. Age 2. Sex 3. Orientation disturbance 4. Respiratory failure 5. Low blood pressure 6. Dehydration 7. Comorbidities 8. Emergency admission via ambulance 9. Use of intensive care units University-affiliated major hospital status 10. Treatment in a pulmonary unit Hospital volume

11. Hospital size and doctor-to-bed and nurse-to-bed ratios.	

Table 45: Clinical evidence profile: Targeted treatment using a combination of tests compared with empirical treatment (no test)

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Combination of tests targeted treatment**	**Empirical treatment (no test)**	**Relative (95% CI)**	**Absolute**	**Quality**
Mortality (follow-up 30 days) [van der Eerden 2005]											
1	randomised trial	very serious[1]	no serious	serious[2]	serious[3]	none	12/152 (14.6%)	22/151 (14.6%)	RR 0.54 (0.28 to 1.06)	67 fewer per 1000 (from 105 fewer to 9 more)	Very low
Mortality (follow-up 3 months) [Lidman 2002]											
1	observational study	very serious[4]	no serious	serious[5]	no serious	none	42/482 (8.7%)	29/123 (23.6%)	RR 0.37 (0.24 to 0.57)	149 fewer per 1000 (from 101 fewer to 179 fewer)	Very low
Mortality (30-day in-hospital) [Uematsu 2014]											
1	observational study	very serious[6]	no serious	serious[5]	no serious	none	-	-	AOR 0.64 (0.56 to 0.74)[14]	-	Very low
Clinical failure (follow-up 30 days) [van der Eerden 2005]											
1	randomised trial	very serious[7]	no serious	serious[8]	very serious[9]	none	32/152 (21.1%)	35/151 (23.2%)	RR 0.91 (0.59 to 1.39)	21 fewer per 1000 (from 95 fewer to 90 more)	Very low
Length of hospital stay (follow-up unclear; Better indicated by lower values) [van der Eerden 2005]											
1	randomised trial	serious[10]	no serious	serious[2]	no serious	none	14.3 (9.4)	13.2 (13.2)	-	MD 1.1 higher (1.48 lower to 3.68 higher)	Low
Length of hospital stay (follow-up unclear) [Lidman 2002]											
1	observational study	serious[10]	no serious	serious[5]	no serious	none	5 (1 to 90)	5 (1 to 34)	-		Very low
Length of hospital stay (time to hospital discharge as a surrogate) [Uematsu 2014]											

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Combination of tests targeted treatment**	**Empirical treatment (no test)**	**Relative (95% CI)**	**Absolute**	**Quality**
1	observational study	very serious[12]	no serious	serious[5, 13]	no serious	none	-	-	AHR 1.04 (1.00 to 1.07)[14]	-	Very low
Quality-of-life; SF-36 - 30 days (follow-up 30 days; Better indicated by lower values) [van der Eerden 2005]											
1	randomised trial	very serious[11]	no serious	serious[2]	no serious	None	59.5 (21.5)	57.3 (20.5)	-	MD 2.2 higher (5.48 lower to 9.88 higher)	Very low
Quality-of-life; SF-36 - 90 days (follow-up 90 days; Better indicated by lower values) [van der Eerden 2005]											
1	randomised trial	very serious[11]	no serious	serious[2]	no serious	None	66.7 (22.9)	67.2 (30.1)	-	MD 0.5 lower (12.32 lower to 11.32 higher)	Low
Quality-of-life; SF-36 - 180 days (follow-up 180 days; Better indicated by lower values) [van der Eerden 2005]											
1	randomised trial	very serious[11]	no serious	serious[2]	serious[3]	None	79.3 (22.4)	64.1 (20.1)	-	MD 15.2 higher (3.68 to 26.72 higher)	Very low
Change in prescription (based on test results) (follow-up unclear) [van der Eerden 2005]											
1	randomised trial	serious[7]	no serious	serious[2]	no serious	None	25/134 (18.7%)	0/128 (0%)	PETO OR 8.61 (3.78 to 19.61)	190 (120 more per 1000 to 250 more]	Low
Change in prescription (based on test results or clinical judgement) [Lidman 2002]											
1	observational study	very serious[4]	no serious	serious[5,6]	serious[3]	None	133/482 (27.6%)	23/123 (18.7%)	RR 1.48 (0.99 to 2.19)	90 more per 1000 (from 2 fewer to 223 more)	Very low
Withdrawal due to adverse events											
0	no evidence available	-	-	-	-	None	-	-	-	-	

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Combination of tests targeted treatment	Empirical treatment (no test)	Relative (95% CI)	Absolute	Quality
Complications											
0	no evidence available	-	-	-	-	none	-	-	-	-	

[1] *Unclear sequence generation and severity higher in empirical group plus missing data rate higher than event rate*
[2] *Indirect intervention: some invasive tests included and treatment could be targeted by clinical presentation as well as test results, pathogens were identified in 66% of patients (not reflecting current UK practice)*
[3] *95% CI crosses 1 default MID*
[4] *Very high risk of selection bias (allocation likely determined by physician), not matched at baseline for age, comorbidities or prior antibiotics (older, more comorbidities and more with prior antibiotic treatment in empirical group) and no controlling for confounders in analysis*
[5] *Study analysed outcomes in the groups who received test compared with no test, no specific information on whether the test was followed by targeted treatment*
[6] *Retrospective database analysis, no information on antibiotic prescription*
[7] *Unclear sequence generation and severity higher in empirical group plus unblinded*
[8] *Indirect intervention: some invasive tests included and treatment could be targeted by clinical presentation as well as test results and surrogate outcome measure*
[9] *95% CI crosses both default MIDs*
[10] *Unclear sequence generation and severity higher in empirical group*
[11] *Unclear sequence generation and severity higher in empirical group plus high rate of missing data and unblinded*
[12] *Analysis excluded patients who died in hospital, HR for hospital discharge as surrogate for length of hospital stay*
[13] *Length of stay in Japan and UK may be different, limiting applicability of findings*
[14] *Multivariate analysis adjusted for age, sex, orientation disturbance, respiratory failure, low blood pressure, dehydration, comorbidities, emergency admission via ambulance, use of intensive care units, university-affiliated major hospital status, treatment in a pulmonary unit, hospital volume, and hospital size and doctor-to-bed and nurse-to-bed ratios*

Table 46: Clinical evidence profile: Targeted treatment using urinary antigen tests compared with empirical treatment (no tests)

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Urinary antigen targeted treatment	Empirical treatment (no test)	Relative (95% CI)	Absolute	Quality
Mortality (follow-up 30 days after treatment) [Falguera 2010]											
1	randomised trial	serious[1]	no serious	serious[2]	very serious[3]	None	1/88 (1.1%)	0/89 (0%)	PETO OR 7.47 (0.15 to 376.66)	10 more (20 fewer per 1000 to 40 more)	Very low
Mortality (30-day in-hospital) [Uematsu 2014]											
1	observational study	very serious[4]	no serious	serious[5]	serious[7]	none	-	-	AOR 0.75 (0.69 to 0.82)[8]	-	Very low
Clinical relapse (follow-up up to 30 days after discharge) [Falguera 2010]											
1	randomised trial	serious[1]	no serious	serious[2]	very serious[3]	none	4/88 (4.5%)	2/89 (2.2%)	RR 2.02 (0.38 to 10.76)	23 more per 1000 (from 14 fewer to 219 more)	Very low
Re-admission (follow-up up to 30 days after discharge) [Falguera 2010]											
1	randomised trial	serious[1]	no serious	serious[2]	very serious[3]	none	4/88 (4.5%)	2/89 (2.2%)	RR 2.02 (0.38 to 10.76)	23 more per 1000 (from 14 fewer to 219 more)	Very low
Treatment withdrawal due to adverse events (follow-up 5 to 10 days) [Falguera 2010]											
1	randomised trial	serious[1]	no serious	serious[2]	very serious[3]	none	1/88 (1.1%)	1/89 (1.1%)	RR 1.01 (0.06 to 15.92)	0 more per 1000 (from 11 fewer to 168 more)	Very low
Length of hospital stay (follow-up unclear; Better indicated by lower values) [Falguera 2010]											
1	randomised trial	serious[1]	no serious	serious[2]	no serious	none	7.1 (4)	7.1 (3.8)	-	MD 0 higher (1.15 lower to 1.15 higher)	Low
Length of hospital stay (assessed by hospital discharge) [Uematsu 2014]											
1	observational study	very serious[4]	no serious	serious[5,6]	no serious	none	-	-	AHR 1.07 (1.05 to 1.10)[8]	-	Very low

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Urinary antigen targeted treatment	Empirical treatment (no test)	Relative (95% CI)	Absolute	Quality
Change in prescription											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Quality-of-life											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Complications											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Withdrawal due to adverse events											
0	no evidence available	-	-	-	-	none	-	-	-	-	

[1] *Unclear sequence generation and allocation concealment*

[2] *Indirect population: Excluded those with risk factors for P. aeruginosa infection or other micro-organisms not susceptible to study drugs; indirect intervention: Only implemented targeting once clinically stable*

[3] *95% CI crosses both default MIDs*

[4] *Retrospective database analysis, no information on antibiotic prescription*

[8] *Study analysed outcomes in the groups who received test compared with no test, no specific information on whether the test was followed by targeted treatment*

[6] *Length of stay in Japan and UK may be different,- limiting applicability of findings, HR for hospital discharge as surrogate for length of hospital stay*

[7] *95% CI crosses 1 default MID*

[8] *Multivariate analysis adjusted for age, sex, orientation disturbance, respiratory failure, low blood pressure, dehydration, comorbidities, emergency admission via ambulance, use of intensive care units, university-affiliated major hospital status, treatment in a pulmonary unit Hospital volume, and hospital size and doctor-to-bed and nurse-to-bed ratios*

Table 47: Clinical evidence profile: Targeted treatment using blood culture compared with empirical treatment (no test)

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Blood culture targeted treatment	Empirical treatment (no test)	Relative (95% CI)	Absolute	Quality
Mortality (follow-up unclear) [Benenson 2007]											
1	observational study	very serious[1]	no serious	serious[2]	very serious[3]	none	32/667 (4.8%)	8/118 (6.8%)	RR 0.71 (0.33 to 1.5)	20 fewer per 1000 (from 45 fewer to 34 more)	Very low
Mortality (30-day in-hospital) [Uematsu 2014]											
1	observational study	very serious[4]	no serious	serious[5]	very serious[3]	none	-	-	AOR 0.78 (0.71 to 1.40)[6]	-	Very low
Mortality (in-hospital) - Blood culture within 24 hours [Dedier 2002]											
1	observational study	serious[7]	no serious	serious[5]	serious[11]	none	54/841 (6.4%)	5/150 (3.3%)	AOR 0.86 (0.36 to 2.05)[12]	-	Very low
Mortality (in-hospital) - Blood culture before antibiotic therapy [Dedier 2002]											
1	observational study	serious[8]	no serious	serious[5]	serious[11]	none	-	-	AOR 1.21 (0.62 to 2.36)[12]	-	Very low
Mortality (30-day) - Blood culture before antibiotic therapy [Lee 2011; Meehan 1997]											
2	observational studies	serious[8]	no serious	serious[5]	very serious[6]	none			AOR 0.92 (0.82 to 1.02)[16]	-	Very low
					serious[11]	none			AOR 0.90 (0.60 to 1.30)[17]	-	
Mortality (30-day) - Blood culture within 24 hours [Meehan 1997]											
1	observational studies	very serious[7]	no serious	serious[5]	no serious	none	4502	9567	AOR 0.90 (0.81 to 1.00)[16]	- -	Very low
Clinical instability at 48 hours - Blood culture within 24 hours (follow-up 48 hours) [Dedier 2002]											

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Blood culture targeted treatment	Empirical treatment (no test)	Relative (95% CI)	Absolute	Quality
1	observational study	serious[9]	no serious	serious[5, 10]	serious[8]	none	186	876	AOR 1.62 (1.13 to 2.32)[12]	-	Very low
Clinical instability at 48 hours - Blood culture before antibiotic therapy (follow-up 48 hours) [Dedier 2002]											
1	randomised trial	serious[9]	no serious	serious[5, 10]	very serious[3]	none	294	768	AOR 1.06 (0.74 to 1.52)[12]	-	Very low
Length of hospital stay (follow-up unclear; Better indicated by lower values) [Benenson 2007]											
1	observational study	very serious[1]	no serious	serious[2, 5]	no serious	none	5.3 (3.4)	5 (4.3)	-	MD 0.3 higher (0.52 lower to 1.12 higher)	Very low
Length of hospital stay (longer than median 4 days) - Blood culture within 24 hours (follow-up unclear) [Dedier 2002]											
1	observational study	serious[9]	no serious	serious[5]	very serious[3]	none	-	-	AOR 1.04 (0.72 to 1.50)[12]	-	Very low
Length of hospital stay (longer than median 4 days) - Blood culture before antibiotic therapy (follow-up unclear) [Dedier 2002]											
1	observational study	serious[9]	no serious	serious[5]	serious[11]	none	-	-	AOR 0.84 (0.60 to 1.18)[12]	-	Very low
Length of hospital stay - Blood culture before antibiotic therapy (follow-up unclear) [Lee 2011]											
1	observational study	serious[8]	no serious	serious[5, 13]	no serious	none	Median 5 (3 to 7)	Median 5 (3 to 8)	AHR 1 (0.90 to 1.20)[17]	-	Very low
Length of hospital stay (time to hospital discharge as a surrogate) [Uematsu 2014]											
1	observational study	very serious[4]	no serious	serious[5, 15]	no serious	none	-	-	AHR 1.00 (0.98 to 1.02)[6]	-	Very low
Hospital re-admission - Blood culture before antibiotic therapy (follow-up unclear) [Lee 2011]											

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Blood culture targeted treatment	Empirical treatment (no test)	Relative (95% CI)	Absolute	Quality
1	observational study	serious[9]	no serious	serious[5, 13]	serious[11]	none	-	-	AOR 0.80 (0.60 to 1.07)[17]	-	Very low
Change in treatment based on test results (follow-up unclear) [Benenson 2007]											
1	observational study	serious[14]	no serious	very serious[2, 5]	very serious[3]	none	3/684 (0.4%)	0/122 (0%)	PETO OR 3.26 (0.14 to 76.9)	0 more per 1000 (from 10 fewer to 10 more)	Very low
Quality-of-life											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Complications											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Withdrawal due to adverse events											
0	no evidence available	-	-	-	-	none	-	-	-	-	

[1] *Allocation by indication, unclear baseline comparability and no accounting for confounding*
[2] *Population indirectness: some may have had HAP and > 20% had prior antibiotics, immunocompromised patients included*
[3] *95% CI crosses both default MIDs*
[4] *Retrospective database analysis, no information on antibiotic prescription*
[5] *Study analysed outcomes in the groups who received test compared with no test, no specific information on whether the test was followed by targeted treatment*
[6] *Multivariate analysis adjusted for age, sex, orientation disturbance, respiratory failure, low blood pressure, dehydration, comorbidities, emergency admission via ambulance, use of intensive care units, university-affiliated major hospital status, treatment in a pulmonary unit, hospital volume, and hospital size and doctor-to-bed and nurse-to-bed ratios*

[7] *Retrospective analysis of medical records and claims database, unclear baseline comparability and not all key confounders accounted for*
[8] *Secondary analysis of trial data, unclear baseline comparability and not all key confounders accounted for*
[9] *Allocation by indication, unclear baseline comparability and not all key confounders accounted for*
[10] *Surrogate outcome measure*
[11] *95% CI crosses 1 default MID*
[12] *Multivariate analysis adjusted for antibiotics administration ≤ 8 hours of hospital arrival, blood culture ≤ 24 hours, blood culture before antibiotics, oxygenation measurement ≤ 24 hours, and PSI*
[13] *Excluded 54% of those screened and 16% had prior antibiotics*
[14] *Non-comparative data*
[15] *Length of stay in Japan and UK may be different, limiting applicability of findings. HR for hospital discharge as surrogate for length of hospital stay*
[16] *Source [Meehan 1997]. Multivariate analysis adjusted for time from hospital arrival to initial antibiotic administration, blood culture prior to initial antibiotic, blood culture within 24 hours of arrival, oxygenation assessment within 24 hours of arrival, demographics (age, sex, nursing home residence), comorbidities (cerebrovascular disease, congestive heart failure, neoplastic disease), physical examination findings, lab/test results*
[17] *Source [Lee 2011]. Multivariate analysis adjusted for PSI risk class, age, guideline implementation (low, moderate or high intensity), nursing home residence, physical examination findings, lab and radiographic findings, treatments before presentation, comorbidities not contained in the PSI – cognitive impairment, history of coronary artery disease, chronic pulmonary disease, diabetes*

Table 48: Clinical evidence profile: Targeted treatment using sputum culture compared with empirical treatment (no test)

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Sputum culture targeted treatment	Empirical treatment (no test)	Relative (95% CI)	Absolute	Quality
Mortality (30-day in-hospital) [Uematsu 2014]											
1	observational studies	very serious[1]	no serious	serious[4]	no serious	none	-	-	AOR 1.06 (0.98 to 1.15)[3]	-	Very low
Clinical cure											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Length of hospital stay (time to hospital discharge as a surrogate) [Uematsu 2014]											
1	observational studies	very serious[1]	no serious	serious[2, 4]	no serious	none	-	-	AHR 0.98 (0.97 to 1.00)[3]	-	Very low
Change in prescription											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Quality-of-life											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Complications											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Withdrawal due to adverse events											
0	no evidence available	-	-	-	-	none	-	-	-	-	

[1] *Retrospective database analysis, no information on antibiotic prescription*
[2] *Length of stay in Japan and UK may be different, limiting applicability of findings. HR for hospital discharge as surrogate for length of hospital stay*
[3] *Multivariate analysis adjusted for age, sex, orientation disturbance, respiratory failure, low blood pressure, dehydration, comorbidities, emergency admission via ambulance, use of intensive care units, university-affiliated major hospital status, treatment in a pulmonary unit, hospital volume, and hospital size and doctor-to-bed and nurse-to-bed ratios*

[4] *Study analysed outcomes in the groups who received test compared with no test, no specific information on whether the test was followed by targeted treatment*

Table 49: Clinical evidence profile: Targeted treatment following urinary pneumococcal antigen compared with targeted treatment not using pneumococcal antigen

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Targeted treatment following PnAG test	Targeted treatment (not using PnAG test)	Relative (95% CI)	Absolute	Quality
Mortality											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Clinical cure											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Length of hospital stay											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Change in prescription (within 48 to 72 hours) [Piso 2012]											
1	observational studies	Serious[1]	no serious	no serious	Serious[2]	none	88/139 (63.3%)	80/147 (54.4%)	RR 1.16 (0.96 to 1.41)	87 more per 1000 (from 22 fewer to 223 more)	Very low
Quality-of-life											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Complications											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Withdrawal due to adverse events											

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Targeted treatment following PnAG test	Targeted treatment (not using PnAG test)	Relative (95% CI)	Absolute	Quality
0	no evidence available	-	-	-	-	none	-	-	-	-	

[1] *Serious risk of selection bias: allocation by time and not all key confounders accounted for*
[2] *95% CI crosses 1 default MID*

Table 50: Clinical evidence of outcomes for different combination of tests compared with no test stratified by severity status (Uematsu 2014)

Severity strata[1]	30-day in hospital mortality - Adjusted odds ratio (95% CI)	Length of stay (assessed by hospital discharge) Adjusted hazard ratio (95% CI)	Quality	Notes
Comparison of combination of tests with no test			Very low (Retrospective database analysis, *post-hoc* subgroup analysis. Length of stay in Japan and UK may be different, limiting applicability of findings).	Multivariate analysis adjusted for age, sex, orientation disturbance, respiratory failure, low blood pressure, dehydration, comorbidities, emergency admission via ambulance, use of ITU, university-affiliated major hospital status, treatment in a pulmonary unit, hospital volume, and hospital size and doctor-to-bed and nurse-to-bed ratios.
Mild	AOR 1.08 (0.36 to 3.26)	AHR 0.95 (0.89 to 1.02)		
Moderate	AOR 0.83 (0.66 to 1.04)	AHR 1.02 (0.98 to 1.07)		
Severe	AOR 0.70 (0.54 to 0.91)	AHR 1.12 (1.03 to 1.22)		
Very severe	AOR 0.51 (0.40 to 0.64)	AHR 1.12 (1.01 to 1.23)		
Comparison of blood cultures with no test				
Mild	AOR 1.67 (0.79 to 3.53)	AHR 0.92 (0.88 to 0.97)		
Moderate	AOR 0.79 (0.68 to 0.93)	AHR 1.03 (1.00 to 1.05)		
Severe	AOR 0.71 (0.60 to 0.85)	AHR 1.05 (0.99 to 1.12)		
Very severe	AOR 0.81 (0.70 to 0.93)	AHR 1.02 (0.95 to 1.09)		
Comparison of urinary antigen tests with no test				
Mild	AOR 0.39 (0.16 to 0.99)	AHR 1.03 (0.98 to 1.07)		
Moderate	AOR 0.80 (0.69 to 0.94)	AHR 1.07 (1.04 to 1.10)		
Severe	AOR 0.75 (0.63 to 0.89)	AHR 1.05 (0.99 to 1.11)		
Very severe	AOR 0.75 (0.64 to 0.87)	AHR 1.15 (1.08 to 1.24)		
Comparison of sputum tests with no test				
Mild	OR 1.00 (0.50 to 2.00)	AHR 0.98 (0.94 to 1.01)		
Moderate	AOR 1.11 (0.98 to 1.26)	AHR 0.97 (0.95 to 0.99)		
Severe	AOR 1.22 (1.05 to 1.41)	AHR 1.02 (0.97 to 1.08)		
Very severe	AOR 0.93 (0.82 to 1.05)	AHR 1.01 (0.95 to 1.07)		

[1] *Severity was assessed based on the A-DROP severity assessment tool*

9.3 Economic evidence

Published literature

One study was included which compared targeted treatment based on microbiological tests with empirical treatment for patients with CAP.[72] This is summarised in the economic evidence profile below (Table 51). See also the study selection flow chart in Appendix E: and study evidence tables in Appendix H:.

Two studies of patients with CAP comparing the addition of urinary antigen test for either *Legionella pneumophila* serotype 1[69] or *S. pneumoniae*[70] to other microbiological tests were excluded as they had very serious limitations (retrospective studies where the comparators were not clearly defined; costs were considered from a non-UK NHS perspective, and the analysis did not take into account the consequences of negative tests). In one of the studies[69] the cost per urinary antigen test for *L. pneumophila* was £19; this test was positive in 2% of patients with CAP, resulting in a number needed to test of 46. In 60% of the cases, the urinary antigen test for *L. pneumophila* was the only test that detected *L. pneumophila* among other microbiological tests including serology. In the other study[70] the cost of adding urinary antigen test for *S. pneumoniae* was £16.88 per patient, which included the savings made from the substitution of targeted treatment for empirical treatment.

Two studies that met the inclusion criteria were selectively excluded due to the availability of more applicable evidence and methodological limitations.[152,184]

The excluded studies are reported in Appendix K: with reasons for exclusion given.

No economic studies on microbiological tests were found for HAP.

Table 51: Economic evidence profile: Targeted treatment compared with empirical treatment

Study	Applicability	Limitations	Other comments	Incremental cost per patient[c]	Incremental effects per patient[d]	Cost effectiveness	Uncertainty
Falguera 2010[72] (Spain)	Partially applicable[a]	Very serious limitations[b]	Cost consequence analysis alongside a prospective, randomised, comparative trial of patients with high severity CAP comparing targeted treatment, using urinary and legionella antigen tests, with empirical treatment.	£33.65	0.0114 deaths 0.0230 clinical relapses - 0.0112 ITU admissions 0.0009 days of hospitalisation 0.0230 re-admissions - 0.0889 adverse events 0.0047 days of antimicrobial treatment 0.0029 days of IV treatment	NA	No sensitivity analysis undertaken

(a) Conducted from a Spanish health care perspective
(b) No ICERs were presented; costs are from a single hospital not national list prices; no quality-of-life information provided; patients had to be stable prior to randomisation and as such some costs and outcomes here may not be representative
(c) Converted from 2010 Euros using purchasing power parity [155]. See economic evidence table for full list of cost components
(d) Health outcomes were converted from cohort level to mean per patient by NCGC

9.3.1 Economic modelling

9.3.1.1 Model overview/Methods

There are multiple microbiological testing strategies for those admitted to hospital with moderate- and high-severity CAP. The most relevant strategies chosen by the GDG due to their common usage in the UK were analysed in this model:

- no testing (clinical judgement)
- blood culture
- sputum culture
- urinary pneumococcal antigen
- urinary legionella antigen
- a combination of a blood culture and a sputum culture
- a combination of a blood culture, a urinary pneumococcal antigen and a urinary legionella antigen
- all tests in combination.

The time horizon chosen for the model was a lifetime time horizon, with a single in-hospital episode including diagnosis and treatment over a short time period with a lifetime extrapolation. The analysis took the perspective of that in the NICE reference case: that of the NHS and personal and social services.

The model is a decision tree, where individuals receive no test/1 test/a combination of tests according to the strategy listed above. Based on the pathogen identified by the tests, patients are given either targeted treatment or empirical treatment is continued. The correct or incorrect identification of the pathogen depends on the sensitivity and specificity of the test/tests used. The appropriateness of antibiotic therapy and the type of pathogen present determine the probability of patients being alive or dead at 30 days (pathogen-specific mortality probabilities are used in the model).

Costs and QALYs were determined by the initial strategy adopted and the probability of incorrect (falsely positive and falsely negative) test results and their outcomes, namely the increase in mortality. After 30 days, the model assumes there is no impact of pneumonia on mortality and standard UK life expectancies were used to generate lifetime QALYs. This model is unable to quantify some benefits of targeted treatment such as a reduction in adverse events or the reduction in antimicrobial resistance.

Key data and assumptions

Due to lack of certain data, and pragmatic constraints relating to model complexity, a number of assumptions were made to facilitate the development of this model. These assumptions were agreed in discussion with the GDG and are detailed below.

<u>Pathogens and tests</u>

- In order to make the model feasible, it was assumed that patients have only a single causative pathogen, so that the overall pathogens prevalence adds up to 1. However, in real clinical practice more than 1 pathogen can be present and this was acknowledged in the treatment management assumptions of the model, where in some circumstances (for example when 2 tests performed in

combination showed positive results to 2 different pathogens) treatment could cover more than 1 organism.

- The only pathogens considered were:
  - *Streptococcus pneumoniae*
  - *Haemophilus influenzae*
  - *Staphylococcus aureus*
    - *'Staphylococcus species' (initial result showing Staphylococci based on Gram stain appearance and awaiting species identification)*
  - *Legionella pneumophila*
  - 'Atypical' pathogens
  - Aerobic Gram-negative rods.
- As the model was concerned with moderate- and high-severity CAP managed in hospital, the prevalence of pathogens noted from patients admitted to hospital with CAP was used rather than community pathogen prevalence.
- The prevalence of pathogens in the UK was taken from the BTS CAP Guidelines.[119] This is described in Table 52.

Table 52: Prevalence of pathogens

Pathogen	Prevalence from BTS (%)	Prevalence for model (%)[a]
S. pneumoniae	39.00	63.41
H. influenzae	5.20	8.46
L. pneumophila	3.60	5.85
S. aureus	1.90	3.09
Atypical pathogens	10.80	17.56
Aerobic Gram-negative rods[b]	1.00	1.63

(a) Scaled up using a factor of 100/61.50 = 1.626 since only 61.5% of cases had an identifiable cause in the BTS audit. We have assumed no difference in the proportion of cases caused by each organism in the proven compared with the unproven cases

(b) Aerobic Gram-negative rods refer to Enterobacteriaceae and other non-fermenting Gram negatives

- Different tests in routine use detect different pathogens as described in Table 53:
  - Blood culture could detect:
    - *S. pneumoniae*, *H. influenzae*, *S. aureus* and aerobic Gram-negative rods
  - Routine sputum culture could detect:
    - *S. pneumoniae*, *H. influenzae*, *S. aureus* and aerobic Gram-negative rods
  - Urinary pneumococcal antigen could detect:
    - *S. pneumoniae*
  - Urinary legionella antigen could detect:
    - *L. pneumophila* serogroup 1
  - No routine test could reliably detect atypical pathogens other than *L. pneumophila*.

Table 53: Detection of pathogens by single test

	S. pneumoniae	***H. influenzae***	***S. aureus***	***L. pneumophila***	**Atypical pathogens**	**Aerobic Gram-negative rods**
Blood culture	Yes	Yes	Yes	No	No	Yes
Routine sputum culture	Yes	Yes	Yes	No	No	Yes
Urinary pneumococcal antigen	Yes	No	No	No	No	No
Urinary legionella antigen	No	No	No	Yes	No	No

- Tests were assumed to produce the following false positive results in certain circumstances:
  - Blood culture could only be false positive for:
    - *'Staphylococcus* species'
  - Sputum culture could only be false positive for:
    - *S. pneumoniae*, *H. influenzae* and aerobic Gram-negative rods.
- Sensitivities and specificities were assumed for some tests, as shown in Table 54.
- Sensitivity for all *Staphylococcus* species was assumed to be the same as the contamination rate for positive blood cultures with 'coagulase negative staphylococci' at 5%.

Table 54: Accuracy of tests to detect specific pathogens

Blood culture and sensitivities		
Sensitivity to *S. pneumoniae*	0.25	GDG expert opinion
Sensitivity to *H. influenzae*	0.25	GDG expert opinion
Sensitivity to *S. aureus*	0.25	GDG expert opinion
Sensitivity to aerobic Gram-negative rods	0.25	GDG expert opinion
Specificity to *Staphylococcus* spp	0.95	GDG expert opinion
Sputum culture		
Sensitivity to *S. pneumoniae*	0.55	GDG expert opinion and Barrett-Connor (1971)[14]
Sensitivity to *H. influenzae*	0.55	GDG expert opinion and Barrett-Connor (1971)[14]
Sensitivity to *S. aureus*	0.80	GDG expert opinion
Sensitivity to aerobic Gram-negative rods	0.80	GDG expert opinion
Specificity to *S. pneumoniae*	0.71	GDG expert opinion and Guckian et al (1978)[88]
Specificity to *H. influenzae*	0.71	GDG expert opinion and Guckian et al (1978)[88]
Specificity to aerobic Gram-negative rods	0.74	GDG expert opinion and Guckian et al (1978)[88]
Urinary pneumococcal antigen		
Sensitivity to *S. pneumoniae*	0.74	Sinclair et al (2013)[185]
Specificity to *S. pneumoniae*	0.97	Sinclair et al (2013)[185]
Urinary legionella antigen		
Sensitivity to *L. pneumophila*	0.74	Shimada et al (2009)[179]
Specificity to *L. pneumophila*	0.99	Shimada et al (2009)[179]

Changes in management

- A change in management was defined as a change in antibiotic prescription only.
- All patients were treated empirically with a broad-spectrum beta-lactam lactam (the cost used in the model was based on patients receiving co-amoxiclav) plus a macrolide.

The pathogen detected dictated the change in antibiotic therapy as per susceptibility described in Table 55:

  - If *S. pneumoniae* was detected, it was assumed that a switch to a narrow-spectrum beta-lactam would be made
  - If *H. influenzae* was detected, it was assumed that the macrolide component of the antibiotic treatment would be stopped
  - If *S. aureus* was detected, it was assumed that antibiotic therapy would be changed to flucloxacillin
    - If *'Staphylococcus species'* was detected, 24 hours of flucloxacillin was added to empirical treatment (to allow for further identification of the *Staphylococcus* species)
  - If *Legionella pneumophila* was detected, it was assumed that treatment would be changed to a fluoroquinolone
  - If an aerobic Gram-negative rod was detected, it was assumed that a switch to piperacillin-tazobactam would be made.

- If a patient tested negative, empirical treatment would be continued without further tests.

Combinations

- If more than 1 pathogen was detected in a combination of tests, treatment would depend on the susceptibility of the second pathogen to the treatment for the first pathogen. For example, if *S. pneumoniae* was detected together with aerobic Gram-negative rods, no further treatment would be required as *S. pneumoniae* is susceptible to piperacillin-tazobactam.
- In the combination of blood culture and sputum culture:
    - the result of the blood culture was trusted over sputum culture, unless the blood culture reported '*Staphylococcus* species' in which case treatment for both organisms would be required.
- In the combination of blood culture and urinary antigen tests:
    - the result of the urinary *Legionella* antigen test over "all tests" was trusted, unless the blood culture reported '*Staphylococcus* species' in which case treatment for both organisms would be required
    - the result of the urinary pneumococcal antigen test was trusted over blood culture even if '*Staphylococcus* species' was reported.
- When all tests were done in combination:
    - as above, the result of the blood culture was trusted over sputum culture
    - the result of the urinary *Legionella* antigen over "all tests" was trusted, unless the blood culture reported '*Staphylococcus* species' in which case treatment for both organisms was required
    - the result of the urinary pneumococcal antigen test was trusted over blood culture even if '*Staphylococcus* species' was reported.

Treatment pathway

Treatments were defined as 'incorrect' if the pathogen was resistant to the antibiotic therapy as defined by Table 55.

- All patients were started on intravenous (IV) antibiotic therapy with switch to oral antibiotic therapy after 2 days.
    - Patients correctly treated with piperacillin-tazobactam would remain on IV antibiotic for 7 days, due to the likely antibiotic susceptibility profile of aerobic Gram-negative rods.
    - Patients who deteriorated, or did not respond to (incorrectly treated) IV piperacillin-tazobactam would be switched to another broad-spectrum beta-lactam (co-amoxiclav) after 24 hours.
- The proportion of those admitted to and time spent in an intensive care unit (ITU) was assumed to be similar across all pathogens, as this parameter is most influenced by severity of pneumonia rather than pathogen. As such, the cost of ITU was not included in the model.
- The model did not allow for recurrence or relapse of pneumonia.
- All patients had a hospital stay of at least 7 days.
- Patients treated 'incorrectly' had an additional 3 days' length of stay (LOS) over those treated 'appropriately'.

Table 55: Antibiotic susceptibility

	S. pneumoniae	*H. influenzae*	*S. aureus*	*L. pneumophila*	Atypical pathogens	Aerobic Gram-negative rods
Empirical	S	S	S	S	S	S/R[b]
Broad-spectrum beta-lactam	S	T	S	R	R	S/R[b]
Narrow-spectrum beta-lactam	T	S[a]	R	R	R	R
Flucloxacillin	S	R	T	R	R	R
Macrolide	S	S/R[C]	S	S	S	R
Fluoroquinolone	S	S	S	T	S	S
Piperacillin-tazobactam	S	S	S	R	R	T

Note: S = susceptible, R = resistant, T = targeted treatment

(a) Susceptible to amoxicillin but not to benzylpenicillin

(b) Some susceptible, some resistant

(c) H. influenzae could be either resistant or have intermediate susceptibility to macrolide

Quality-of-life

- It was assumed that patients with moderate- and high-severity CAP would only ever return to 95% of their pre-pneumonia quality-of-life, which would occur after 6 months.
- Severe sepsis was used a proxy for moderate- and high-severity pneumonia due to quality-of-life data limitations.

Mortality

- Due to mortality data limitations, the GDG refined mortality estimates, using published and unpublished data and clinical experience. See Table 56 for parameters used in the model.
- Death was assumed to occur within 30 days. After 30 days, the model assumes mortality is not affected by pneumonia.

Table 56 Probability of pathogen-specific mortality

	Non-targeted treatment	Targeted treatment	Source
S. pneumoniae	0.14	0.14	Lim et al (2001)[120]
H. influenzae	0.05	0.05	Lim et al (2001)[120]
S. aureus	0.50	0.30	Lim et al (2001)[120]
L. pneumophila	0.11	0.11	Lim et al (2001)[120]
Atypical	0.05	0.05	Lim et al (2001)[120]
Aerobic Gram-negative rods	0.4	0.25	Lim et al (2001)[120] and GDG expert opinion

9.3.1.2 Results

In the base case (moderate-severity CAP), the most cost-effective microbiological testing strategy was to perform a blood culture and a sputum culture (see Table 57). This remained the same in a number of sensitivity analyses; when all mortality probabilities were doubled (to account for high-severity CAP), quality-of-life returned to pre-pneumonia levels and a range of specific pathogen mortality probabilities were used.

However, for patients in whom sputum was not available, the most cost-effective strategy was blood culture alone and when ITU pathogen prevalence was used, the most cost-effective strategy was all tests in combination.

When base case test sensitivities were reduced by more than 88%, blood culture replaced the combination of blood culture and sputum culture as the most optimal strategy. When ITU prevalence of pathogens was used, sensitivities of tests needed to be only reduced by 25% in order for the combination of blood culture and sputum culture to replace all tests in combination as the optimal strategy.

If there were to be a QALY gain from targeted treatment it would need to be above 0.0134 QALYs before all tests in combination would become the most cost-effective strategy compared with the blood culture and sputum culture strategy.

Table 57: Base case (moderate-severity community-acquired pneumonia) – probabilistic results

Strategy	Cost (£)	QALYs	NMB	Rank[(a)]	Probability optimal strategy[(b)]
Blood culture and sputum culture	£2,683	7.4103	145,524	1	58%
All tests	£2,731	7.4103	145,475	2	5%
Sputum culture	£2,664	7.4066	145,468	3	18%
Blood culture	£2,582	7.3670	144,758	4	3%
Blood culture and urinary antigen tests	£2,642	7.3670	144,698	5	0%
No testing	£2,570	7.3488	144,406	6	15%
Urinary pneumococcal antigen	£2,589	7.3488	144,387	7	2%
Urinary legionella antigen	£2,610	7.3488	144,36	8	0%

Strategy	Cost (£)	QALYs	NMB	Rank[a]	Probability optimal strategy[b]
			6		

(a) Ranked by average NMB (£20,000 per QALY threshold)
(b) Percentage of simulations in which the microbiological testing strategy was the optimal strategy

Major limitations

Due to the lack of evidence and pragmatic constraints relating to model complexity, a number of assumptions were made to facilitate this model, relating both to the data inputs and the model structure. A considerable number of inputs within this model used data that is an assumption by the GDG, indirect evidence, or not from high quality randomised controlled trials. This data limitation does cause uncertainty around the model results, yet the probabilistic nature of the model and the sensitivity analyses undertaken minimises this risk.

A key assumption that may not translate to clinical practice is that this model assumed that patients had only a single causative pathogen. Moderate- and high-severity CAP can be caused by multiple pathogens and it is possible that it may be more acceptable to undertake additional tests to identify the rarer pathogens in this scenario. Further to this, with 30% of cases having unidentified aetiology, the true prevalence of these pathogens may be different to that within the model. Patients may also have a bacteraemia due to other undiagnosed causes (such as an urinary tract infection) which will still require treatment despite a positive urinary antigen or sputum culture result.

The model also assumed that except for mortality there were no other causes of treatment failure and that there were no adverse events, which would be likely to impact both the cost of some strategies and their QALYs gained. However, it was considered that estimating the incidence of treatment failure (other than mortality) and adverse events would have introduced too many unnecessary complications given the relatively limited impact of these effects compared with the impact of mortality.

In addition, there is no accepted method of estimating a cost for the advantages of antimicrobial stewardship. Reducing the need for inappropriate antibiotic therapy may lead to long-term economic benefits, on both an individual and societal level, through the use of lower cost antibiotics and the continued ability to use basic antibiotics for common conditions. With the development of new antibiotics slowing, this is a key issue, both in terms of costs and quality-of-life.

The evidence on quality-of-life reductions associated with high-severity CAP is extremely limited. Using severe sepsis as a proxy does have limitations. This may either under- or over-value the true quality-of-life reductions associated with moderate- and high-severity CAP and ineffective treatment.

Further to this, the model was unable to capture the fact that Legionnaires' disease became a notifiable disease in early 2010 in England. For those with high-severity CAP, legionella urinary antigen tests should still be considered for surveillance reasons.

The model may not have fully captured the benefits of urinary pneumococcal and legionella antigen tests as these pathogens are susceptible to empirical treatment and hence no decrease in mortality was assumed with targeted treatment for these 2 pathogens. The health benefit of all tests in combination may be underestimated by the model, as the paper by Uematsu et al (2014)[194] included in the clinical review suggests - a lower mortality is evident in the all tests strategy in this paper, while in our model there is no QALY gain associated with conducting urinary antigen tests in addition to blood and sputum culture tests. However, it should be noted that the design of the study by Uematsu and colleagues demonstrates only an association between mortality and test strategy, and a number of confounding factors could explain this association.

9.4 Evidence statements for patients with community acquired pneumonia

9.4.1 Clinical

9.4.1.1 Empirical compared with targeted treatment using a combination of tests

- Very low quality evidence from 1 RCT of more than 200 patients and 2 non-randomised studies (N = 605 and N = 65,145) showed a consistent effect in favour of targeted treatment following a combination of tests for reducing mortality for patients with CAP.A *post-hoc* subgroup analysis stratified by severity using A-DROP suggested this survival benefit was greater in patients with severe and very severe CAP than in patients with milder disease. However, no clear differences were seen for clinical failure, length of hospital stay or SF-36 score. One non-randomised study showed that a clinically relevant increase in the proportion of people with a change in prescription occurred when microbiological tests were performed.

9.4.1.2 Empirical compared with targeted treatment using urinary antigen tests

- Very low quality evidence from 1 RCT (N = 177) of hospitalised patients with CAP showed that there may be no clinical difference between empirical treatment and urinary antigen-(pneumococcal or legionella) targeted treatment for the outcomes of mortality, clinical relapse or re-admission.
- A large retrospective database analysis of over 65,000 patients with CAP suggested a reduction in 30-day in-hospital mortality for patients receiving urine antigen tests across all severity groups. This effect was greater in the subgroup of patients with low-severity CAP, but the evidence was considered to be very low quality. This study reported no significant difference in length hospital stay between the 2 groups.

9.4.1.3 Empirical compared with targeted treatment using blood culture

- The majority of the evidence suggested that there may be a benefit associated with performing blood cultures for reducing mortality; however, the size of this effect was small and the quality of the evidence was regarded as very low.
    - One study also suggested that hospital re-admission may be reduced by performing blood culture in patients with CAP. However, no clinically relevant impact of performing blood culture was seen for length of hospital stay, and findings for clinical instability differed depending on whether the blood culture was performed within 24 hours of hospital arrival or before antibiotic administration.

9.4.1.4 Targeted treatment using a combination of tests with or without pneumococcal urinary antigen

- Very low quality evidence from one non-randomised study demonstrated that adding the pneumococcal urinary antigen test to microbiological tests may result in a clinically relevant increase in the proportion with a test positive for pneumococcus; however this may not translate into a clear benefit in terms of the proportion of patients treated with a narrowed antibiotic spectrum.

9.4.2 Economic

- One cost-consequence analysis found that targeted treatment was more costly than empirical treatment for treating high-severity CAP (£33 more per patient) and had 0.0114 more deaths per patient; 0.0230 more clinical relapses per patient; 0.0009 more days of hospitalisation; 0.0230 more re-admissions; 0.3 more days of antimicrobial treatment per patient; 0.2 more days of intravenous treatment per patient; but 0.0112 fewer ITU admissions per patient; 0.0889 fewer

adverse events per patient and the same overall length of stay per patient. This analysis was assessed as partially applicable with very serious limitations.

- One cost–utility analysis found that blood and sputum cultures in combination were cost effective compared with no test, blood culture, sputum culture, urinary pneumococcal antigen, urinary legionella antigen, a combination of a blood culture and a sputum culture, a combination of a blood culture, a urinary pneumococcal antigen and a urinary legionella antigen, and all tests in combination for detecting pneumonia pathogen in moderate- and high-severity patients with CAP admitted to hospital. It also found that blood and sputum cultures were dominant (less costly and equally effective) compared with all tests, no test was dominant compared with urinary pneumococcal antigen and urinary legionella antigen tests, and blood culture was dominant compared with blood culture in combination with urinary antigen tests. However there needs to be a relatively modest QALY gain from targeted treatment in order for all tests in combination to be the optimal strategy. This analysis was assessed as directly applicable with potentially serious limitations.

9.5 Recommendations and link to evidence

Table 58: Linking evidence to recommendations– microbiological tests for moderate- and high-severity community-acquired pneumonia

Recommendations	**7. Do not routinely offer microbiological tests to patients with low-severity community-acquired pneumonia.** **8. For patients with moderate- or high-severity community-acquired pneumonia:** • **take blood and sputum cultures and** • **consider pneumococcal and legionella urinary antigen tests.**
Relative values of different outcomes	The GDG considered that evidence of an appropriate change in management as a result of the use of microbiological tests (for example, the narrowing of antibiotic treatment spectrum, or switching to a different antibiotic regimen for pathogens not covered by empirical treatment) was the most relevant outcome. A positive impact (or lack of negative impact) on mortality, clinical cure, treatment failure, complications or length of stay were considered other relevant outcomes.
Trade-off between clinical benefits and harms	Three studies, 1 of which was randomised, examined empirical compared with targeted treatment guided by a combination of microbiological tests. More changes in prescription were seen in the targeted treatment group. All studies suggested reduced mortality in patients who received targeted treatment. However, there was no important difference in clinical failure which would be expected if the reported differences in mortality were a true effect. There was a reduced length of stay (by 1 day) in the targeted treatment group. There was no difference in SF-36 quality-of-life scores at 30 or 90 days between the groups, but at 180 days the targeted treatment group had favourably higher scores compared with the empirical treatment group (although the number of responders at 180 days was extremely low – 20% of the full sample). One RCT and 4 multivariate analyses examined empirical treatment compared with targeted treatment based on blood culture results. There were no differences in mortality, length of stay or re-admission rates between the groups. In 1 retrospective study, a higher proportion of patients achieved clinical stability at 48 hours when blood cultures were performed within 24 hours (blood culture results usually become available after 48 hours, but the Gram stain may be available within 24 hours). However, the GDG noted that performance of blood cultures may be a marker of a generally high standard of care and agreed that the outcome could be a result of good overall clinical practice rather than the independent utility of the test. One randomised study found no substantial differences in mortality, clinical relapse, length of stay or other clinical outcomes between patients treated with empirical antibiotic therapy and those who received targeted treatment based on urinary pneumococcal and legionella antigen tests. One non-randomised comparative cohort study used empirical then targeted antibiotic therapy for all patients, with targeting based on a combination of tests with or without pneumococcal urinary antigen testing. The study found that testing for pneumococcal urinary antigen increased the likelihood of identifying pneumococcal infection, but there was no difference in the proportion of patients with a change in prescription.

Trade-off between net health benefits and resource use	One suitable economic evaluation was considered. This examined targeted treatment using urinary pneumococcal and legionella antigen testing compared with empirical treatment. No incremental cost analysis was reported in the paper but it was possible to use the data to perform such an analysis; this showed an incremental cost of £33 per patient in the targeted group. However, the study had very serious limitations and was partially applicable. The study used costs derived from a single hospital in Spain, and significant limitations were noted pertaining to the clinical paper on which the cost analysis was based. An original model developed for this guideline showed that blood culture in combination with sputum culture is the optimal strategy for patients with confirmed moderate- and high-severity CAP, managed in a hospital setting. Compared with all tests in combination, this strategy yielded the same amount of QALYs at a lower cost. However this analysis assumes there to be no benefit in terms of lower mortality from targeted treatment for those pathogens detected by the antigen tests (*Legionella* spp and *S. pneumoniae*). In a sensitivity analysis, all tests in combination became cost effective when targeted treatment reduces mortality of *L. pneumophila* to 10.4% (from 11.0%) or targeted treatment reduces mortality from *S. pneumoniae* to 13.8% (from 14.0%). Another threshold analysis showed that if there was a QALY gain from targeted treatment of more than 0.0134 over the lifetime of a patient, all tests in combination is the most cost-effective strategy. Other sensitivity analyses showed that when patients are unable to produce sputum, blood culture alone is the optimal strategy, and if the prevalence of pathogens is closer to that observed in the ITU, all tests in combination becomes the optimal strategy. Our analysis advocates that there needs to be a relatively modest QALY gain from targeted treatment in order for all tests in combination to be the optimal strategy. Also, the GDG have acknowledged that the model did not consider the benefit from targeted treatment in terms of decreased antibiotic resistance and decreased adverse events from antibiotic treatment. The model may not have fully captured the benefits of urinary pneumococcal and legionella antigen tests as these pathogens are susceptible to empirical treatment and hence no decrease in mortality was assumed with targeted treatment for these 2 pathogens. The health benefit of all tests in combination may be underestimated by the model, as the paper by Uematsu et al (2014)[194] included in the clinical review suggests - a lower mortality is evident in the all tests strategy in this paper, while in our model there is no QALY gain associated with conducting urinary antigen tests in addition to blood and sputum culture tests. However, it should be noted that the design of the study by Uematsu and colleagues demonstrates only an association between mortality and test strategy, and a number of confounding factors could explain this association.
Quality of evidence	The studies presented evaluated the difference in the outcomes between the groups of patients who were tested with different microbiological tests compared with those who did not undergo these tests. Because of limited data available from randomised studies, the GDG considered data from other studies in which groups of patients had either undergone microbiological testing of some form, or had received no tests. However, the GDG was aware that these studies can only show associations between microbiological testing and clinical outcome. The assumption that the outcome is the result of having had the microbiological tests is much weaker in these studies than it would be with RCT results. Some of the comparative non-randomised studies were of reasonable quality, but others did not adjust for confounders and so were considered to be at very high risk of bias for clinical outcomes. The evidence comparing empirical with targeted antibiotic therapy using a combination of tests was of low or very low quality by GRADE criteria. The GDG

	noted that whilst both studies (1 RCT and 1 observational study) reported a lower mortality with targeted treatment, neither study specified mortality as their primary outcome and were not powered to detect a difference in this outcome. In addition, the pathogen identification rate was higher than that typically seen in clinical practice; some patients had pathogens identified on a "presumptive" basis, the criteria for which were unclear. The evidence examining blood cultures was of very low quality by GRADE criteria. The GDG commented that findings were inconsistent. The study examining both legionella and pneumococcal urinary antigen test usage was of very low quality by GRADE criteria. Low event rates led to a high degree of imprecision in results. The study examining pneumococcal urinary antigen testing alone was of very low quality by GRADE criteria. The GDG noted that the outcomes reported were extremely limited. The economic evidence on targeted treatment was assessed as partially applicable with very serious limitations, while the original model on microbiological tests was assessed as directly applicable with potentially serious limitations.
Other considerations	The GDG agreed that routine performance of microbiological tests was unlikely to be useful in low-severity CAP. Low-severity CAP is usually treated with a narrow-spectrum antibiotic, so there is little scope to narrow the spectrum of antibiotic therapy further. In addition, in patients with low-severity CAP the consequences of treatment failure due to the pathogen not being sensitive to empirical treatment are less likely to be serious, so microbiological testing for this reason is unlikely to be cost effective. The recommendation pertaining to moderate- and high-severity CAP was debated at length. Acknowledging the limited evidence available, the GDG discussed the potential advantages and disadvantages of microbiological tests in CAP, including those that may be difficult to capture and quantify in studies. The advantages of microbiological tests may include (1) confirmation of a pathogen covered by empirical treatment, allowing the antibiotic spectrum to be narrowed or optimised, with potential associated benefits of minimising side effects of treatment and minimising resistance of pathogens in the wider population; (2) identification of pathogen not covered by empirical treatment, allowing treatment to be altered to cover the pathogen with associated improvement in outcomes; and (3) identification of a non-respiratory pathogen in blood cultures which may lead to an alternative (or additional) diagnosis to CAP. Conversely, in some patients, more than 1 bacterial pathogen may be implicated. In these instances, narrowing the spectrum of treatment could potentially cause harm. However, the GDG agreed that none of the evidence suggested that targeted treatment was likely to lead to significantly worse outcomes compared with empirical treatment, and that targeted treatment was therefore usually desirable on the grounds of antibiotic stewardship. The disadvantages of microbiological testing may include the time and cost associated with performing such tests, in addition to the risk of false positive and false negative results leading to detrimental changes (or lack of changes) in treatment. In patients with moderate- and high-severity CAP, where broad-spectrum antibiotic therapy is used for empirical treatment, there is more scope for narrowing the

	antibiotic spectrum if a specific pathogen is identified. In addition, treatment failure in patients with high-severity CAP is likely to be associated with significant morbidity and mortality, therefore identification of pathogens insensitive to empirical treatment is highly desirable. Patients who are misdiagnosed with high-severity CAP when they actually have some other infective illness are likely to be seriously ill with a high risk of morbidity and mortality, so the added benefit of potentially identifying an alternative diagnosis as a result of a positive blood culture in these circumstances was acknowledged. The decision of the GDG thus depended on the outcome of the balance of benefits and harms. The group was particularly cognisant of the results of the associated health economic modelling analysis and noted its sensitivity to small changes in QALY gain relating to the (as yet unquantifiable) benefits of antibiotic stewardship linked with targeted therapy for CAP. The GDG therefore concluded by consensus that in patients with moderate- and high-severity CAP blood and sputum culture should be offered and urinary antigen tests only "considered", as the evidence was not strong enough to support a stronger recommendation. The GDG agreed that the importance of public health principles relating to this consider recommendation behove the need for further research in order to resolve the uncertainty. **Key priority for implementation** The GDG agreed that implementing urinary antigen testing would set challenging but achievable expectations of health services and lead to more efficient use of NHS resources through the reduction of antimicrobial resistance at a population level.

9.6 Research recommendation

1. **In moderate- to high-severity community-acquired pneumonia does using legionella and pneumococcal urinary antigen testing in addition to other routine tests improve outcomes?**

Why this is important:

Current practice and evidence suggests that giving a combination of antibiotics to patients with moderate- to high-severity community-acquired pneumonia reduces mortality. However, no randomised controlled trial has looked at using urinary antigen testing to target treatment. If effective, such targeted treatment could improve antibiotic stewardship, increase compliance and potentially reduce costs.

10 Antibiotic therapy

Antibiotic therapy is the cornerstone of management of community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP). In an ideal world it would be possible to ensure that the causative organism in that individual is sensitive to the choice of antibiotic prescribed. However, the causative bacterium is not known when the patient first presents for medical attention and in many patients it is never known. Initial antibiotic therapy is therefore commenced on an empirical basis. In many patients this remains the basis of treatment throughout their illness. This empirical choice is based on knowledge of the common causative bacteria and their usual antibiotic sensitivities.

However pneumonia can be caused by a number of different bacteria each with different antibiotic sensitivity profiles. The bacterial causes of CAP and their antimicrobial sensitivities are similar throughout the UK. The bacterial causes of HAP (with the exception of that which occurs after intubation) are not well described, and the bacteria and their resistance profiles may vary from hospital to hospital. A large number of antibiotics are available to which the causative bacteria may or may not be sensitive. Each antibiotic will have a different spectrum of antibacterial activity, pharmacodynamic characteristics, potentially harmful side effects and costs. A combination of 2 or more antibiotics might be better (improved outcomes or less harms or both) than any single antibiotic given alone. The balance between benefits and harms may be different in different settings. A minor side effect might be important in a patient with low-severity pneumonia where a number of different antibiotics could produce the same benefit. The same side effect might be less important in a severely ill patient with a higher risk of death where the antibiotic with this side effect is the only one with the capacity to reduce the risk of death. Choice of empirical antibiotic therapy is therefore not straightforward and should be based on a balanced comparison of benefits and harms of each regimen in the treatment of pneumonia, ideally obtained from controlled, comparative, clinical trials.

The GDG recognises that viruses may also be important causes of pneumonia. With the exception of antiviral agents active against the influenza viruses there are currently few available antiviral agents for the known causative respiratory viruses. It is accepted that use of neuraminidase inhibitors may be appropriate additional treatment for adults with influenza-related pneumonia, but detailed evaluation of this is beyond the scope of this guideline.

Common sense suggests that if an antibiotic is to be given, it should be given as early as possible in the course of the illness. However it is not clear whether such early administration does improve outcomes. There may be practical limitations as to how early antibiotic therapy can be given. If the benefit of early administration is demonstrated to be large then investment to overcome the practical hurdles might be worthwhile.

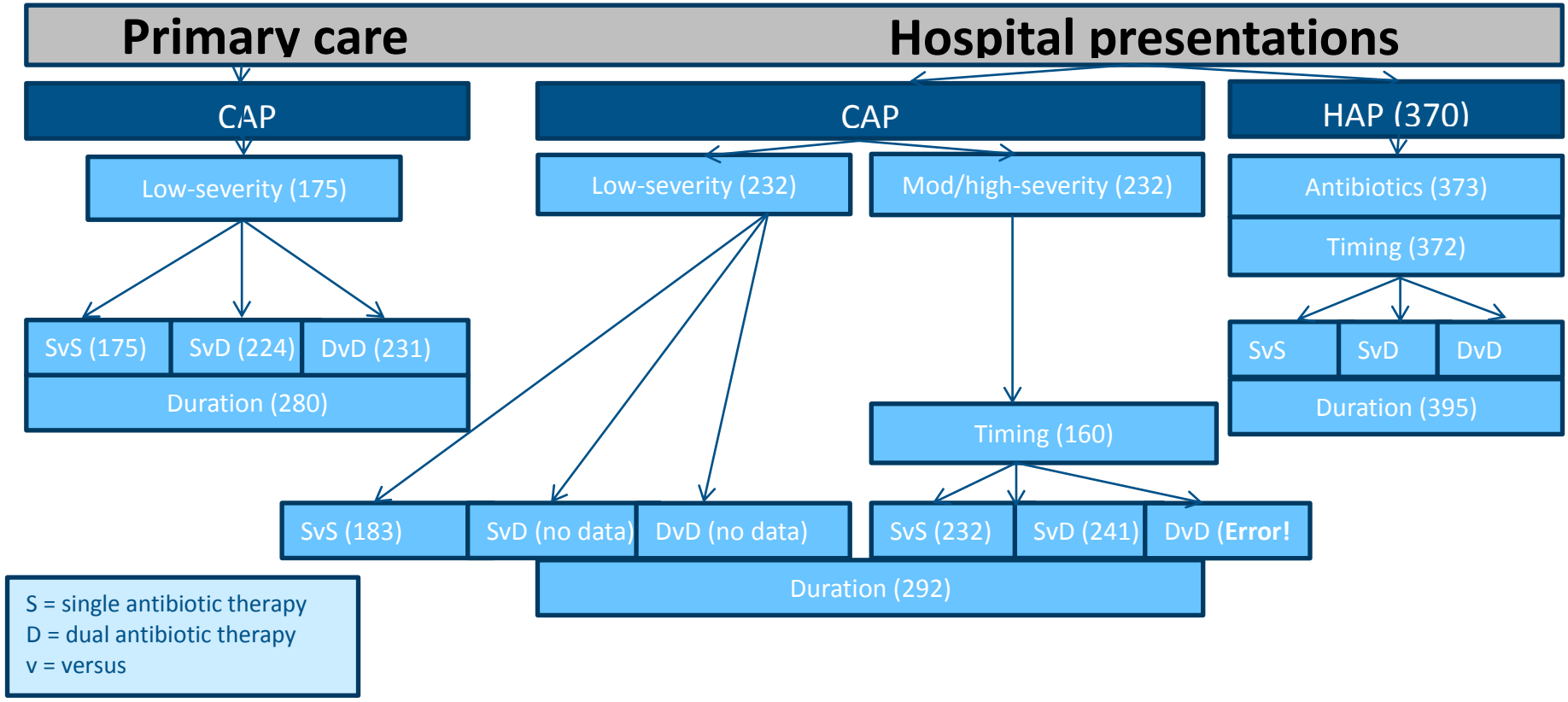
The most appropriate duration for antibiotic therapy in an adult with CAP or HAP is not known. A prolonged course has the advantages of being more likely to have killed the causative bacteria, but the disadvantages include increased harmful side effects and increased cost. A short course is less likely to be harmful and cheaper, but only if it is given for long enough to kill the bacteria and cure the illness. A course of antibiotic therapy that is too short could result in relapse or recurrence of illness, which could be more expensive and more likely to result in death. Currently-used durations of antibiotic therapy are based on historical practice rather than strong evidence, and it may be that shorter treatment durations can produce the same benefits with less harm and cost.

Because of these uncertainties, the GDG requested a comprehensive assessment of the evidence base for empirical antibiotic therapy and posed questions to clarify when and which empirical antibiotic choice would be the most cost-effective treatment for 2 severity strata in CAP (low, and moderate- to –high severity), and HAP, as well as for how long the treatment should optimally be offered.

The questions and data relating to therapy for hospital-acquired pneumonia can be found in chapter 18.

Please see Figure 5 for assistance in navigating this chapter.

Figure 5: Map of antibiotic therapy chapters (numbers in brackets are page numbers and are hyperlinked to the relevant sections)



10.1 Timing of antibiotic therapy

10.2 Review question: In adults with suspected community-acquired pneumonia is earlier rather than later antibiotic administration more clinically and cost effective?

We searched for evidence from systematic reviews, RCTs and observational studies, as the GDG considered it unlikely that RCTs would be available (due to ethical concerns related to treatment delay). As the effect of timing of antibiotic therapy on outcomes may be moderated by other factors, only cohort studies reporting results with a multivariate analysis that adjusted for important confounders were considered as the least biased study design to answer this review question.

For full details see review protocol in Appendix C:.

Where possible, data were stratified for severity. Ideally this would be done on the basis of formal assessment tools (see chapter 8) but it was sometimes necessary to accept other methods used by the authors of the included papers (for example, severity based on site of care).

10.2.1 Clinical evidence

No RCTs comparing the effectiveness and safety of different timings of antibiotic therapy were found.

We included only observational studies that employed a multivariate type of analysis. Thirteen cohort studies were included in this review with the majority of patients reported to have moderate-to high-severity CAP. No observational studies were found for patients with low-severity CAP with the exception of one study (Houck 2004) which gave subgroup analysis for patients with low to moderate risk and those with high risk. The majority of the included studies employed formal severity assessment tools (such as PSI) to categorise the severity status of patients. Only 7 studies used place of care (community, hospital, ITU) as surrogates for assessing severity status.

Explanatory factors assessed in the multivariate analysis in the included observational studies were determined in 2 ways:

- Pre-specified multivariate analysis conducted in 1 stage: explanatory factors (confounders) were included based on the well-established findings of previous studies or clinical judgement
- Multivariate analysis conducted in 2 stages: in the first stage, a univariate analysis was performed to detect if any of the explanatory factors were associated with the outcomes of interest (this is usually defined at a certain level of p-value, for example $p < 0.20$) and in a second stage, a multivariate analysis was conducted by including only the confounding factors that remained associated in the first step.

Among the observational studies that conducted the multivariate analysis in 2 stages, some did not find timing of antibiotic therapy to be a significant factor affecting the outcome of interest in their univariate analysis (first stage) and therefore this factor (timing of antibiotic therapy) was excluded from the multivariate analysis. A summary of these studies is shown in the appendix of supplementary evidence (Appendix P:). A summary of studies in which timing of antibiotic administration entered the multivariate analysis is presented in Table 59.

For consistent evidence interpretation, we inverted the adjusted ORs or RRs given for some studies in a direction of early compared with later administration of antibiotic even if this was not the direction of results reported by the authors (this is noted in the results where applicable).

See also the study selection flow chart in Appendix D:, forest plots in Appendix I:, study evidence tables in Appendix G:and exclusion list in Appendix J:.

Table 59: Summary of included studies with multivariate analysis including timing of antibiotic therapy

Study	Study type, population	Setting/ Source of data	Sample size	Factors included in multivariate analysis	Outcomes available	Comments
Simonetti 2012[183]	Prospective cohort study. High-severity CAP (> 50% of patients with PSI ≥ IV). Excluded patients with pre-hospital antibiotic therapy.	Barcelona (800 bed hospital) between 2001 and 2009	1274	1. Age 2. Sex 3. Comorbidities (unclear which were included) 4. Initial appropriate antibiotic therapy 5. Severity 6. Timing – 4 and 8 hours	• 30-day mortality (following admission)	• Multivariate logistic regression analysis included variables "potentially associated" with 30-day mortality in the univariate analysis, regardless of statistical significance. • Number of variables restricted so that there were at least 5 to 9 events per variable. • Mean TFAD 5.9 hours. • Excluded those with prior antibiotic therapy.
Houck 2004[97]	Retrospective chart review. High-severity CAP (> 50% of patients with PSI ≥ IV). Patients with pre-hospital antibiotic therapy analysed separately.	USA, national random sample Medicare patients in 1998 and 1999, 850 cases per state	18,209 included from 39,242 cases assessed	1. Antibiotic timing 2. PSI score 3. Admission to an ITU during the first 24 hours 4. Census region of hospitalisation 5. Arterial oxygenation 6. Blood culture within 24 hours of arrival 7. Initial antibiotic regimen consistent with IDSA or ATS guidelines 8. Ethnicity	• 30-day mortality (following admission) • mortality during hospitalisation • prolonged length of stay (> 5 days) • Re-admission after discharge (within 30 days)	• Multivariate analysis included pre-specified factors found in the univariate analysis. These were factors known to be associated with outcomes as reported in previous studies or found in univariate analysis. • 24.4% prior antibiotic therapy.

Study	Study type, population	Setting/ Source of data	Sample size	Factors included in multivariate analysis	Outcomes available	Comments
Battleman 2002[16]	Retrospective chart review. Moderate- to high-severity CAP (hospital setting, no formal severity assessment). Excluded patients with pre-hospital antibiotic therapy.	New York Presbyterian Healthcare (NYPH) system, 100 per institution in 1998.	609 from 700 assessed	1. Age 2. Ethnicity 3. Payer – Medicaid or self-pay 4. COPD 5. Comorbid illness 6. White blood cell count at admission 7. Respiratory rate at admission 8. Site of initial antibiotic administration 9. Appropriateness of antibiotic 10. Timing of antibiotic (8 hours or later)	• prolonged length of stay (> 9 days, the 75th percentile)	• Two-stage analysis: Univariate analysis included 13 pre-specified factors. Any variable significant at $p \leq 0.2$ from the univariate analyses were included in the multivariate logistic regression analysis. • Included 18% of patients admitted from a nursing home. • Patients with antibiotic therapy prior to admission were excluded. • Mean TFAD 3.5 hours for those treated in ED; 9.5 hours for those treated on the inpatient ward.
Waterer 2006[203]	Prospective observational study. Moderate- to high-severity CAP (majority of patients with PSI III or ≥ IV[1]).	Patients admitted to USA hospital between 1998 and July 2001	451	1. Altered mental state 2. Age 3. Time to antibiotics > 4 hours 4. Absence of hypoxia 5. Absence of fever	• mortality (not defined)	• Mortality – not defined. • Factors that reached a threshold of $p < 0.1$ were included in multivariate analysis model. • Mean TFAD 4.75 hours.
Dedier 2001[59]	Retrospective chart review/ database	US 1997 to 1998	1062	• Antibiotic administration ≤ 8 hours of hospital arrival	• mortality (inpatient) • length of stay (> median)	• Timing was one of the 4 pre-specified processes of care factors analysed.

Study	Study type, population	Setting/ Source of data	Sample size	Factors included in multivariate analysis	Outcomes available	Comments
	(cohort). High-severity CAP (> 50% of patients with PSI ≥ IV).			• Blood culture ≤ 24 hours • Blood culture before antibiotic • Oxygenation measurement ≤ 24 hours • PSI	• clinical instability at 48 hours	• Cut-off 8 hours, one of 4 process markers analysed. • Median TFAD 4.2 hours. • Excluded those with prior antibiotic therapy.
Wilson 2005[205]	Retrospective medical record review. High-severity CAP (requiring ITU admission, no formal severity assessment).	Two Australian hospital databases, 2001 to 2003.	96	1. Age 2. Antibiotic therapy prior to admission 3. Treatment delay > 4 hours 4. Multilobar or bilateral disease 5. PSI 6. Smoking	• mortality (inpatient)	• Cut-off 4 hours. • Unclear how factors were selected for entry into the multivariate analysis - most likely dependent on univariate data. • PSI was not associated with mortality rate unless age was left of out the analysis. • Mean TFAD 3.3 hours. • 23% had prior antibiotic therapy.
Huang 2006[99]	Prospective cohort. Suspected CAP (hospital setting, no formal severity assessment).	Seven 'Capital Health' hospitals in Canada, 2000 to 2002.	2757 of 3473 before exclusions.	1. Age 2. Study site 3. Residence on admission 4. Weight loss 5. Functional status 6. CAP pathway used 7. Oxygen saturation 8. Symptoms – sweats/fever/ shaking/cough/sputum/altered mental state/wheeze 9. Comorbidities – heart disease, dementia, stroke, neoplastic,	• length of stay ([LOS] > 7 days).	• Variables with $p < 0.1$ in univariate analysis used in multivariate analysis. • Also conducted multiple linear regression on factors associated with median LOS – hours presenting to Emergency Department to first antibiotic dose (per additional hour). • Ratio (all suspected CAP): 1.01 (1.0 to 1.01), $p < 0.03$; Ratio (definite CAP) same

Study	Study type, population	Setting/ Source of data	Sample size	Factors included in multivariate analysis	Outcomes available	Comments
				cerebrovascular, congestive heart failure, renal disease. 10. Mean hours from presenting to E D to first antibiotic.		as above at p = 0.003. • Mean TFAD 8.3 hours.
Lee 2011[112]	Retrospective observation (secondary analysis) of a prospective RCT. Moderate- to high-severity CAP (PSI III: 24.4%, PSI ≥ IV: 48.5%).	Hospitalised for CAP in 32 EDs in Connecticut and Pennsylvania in 2001.	2076 of 4506 before exclusions.	1. PSI risk class 2. Age 3. Low, moderate or high intensity guideline implementation 4. Nursing home residence 5. Physical examination findings 6. Lab and radiographic findings 7. Treatments before presentation 8. Comorbidities not contained in the PSI – cognitive impairment, history of coronary artery disease, chronic pulmonary disease, diabetes.	• 30-day mortality (after presentation) • length of stay • hospital re-admission	• Multivariate analysis • Some comorbidities assumed to be covered in PSI risk class (neoplastic, liver, cerebrovascular, congestive heart failure, renal) not adjusted for in multivariate analysis. • 15.5% had prior antibiotic therapy.
Meehan 1997[130]	Retrospective medical record review. Elderly (≥ 65 years) pneumonia, moderate- to high-severity CAP (hospital setting, no formal severity assessment). Patients with HAP were	3555 acute care hospitals throughout the USA, Colombia and Puerto Rico. 1994-1995.	14069 of 25561 before exclusions.	1. Severity-of-illness status (assumed to incorporate age, sex, nursing home, cerebrovascular disease, congestive heart failure, neoplastic disease, liver disease and renal disease, physical examination findings and lab results) 2. Other processes of care (blood culture prior to antibiotic therapy, blood culture within 24 hours, oxygenation within 24 hours)	• 30-day mortality	• Multivariate analysis only adjusted for patient risk status (PSI) and performance of other processes of care. • Approximately 13% had prior antibiotic therapy. • Median TFAD 4.2 hours.

Study	Study type, population	Setting/ Source of data	Sample size	Factors included in multivariate analysis	Outcomes available	Comments
	excluded (hospitalisation in the previous 10 days), proportion of nursing home residents not stated.					
Bader 2011[12]	Retrospective observational cohort. Diabetes patients with moderate- to high-severity CAP (PSI III: 44.2%, PSI ≥ IV: 28.2%).	Two tertiary hospitals in Newfoundland, Canada between 2002 and-2007	206 of 596 before exclusions.	1. PSI class 2. Comorbid conditions	• in-hospital mortality	• Multivariate analysis • All patients had diabetes. • No detailed list of factors other than PSI class and comorbid conditions included in multivariate analysis. • Mean TFAD 6.3 hours.
Jo 2012[103]	Retrospective observational study. Moderate- to high-severity CAP (PSI III: 20.6%, PSI ≥ IV: 33.5%).	All adult patients diagnosed in the ED of 2 tertiary hospitals in Korea, April 2008 to Sept 2009.	477 of 597 before exclusions.	1. Low/med/high ED overcrowding level 2. C-reactive protein 3. Serum creatinine 4. Albumin 5. Total cholesterol 6. PaO_2/FiO_2 ratio 7. PSI 8. Time to first antibiotic dose (TFAD).	• 28-day mortality	• Unclear time cut-offs of TFAD included in multivariate analysis. • Unclear whether comorbidities were considered in multivariate analysis. • Median TFAD 2.8 hours.
Mortensen 2008[141]	Retrospective observational cohort (chart review).	All patients admitted to 2 academic tertiary	733 (exclusion details not provided)	1. PSI 2. Process of care measures (initial antibiotic therapy within 8 hours) 3. Receipt of antibiotic therapy within	• 30-day mortality	• No specific mention of CAP although exclusions include HAP.

Study	Study type, population	Setting/ Source of data	Sample size	Factors included in multivariate analysis	Outcomes available	Comments
	Low- to moderate-severity CAP (PSI I-III: 55%, PSI ≥ IV: 45%)	hospitals in San Antonio, Texas 1999 to 2002.		30 days prior to presentation.		
Bordon 2013[24]	Retrospective observational study Moderate- to high-severity CAP (PSI ≥ IV 55.6%)	Consecutive adult patients hospitalised with CAP at a Veterans Affairs Medical Centre in the USA.	372	1. age, platelet count, albumin, creatinine, diabetes mellitus, arterial hypertension, glucocorticosteroids, blood urea nitrogen, AMI, gender, ITU admission, respiratory rate, blood pressure, sodium, O2 saturation, heart rate, 2. nursing home residence 3. co-morbidities (such as cancer, liver disease, CHF, CVA, renal disease, AMI, COPD and HIV infection) 4. indicators of complex pneumonia such as multilobar infiltrates, pleural effusion and cavitatory lesions **5.** Time to first antibiotic dose (TFAD).	• mortality • hospital stay • time to clinical stability	• Adjusted effect size of timing on mortality not reported.

[1] *The reported severity breakdown by PSI does not add up to 100% (81.5%), but the majority of patients (48%) had PSI III or ≥ IV at baseline*

Table 60: Summary of evidence from observational studies with multivariate analysis including timing of antibiotic therapy as explanatory factor

Study (design)	Quality assessment					Outcomes					Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Study ID	No of patients	Outcome definition	Timing definition (hours)	Adjusted HR/OR/RR (95% CI)	
All-cause mortality											
9 retrospective chart reviews (Houck 2004, Bader 2011, Dedier 2001, Jo 2012, Lee 2011, Meehan 1997, Mortensen 2008, Wilson 2005, Bordon 2013) 2 prospective observational studies (Waterer 2006, Simonetti 2012)	Serious[1]	Serious[2]	No serious	Serious[3]	None	Houck 2004	18, 209	30 days	≤ 4 vs. > 4 h	**Overall**: AOR 0.85 (0.76 to 0.95) **PSI II-III**: AOR 0.62 (0.42 to 0.92) **PSI IV-V**: AOR 0.87 (0.78 to 0.97)	Very low
						Lee 2011	2076	30 days	< 4 vs. ≥ 4 h	AOR 0.7 (0.5 to 1.1)	
						Wilson 2005	96	In-hospital death	≤ 4 vs. > 4 h	AOR 0.29 (0.09 to 0.92) (inverted)	
						Waterer 2006	451	Unclear definition	≤ 4 vs. > 4 h	AOR 0.54 (0.2 to 1.19) (inverted)	
						Simonetti 2012 – CAP	1274	30 days	≤ 4 vs. > 4 h	AOR 1.12 (0.38 to 3.33)	
						Bader 2011	206	In-hospital death	≤ 8 vs. > 8 h	AOR 0.25 (0.08 to 0.83) (inverted)	
						Meehan 1997	14069	30 days	≤ 8 vs. > 8 h	AOR 0.85 (0.75 to 0.96)	
						Mortensen 2008	733	30 days	≤ 8 vs. > 8 h	AOR 1.2 (0.7 to 2.1)	
						Dedier 2001	1062	In-hospital death	≤ 8 vs. > 8 h	AOR 1. 69 (0.78 to 3.66)	
						Houck 2004	18, 209	30 days	≤ 8 vs. > 8 h	AOR 0.85 (0.73 to 0.99)	
						Simonetti 2012 – CAP	1274	30 days	≤ 8 vs. > 8 h	AOR 1.58 (0.64 to 3.88)	

Study (design)	Quality assessment					Outcomes					Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Study ID	No of patients	Outcome definition	Timing definition (hours)	Adjusted HR/OR/RR (95% CI)	
						Houck 2004[4]	18, 209	30 days	≤ 12 vs. > 12 h	AOR 0.97 (0.79 to 1.19)	
						Jo 2012	477	28 days	Continuous variable	AOR 1 (0.99 to 1.00)	
						Bordon 2013	372	30 days	Continuous variable	AHR not reported (p = 0.148)	
Length of stay (prolonged)											
5 retrospective chart reviews (Battleman 2002, Dedier 2001, Houck 2004, Lee 2011, Bordon 2013), 1 prospective cohort (Huang 2006)	Serious[1]	No serous	No serious	Serious[5]	None	Houck 2004	18,209	> 5 days (median)	≤ 4 vs. ≥ 4 h	**Overall**: AOR 0.90 (0.83 to 0.96) **PSI II-III**: AOR 0.86 (0.75 to 0.99) **PSI IV-V**: AOR 0.92 (0.84 to 1.01)	Low
						Lee 2011	2076	Unclear – discrete data model	≤ 4 vs. ≥ 4 h	AOR 1.2 (1.1 to 1.4)	
						Dedier 2001	1062	> 4 days (median) LOS	≤ 8 vs. > 8 h	AOR 0.89 (0.65 to 1.22)	
						Battleman 2002	609	> 9 days: (75th percentile)	≤ 8 vs. > 8 h	AOR 0.57 (0.44 to 0.75) (inverted)	
						Huang 2006	2757	> 7 days (median = 6.4 days)	≤ 4 vs. 4 to 8 h	AOR 1.02 (0.83 to 1.25) (inverted)	
						Huang 2006	2757	> 7 days (median = 6.4 days)	≤ 4 vs. > 8 h	AOR 0.78 (0.63 to 0.97) (inverted)	

Study (design)	Quality assessment					Outcomes					Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Study ID	No of patients	Outcome definition	Timing definition (hours)	Adjusted HR/OR/RR (95% CI)	
						Bordon 2013	372		Continuous	AHR 0.99 (0.97 to 1.02)	
Re-admission after discharge											
2 retrospective chart reviews (Houck 2004, Lee 2011)	Serious[6]	Serious[7]	No serious	No serious	None	Houck 2004	18,209	30 days	≤ 4 vs. > 4 h	**Overall**: AOR 0.95 (0.85 to 1.06) **PSI II-III**: AOR 0.87 (0.70 to 1.08) **PSI IV-V**: AOR 0.99 (0.88 to 1.11)	Low
						Lee 2011	2076	30 days	≤ 4 vs. ≥ 4 h	AOR 1.4 (0.9 to 2.2)	
Clinical instability at 48 hours											
1 retrospective chart review (Dedier 2001)	Serious[8]	No serious	Serious[9]	No serious	None	Dedier 2001	1062	Objective criteria	≤ 8 vs. > 8 h	AOR 1.04 (0.75 to 1.44)	Low

[1] *Not all key confounders adjusted for in majority of studies*
[2] *Effect estimate range from large effect in favour of earlier antibiotic therapy to no clinically relevant effect (although 95% CIs largely overlap)*
[3] *Majority of studies small and wide 95% CIs*
[4] *See also Houck forest plot in Appendix I: for more time-points*
[5] *95% CI crosses default MIDs for majority of studies*
[6] *Both studies < 50% of cases remain included after applying exclusion criteria; larger study (Houck) restricted to age over 65 years. Unclear if patients still representative of the CAP population in UK.*
[7] *Two studies show opposite direction of effect*
[8] *Not all key confounders were adjusted for in the analysis*
[9] *Surrogate outcome measure*

10.2.2 Economic evidence

Published literature

No relevant economic evaluations comparing early or late antibiotic administration in the community or the hospital were identified.

Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided in Appendix O: to aid consideration of cost effectiveness.

10.2.3 Evidence statements

10.2.3.1 Clinical

- For the key outcome of mortality, the majority of the studies (mainly retrospective chart reviews) suggested that administering antibiotic therapy within the first 4 hours of admission was beneficial in reducing mortality; however, there was inconsistency in the size of the effect and the evidence was of very low quality. When using a threshold of 8 hours there was heterogeneity in both the size and direction of effect, with some studies suggesting that delayed antibiotic therapy administered more than 8 hours after admission reduced mortality.
  - Subgroup data from 1 retrospective study of almost 19,000 patients suggested that for the outcomes of 30-day mortality, length of hospital stay and re-admission after discharge the benefit of antibiotic administration within the first 4 hours of admission was slightly greater for patients with low-to moderate-severity CAP (PSI -III) compared with the high-severity group (PSI IV-V), although the quality of the evidence was low.
- One retrospective study of almost 500 patients with CAP examined the influence of timing of antibiotic administration on mortality by splitting the data into 1 hour intervals. The association between increasing time to first antibiotic dose and mortality was not linear, but those treated with antibiotics between 4 and 8 hours after admission had the lowest risk of death (very low quality evidence).
- Heterogeneous data from retrospective studies showed inconsistent results regarding the outcome of length of stay.
- Limited data were available for clinical instability at 48 hours and re-admissions.

10.2.3.2 Economic

- No relevant economic evaluations were identified.

10.2.4 Recommendations and link to evidence

Table 61: Linking evidence to recommendations – timing of antibiotic therapy

Recommendations	**Put in place processes to allow diagnosis (including X-rays) and treatment of community-acquired pneumonia within 4 hours of presentation to hospital.** **Offer antibiotic therapy as soon as possible after diagnosis, and certainly within 4 hours to all patients with community-acquired pneumonia who are admitted to hospital.**
Relative values of	The GDG considered mortality the most important outcome. Clinical cure, length of

different outcomes	hospital stay and adverse events were also regarded as important although the GDG reflected that timing of antibiotic administration was likely to have a more direct effect on mortality than these other outcomes.
Trade-off between clinical benefits and harms	No RCTs examining timing of antibiotic administration were available. Eighteen cohort studies were considered investigating the role of timing of antibiotic therapy for patients with moderate--to high-severity CAP in a multivariate analysis. No suitable data were available for low-severity CAP with the exception of 1 subgroup analysis of a retrospective study that reported results for patients with low-to moderate-severity. In relation to mortality, most of the studies that compared the administration of antibiotic therapy at less than 4 hours from presentation compared with later antibiotic administration were heterogeneous and adjusted for different confounders. Nevertheless, they showed that there was a clinically important reduction in this outcome favouring administration of antibiotic therapy within 4 hours. On the contrary, when the timing of administration of antibiotic therapy was set at an 8-hour threshold, no consistent evidence was found favouring earlier rather than later than 8-hours administration for the outcomes of mortality, length of stay and clinical stability at 48 hours. One study reported an hour-by-hour analysis for antibiotic administration. This produced a J-shaped curve, with improved mortality with antibiotic administration within the first 4 to 8 hours, but not when first antibiotic administration was earlier or later than this. There was evidence in the studies that sought such information to indicate that patient factors influenced the timing of antibiotic administration (more severely ill patients were more likely to receive antibiotics early and less severe and confused patients were more likely to receive antibiotic therapy later). Thus, the advantage of receiving antibiotic therapy quickly is only manifest in the moderate-severity group.
Trade-off between net health benefits and resource use	Earlier antibiotic prescribing could be associated with higher rates of misdiagnosis and inappropriate prescribing, which could result in harm to patients (such as adverse events due to antibiotic therapy) and to the wider population (such as increased antibiotic resistance) as well as being wasteful from an economic standpoint. However, the GDG considered that the cost of adverse events and inappropriate prescribing were likely to be outweighed by the additional risk of mortality associated with inappropriately delayed antibiotic therapy. In fact, the clinical review showed that the majority of studies reported lower mortality rates for antibiotic administration within 4 hours.
Quality of evidence	No RCTs examining timing of antibiotic administration were available. The GDG acknowledged that the ethical implications of deliberately delaying antibiotic therapy are likely to preclude such studies being performed. The evidence from the observational studies was considered of low to very low quality by modified GRADE criteria. The studies used a variety of outcomes and timing cut-offs that made direct comparisons difficult, as well as adjusting for different variables (the majority of studies did not account for all key potential confounders as identified by the GDG in their analysis). The average time to antibiotic administration varied between studies, a variety of antibiotic therapy was used across studies, and these were often not in accordance with relevant guidance. Inconsistency and imprecision were seen in many results, and some studies did not adequately adjust for confounding factors. Sample sizes varied widely across the

	studies. The largest study (Houck) included only patients over the age of 65. Some studies excluded patients admitted directly to ITU, which is likely to lead to the exclusion of some patients at the severe end of the disease spectrum.
Other considerations	The GDG agreed that the evidence supported early antibiotic administration, notwithstanding the failure to demonstrate this in patients who received antibiotic therapy very quickly, this being accounted for by severity confounding in these retrospective studies. However, the group also acknowledged that making an early confident diagnosis of CAP is not always straightforward. It was concluded that when a diagnosis of CAP has been made with reasonable confidence, it is desirable to administer antibiotic therapy as soon as possible. However, the GDG wished to balance this with avoiding inappropriate antibiotic prescribing for patients who do not have CAP, but in whom this is considered a potential differential diagnosis (for example, patients with LRTI who have not yet had a chest X-ray, in whom the benefit of antibiotic therapy is not as clear-cut). They felt that swift diagnostic procedures should be encouraged as part of the timing recommendation wherever possible, without discouraging clinical judgement. In patients with suspected CAP who are severely ill, antibiotic therapy should not necessarily be withheld until investigations such as chest X-ray are performed. Early appropriate antibiotic administration in hospital relies on making an early accurate diagnosis of CAP. The pathway to achieving this requires the same elements (clinical assessment, performing and reviewing a chest X-ray, making a diagnosis, and prescribing and administering antibiotic therapy) regardless of the speed of their undertaking. The GDG anticipated that the implementation of 4-hour patient processing targets in Accident & Emergency departments should make the above sequence of events achievable within 4 hours (without requiring more resources than those already available.) All studies considered patients treated in a hospital setting. The GDG felt that it was also desirable for antibiotic therapy to be commenced as soon as reasonably possible for patients with CAP treated outside hospital, though due to the lower severity and adverse outcome rates in this group any benefits of early antibiotic administration are likely to be smaller. In addition, patients currently obtain their medication by various pathways when they are not admitted to hospital. For example, some patients may be given a prescription for a course of antibiotic in primary care and subsequently obtain them from a pharmacy on a separate site, with potential delays at each stage of the process. This is in contrast to current practice in, for example, suspected meningococcal septicaemia, where an immediate dose of antibiotic is usually given during the consultation in primary care. The difficulty associated with getting quick X-ray confirmation of the diagnosis was also noted. In the absence of any evidence in patients not admitted to hospital, the GDG did not conclude that a specific time target (and the subsequent implications for service provision) should be stated for this group. **Key priority for implementation** The GDG agreed that structuring clinical care pathways to allow diagnosis and treatment of community-acquired pneumonia within 4 hours of presentation to hospital would have a high impact on reducing variation in care and outcomes, set challenging but achievable expectations of health services, include actions that are measurable and promote equality.

10.3 Review question: In adults with community-acquired pneumonia what is the most clinically- and cost-effective empirical antibiotic choice?

Although the earlier review of the severity assessment tools (see chapter 8) demonstrated 3 clear strata of mortality risk, the evidence base identified for empirical antibiotic therapy did not map precisely to these parameters. The GDG pragmatically divided the evidence base into 2 groups relevant to primary care and hospital physicians: low-severity CAP and moderate- to high-severity CAP respectively (although clearly there are some caveats to this generalisation). Literature searches were based either on designation of severity by the authors or on stated place of care, but stratification was refined according to factors such as ITU admission and death rates as well as formal severity scores when reported. Data were stratified for low- and moderate- to- high-severity CAP.

The presentation of evidence is organised into 3 sections.

- Firstly, a single antibiotic is compared with a single antibiotic from a different class (please see protocols in Appendix C: for further information and exceptions).
- In the second section, a single antibiotic is compared with dual-antibiotic therapy (from different classes).
- In the third section, dual-antibiotic therapy (from different classes) is compared with other dual-antibiotic therapy (from different classes).

Dual therapy is the current standard of care for moderate- to high-severity CAP. Combinations of more than 2 antibiotics are not usually used for CAP in the UK and studies of such therapy were not included in this review. Dual therapy was defined as the administration of 2 antibiotics from different classes.

The GDG considered whether a Network Meta-analysis (NMA) would help interpret these data. In theory this would be a highly appropriate step, enabling a tentative hierarchy of benefit to be established between the antibiotics included in these disparate head-to-head studies. However, after considering the heterogeneity of the patient groups in the different studies, the non-representative nature of the patients in most of the studies (particularly the age difference when compared with those with pneumonia in the general population), different definitions of outcomes (such as clinical cure) and the mixture of non-inferiority and superiority studies, the GDG agreed that they would not have any confidence in the results of an NMA. In addition, no RCT data were found for the comparison of the most common antibiotic therapies used in UK clinical practice (beta-lactam compared with macrolide plus beta-lactam), thus limiting the applicability of findings from a NMA which would include only RCTs. It was therefore concluded that performing a NMA would not be an appropriate use of resource

Low-severity community-acquired pneumonia

10.4 Single-compared with other single-antibiotic therapy for low-severity community-acquired pneumonia

For full details see review protocol Appendix C:.

10.4.1 Clinical evidence

We searched for systematic reviews and randomised trials (RCTs) of the effectiveness and safety of empirical treatment with a single antibiotic from one class compared with a single antibiotic from a different class, for low-severity CAP. We did not compare within classes, with the exception of azithromycin (macrolide). Azithromycin was assessed individually as its relative efficacy compared with other macrolides was considered of importance by the GDG due to its substantially different pharmacokinetic profile.

Data from studies comparing the same classes of antibiotics were pooled into a single analysis (see Appendix N: for classification). Data were accepted for antibiotic administered by the oral or intravenous routes. This section is divided in 2 parts:

- Studies of patients with low-severity CAP managed in the community and/or assessed as having low-severity CAP by the application of severity assessment tools.
- Studies of patients with low-severity CAP (assessed by the GDG) managed in the hospital and/or receiving intravenous antibiotic therapy. These studies were initially grouped into the high-severity CAP stratum based on protocol criteria and the literature search. However the GDG decided that these studies were more applicable to a low-severity CAP population based on the morbidity profiles of the patients included in the studies.

Low-severity community-acquired pneumonia managed in the community

Eighteen RCTs[9,23,42,78,87,92,93,124,140,146-148,156,158,159,166,187,204] were included in the review.

A matrix of included comparisons is presented to facilitate navigation of the evidence in Figure 6.

The randomised evidence was heterogeneous with a variety of antibiotics used across the studies coming from mixed populations (with prior antibiotic treatment, mixed populations of CAP and HAP and different age profiles) and different definitions of clinical cure (Table 62).

In addition, most of the included RCTs were non-inferiority trials. Only 1 of the studies[158] included the UK current standard of antibiotic therapy for low-severity CAP (amoxicillin).

Given that the available randomised evidence did not include a direct comparison of 2 of the most commonly used single antibiotic therapies for CAP in current UK clinical practice, amoxicillin and clarithromycin, an indirect comparison was performed to review their relative efficacy. Two randomised studies were included for this indirect comparison.[140,147]

Evidence from the included studies is summarised in the clinical GRADE evidence profiles below (Table 64, Table 65, Table 66, Table 67, Table 68, Table 69, Table 70, Table 71, Table 72, and Table 73). None of the available studies for any comparison reported *C. difficile*-associated diarrhoea, complications, health-related quality-of-life or hospital admission.

Low-severity community-acquired pneumonia (assessed by the GDG) managed in the hospital and/or receiving intravenous antibiotic therapy

Site of care was included as a surrogate for severity assessment in the protocol. Six studies[21,26,85,91,116,151] included patients treated in hospital but the GDG decided these patients should be categorised as having low-severity CAP given the patients' morbidity profiles. This population was not sufficiently homogeneous to be merged with the patients with low-severity CAP treated in the community (described in the previous section) and their results are presented separately below.

A matrix of included comparisons is presented to facilitate navigation of the evidence (Figure 7). A summary of these studies is included in Table 63. Evidence from the included studies is summarised in the clinical GRADE evidence profiles following the first set of results (Table 73, Table 74, Table 75, Table 76, Table 77, Table 78 and Table 79).

See also the study selection flow chart in Appendix D:, forest plots in Appendix I:, study evidence tables in Appendix G: and exclusion list in Appendix J:.

Figure 6: Single- compared with single-antibiotic therapy for low-severity community-acquired pneumonia (click on hyperlinks or refer to page numbers)

	Tetracycline	Beta-lactamase stable penicillin	Narrow-spectrum beta-lactam	Macrolide
Cephalosporin	• Cephalexin vs demeclocycline Table 65, page 187	• Cefuroxime vs co-amoxiclav Table 66, page 189		
Respiratory fluoroquinolone		• Levofloxacin vs co-amoxiclav Table 69, page 195	• Moxifloxacin vs amoxicillin Table 68, page 193	• Moxifloxacin vs clarithromycin • Levofloxacin vs clarithromycin Table 70, page 197
Non-respiratory fluoroquinolone				• Ofloxacin vs erythromycin Table 71 page 199
Macrolide	• Erythromycin vs doxycycline Table 64, page 185	• Clarithromycin vs co-amoxiclav • Erythromycin vs co-amoxiclav • Azithromycin vs co-amoxiclav Table 67, page 191		• Azithromycin vs clarithromycin Table 72, page 201

Figure 7: Single- compared with other single-antibiotic therapy for low-severity community-acquired pneumonia managed in hospital and/or treated with intravenous antibiotic therapy (click on hyperlinks or refer to page numbers)

	Narrow spectrum beta-lactam	Beta-lactamase stable penicillin	Macrolide	Tetracycline
Cephalosporin	• Cefaclor vs amoxicillin Table 78, page 213	• Cefuroxime vs co-amoxiclav • Cefuroxime vs co-amoxiclav Table 77, page 211		
Non-respiratory fluoroquinolone				• Ofloxacin vs doxycycline Table 79, page 215
Macrolide	• Azithromycin vs benzylpenicillin Table 74, page 205	• Clarithromycin vs co-amoxiclav Table 75, page 207	• Azithromycin vs erythromycin Table 76, page 209	

Table 62: Summary of studies included in the review for low-severity community-acquired pneumonia managed in the community

Study	Intervention (N randomised)	Comparison (N randomised)	Severity definition(a)	Outcomes	Comments
Macrolide compared with tetracycline					
Wiesner 1993[204]	Erythromycin 800 mg daily in 2 doses. Route of administration: oral Duration: 7 to 14 days. (N only with CAP = 11).	Doxycycline 100 mg daily plus identical placebo tablet Route of administration: oral Duration: 7 to 14 days. (N only with CAP = 13).	Managed in the community.	• clinical cure at end of treatment	• Unclear how differentiated CAP and HAP and diagnosis not confirmed by x-ray. • Mixed LRTI study – not stratified for pneumonia before randomisation. • Age range included children from 10 years of age and excluded those > 70 years. • Concomitant antibacterial treatment not permitted.
Cephalosporin compared with tetracycline					
Antani 1991[9]	Cephalexin 500 mg twice daily Route of administration: oral Duration: 10 days. N = 31).	Demeclocycline 300 mg twice daily Route of administration: oral Duration: 10 days. (N = 29).	Managed in the community.	• overall efficacy at end of treatment • withdrawal due to adverse events	• Young population, no details on other baseline characteristics. • Unclear how differentiated CAP and HAP.
Cephalosporin compared with beta-lactamase stable penicillin					
Higuera 1996[92]	Cefuroxime axetil 500 mg twice daily Route of administration: oral Duration: 10 days. (N = 84).	Co-amoxiclav 500 mg/125 mg 3-times daily Route of administration: oral Duration: 10 days. (N = 78).	Managed in the community	• clinical cure at end of follow-up	• Young population, no details on other baseline characteristics. • Included children from 12 years.
Macrolide compared with beta-lactamase stable penicillin					
Bonvehi 2003[23]	Clarithromycin 500 mg immediate-release twice daily. Route of	Co-amoxiclav 875 mg/125 mg twice daily Route of administration: oral	Managed in the community	• clinical cure (resolution of signs and symptoms with no need for additional	• Children were included. • Patients with known Legionella were excluded.

Study	Intervention (N randomised)	Comparison (N randomised)	Severity definition(a)	Outcomes	Comments
	administration: oral. Duration: 7 days. (N = 160).	Duration: 7 days or more (N = 167).		antibiotic therapy) at end of follow up • withdrawal due to adverse events	
Lode 1995[124]	Erythromycin 1,000 mg twice daily. Route of administration: oral. Duration: 7 to 14 days. (N = 87).	Co-amoxiclav 500/125 mg 3-times daily. Route of administration: oral. Duration: 7 to 14 days. (N = 79).	Low-severity CAP.	• mortality • efficacy (clinical and radiological response) at end of treatment • overall efficacy at end of follow-up • withdrawal due to adverse events	Inpatients and outpatients were included.
Paris 2008[156]	Azithromycin 1 g once daily. Route of administration: oral Duration: 3 days. (N = 136).	Co-amoxiclav 875/125 mg twice daily. Route of administration: oral Duration: 7 days. (N = 132).	PSI classes I-II outpatients.	• mortality • clinical success (complete resolution of all signs and symptoms with no need for additional antibiotics) at end of treatment • clinical success at end of follow-up • withdrawal due to adverse events	• Included some aged < 18 years. • 39% of identified pathogens were *M. pneumoniae.* • 49% were smokers.
Respiratory fluoroquinolone compared with narrow-spectrum beta-lactam (class 2)					
Petitpretz 2001 [158]	Moxifloxacin 400 mg once daily Route of administration: oral. Duration: 10 days. (N = 203).	Amoxicillin 1 g 3-times daily Route of administration: oral. Duration: 10 days. (N = 208).	Severe infection requiring IV antibiotic therapy excluded Low number of patients with infiltrate involving more than 1 lobe at baseline CXR.	• mortality • clinical cure (complete resolution of signs and symptoms at end of treatment • clinical cure at end of follow-	• Limited to suspected pneumococcal. • 57% were past or present smokers.

Study	Intervention (N randomised)	Comparison (N randomised)	Severity definition(a)	Outcomes	Comments
				up • withdrawal due to adverse events • complications (superinfection)	
Respiratory fluoroquinolone compared with beta-lactamase stable penicillin					
Carbon 1999[42]	Levofloxacin 500 mg once or twice daily. Route of administration: oral. Duration: 7 to 10 days (mean 8.1 days). (N = 348).	Co-amoxiclav 625 mg 3 times daily. Route of administration: oral. Duration: 7 to 10 days (mean 8.1 days). (N = 168).	Low- to moderate-severity pneumonia inpatients or out-patients.	• mortality • clinical cure (resolution of signs and symptoms and CXR improvement) at end of treatment • withdrawal due to adverse events	• Excluded those aged > 65 years. • 42.2% received concomitant non-anti-infective medications. • 57.6% had concomitant illnesses (mostly respiratory). • 10.5% had prior antibiotic therapy. • 57.2% were smokers.
Respiratory fluoroquinolone compared with macrolide					
Fogarty 1999[78]	Moxifloxacin 400 mg once daily plus placebo once daily. Route of administration: oral. Duration: 10 days. (N = 194).	Clarithromycin, 500 mg twice daily. Route of administration: oral. Duration: 10 days. (N = 188).	Managed in the community.	• clinical cure at end of treatment • withdrawal due to adverse events	• High proportion with *C. pneumoniae* infection. • High-severity pneumonia was excluded. • 4% prior antibiotic therapy.
Hoeffken 2001[93]	Moxifloxacin (400 mg once daily) - 1 active and 1 placebo capsule in the morning and 2 placebo capsules in the evening Route of administration: oral Duration: 10 days. (N = 224).	Clarithromycin 500 mg twice daily. Route of administration: oral. Duration: 10 days. (N = 222).	Managed in the community.	• mortality • clinical cure (resolution of signs and symptoms) at end of treatment • withdrawal due to adverse events	• Concomitant antibacterial therapy not permitted.

Study	Intervention (N randomised)	Comparison (N randomised)	Severity definition(a)	Outcomes	Comments
Gotfried 2002[87]	Levofloxacin - 2 250-mg tablets once daily. Route of administration: oral Duration: 7 days. (N = 143).	Clarithromycin extended release - 2 500 mg tablets. Route of administration: oral Duration: 7 days. (N = 156).	Managed in the community.	• clinical cure (clinical resolution and improvement on CXR or lack of progression) at end of treatment • withdrawal due to adverse events	• Required qualified sputum sample to be included, which may limit the sample to a narrower range of pathogens. • High proportion *M. pneumoniae* and *C. pneumoniae.*
Non-respiratory fluoroquinolone compared with macrolide					
Nielsen 1993[146]	Ofloxacin (400 mg once daily). Route of administration: oral. Duration: 7 days. (N = 73).	Erythromycin (500 mg twice daily). Route of administration: oral. Duration: 7 days. (N = 58).	Managed in the community.	• clinical cure (unclear definition) at end of treatment	• *Post hoc* subgroup analysis on pneumonia group. • 21.3% had concomitant medication. • Diagnosis of pneumonia based on clinical signs and symptoms only. • Limited to those not eligible for penicillin. • May have been a substantial number of viral, Mycoplasma or Legionella cases.
Peugeot 1991[159]	Ofloxacin (400 mg q12h) Route of administration: oral. Duration: 10 days. (N = 19).	Erythromycin (400 mg q6h) Route of administration: oral. Duration: 10 days. (N = 13).	Managed in the community.	• clinical cure at end of treatment • withdrawal due to adverse events	• *Post hoc* subgroup analysis on pneumonia group (mixed LRTI study). • 45% had existing pulmonary problems.
Azithromycin (macrolide) compared with other macrolide					
O'Doherty 1998[148]	Azithromycin 500 mg once daily Route of administration: oral Duration: 3 days.	Clarithromycin 250 mg twice daily Route of administration: oral Duration: 10 days.	Low- to moderate-severity CAP managed in the community.	• clinical cure (plus improvement) at end of treatment • maintaining clinical cure at end of follow-	• High-severity pneumonia was excluded. • Age range included children from 12 years of age and excluded those > 75 years.

Study	Intervention (N randomised)	Comparison (N randomised)	Severity definition(a)	Outcomes	Comments
	(N = 101).	(N = 102).		up • withdrawal due to adverse events	
Rizzato 1995[166]	Azithromycin 500 mg once daily. Route of administration: oral Duration: 3 days. (N = 20).	Clarithromycin 250 mg twice daily Route of administration: oral Duration: at least 8 days. (N = 20).	Low- to moderate-severity CAP (as exclusion criteria for severe pneumonia: pneumonia in more than 1 lobe; > 75 years of age; WBC < 3 x 10(9)/l; PaO_2 < 7.3 kPa (< 55 mmHg); and bacteraemia).	• clinical cure at end of treatment • length of hospital stay	• 50% had failed prior antibiotic therapy. • 41% of identified pathogens were *M. pneumoniae*.
Sopena 2004[187]	Azithromycin, once-daily 500 mg dose. Route of administration: oral Duration: 3 days. (N = 34).	Clarithromycin twice daily 250 mg dose. Route of administration: oral Duration: 10 to 14 days. (N = 36).	Mild to moderate CAP.	• clinical cure at end of treatment (10 to 13 days) • clinical cure at end of follow-up (25 to 30 days)	• Severe pneumonia was excluded. • 38% of identified pathogens were *M. pneumoniae*.
Comparison of 2 of the most common single antibiotic therapies for CAP: Amoxicillin compared with clarithromycin (from indirect comparison)					
Moola 1999[140]	Grepafloxacin 600 mg daily Route of administration: oral Duration: 10 days. (N = 251).	Clarithromycin 500 mg twice daily Route of administration: oral Duration: 10 days. (N = 253).	Formal assessment.	• mortality • clinical cure at end of follow-up • withdrawal due to adverse events	• Unclear how differentiated CAP and HAP. • 28% of identified pathogens were *M. pneumoniae*.
O'Doherty 1997[147]	Grepafloxacin 600 mg daily Route of administration: oral Duration: 7 to 10 days. (N = 127).	Amoxicillin, 500 mg tree-times daily Route of administration: oral Duration: 7 to 10 days. (N = 137).	Managed in the community.	• Mortality • clinical cure at end of follow-up • withdrawal due to adverse events	• Unclear how differentiated CAP and HAP. • UK and Ireland. • Excluded if required inhalation of, or increase in dose of, systemic glucocorticosteroids for RTIs.

(a) *All studies used some method of excluding severe pneumonia, although these varied between the studies (e.g. requiring parenteral therapy or hospital admission)*

Table 63: Summary of studies included in the review for low severity community-acquired pneumonia managed in the in hospital and/or treated with intravenous antibiotic

Study	Intervention	Comparison	Severity definition	Outcomes	Comments
Azithromycin (macrolide) compared with narrow-spectrum beta-lactam (class 1)					
Bohte 1995-pneumococcal[21]	Azithromycin 500 mg twice on first day and once daily for the next 4 days Route of administration: oral Duration: 5 days. (N = 35).	Benzylpenicillin 1 x 10^6 IU 4 times daily. Route of administration: IV Duration: until 5 days after body temperature had normalised. (N = 29).	Hospital setting.	• clinical cure (disappearance of all signs and symptoms) at end of treatment • clinical cure at end of follow-up • withdrawal/ • switching due to adverse events	• Only for patients with suspected pneumococcal. • Drugs compared used different routes of administration. • High-dose azithromycin on day 1. • Excluded those aged > 75 years.
Macrolide compared with beta-lactamase stable penicillin					
Genne 1997[85]	Clarithromycin lactobionate 500 mg twice daily IV for 3 to 5 days followed by 500 mg orally twice daily Route of administration: IV then oral Duration: at least 10 days. (N = 56).	Co-amoxiclav 1.2 g IV 4 times daily for 3 to 5 days followed by 625 mg orally 3-times daily Route of administration: IV then oral Duration: at least 10 days. (N = 56).	Hospital setting.	• mortality • clinical cure (clinical, microbiological and radiological cure) at end of treatment • withdrawal due to adverse events	• High-dose amoxicillin. • Physician was free to change treatment according to the patient's condition.
Azithromycin (macrolide) compared with other macrolide					
Bohte 1995-non-pneumococcal[21]	Azithromycin 500 mg twice on first day and once daily for the next 4 days Route of administration: oral Duration: 5 days (N = 19).	Erythromycin 500 mg 4 times daily Route of administration: oral Duration: 10 days. (N = 21).	Hospital setting.	• mortality • clinical cure (disappearance of all signs and symptoms) at end of treatment • clinical cure at end of follow-up • withdrawal/switching due to adverse events	• Only for patients with suspected non-pneumococcal. • High-dose azithromycin on day 1. • Excluded those aged > 75 years.
Cephalosporin compared with narrow-spectrum beta-lactam (class 2)					
Leuenberger 1983[116]	Cefaclor 500 mg 3-times daily Route of administration:	Amoxicillin 750 mg 3-times daily Route of administration:	Hospital setting.	• clinical cure (disappearance of all signs and	• Route of administration unclear. • Number

Study	Intervention	Comparison	Severity definition	Outcomes	Comments
	unclear Duration: 8 days. (N = 16).	unclear Duration: 8 days. (N = 18).		symptoms) at end of treatment	randomised to each group unclear. • Limited to those who produced sputum.
Cephalosporin compared with beta-lactamase stable penicillin					
Brambilla 1992[26]	Cefuroxime 750 mg 3 times daily IV for 48 to 72 hours, followed by cefuroxime axetil tablets 500 mg twice daily for at least 5 days Route of administration: IV then oral Duration: at least 7 days. (N = 137).	Co-amoxiclav 1.2 g 3-times daily IV, followed by 625 mg 3-times daily orally Route of administration: IV than oral Duration: at least 7 days. (N = 134).	Hospital setting.	• clinical cure at end of treatment • maintaining clinical cure at end of follow-up	• Mixed CAP and HAP: 8.5% HAP; 91.5% CAP.
Oh 1996[151]	Cefuroxime 750 mg IV every 8 hours for 48 hours followed by 500 mg orally twice daily Route of administration: IV then oral Duration: 7 to 14 days (N = 24).	Co-amoxiclav 1.2 g IV every 8 hours for 48 hours followed by 750 mg orally 3-times daily Route of administration: IV then oral Duration: 7 to 14 days. (N = 24).	Hospital setting.	• clinical cure (resolution of signs and symptoms) at end of treatment • withdrawal due to adverse events	• Dose of co-amoxiclav slightly high. • Unclear if any children were included.
Non-respiratory fluoroquinolone compared with tetracycline					
Harazim 1987[91]	Ofloxacin 200 or 400 mg twice daily Route of administration: oral Duration: 10 days. (N = 62).	Doxycycline 100 mg twice daily Route of administration: oral Duration: 10 days. (N = 69).	Hospital setting.	• clinical cure (disappearance of cough and sputum production) at end of treatment	• Mixed LRTI study with results stratified for pneumonia (57% pneumonia, 43% bronchitis). • Limited reporting of baseline characteristics.

Table 64: Clinical evidence profile: Macrolide compared with tetracycline for low-severity community-acquired pneumonia in the community

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Macrolide	Tetracycline	Relative (95% CI)	Absolute	Quality
Mortality											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Clinical cure at end of treatment (follow-up 7 to 14 days) [Wiesner 1993]											
1	randomised trials	very serious[1]	no serious	serious[2]	serious[3]	none	9/11 (81.8%)	12/13 (92.3%)	RR 0.89 (0.64 to 1.22)	102 fewer per 1000 (from 332 fewer to 203 more)	Very low
Withdrawal due to adverse events											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Hospital admission											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Length of hospital stay											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Health-related quality- of-life											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Complications											
0	no	-	-	-	-	none	-	-	-	-	

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Macrolide	Tetracycline	Relative (95% CI)	Absolute	Quality
	evidence available										
***C. difficile*-associated diarrhoea**											
0	no evidence available	-	-	-	-	none	-	-	-	-	

[1] *Serious risk of selection bias and post-hoc subgroup analysis of broader population (CAP population was only 15% of the whole LRTI sample)*
[2] *Indirect population: excluded those > 70 years*
[3] *95% CI crosses 1 default MID*

Table 65: Clinical evidence profile: Cephalosporin compared with tetracycline for low-severity community-acquired pneumonia in the community

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cephalosporin	Tetracycline	Relative (95% CI)	Absolute	Quality
Mortality											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Clinical cure at end of treatment (follow-up 10 days) [Antani 1991]											
1	randomised trial	serious[1]	no serious	serious[2]	very serious[3]	none	9/31 (29%)	9/29 (31%)	RR 0.94 (0.43 to 2.03)	19 fewer per 1000 (from 177 fewer to 319 more)	Very low
Withdrawal due to adverse events (follow-up 10 days) [Antani 1991]											
1	randomised trial	no serious	no serious	serious[2]	very serious[3]	none	1/31 (3.2%)	0/29 (0%)	PETO OR 6.93 (0.14 to 349.88)	32 more per 1000 (from 54 fewer to 119 more)[4]	Very low
Hospital admission											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Mean length of hospital stay											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Health-related quality-of-life											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Complications											
0	no evidence available	-	-	-	-	none	-	-	-	-	
***C. difficile*-associated diarrhoea**											

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cephalosporin	Tetracycline	Relative (95% CI)	Absolute	Quality
0	no evidence available	-	-	-	-	none	-	-	-	-	

[1] *Unclear how outcome defined and measured*
[2] *Young age profile in both groups (mean age 36.3 years and 38.6 years respectively)*
[3] *95% CI crosses both default MIDs*
[4] *Calculated from risk difference*

Table 66: Clinical evidence profile: Cephalosporin compared with beta-lactamase stable penicillin for low-severity community-acquired pneumonia in the community

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cephalosporin	Beta-lactamase stable penicillin	Relative (95% CI)	Absolute	Quality
Mortality											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Clinical cure at end of treatment											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Clinical cure at end of follow-up (follow-up 14 days after treatment) [Higuera 1999]											
1	randomised trial	serious[1]	no serious	serious [2]	no serious	none	49/55 (89.1%)	46/51 (90.2%)	RR 0.99 (0.87 to 1.12)	9 fewer per 1000 (from 117 fewer to 108 more)	Low
Withdrawal due to adverse events											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Hospital admission											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Length of hospital stay											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Health-related quality-of-life											

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cephalosporin	Beta-lactamase stable penicillin	Relative (95% CI)	Absolute	Quality
0	no evidence available	-	-	-	-	none	-	-	-	-	
Complications											
0	no evidence available	-	-	-	-	none	-	-	-	-	
***C. difficile*-associated diarrhoea**											
0	no evidence available	-	-	-	-	none	-	-	-	-	

[1] *Unclear allocation concealment and no information on the comparability of baseline severity between the 2 groups*
[2] *Young age profile*

Table 67: Clinical evidence profile: Macrolide compared with beta-lactamase stable penicillin for low-severity community-acquired pneumonia in the community

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Macrolide	Beta-lactamase stable penicillin	Relative (95% CI)	Absolute	Quality
Mortality (follow-up 22 to 26 days in one study and 42 days in another) [Lode 1995, Paris 2008]											
2	randomised trials	serious[1]	no serious	serious[2]	serious[3]	none	10/344 (2.9%)	4/331 (1.2%)	RR 2.39 (0.76 to 7.5)	17 more per 1000 (from 3 fewer to 79 more)	Very low
Clinical cure at end of treatment (follow-up 7 to 14 days in 1 study and 8 to 12 days in another) [Lode 1995, Paris 2008]											
2	randomised trials	serious[4]	no serious	serious[2]	no serious	none	280/344 (81.4%)	276/330 (83.6%)	RR 0.97 (0.91 to 1.04)	25 fewer per 1000 (from 75 fewer to 33 more)	Low
Clinical cure at end of follow-up (follow-up 22 to 42 days) [Lode 1995, Paris 2008, Bonvehi 2003]											
3	randomised trials	serious[5]	no serious	serious[2]	no serious	none	368/467 (78.8%)	367/457 (80.3%)	RR 0.98 (0.93 to 1.05)	16 fewer per 1000 (from 56 fewer to 40 more)	Low
Withdrawal due to adverse events (follow-up 22 to 42 days) [Lode 1995, Paris 2008, Bonvehi 2003]											
3	randomised trials	serious[5]	no serious	serious[2]	serious[6]	none	24/504 (4.8%)	11/498 (2.2%)	RR 2.12 (1.05 to 4.29)	25 more per 1000 (from 1 more to 73 more)	Very low
Hospital admission											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Length of hospital stay											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Health-related quality-of-life											

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Macrolide	Beta-lactamase stable penicillin	Relative (95% CI)	Absolute	Quality
0	no evidence available	-	-	-	-	none	-	-	-	-	
Complications											
0	no evidence available	-	-	-	-	none	-	-	-	-	
***C. difficile*-associated diarrhoea**											
0	no evidence available	-	-	-	-	none	-	-	-	-	

[1] *Unclear sequence generation and allocation concealment and 25% of missing information in 1 study (which was imputed as treatment failure)*
[2] *One study included inpatients*
[3] *95% CI crosses 1 default MID*
[4] *High risk of bias as 1 study was unblinded with unclear sequence generation and allocation concealment*
[5] *The majority of the evidence was from studies at high risk of bias*
[6] *Confidence interval crosses 1 default MID*

Table 68: Clinical evidence profile: Respiratory fluoroquinolone compared with narrow spectrum beta-lactam (class 2) for low-severity community-acquired pneumonia in the community

Quality assessment							No of patients		Effect		
No of studies	Design evidence	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Respiratory fluoroquinolone	Narrow spectrum beta-lactam (class 2)	Relative (95% CI)	Absolute	Quality
Mortality [Petitpretz 2001]											
1	randomised trial	serious[1]	no serious	no serious	very serious[2]	none	3/200 (1.5%)	4/208 (1.9%)	RR 0.78 (0.18 to 3.44)	4 fewer per 1000 (from 16 fewer to 47 more)	Very low
Clinical cure at end of treatment [Petitpretz 2001]											
1	randomised trial	serious[1]	no serious	no serious	no serious	none	173/200 (86.5%)	171/208 (82.2%)	RR 1.05 (0.97 to 1.14)	41 more per 1000 (from 25 fewer to 115 more)	Moderate
Clinical cure at end of follow-up (3 to 4 weeks after end of treatment) [Petitpretz 2001]											
1	randomised trial	serious[1]	no serious	no serious	no serious	none	154/200 (77%)	164/208 (78.8%)	RR 0.98 (0.88 to 1.08)	16 fewer per 1000 (from 95 fewer to 63 more)	Moderate
Complications – superinfection [Petitpretz 2001]											
1	randomised trial	serious[1]	no serious	no serious	serious[3]	none	0/200 (0%)	1/208 (0.48%)	Peto OR 0.14 (0.00 to 7.09)	4 fewer per 1000 (from 5 fewer to 66 more)	Low
Withdrawal or treatment discontinuation due to adverse events [Petitpretz 2001]											
1	randomised trial	serious[1]	no serious	no serious	very serious[2]	none	8/200 (4%)	8/208 (3.8%)	RR 1.04 (0.4 to 2.72)	2 more per 1000 (from 23 fewer to 66 more)	Very low
Hospital admission											
0	no	-	-	-	-	none	-	-	-	-	

Quality assessment							No of patients		Effect		
No of studies	Design evidence	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Respiratory fluoroquinolone	Narrow spectrum beta-lactam (class 2)	Relative (95% CI)	Absolute	Quality
	available										
Length of hospital stay											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Health-related quality-of-life											
0	no evidence available	-	-	-	-	none	-	-	-	-	
***C. difficile*-associated diarrhoea**											
0	no evidence available	-	-	-	-	none	-	-	-	-	

[1] *High risk of selection bias (due to unclear randomisation and allocation concealment)*
[2] *Confidence interval crossed both default MIDs*
[3] *Confidence interval crossed 1 default MID*

Table 69: Clinical evidence profile: Respiratory fluoroquinolone compared with beta-lactamase stable penicillin for low-severity community-acquired pneumonia in the community

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Respiratory fluoroquinolone	Beta-lactamase stable penicillin	Relative (95% CI)	Absolute	Quality
Mortality (follow-up up to 42 days after end of treatment) [Carbon 1999]											
1	randomised trial	serious[1]	no serious	serious[2]	serious[3]	none	0/348 (0%)	2/168 (1.2%)	PETO OR 0.05 (0 to 0.89)	11 fewer per 1000 (from 1 fewer to 12 fewer)	Very low
Clinical cure at end of treatment (follow-up 2 to 5 days after end of treatment) [Carbon 1999]											
1	randomised trial	serious[1]	no serious	serious[2]	no serious	none	286/348 (82.2%)	144/168 (85.7%)	RR 0.96 (0.89 to 1.04)	34 fewer per 1000 (from 94 fewer to 34 more)	Low
Withdrawal due to adverse events (follow-up 7 to 10 days) [Carbon 1999]											
1	randomised trial	serious[1]	no serious	serious[2]	very serious[4]	none	13/348 (3.7%)	5/168 (3%)	RR 1.26 (0.45 to 3.46)	8 more per 1000 (from 16 fewer to 74 more)	Very low
Hospital admission											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Length of hospital stay											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Health-related quality-of-life											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Complications											
0	no	-	-	-	-	none	-	-	-	-	

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Respiratory fluoroquinolone	Beta-lactamase stable penicillin	Relative (95% CI)	Absolute	Quality
	evidence available										
***C. difficile*-associated diarrhoea**											
0	no evidence available	-	-	-	-	none	-	-	-	-	

[1] *Unclear allocation concealment and unclear if comparable numbers with prior antibiotic therapy*
[2] *Indirect population: excluded those aged > 65 years and 2 groups of different dosages of respiratory fluoroquinolone (500 mg and 2 x 500 mg per day levofloxacin were merged in terms of presentation of results)*
[3] *95% CI crosses 1 default MID*
[4] *95% CI crosses both default MIDs*

Table 70: Clinical evidence profile: Respiratory fluoroquinolone compared with macrolide for low-severity community-acquired pneumonia in the community

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Respiratory fluoroquinolone	Macrolide	Relative (95% CI)	Absolute	Quality
Mortality (21 to 28 days after end of treatment) [Hoeffken 2001]											
1	randomised trial	serious[1]	no serious	no serious	very serious[2]	none	2/224 (0.9%)	5/222 (2.3%)	RR 0.4 (0.08 to 2.02)	14 fewer per 1000 (from 21 fewer to 23 more)	Very low
Clinical cure at end of treatment (10 to 16 days in 1 study and 13 to 15 days in another) [Fogarty 1999; Hoeffken 2001]											
2	randomised trials	serious[3]	no serious	no serious	no serious	none	344/371 (92.7%)	337/362 (93.1%)	RR 1 (0.96 to 1.04)	0 fewer per 1000 (from 37 fewer to 37 more)	Moderate
Clinical cure at end of follow-up (14 to 35 days after treatment) [Fogarty 1999; Gotfried 2002; Hoeffken 2001]											
3	randomised trials	serious[3]	no serious	serious[4]	no serious	none	432/470 (91.9%)	432/469 (92.1%)	RR 1 (0.96 to 1.04)	0 fewer per 1000 (from 37 fewer to 37 more)	Moderate
Withdrawal due to adverse events (follow-up 7 to 10 days) [Fogarty 1999; Gotfried 2002; Hoeffken 2001]											
3	randomised trials	serious[3]	no serious	no serious	serious[5]	none	18/608 (3%)	28/610 (4.6%)	RR 0.64 (0.36 to 1.14)	18 fewer per 1000 (from 32 fewer to 7 more)	Low
Hospital admission											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Length of hospital stay											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Health-related quality-of-life											

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Respiratory fluoroquinolone**	**Macrolide**	**Relative (95% CI)**	**Absolute**	**Quality**
0	no evidence available	-	-	-	-	none	-	-	-	-	
Complications											
0	no evidence available	-	-	-	-	none	-	-	-	-	
***C. difficile*-associated diarrhoea**											
0	no evidence available	-	-	-	-	none	-	-	-	-	

[1] *Unclear sequence generation and allocation concealment*
[2] *95% CI crosses both default MIDs*
[3] *All studies had unclear sequence generation and allocation concealment*
[4] *Different definitions of cure used across studies*
[5] *95% CI crosses 1 default MID*

Table 71: Clinical evidence profile: Non-respiratory fluoroquinolone compared with macrolide for low-severity community-acquired pneumonia in the community

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Non-respiratory fluoroquinolone	Macrolide	Relative (95% CI)	Absolute	Quality
Mortality											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Clinical cure at end of treatment (from 7 days to 13 to 15 days) [Nielsen 1993; Peugeot 1991]											
2	randomised trials	very serious[1]	no serious	serious[2]	serious[3]	none	52/88 (59.1%)	30/63 (47.6%)	RR 1.24 (0.91 to 1.69)	113 more per 1000 (from 42 fewer to 325 more)	Very low
Withdrawal due to adverse events (Peugeot 1991)											
1	randomised trial	very serious[1]	no serious	no serious	serious[3]	none	2/19 (10.5%)	0/13 (0%)	PETO OR 5.70 (0.32 to 100.37)	110 more per 1000 (from 70 lower to 280 more)	Low
Hospital admission											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Length of hospital stay											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Health-related quality-of-life											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Complications											

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Non-respiratory fluoroquinolone	Macrolide	Relative (95% CI)	Absolute	Quality
0	no evidence available	-	-	-	-	none	-	-	-	-	
***C. difficile*-associated diarrhoea**											
0	no evidence available	-	-	-	-	none	-	-	-	-	

[1] *Post hoc subgroup analyses; 1 study was unblinded*
[2] *One study had no definition of outcome and differential follow ups (7 days in 1 study and 13 to 15 days in the other)*
[3] *95% CI crosses 1 default MID*

Table 72: Clinical evidence profile: Azithromycin (macrolide) compared with other macrolide for low-severity community-acquired pneumonia in the community

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azithromycin	Other macrolide	Relative (95% CI)	Absolute	Quality
Mortality											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Clinical cure at end of treatment (follow-up between 10 and 16 days) [O'Doherty 1998; Rizzato 1995; Sopena 2004]											
3	randomised trials	very serious[1]	no serious	no serious	no serious	none	95/138 (68.8%)	100/140 (71.4%)	RR 0.96 (0.83 to 1.12)	28 fewer per 1000 (from 118 fewer to 83 more)	Very low
Clinical cure at end of follow-up (follow-up 19 to 23 days in one and 25 to 30 days in the other) [O'Doherty 1998; Sopena 2004]											
2	randomised trials	very serious[1]	no serious	no serious	serious[2]	none	47/54 (87%)	43/54 (79.6%)	RR 1.1 (0.93 to 1.3)	78 more per 1000 (from 54 fewer to 233 more)	Very low
Withdrawal due to adverse events (follow-up 12 to 16 days) [O'Doherty 1998]											
1	randomised trial	serious[3]	no serious	no serious	very serious[4]	none	0/101 (0%)	2/102 (2%)	PETO OR 0.14 (0.01 to 2.18)	17 fewer per 1000 (from 20 fewer to 23 more)	Very low
Hospital admission											
0	no available evidence	-	-	-	-	none	-	-	-	-	
Length of hospital stay (follow-up unclear; Better indicated by lower values) [Rizzato 1995]											
1	randomised trial	serious[5]	no serious	no serious	serious[2]	none	12.7 (5.7)	14.3 (7.6)	-	MD 1.6 lower (5.76 lower to 2.56 higher)	Low
Health-related quality-of-life											
0	no	-	-	-	-	none	-	-	-	-	

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azithromycin	Other macrolide	Relative (95% CI)	Absolute	Quality
	available evidence										
Complications											
0	no available evidence	-	-	-	-	none	-	-	-	-	
***C. difficile*-associated diarrhoea**											
0	no available evidence	-	-	-	-	none	-	-	-	-	

[1] *All studies were of high risk of selection bias and 1 was unblinded*
[2] *95% CI crosses 1 default MID*
[3] *Unclear sequence generation and allocation concealment*
[4] *95% CI crosses both default MIDs*
[5] *High risk of selection bias: unclear allocation concealment and groups not matched at baseline for comorbidities*

Table 73: Clinical evidence profile: Clarithromycin compared with amoxicillin (indirect comparison) for low-severity community-acquired pneumonia in the community

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clarithromycin	Amoxicillin	Relative[1] (95% CI)	Absolute	Quality
Mortality (follow-up 65 to 40 days after treatment) [Moola 1999, O'Doherty 1997]											
2	randomised trials	very serious[2]	no serious	serious[3]	very serious[3]	none	0/253 (0%)	0/137 (0%)	RR 1.07 (0.01 to 77.18)	0 more per 1000 (from 1 fewer to 1 more)	Very low
Cure at end of follow-up (follow-up 28 to 42 days after treatment) [Moola 1999, O'Doherty 1997]											
2	randomised trials	very serious[2]	no serious	serious[3]	no serious	none	192/253 (75.9%)	85/111 (76.6%)	RR 1.05 (0.9 to 1.23)	38 more per 1000 (from 77 fewer to 176 more)	Very low
Withdrawal due to adverse events (follow-up 7 to10 days) [Moola 1999, O'Doherty 1997]											
2	randomised trials	very serious[2]	no serious	serious[3]	no serious	none	18/253 (7.1%)	2/137 (1.5%)	RR 4.79 (1.6 to 14.32)	55 more per 1000 (from 9 more to 194 more)	Very low
Hospital admission											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Length of hospital stay											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Health-related quality-of-life											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Complications											
0	no evidence available	-	-	-	-	none	-	-	-	-	

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clarithromycin	Amoxicillin	Relative[1] (95% CI)	Absolute	Quality
***C. difficile*-associated diarrhoea**											
0	no evidence available	-	-	-	-	none	-	-	-	-	

[1] Indirect comparison based on 2 trials of grepafloxacin compared with clarithromycin and amoxicillin. RR for the indirect comparison is obtained through dividing the RR of comparison of grepafloxqcin with clarithromycin by the RR of comparison of grepafloxacin with amoxicillin
[2] Both studies were of high risk of selection bias and attrition bias
[3] 95% CI crossed both default MIDs

Table 74: Clinical evidence profile: Macrolide compared with narrow-spectrum beta-lactam (class 1) for low-severity community-acquired pneumonia treated in hospital

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Macrolide	Narrow-spectrum beta-lactam (class 1)	Relative (95% CI)	Absolute	Quality
Mortality											
0	no evidence available					none	-	-	-	-	
Clinical cure at end of treatment (follow-up at discharge or 12 to 15 days) [Bohte 1995]											
1	randomised trials	very serious[1]	no serious	serious[2]	serious[3]	none	24/35 (68.6%)	14/29 (48.3%)	RR 1.42 (0.92 to 2.2)	203 more per 1000 (from 39 fewer to 580 more)	Very low
Cure at end of follow-up (follow-up up to 21 days after discharge) [Bohte 1995]											
1	randomised trials	very serious[1]	no serious	serious[2]	serious[4]	none	29/35 (82.9%)	19/29 (65.5%)	RR 1.26 (0.93 to 1.71)	170 more per 1000 (from 46 fewer to 465 more)	Very low
Withdrawal/switching of treatment due to adverse events (follow-up up to 21 days after discharge) [Bohte 1995]											
1	randomised trials	very serious[5]	no serious	serious[2]	very serious[6]	none	2/35 (5.7%)	0/29 (0%)	PETO OR 6.41 (0.39 to 106.11)	57 more per 1000 (from 38 fewer to 152 more)[7]	Very low
Hospital admission											
0	no evidence available					none	-	-	-	-	
Length of hospital											
0	no evidence available					none	-	-	-	-	
Health-related quality-of-life											

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Macrolide	Narrow-spectrum beta-lactam (class 1)	Relative (95% CI)	Absolute	Quality
0	no evidence available					none	-	-	-	-	
Complications											
0	no evidence available					none	-	-	-	-	
***C. difficile*-associated diarrhoea**											
0	no evidence available					none	-	-	-	-	

[1] *High risk of selection bias, unblinded and differential switching rates*
[2] *Suspected pneumococcal and non-pneumococcal randomised to different interventions; high dose azithromycin on day 1*
[3] *95% CI crosses 1 default MID*
[4] *No explanation was provided*
[5] *High risk of selection bias, and differential switching rates*
[6] *95% CI crosses both default MIDs*
[7] *Calculated from risk difference*

Table 75: Clinical evidence profile: Macrolide compared with beta-lactamase stable penicillin for low-severity community-acquired pneumonia treated in hospital

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Macrolide	Beta-lactamase stable penicillin	Relative (95% CI)	Absolute	Quality
Mortality (during treatment) [Genne 1997]											
1	randomised trial	very serious[1]	no serious	no serious	very serious[2]	none	1/56 (1.8%)	1/56 (1.8%)	RR 1 (0.06 to 15.59)	0 fewer per 1000 (from 17 fewer to 263 more)	Very low
Clinical cure - End of treatment [Genne 1997]											
1	randomised trial	serious[3]	no serious	no serious	no serious	none	48/56 (85.7%)	47/56 (83.9%)	RR 1.02 (0.87 to 1.19)	17 more per 1000 (from 109 fewer to 159 more)	Moderate
Withdrawal due to adverse events [Genne 1997]											
1	randomised trial	serious[3]	no serious	no serious	very serious[2]	none	1/56 (1.8%)	3/56 (5.4%)	RR 0.33 (0.04 to 3.11)	36 fewer per 1000 (from 52 fewer to 114 more)	Very low
Hospital admission											
0	no evidence available					none	-	-	-	-	
Length of hospital stay (follow-up unclear) [Genne 1997]											
1	randomised trial	serious[3]	no serious	no serious	very serious[4]	none	56	56	-	authors stated that length of hospital stay did not differ between groups	Very low
Health-related quality-of-life											

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Macrolide	Beta-lactamase stable penicillin	Relative (95% CI)	Absolute	Quality
0	no evidence available					none	-	-	-	-	
Complications											
0	no evidence available					none	-	-	-	-	
***C. difficile*-associated diarrhoea**											
0	no evidence available					none	-	-	-	-	

[1] *Very serious reporting bias: 1 additional patient death reported but treatment group not stated*
[2] *95% CI crosses both default MIDs*
[3] *Unblinded study with no details on randomisation and allocation concealment*
[4] *Results were not reported by group and no overall assessment of relative effect; not possible to assess imprecision*

Table 76: Clinical evidence profile: Azithromycin compared with other macrolide for low-severity community-acquired pneumonia treated in hospital

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consideration	Azithromycin	Other macrolide	Relative (95% CI)	Absolute	Quality
Mortality (during treatment) [Bohte 1995]											
1	randomised trials	serious[1]	no serious	serious[2]	very serious[3]	none	1/20 (5%)	1/22 (4.5%)	RR 1.1 (0.07 to 16.45)	5 more per 1000 (from 43 fewer to 711 more)	Very low
Clinical cure at end of treatment [Bohte 1995]											
1	randomised trials	very serious[1]	no serious	serious[2]	very serious[3]	none	14/19 (73.7%)	14/21 (66.7%)	RR 1.11 (0.74 to 1.66)	73 more per 1000 (from 173 fewer to 440 more)	Very low
Clinical cure at end of follow-up (21 days after discharge) [Bohte 1995]											
1	randomised trial	very serious[1]	no serious	serious[2]	serious[4]	none	15/19 (78.9%)	15/21 (71.4%)	RR 1.11 (0.77 to 1.58)	79 more per 1000 (from 164 fewer to 414 more)	Very low
Withdrawal/switching of treatment due to adverse events (21 days after discharge) [Bohte 1995]											
1	randomised trial	very serious[1]	no serious	serious[2]	very serious[3]	none	0/19 (0%)	2/21 (9.5%)	PETO OR 0.14 (0.01 to 2.36)	81 fewer per 1000 (from 94 fewer to 104 more)	Very low
Hospital admission											
0	no evidence available					none	-	-	-	-	
Length of hospital stay											
0	no evidence available					none	-	-	-	-	
Health-related quality-of-life											

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consideration	Azithromycin	Other macrolide	Relative (95% CI)	Absolute	Quality
0	no evidence available					none	-	-	-	-	
Complications											
0	no evidence available					none	-	-	-	-	
***C. difficile*-associated diarrhoea**											
0	no evidence available					none	-	-	-	-	

[1] *High risk of selection bias and difference in baseline comparability of the group (higher proportion of patients with comorbidities in the erythromycin group)*
[2] *Patients were suspected to have pneumonia of non-pneumococcal origin; high-dose azithromycin on day 1*
[3] *95% CI crosses both default MIDs*
[4] *95% CI crosses 1 default MID*

Table 77: Clinical evidence profile: Cephalosporin compared with beta-lactamase stable penicillin for low-severity community-acquired pneumonia treated in hospital

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cephalosporin	Beta-lactamase stable penicillin	Relative (95% CI)	Absolute	Quality
Mortality											
0	no evidence available					none	-	-	-		
Clinical cure - end of treatment [Brambilla 1992; Oh 1996]											
2	randomised trials	very serious[1]	no serious	no serious	serious[2]	none	100/161 (62.1%)	81/158 (51.3%)	RR 1.21 (1 to 1.47)	128 more per 1000 (from 0 more to 287 more)	Very low
Clinical cure (maintenance) - end of follow-up (7 to 28 days after treatment) [Brambilla 1992]											
1	randomised trial	very serious[3]	no serious	no serious	no serious	none	101/117 (86.3%)	94/108 (87%)	RR 0.99 (0.9 to 1.1)	9 fewer per 1000 (from 87 fewer to 87 more)	Low
Hospital admission											
0	no evidence available					none					
Length of hospital stay											
0	no evidence available					none		-			
Health-related quality-of-life											
0	no evidence available					none		-			
Withdrawal due to adverse events (follow-up 7 to 28 days) [Oh 1996]											

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Cephalosporin**	**Beta-lactamase stable penicillin**	**Relative (95% CI)**	**Absolute**	**Quality**
1	randomised trials	serious[4]	no serious	no serious	very serious[5]	none	0/24 (0%)	2/24 (8.3%)	OR 0.13 (0.01 to 2.13)	71 fewer per 1000 (from 82 fewer to 79 more)	Very low
Complications											
0	no evidence available					none					
***C. difficile*-associated diarrhoea**											
0	no evidence available					none					

[1] *2/2 studies unblinded and 1/2 (78% weighted) high risk of selection bias*
[2] *95% CI crosses 1 default MID*
[3] *High risk of selection bias and unblinded*
[4] *Unclear allocation concealment and baseline comparability*
[5] *95% CI crosses both default MIDs*

Table 78: Clinical evidence profile: Cephalosporin compared with narrow-spectrum beta-lactam (class 2) for low-severity community-acquired pneumonia treated in hospital

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cephalosporin	Narrow-spectrum beta-lactam (class 2)	Relative (95% CI)	Absolute	Quality
Mortality											
0	no evidence available					none	-	-	-	-	
Clinical cure - End of treatment [Leuenberger 1983]											
1	randomised trial	serious[1]	no serious	serious[2]	serious[3]	none	15/16 (93.8%)	16/18 (88.9%)	RR 1.05 (0.86 to 1.3)	44 more per 1000 (from 124 fewer to 267 more)	Very low
Clinical cure											
0	no evidence available					none	-	-	-	-	
Withdrawal due to adverse events											
0	no evidence available					none	-	-	-	-	
Hospital admission											
0	no evidence available					none	-	-	-	-	
Length of hospital stay											
0	no evidence available					none	-	-	-	-	
Health-related quality-of-life											

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cephalosporin	Narrow-spectrum beta-lactam (class 2)	Relative (95% CI)	Absolute	Quality
0	no evidence available					none	-	-	-	-	
Complications											
0	no evidence available					none	-	-	-	-	
***C. difficile*-associated diarrhoea**											
0	no evidence available					none	-	-	-	-	

[1] *Unclear allocation concealment*
[2] *Included patients had either acute bacterial pneumonia or bronchopneumonia and the clinical diagnosis was either based on signs and symptoms or CXR findings*
[3] *95% CI crosses 1 default MID*

Table 79: Clinical evidence profile: Non-respiratory fluoroquinolone compared with tetracycline for low-severity community-acquired pneumonia treated in hospital

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Non-respiratory fluoroquinolone	Tetracycline	Relative (95% CI)	Absolute	Quality
Mortality											
0	no evidence available					none	-	-	-	-	
Clinical cure at end of treatment [Harazim 1987]											
1	randomised trial	very serious[1]	no serious	no serious	very serious[2]	none	34/62 (54.8%)	39/69 (56.5%)	RR 0.97 (0.71 to 1.32)	17 fewer per 1000 (from 164 fewer to 181 more)	Very low
Withdrawal due to adverse events											
0	no evidence available					none	-	-	-	-	
Hospital admission											
0	no evidence available					none	-	-	-	-	
Length of hospital stay											
0	no evidence available					none	-	-	-	-	
Health-related quality-of-life											
0	no evidence available					none	-	-	-	-	
Complications											

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Non-respiratory fluoroquinolone	Tetracycline	Relative (95% CI)	Absolute	Quality
0	no evidence available					none	-	-	-	-	
***C. difficile*-associated diarrhoea**											
0	no evidence available					none	-	-	-	- -	

[1] *Post hoc subgroup analysis. Unblinded study with no details on randomisation and allocation concealment*
[2] *95% CI crosses both default MIDs*

10.4.2 Economic evidence

Published literature

No studies were included with the relevant comparisons for low-severity CAP.

Three studies that met the inclusion criteria were selectively excluded due to methodological limitations[15,145,163]– these are reported in Appendix K: with reasons for exclusion given.

Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided in Appendix O: to aid consideration of cost effectiveness.

10.4.3 Evidence statements

10.4.3.1 Clinical

10.4.3.2 Patients with low-severity community-acquired pneumonia treated in the community

10.4.3.2.1 Macrolide compared with tetracycline

Subgroup analysis in a very small sample of 24 patients showed that treatment with a macrolide may be less beneficial compared with tetracycline in improving clinical cure rate (very low quality).

10.4.3.2.2 Non-respiratory fluoroquinolone compared with macrolide

Very low quality evidence from 2 trials including 150 patients showed that antibiotic therapy with a non-respiratory fluoroquinolone may improve clinical cure at the end of treatment compared with a macrolide.

10.4.3.2.3 Azithromycin compared with other macrolide

When comparing macrolides, azithromycin may be more beneficial in improving clinical cure at follow-up compared with other macrolides. However, this finding was based on very low quality evidence from 2 trials.

10.4.3.2.4 Respiratory fluoroquinolone compared with narrow-spectrum beta-lactam (class 2)

One RCT of over 400 patients suggested a small survival benefit associated with respiratory fluoroquinolone compared with amoxicillin, but the evidence was of very low quality. There were no significant differences between the 2 groups for the outcomes of clinical cure or adverse events.

10.4.3.2.5 Clarithromycin compared with amoxicillin

An indirect comparison of clarithromycin compared with amoxicillin using 2 randomised trials of almost 400 participants indicated that patients treated with clarithromycin may be at higher risk of withdrawing due to adverse events compared with patients treated with amoxicillin but no clinical difference was found for the outcomes of mortality and clinical cure. This was very low quality evidence.

No clinical difference in any of the outcomes (most reported were clinical cure and withdrawal due to adverse events) was found for the comparisons of:

- cephalosporin compared with tetracycline (low quality evidence from a randomised trial of 60 participants)
- cephalosporin compared with beta-lactam (low quality evidence from a trial of 100 participants)

- macrolide compared with beta-lactam (low to very low quality evidence from 3 trials of over 600 participants)
- respiratory fluoroquinolone compared with beta-lactam (class 2) (moderate to very low quality from 1 trial of over 400 participants)
- respiratory fluoroquinolone compared with beta-lactamase stable penicillin (very low quality evidence from 1 trial of over 500 participants)
- respiratory fluoroquinolone compared with macrolide (moderate to very low quality evidence from 3 trials of over 900 participants).

10.4.3.3 Patients with low-severity community-acquired pneumonia treated in hospital

10.4.3.3.1 Macrolide compared with narrow-spectrum beta-lactam (class 1)

- Very low quality evidence from 1 study of 60 participants showed that although more patients who received a macrolide may benefit from clinical cure than patients treated with a narrow-spectrum beta-lactam (class 1), they may have a higher risk of experiencing withdrawal due to adverse events.

10.4.3.3.2 Azithromycin compared with other macrolide

- Low quality evidence from 1 small trial of 40 participants showed that azithromycin may have a beneficial effect on improving clinical cure and reducing withdrawals due to adverse events compared with the other macrolides.

10.4.3.3.3 Cephalosporin compared with beta-lactamase stable penicillin

- Very low quality evidence from 1 trial of over 100 patients found that treatment with a cephalosporin may have a significant clinical benefit on improving clinical cure at the end of treatment and reducing withdrawals due to adverse events compared with a beta-lactamase stable penicillin.

No clinical difference in any of the outcomes (mortality [not reported in all comparisons], clinical cure and withdrawal due to adverse events) was found for the comparisons of:

- cephalosporin and narrow beta-lactam (class 2) (very low quality evidence from a very small study of 34 participants)
- macrolide and beta-lactamase stable penicillin (moderate to low quality evidence from 1 trial of over 100 participants)
- non-respiratory fluoroquinolone and tetracycline (very low quality evidence from 1 trial of 130 participants).

10.4.3.4 Economic

- No relevant economic evaluations were identified.

10.4.4 Recommendations and link to evidence

Table 80: Linking evidence to recommendations: single- compared with other single-antibiotic therapy for low-severity community-acquired pneumonia managed in the community

Recommendations	**Offer single antibiotic therapy to patients with low-severity community-acquired pneumonia.** **Consider amoxicillin in preference to a macrolide or a tetracycline for patients with low-severity community-acquired pneumonia. Consider a macrolide or a tetracycline for patients who are allergic to penicillin.** **Do not routinely offer a fluoroquinolone to patients with low-severity community-acquired pneumonia.**
Relative values of different outcomes	The GDG considered mortality the most important outcome, though acknowledged that this was likely to be a rare event in low-severity CAP. Clinical cure and withdrawal due to adverse events were considered other important outcomes.
Trade-off between clinical benefits and harms	Various comparisons between different antibiotics were considered. The GDG noted that amoxicillin is the current UK standard treatment for low-severity CAP. No studies matching the protocol included amoxicillin in usual UK doses as a comparator. There was very slight reduction in mortality with beta-lactamase stable penicillin compared with macrolide, though event rates were low leading to imprecision around this result which the GDG judged to be of debatable clinical significance. No clinically relevant difference in clinical cure was seen. There were also fewer withdrawals from studies due to adverse events with beta-lactamase stable penicillin than with macrolide, though the study that showed the largest difference included erythromycin as the macrolide arm. Erythromycin is often poorly tolerated compared with other macrolide antibiotics due to gastro-intestinal side effects, and is now not commonly used as a first-line treatment for CAP. The GDG concluded that the evidence for a beta-lactamase stable penicillin benefit over a macrolide was not compelling. There were a small amount of data comparing cephalosporin with beta-lactamase stable penicillin and tetracycline. No data on mortality and little data on withdrawal from studies due to adverse events were available, and there was no difference in clinical cure between the groups. The GDG's clinical experience with cephalosporins, excepting later-generation cephalosporins (which are not routinely used for low-severity CAP, require intravenous administration and are more expensive) is that these are inferior to alternative antibiotics for low-severity CAP. Two studies suggested that patients treated with a non-respiratory fluoroquinolone may benefit in terms of clinical cure compared with a macrolide, although there was imprecision around the effect size. Azithromycin was compared with other antibiotics from the same class (macrolides) because of its different pharmacokinetic profile. No mortality data were available. It was found that treatment with azithromycin may produce a benefit in clinical cure at the end of follow-up (12 to 16 days after treatment) compared with the other macrolides. No clinical difference was found for the outcomes of clinical cure at the end of treatment and withdrawal due to adverse events. There was also a reduced length of stay with azithromycin, though the GDG noted that this was not surprising due to the shorter duration of a standard azithromycin course, and that this was not strongly relevant because most patients with low-severity CAP can be managed

	without admission. No mortality data were available for studies comparing tetracyclines with other antibiotic groups. Studies comparing tetracycline with cephalosporin and macrolide included small numbers of patients, with little difference seen in the outcomes of different groups. Four studies considered respiratory fluoroquinolone. The licence for these antibiotics for CAP is currently limited due to safety concerns regarding hepatotoxicity, skin reactions, cardiac arrhythmias and tendon rupture. No clinically important difference was found for any outcomes when respiratory fluoroquinolone was compared with macrolide or amoxicillin. The GDG agreed that safety concerns outweighed any potential benefit seen in these studies. As such, the GDG concluded that respiratory fluoroquinolones should not be offered routinely as first-line treatment. The GDG acknowledged data from an indirect comparison of amoxicillin and clarithromycin, using 2 trials with a common comparator. There was no clinically relevant difference in mortality or clinical cure between the groups. The indirect comparison showed that a higher proportion of patients treated with clarithromycin may experience withdrawals due to adverse events compared with those treated with amoxicillin. GDG experience corroborated this result and the GDG determined that more extensive investigation of indirect comparisons would not be helpful.
Trade-off between net health benefits and resource use	No economic studies comparing a single antibiotic with another single antibiotic were found. Unit costs were presented to the GDG and, in comparison with other elements of clinical care, the GDG noted the relatively low cost of antibiotic therapy and the small difference in costs between classes when IV delivery is not required. The GDG agreed that given the potential mortality and complications associated with ineffective treatment, clinically effective antibiotics were likely to be cost effective. No convincing clinical evidence was found which proved one or another single antibiotic to be more clinically effective than the current UK standard treatment for low-severity CAP (amoxicillin). Therefore the GDG did not find there was any evidence to suggest another option might be more cost effective than amoxicillin for patients with low-severity CAP who do not require intravenous antibiotic treatment.
Quality of evidence	The GDG noted that the majority of studies were non-inferiority studies not designed to detect superiority of one antibiotic over another and in some cases not adequately powered to detect any differences in the outcomes between the 2 treatment groups. The majority of studies were funded by the pharmaceutical industry and were not blinded. There was considerable heterogeneity in the populations studied. Only 3 studies included any UK patients, and even then only as a minority in multi-national studies. In 3 studies, patients with CAP were a subgroup of a larger population being studied. The patients in the studies were younger than the usual population with low-severity CAP, which limits the generalisability of the results to older people. The GRADE rating of the evidence ranged from moderate to very low, with risk of bias and imprecision the quality assessment domains most affected by downgrading. The GDG considered whether other potential sources of data, by performing a network meta-analysis would be of value to indirectly compare further antibiotic therapy. However, concerns regarding the comparability of the populations in

	different studies led the GDG to conclude that this was unlikely to be helpful so a NMA was not performed (see section 10.3).
Other considerations	Overall, the GDG concluded that there was little convincing evidence to support the use of any one group of antibiotics over another. In the absence of any convincing evidence to the contrary, the GDG reached consensus that amoxicillin should be recommended as first-line treatment for low-severity CAP. This was based on a number of factors. Without compelling evidence of benefit of broad- over narrow-spectrum antibiotic therapy, the GDG considered it desirable to recommend a relatively narrow-spectrum antibiotic. (Broad-spectrum antibiotic therapy such as beta-lactamase stable penicillin or cephalosporin is more likely to be associated with adverse effects and is more likely to lead to increased resistance of pathogens at a population level). This was thought to outweigh the theoretical risk of increased treatment failure with a narrow-spectrum antibiotic. Whilst the GDG acknowledged that a proportion of patients would have pneumonia caused by organisms resistant to amoxicillin, the lower severity of disease in these patients would mean that some would have self-limiting illness, while there would usually be opportunity to alter treatment without severe repercussions in those who did not improve. The GDG agreed to recommend amoxicillin in preference to a macrolide or tetracycline as the first-choice antibiotic by consensus, with the emergence of macrolide-resistance in other countries such as the USA (though not currently a major problem in the UK) being 1 factor taken into account. The GDG suggested that for patients who are unable to take amoxicillin (for example, due to a penicillin allergy), a macrolide or tetracycline would be reasonable alternatives. **Key priority for implementation** The GDG prioritised offering a 5-day course of a single antibiotic to patients with low-severity community-acquired pneumonia because it would lead to more efficient use of NHS resources.

10.4.5 Recommendations and link to evidence

Table 81: Linking evidence to recommendations – low-severity community-acquired pneumonia treated in hospital: single-compared with other single-antibiotic therapy

Recommendations	No recommendation made.
Relative values of different outcomes	The GDG considered mortality the most important outcome, with clinical cure, length of hospital stay and adverse events as other important outcomes.
Trade-off between clinical benefits and harms	Six randomised studies were considered. Mortality was rarely reported. In the studies that did report mortality, no antibiotic group was superior to any other. Narrow-spectrum beta-lactam was compared with macrolide and cephalosporin. Azithromycin (macrolide) had a higher rate of clinical cure and withdrawals due to adverse events than benzylpenicillin (narrow-spectrum beta-lactam, class 1), though event rates were low leading to imprecision around the results. A comparison of cefaclor (cephalosporin) and amoxicillin (narrow-spectrum beta-lactam, class 2) only reported clinical cure at end of treatment, for which there was no clinically important difference. Beta-lactamase stable penicillin was compared with macrolide. There was no difference in mortality or clinical cure. There was a slightly higher rate of withdrawal due to adverse events with beta-lactam stable penicillin, though event rates were low leading to a large degree of imprecision around the result. Beta-lactamase stable penicillin was compared with cephalosporin. More patients with CAP were clinically cured at end of treatment with cephalosporins, though not at end of follow-up which was within several weeks of commencing treatment. The rate of withdrawal due to adverse events was low in both groups. Azithromycin was compared with other macrolides. Only a small number of patients were included resulting in a large degree of imprecision around results and causing the GDG to afford little value to the findings. The comparison of non-respiratory fluoroquinolone with tetracycline only reported clinical cure at end of treatment, for which there was no clinically important difference.
Trade-off between net health benefits and resource use	In comparison with other elements of clinical care, the GDG noted the relatively low cost of antibiotics and the small difference between classes, especially when intravenous treatment is not required. The GDG noted that given the potentially high rate of mortality from ineffective treatment, clinically effective antibiotic therapy was likely to be cost-effective. Intravenous antibiotic therapy is more expensive than oral antibiotic therapy and there are differences in costs between classes. Recommending a more costly treatment would need to be justified by an acceptable increase in effectiveness. As the clinical effective review was judged to be inconclusive, the GDG was not able to identify which intravenous antibiotic would be most cost effective and decided not to make a recommendation in this area.
Quality of evidence	The majority of the evidence was of very low quality by GRADE criteria due to risk of bias and imprecision of effect. In addition, most studies were small, non-inferiority studies. The route of antibiotic administration was intravenous in most studies. This was notably different to the previously reviewed section comparing single-antibiotic therapy for patients with low-severity CAP in community.

	The GDG noted that low-severity CAP is usually managed in the community in the UK, though a significant proportion of admissions to hospital with CAP are patients with low-severity CAP requiring admission for other reasons. However, such patients are not usually managed with intravenous antibiotic therapy, and this limits the direct relevance of these studies. No economic evidence was found on this question.
Other considerations	The GDG discussed whether a separate recommendation for antibiotic therapy for low-severity CAP treated in hospital was necessary. Such patients are likely to represent a distinct subpopulation of patients with low-severity CAP – admission is most commonly required because of comorbidity or frailty; as such, treatment failure may be more serious, but so too may be adverse events from antibiotic therapy. The GDG concluded that in the absence of relevant evidence, no separate recommendation was required from that already made for low-severity CAP (see section 10.4).

10.5 Single- compared with dual-antibiotic therapy for low-severity community-acquired pneumonia

For low-severity pneumonia, current clinical practice is to use single antibiotic regimens rather than a combination of antibiotics. In this group the need to cover as many possible causative organisms from the onset is less pressing than in moderate-to high-severity CAP, since there is more scope for subsequent adjustment of treatment based on clinical response. The "failsafe" use of more than 1 antibiotic must be set against the greater risk to the individual of side effects with additional agents, and against the public health concerns of increasing antibiotic resistance. However, although this is currently standard practice the GDG felt it important to consider any studies comparing single-with dual-antibiotic therapy in low-severity, as well as moderate – to high-severity pneumonia.

10.5.1 Clinical evidence

We searched for systematic reviews and randomised trials (RCTs) comparing the effectiveness and safety of single- compared with dual-antibiotic therapy for the treatment of low-severity pneumonia acquired in the community. Dual therapy was defined as the administration of 2 antibiotics from different classes. Data from studies comparing the same classes of antibiotics were pooled into a single analysis (see Appendix N: for classifications). Data were accepted for antibiotic therapy administered by the oral or intravenous routes.

Two RCTs for low-severity CAP[111,170] were included in the review (Table 82).

- The study by Rovira et al. included some participants with prior antibiotic, making the population potentially indirect for the selection of empirical therapy, although this is in line with the spectrum of clinical presentations in practice.
- The study by Lee et al. examined a high dose of levofloxacin, which is not licensed in the UK, but the GDG considered it for inclusion in the review given the lack of evidence for this section.

A matrix of included comparisons is presented to facilitate navigation of the evidence (Figure 8). A summary of the included studies is presented in Table 82. Evidence from the included studies is summarised in the clinical GRADE evidence profiles below (Table 83 and Table 84).

See also the study selection flow chart in Appendix D:, forest plots in Appendix I:, study evidence tables in Appendix G: and exclusion list in Appendix J:.

Figure 8: Single- compared with dual-antibiotic therapy for low-severity community-acquired pneumonia (click on hyperlinks or refer to page numbers)

	Macrolide plus cephalosporin
Macrolide	• Clarithromycin vs clarithromycin + cefuroxime Table 83, 226
Respiratory fluoroquinolone	• Levofloxacin vs azithromycin + ceftriaxone Table 84, 228

Table 82: Summary of studies in the low-severity community-acquired pneumonia review: single- compared with dual-antibiotic therapy

Study	Intervention	Comparison	Severity definition	Outcomes	Comments
Macrolide compared with macrolide plus cephalosporin					
Rovira 1999[170]	Clarithromycin 500 mg b.i.d. orally. Duration 14 days. (N = 45)	Clarithromycin 500 mg b.i.d. orally plus cefuroxime 500 mg b.i.d. orally. Duration 7 days. (N = 45).	Managed in community.	• Mortality • treatment failure • complications (pleural effusion)	• Older than 15 years of age. • A previous antibiotic treatment (at least 1 dose and less than 24-hour duration) had been administered in 31 patients (34%). • Monotherapy duration longer than dual therapy.
Respiratory fluoroquinolone compared with macrolide (azithromycin) plus cephalosporin					
Lee 2012[111]	Levofloxacin 750 mg intravenously once daily, followed by the same dose orally at discharge when clinically improved Duration: 7 days or more	Azithromycin plus ceftriaxone 2.0 g intravenously once daily plus oral azithromycin 500 mg for 3 consecutive days, followed by oral cefpodoxime 200 mg per day at discharge after clinical improvement Duration: 7 days or more	Low-severity CAP (61% of patients with PSI I or II) managed in hospital.	• clinical cure or improvement (no further antibiotic therapy required but clinical symptoms or signs may or may not remain) at end of treatment • withdrawal due to adverse events • complications (pleural effusion)	• Limited to those able to produce sputum. • High-dose levofloxacin.

Table 83: Clinical evidence profile: Macrolide compared with macrolide plus cephalosporin for low-severity community-acquired pneumonia managed in the community

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Macrolide	Macrolide plus cephalosporin	Relative (95% CI)	Absolute	Quality
Mortality (CAP-related) (follow-up unclear) [Rovira 1999]											
1	randomised trial	very serious[1]	no serious	no serious	no serious	none	0/45 (0%)	0/45 (0%)	not pooled	not pooled	Low
Clinical cure											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Withdrawal due to adverse											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Treatment failure (follow-up unclear) [Rovira 1999]											
1	randomised trial	very serious[2]	no serious	no serious	very serious[3]	none	0/45 (0%)	2/45 (4.4%)	PETO OR 0.13 (0.01 to 2.15)	38 fewer per 1000 (from 44 fewer to 46 more)	Very low
Health-related quality-of-life											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Complications (pleural effusion) (follow-up unclear) [Rovira 1999]											
1	randomised trial	very serious[3]	no serious	no serious	very serious[3]	none	1/45 (2.2%)	0/45 (0%)	PETO OR 7.39 (0.15 to 372.38)	22 more per 1000 (from 37 fewer to 82 more)	Very low
***C. difficile*-associated diarrhoea**											
0	no evidence	-	-	-	-	none	-	-	-	-	

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Macrolide	Macrolide plus cephalosporin	Relative (95% CI)	Absolute	Quality
	available										

[1] *High risk of selection bias (unclear allocation concealment)*
[2] *High risk of selection bias (unclear allocation concealment) and unblinded*
[3] *95% CI crosses both default MIDs*

Table 84: Clinical evidence profile: Respiratory fluoroquinolone compared with cephalosporin plus macrolide (azithromycin) for low-severity community-acquired pneumonia managed in the hospital

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Respiratory fluoroquinolone (new)	Cephalosporin plus azithromycin	Relative (95% CI)	Absolute	Quality
Clinical cure or improvement at end of treatment [Lee 2012]											
1	randomised trial	serious[1]	no serious	serious[2]	serious[3]	none	16/17 (94.1%)	16/19 (84.2%)	RR 1.12 (0.89 to 1.4)	101 more per 1000 (from 93 fewer to 337 more)	Very low
Withdrawal due to adverse events [Lee 2012]											
1	randomised trial	serious[1]	no serious	serious[2]	very serious[4]	none	3/20 (15%)	1/20 (5%)	RR 3 (0.34 to 26.45)	100 more per 1000 (from 33 fewer to 1000 more)	Very low
Complications (pleural effusion) [Lee 2012]											
1	randomised trial	serious[1]	no serious	serious[2]	very serious[4]	none	0/20 (0%)	1/20 (5%)	RR 0.33 (0.01 to 7.72)	34 fewer per 1000 (from 49 fewer to 336 more)	Very low
Mortality											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Health-related quality-of-life											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Complications											
0	no evidence available	-	-	-	-	none	-	-	-	-	
***C. difficile*-associated diarrhoea**											

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Respiratory fluoroquinolone (new)	Cephalosporin plus azithromycin	Relative (95% CI)	Absolute	Quality
0	no evidence available	-	-	-	-	none	-	-	-	-	

[1] *High risk of selection bias (unblinded, unclear allocation concealment, higher proportion of patients with low-severity in the levofloxacin group)*
[2] *Limited to those able to produce sputum, high dose of levofloxacin*
[3] *Confidence interval crossed 1 default MID*
[4] *Confidence interval crossed both default MIDs*

10.5.2 Economic evidence

Published literature

No relevant economic evaluations comparing single- with dual-antibiotic therapy were identified for low-severity CAP.

Four studies that met the inclusion criteria were selectively excluded due to methodological limitations[11,164,165,197]– these are reported in Appendix K: with reasons for exclusion given.

Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided in Appendix O: to aid consideration of cost effectiveness.

10.5.3 Evidence statements

10.5.3.1 Clinical

10.5.3.1.1 Macrolide compared with macrolide plus cephalosporin

- Very low quality evidence from a randomised study of 90 patients with low-severity CAP managed in the community showed that there was no clinical difference in any of the outcomes (mortality, treatment failure, complications) between the groups of patients who received a macrolide compared with those who received macrolide plus cephalosporin.

10.5.3.1.2 Respiratory fluoroquinolone compared with macrolide plus cephalosporin

- A small randomised study including patients with low-severity CAP managed in hospital showed that although there may be a benefit in terms of clinical cure for patients who received a respiratory fluoroquinolone compared with those who received macrolide plus cephalosporin (azithromycin), the first group may experience more withdrawals due to adverse events. However, the quality of this evidence was very low with very serious imprecision of the effects.

10.5.3.2 Economic

- No relevant economic evaluations were identified.

10.5.4 Recommendations and link to evidence

Table 85: Linking evidence to recommendations – low-severity community-acquired pneumonia: single- compared with dual-antibiotic therapy

Recommendations	**Do not routinely offer patients with low-severity community-acquired pneumonia:** • **a fluoroquinolone** • **dual antibiotic therapy.**
Relative values of different outcomes	The GDG considered mortality the most important outcome in any severity grouping (although the baseline risk is clearly greater with increasing severity) with clinical cure, length of hospital stay and adverse events as other important outcomes.
Trade-off between clinical benefits and harms	Possible clinical benefit in improving clinical cure by the use of a respiratory fluoroquinolone compared with cephalosporin plus macrolide was seen, though more patients withdrew due to adverse events in the respiratory fluoroquinolone group. The licence for fluoroquinolones for CAP is currently limited due to safety

	concerns regarding hepatotoxicity, skin reactions, cardiac arrhythmias and tendon rupture. The GDG decided that safety concerns outweighed any potential benefit seen in these studies. As such, the GDG resolved that respiratory fluoroquinolones should not be offered routinely as first-line treatment. No difference was found in the clinical outcomes of patients treated with a single macrolide and patients who received macrolide plus cephalosporin. The results were not convincing enough to strongly influence the deliberations of the GDG. There was also very little evidence pertaining to specific harms of dual-antibiotic therapy.
Trade-off between net health benefits and resource use	No economic evidence was available on patients with low-severity CAP. The GDG considered the increased costs and adverse effects of dual therapy to be unjustified by the available clinical evidence in this population and therefore they did not have enough evidence to conclude that dual therapy is cost effective compared with single antibiotic therapy.
Quality of evidence	The randomised study comparing macrolide to macrolide plus cephalosporin was of small sample size, with very low-quality evidence by GRADE criteria across the outcomes and only reported negative outcomes (mortality, treatment failure and complications). The event rates were low resulting in uncertainty around the estimate of effect size. In addition, the monotherapy arm had a longer duration of therapy than the dual therapy arm. The study comparing respiratory fluoroquinolone with macrolide plus cephalosporin included patients with low-severity CAP treated in hospital and included evidence of very low quality by GRADE criteria due to high risk of bias including baseline imbalance of severity status between the 2 groups and issues of indirectness.
Other considerations	The GDG felt that the consequences of treatment failure for low-severity CAP are likely to be less serious than treatment failure of moderate- or high-severity CAP, resulting in the benefit-to-harm ratio of dual-antibiotic therapy being less attractive. There is also a slight additional cost when 2 antibiotics are used. The GDG therefore felt that single-antibiotic therapy was likely to be appropriate for most cases of low-severity CAP and agreed that a recommendation discouraging dual-antibiotic therapy for low-severity CAP was appropriate. The GDG was cognisant of the restricted licence for fluoroquinolones for CAP in the UK due to safety concerns and agreed that a 'do not' recommendation for this class of antibiotic was appropriate. **Key priority for implementation** The GDG agreed that discouraging the use of dual antibiotic therapy for low-severity CAP would have a high impact on outcomes that are important to patients (by reducing the risk of treatment-related adverse events), include actions that are measurable and lead to more efficient use of NHS resources through reduction of antimicrobial resistance.

10.6 Dual- compared with other dual-antibiotic therapy for low-severity community-acquired pneumonia

We searched for systematic reviews and randomised trials (RCTs) comparing the effectiveness and safety of empirical treatment with 2 antibiotics from different classes with 2 other antibiotics for the treatment of low-severity pneumonia acquired in the community. No data were identified.

Moderate- to high-severity community-acquired pneumonia

10.7 Single- compared with other single-antibiotic therapy for moderate- to high-severity community-acquired pneumonia

For full details see review protocol in Appendix C:.

A recommendation for dual antibiotic therapy for moderate- to high-severity CAP was agreed by GDG consensus after reviewing the evidence for single compared with dual antibiotics. However, the GDG wished to ensure that there was no superior single antibiotic regimen for moderate- or high-severity CAP that would be overlooked due to no study directly comparing it with dual-antibiotic therapy.

10.7.1 Clinical evidence

We searched for randomised studies comparing the effectiveness and safety of empirical treatment with single antibiotic therapy from different classes for the treatment of moderate- to high-severity pneumonia acquired in the community. The only comparison found was between cephalosporin and beta-lactam (see Appendix N: for classifications). Data were accepted for antibiotic therapy administered by the oral, intravenous or intramuscular routes.

A matrix of included comparisons is presented to facilitate navigation of the evidence (Figure 9).Two studies of moderate- to high-severity CAP[145,169] were included in the review.

Table 86 summarises the details of studies in patients with moderate- to high-severity CAP. Evidence from the included studies is summarised in the clinical GRADE evidence profiles below (Table 87 and Table 88). No data were reported for health-related quality-of-life for any comparison.

See also the study selection flow chart in Appendix D:, forest plots in Appendix I:, study evidence tables in Appendix G: and exclusion list in Appendix J:.

Figure 9: Single compared with other single antibiotics for moderate- to high-severity community-acquired pneumonia (click on hyperlinks or refer to page numbers)

	Narrow spectrum beta-lactam (class 2)	Beta-lactamase stable penicillin
Cephalosporin	Table 88, 236	Table 87, 234

Table 86: Summary of studies comparing single- with other single-antibiotic therapy in the review of high-severity community-acquired pneumonia

Study	Intervention	Comparison	Severity definition	Outcomes	Comments
Cephalosporin compared with narrow-spectrum beta-lactam (class 2)					
Nicolle 1996[145]	Ceftriaxone 1 g IV daily, plus 2 daily infusions of saline. After 4 days an assessment was made to determine whether to intensify, maintain or modify to oral therapy **Route of administration**: IV to oral **Duration**: 7 days or more (mean: 8.1 days). (N = 17).	Ampicillin 1 g IV every 8 hours. After 4 days an assessment was made to determine whether to intensify, maintain or modify to oral therapy (could be switched to oral amoxicillin if considered appropriate) **Route of administration**: IV to oral **Duration**: Mean 10.2 days. (N = 20).	Moderate-to-high-severity pneumonia in long-term care facility.	• mortality • clinical cure (improvement of clinical findings) at end of follow-up • *C. difficile*-associated diarrhoea	• Limited to those aged > 65 years. • All from long-term care facilities. • 50% of those screened not included.
Cephalosporin compared with beta-lactamase stable penicillin					
Roson 2001[169]	Ceftriaxone IV 1 g every 24 hours for at least 72 hour followed by IM ceftriaxone 1 g every 24 hours **Route of administration**: IV then IM **Duration**: Mean 10.1 days.	Co-amoxiclav IV 2 g/200 mg every 8 hours for at least 72 hours, followed by oral co-amoxiclav 1 g/125 mg every 8 hours (after significant clinical improvement was achieved) **Route of administration**: IV then oral **Duration**: Mean 10.9 days.	Moderate- to high-severity pneumonia in hospital (59% were PSI class IV or V).	• 30-day mortality • clinical cure (clinical and CXR resolution) at end of treatment and follow-up • ITU admission • length of hospital stay • Withdrawal due to adverse events	• Intravenous erythromycin IV received as combination therapy in 12.9% and 9.2% of patients in experimental and control groups respectively. No other antibiotic therapy was allowed. • High dose of co-amoxiclav. • Excluded those suspected of having *Legionella* or atypical

Study	Intervention	Comparison	Severity definition	Outcomes	Comments
	(N = 194).	(N = 184).		• complications (empyema)	pneumonia.

Table 87: Clinical evidence profile: Cephalosporin compared with beta-lactamase stable penicillin for moderate- to high-severity community-acquired pneumonia in hospital

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cephalosporin	Beta-lactamase stable penicillin	Relative (95% CI)	Absolute	Quality
Mortality (follow-up 30 days) [Roson 2001]											
1	randomised trial	serious[1]	no serious	serious[2]	very serious[3]	none	17/194 (8.8%)	19/184 (10.3%)	RR 0.85 (0.46 to 1.58)	15 fewer per 1000 (from 56 fewer to 60 more)	Very low
Clinical cure - End of treatment (11 to 13 days) [Roson 2001]											
1	randomised trial	serious[1]	no serious	serious[2]	no serious	none	157/194 (80.9%)	146/184 (79.3%)	RR 1.02 (0.92 to 1.13)	16 more per 1000 (from 64 fewer to 103 more)	Low
Clinical cure - End of follow-up (1 month after discharge) [Roson 2001]											
1	randomised trial	serious[1]	no serious	serious[2]	no serious	none	144/194 (74.2%)	136/184 (73.9%)	RR 1 (0.89 to 1.13)	0 fewer per 1000 (from 81 fewer to 96 more)	Low
Withdrawal due to adverse events [Roson 2001]											
0	no evidence available					none	-	-	-	-	
ITU admission [Roson 2001]											
1	randomised trial	serious[1]	no serious	serious[2]	very serious[3]	none	14/194 (7.2%)	14/184 (7.6%)	RR 0.95 (0.46 to 1.93)	4 fewer per 1000 (from 41 fewer to 71 more)	Very low
Length of hospital stay (Better indicated by lower values) [Roson 2001]											
1	randomis	serious[1]	no	serious[2]	serious[4]	none	11.3	10.7	-	not pooled	Very

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cephalosporin	Beta-lactamase stable penicillin	Relative (95% CI)	Absolute	Quality
	ed trial		serious								low
Health-related quality-of-life											
0	no evidence available					none	-	-	-	-	
Complications (empyema) (follow-up up to 1 month after discharge) [Roson 2001]											
1	randomised trial	serious[1]	no serious	serious[2]	very serious[3]	none	11/194 (5.7%)	10/184 (5.4%)	RR 1.04 (0.45 to 2.4)	2 more per 1000 (from 30 fewer to 76 more)	Very low
***C. difficile*-associated diarrhoea**											
0	no evidence available					none	-	-	-	-	

[1] *Unclear randomisation. 15% of the original sample had missing data*
[2] *Study excluded those with suspected Legionella/atypical CAP; additional erythromycin permitted (but only received in a minority) and high dose of co-amoxiclav*
[3] *95% CI crosses both default MIDs*
[4] *Imprecision could not be estimated because variance (SD) not reported*

Table 88: Clinical evidence profile: Cephalosporin compared with narrow-spectrum beta-lactam (class 2) for moderate- to high-severity community-acquired pneumonia in long-term facilities

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cephalosporin	Narrow-spectrum beta-lactam (class 2)	Relative (95% CI)	Absolute	Quality
Mortality (follow-up up to 15 days after treatment) [Nicolle 1996]											
1	randomised trial	serious[1]	no serious	serious[2]	very serious[3]	none	1/17 (5.9%)	2/20 (10%)	RR 0.59 (0.06 to 5.94)	41 fewer per 1000 (from 94 fewer to 494 more)	Very low
Clinical cure - End of follow-up (10 to 15 days after treatment) [Nicolle 1996]											
1	randomised trial	serious[1]	no serious	serious[2]	serious[4]	none	16/17 (94.1%)	14/20 (70%)	RR 1.34 (0.99 to 1.83)	238 more per 1000 (from 7 fewer to 581 more)	Very low
Withdrawal due to adverse events											
0	no evidence available					none	-	-	-	-	
Hospital admission											
0	no evidence available					none	-	-	-	-	
Length of hospital stay											
0	no evidence available					none	-	-	-	-	
Health-related quality-of-life											
0	no evidence available					none	-	-	-	-	
Complications											

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cephalosporin	Narrow-spectrum beta-lactam (class 2)	Relative (95% CI)	Absolute	Quality
0	no evidence available					none	-		-	-	
***C. difficile*-associated diarrhoea (follow-up up to 15 days after treatment) [Nicolle 1996]**											
1	randomised trial	serious[1]	no serious	serious[2]	very serious[3]	none	2/17 (11.8%)	1/20 (5%)	RR 2.35 (0.23 to 23.75)	67 more per 1000 (from 38 fewer to 1000 more)	Very low

[1] *High risk of selection bias as study was single blinded only for the first 4 days; unclear randomisation and allocation concealment*
[2] *Limited population: all elderly (mean age 81 years and in nursing home)*
[3] *95% CI crosses both default MIDs*
[4] *95% CI crosses 1 default MID*

10.7.2 Economic evidence

Published literature

One study was included with the relevant comparison.[82] This is summarised in the economic evidence profile below (Table 89). See also the study selection flow chart in Appendix E: and study evidence tables in Appendix H:.

Three studies that met the inclusion criteria were selectively excluded due to methodological limitations[15,145,163] – these are reported in Appendix K:, with reasons for exclusion given.

Table 89: Economic evidence profile: cephalosporin compared with respiratory fluoroquinolone

Study	Applicability	Limitations	Other comments	Incremental cost[c]	Incremental effects (QALYs)	Cost effectiveness[d]	Uncertainty
Frei2005[82] (USA)	Partially applicable[a]	Very serious limitations[b]	This study compared 4 strategies. Only the monotherapy comparison is shown here. The respiratory fluoroquinolone is levofloxacin and the cephalosporin is ceftriaxone.	£260	-0.440[d]	Cephalosporin is dominated by respiratory fluoroquinolone.	Mortality rate was varied by ± 5% according to a normal distribution, and the total hospital cost was fit to a log-normal distribution and varied over the entire interval. No overall conclusion can be drawn from the analysis.

(d) Study conducted in the US with no quality-of-life considerations

(e) Clinical data based on a cohort study, information on drug doses not given, billing data used as proxy for costs, only conducted in a single hospital

(a) 2005 US$ converted into GBP using the purchasing power parities[155]

(b) QALYs gained and incremental analyses calculated by the NCGC as a complete incremental analysis was not performed in the study. QALYs were estimated based on the survival reported in the study, the average EQ-5D scores for general UK population (70 to 80 years) from Kind et al (1998)[107], and the life expectancy for the general population reported in the England and Wales Life Tables.[150] QALYs have been discounted by 3.5% per year

Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided in Appendix O: to aid consideration of cost effectiveness.

10.7.3 Evidence statements

10.7.3.1 Clinical

10.7.3.1.1 Cephalosporin compared with beta-lactamase stable penicillin

- Low to very low quality evidence from a randomised trial of over 300 participants with moderate- to high-severity CAP comparing cephalosporin with beta-lactamase stable penicillin showed that although there were fewer deaths in the cephalosporin arm, no clinical difference was found for the other outcomes (clinical cure, ITU admission, length of hospital stay and complications).

10.7.3.1.2 Cephalosporin compared with narrow-spectrum beta-lactam

- One small randomised study of 40 participants found that although patients with moderate-to high-severity CAP may experience a clinical benefit (lower mortality and higher cure rate at follow-up) from treatment with cephalosporin compared with those receiving narrow-spectrum beta-lactam (class 2), they may also have a higher risk of *C. difficile*-associated diarrhoea. The quality of evidence was very low for all outcomes reported.

10.7.3.2 Economic

- One cost-effectiveness analysis found that respiratory fluoroquinolone was dominant (less costly and more effective) compared with cephalosporin for treating high-severity CAP. This study was assessed as partially applicable with very serious limitations.

10.7.4 Recommendations and link to evidence

Table 90: Linking evidence to recommendations – single- compared with other single-antibiotic therapy for moderate- to high-severity community-acquired pneumonia

Recommendations	No recommendation made.
Relative values of different outcomes	The GDG considered mortality the most important outcome, with clinical cure, length of hospital stay and adverse events as other important outcomes.
Trade-off between clinical benefits and harms	Two studies comparing single-antibiotic therapy for moderate- to high-severity CAP were considered: 1 compared ceftriaxone with co-amoxiclav and the other compared ceftriaxone with ampicillin (in the elderly). The study comparing cephalosporin with narrow-spectrum beta-lactam suggested that cephalosporin may reduce mortality and improve clinical cure rate at follow-up at the cost of a higher incidence of *C. difficile*-associated diarrhoea, though the study was small and there was uncertainty around the estimates of effects. Although there were fewer deaths in the cephalosporin arm, the study comparing cephalosporin with broad-spectrum beta-lactam found no important clinical difference between the 2 groups across all reported outcomes (mortality, clinical cure, ITU admission, length of hospital stay and complications). There was no information on adverse events in either study other than the *C. difficile*-associated diarrhea.

	On balance the GDG considered that there was no consistent evidence to reliably distinguish the interventions in terms of whether any had a favourable benefit/harm profile.
Trade-off between net health benefits and resource use	One economic study showed that respiratory fluoroquinolone was dominant (less costly and more effective) compared with cephalosporin for treating high-severity CAP. However the same study also reported that dual therapy was more cost-effective than single therapy in high-severity CAP. Therefore no recommendation was made on single therapy for patients with moderate-or high-severity CAP as dual therapy was a more cost-effective strategy.
Quality of evidence	Evidence was of low to very low quality by GRADE criteria. For the majority of outcomes there was serious or very serious imprecision so the GDG had little confidence in the estimates. The GDG acknowledged the lack of evidence for single antibiotic regimens in moderate- or high-severity CAP. The studies that were available were limited by indirectness; 1 considered patients over the age of 65 years from long-term care facilities in the USA, where pathogens may not reflect those found in patients with CAP in the UK. In addition, half of the screened patients were not included in the final analysis and patient numbers were small. This study was also at high risk of bias. The other study excluded patients with suspected Legionella or atypical pathogens, and addition of a second antibiotic was optional for both groups. The generalisability of the findings of both studies need caution as both were old (published over 10 years ago) and neither was conducted in the UK. The economic evidence was assessed as partially applicable with very serious limitations.
Other considerations	The GDG noted that in the extremely limited evidence base available, no single antibiotic appeared significantly superior to any other. Current practice in the UK is to treat moderate- to high-severity CAP with dual antibiotic therapy. The GDG felt that the evidence seen in this section did not highlight any single antibiotic that required stronger consideration than those already examined in the single- compared with dual-antibiotic therapy section (Section10.8).

10.8 Single- compared with dual-antibiotic therapy for moderate-to high-severity community-acquired pneumonia

For full details see review protocol in Appendix C:.

The current standard antibiotic treatment for moderate- to high-severity pneumonia in most centres in the UK is the combination of beta-lactam plus macrolide. This is based on an assessment of bacterial causes and their sensitivity profiles; it gives good cover against most common pathogens including Legionella and Mycoplasma. The original rationale for using these 2 antibiotics together is that in patients who have markers of severe disease at presentation it is sensible to cover all the most likely causative organisms since any further deterioration could be catastrophic. The GDG was therefore particularly interested in clinical trials which compared the combination to either of its component parts, or in trials which directly compared other alternatives to this regimen.

10.8.1 Clinical evidence

We searched for systematic reviews and randomised trials (RCTs) comparing the effectiveness and safety of single- and dual-antibiotic therapy for the treatment of pneumonia acquired in the community. Data from studies comparing the same classes of antibiotics were pooled into a single

analysis (see Appendix N: for classifications). Data were accepted for antibiotic therapy administered by the oral or intravenous routes.

A matrix of included comparisons is presented to facilitate navigation of the evidence (Figure 10). Eight RCTs for CAP[79,81,115,121,193,201,202,208] were included in the review. A variety of antibiotic therapy was used and population characteristics varied (see Table 91).

- With the exception of 1 study[193], the included studies were not placebo-controlled. The majority were funded by industry and designed to detect non-inferiority between the comparisons. In addition, some participants in the included studies had a prior antibiotic treatment, which makes the evidence indirect to answer this review question (which focuses on first empirical treatment) although this is currently in line with the spectrum of clinical presentations in UK practice.

The GDG noted in the protocol stage the potential lack of randomised data for the comparison of beta-lactam and beta-lactam plus macrolide (the current standard therapy used in the UK). Given the availability of randomised evidence for the other comparisons, the GDG agreed to review observational studies with multivariate analysis only for the comparison of a beta-lactam and beta-lactam plus macrolide and a summary of these 7 studies is included in Table 92.

Evidence from the included studies is summarised in the clinical GRADE evidence profiles below (Table 93, Table 94, Table 95, Table 96 and Table 97). Evidence from the observational studies with multivariate analysis for beta-lactam compared with beta-lactam plus macrolide is available in Table 98.

See also the study selection flow chart in Appendix D:, forest plots in Appendix I:, study evidence tables in Appendix G: and exclusion list in Appendix J:.

Figure 10: Single- compared with dual-antibiotic therapy for moderate- to high-severity community-acquired pneumonia (click on hyperlinks or refer to page numbers)

	Cephalosporin plus macrolide	Beta-lactamase stable penicillin plus macrolide	Cephalosporin plus respiratory fluoroquinolone	Cephalosporin plus non-respiratory fluoroquinolone
Macrolide	• Azithromycin vs. cefuroxime + erythromycin • Clarithromycin vs. cefuroxime + erythromycin Table 93, 250			
Respiratory fluoroquinolone	• Levofloxacin vs. ceftriaxone + azithromycin • Levofloxacin vs ceftriaxone + erythromycin Table 94, page 252	• Levofloxacin vs. co-amoxiclav + clarithromycin Table 95, page 254	• Moxifloxacin vs. ceftriaxone + levofloxacin Table 96, page 256	• Levofloxacin vs. cefotaxime + ofloxacin Table 97, page 258

Table 91: Summary of studies comparing single- with dual-antibiotic therapy included in the review of moderate- to high-severity community-acquired pneumonia

Study	Intervention (monotherapy)	Comparison (dual therapy)	Population/severity	Outcomes	Comments
Macrolide compared with cephalosporin plus macrolide					
Vergis 2000[201]	Azithromycin dihydrate IV as a 1-hour infusion 500 mg once daily for 2 to 5 days, followed by 500 mg orally **Duration** 7 to 10 days. (N = 67).	Cefuroxime combined with erythromycin. Cefuroxime was IV 750 mg q8v h for 2 to 7 days, followed by cefuroxime axetil 500 mg orally twice daily to complete a total of 7 to 10 days. Erythromycin lactobionate or erythromycin base 500 to 1000 mg IV or orally q6 h for up to 21 days. **Duration** 7 to 10 days. (N = 78)	Managed in hospital.	• Mortality • clinical cure (receipt of a minimum of 3-day therapy and resolution of symptoms and signs) at end of treatment • ITU admission	• The decision to switch to oral therapy was made on the basis of improvement in cough, diminution in purulent sputum production, defervescence, and reduction in leukocytosis. • 24% had *L. pneumophila* infection.
Vetter 1997[202]	Clarithromycin, IV 500 mg twice daily for 2 to 5 days followed by oral clarithromycin 500 mg twice daily. **Duration** 10 days in total (2 to 5 days IV). (N = 118).	Erythromycin, IV 1 g t.i.d plus cefuroxime sodium 1.5 g t.i.d for 2 to 5 days followed by oral erythromycin base 500mg 4 times daily and cefuroxime axetil 500 mg twice daily. **Duration** 10 days in total (2 to 5 days IV). (N = 117).	Managed in hospital and requiring initial IV therapy.	• Mortality • clinical cure (resolution of signs and symptoms) at end of treatment and at follow-up • withdrawal due to adverse events	• Switch from intravenous to oral antibiotic therapy after 3 to 5 days of treatment. • Patients requiring more than 5 days of intravenous therapy were withdrawn from the study.
Respiratory fluoroquinolone compared with cephalosporin plus macrolide					
Fogarty 2004[79]	Levofloxacin, 500 mg IV, followed by oral administration, q24 h. **Duration:** 7 to 14 days. (N = 134).	Ceftriaxone sodium, 1–2 g IV or IM q24 h, with erythromycin, 500–1000 mg IV q6 h, and then switched to co-amoxiclav, 875 mg PO b.i.d., with clarithromycin, 500 mg PO b.i.d. **Duration:** 7 to 14 days. (N = 135).	High-severity CAP (ATS ≥ 3) managed in hospital.	• Mortality • clinical success (cure or improvement) at follow-up (3 to 12 days) • withdrawal due to adverse events	• Antibiotic agents switched when transitioned from IV to oral administration at the investigator's discretion based on signs of clinical improvement. • Nursing home patients were eligible for inclusion.

Study	Intervention (monotherapy)	Comparison (dual therapy)	Population/severity	Outcomes	Comments
Frank 2002[81]	Levofloxacin 500 mg PO or IV q24 h. **Duration:** 10 days. (N = 85).	Azithromycin 500 mg IV q24 h for 2 days plus ceftriaxone 1 g IV q24 h for more than 2 days, followed by an optional transition to azithromycin 500 mg PO q24 h at the investigator's discretion. **Duration:** 10 days. (N = 78).	Moderate- to high-severity CAP (PSI of 71 to 130) managed in hospital.	• clinical success (cure or improvement) at end of treatment • withdrawal due to adverse events	• Comparator arm switched to monotherapy when transitioned from IV to oral administration (at investigators discretion). • Patients with prior antibiotic therapy were allowed to participate.
Zervos 2004[208]	Levofloxacin IV 500 mg/day for 2 to 5 days followed by oral levofloxacin 500 mg/day. **Duration:** 7 to 14 days. (N = 107).	Azithromycin IV 500 mg once daily plus ceftriaxone IV 1 g daily for 2 to 5 days, followed by oral azithromycin 500 mg once daily. **Duration:** 7 to 10 days. (N = 112).	Moderate- to high-severity CAP (> 95% PSI III-V) managed in hospital and requiring initial intravenous therapy.	• Mortality • clinical cure (resolution of signs and symptoms) at end of treatment and at end of follow-up • withdrawal due to adverse events • length of hospital stay	• Comparator arm switched to monotherapy when transitioned from IV to oral administration.
Respiratory fluoroquinolone compared with beta-lactamase stable penicillin plus macrolide					
Lin 2007[121]	Levofloxacin 500 mg IV q24 h transitioning to oral levofloxacin 500 mg q24 h when the patients' condition was compatible. **Duration** 7 to 14 days. (N = 26).	Co-amoxiclav 500 mg/100 mg IV q8 h with oral clarithromycin 500 mg q12 h and then switched to oral co-amoxiclav 250 mg/125 mg q8 h with oral clarithromycin 500 mg q12 h. **Duration** 7 to 14 days. (N = 24).	Moderate- to high-severity CAP (PSI ≥ 71:71%) requiring hospitalisation and initial intravenous therapy (not ITU).	• clinical success (cure or improvement)at end of treatment and t end of follow-up • length of hospital stay	• Analysis performed before calculated sample size reached. • Included subgroup analysis for different PSI classes. • Switch to the oral therapy permitted if: (1) cough and respiratory distress are improving; (2) patient has been afebrile for a minimum of 8 hours; (3) the white

Study	Intervention (monotherapy)	Comparison (dual therapy)	Population/severity	Outcomes	Comments
					blood cell count is returning to normal; (4) there is no evidence of abnormal gastrointestinal absorption.
Respiratory fluoroquinolone compared with cephalosporin plus respiratory fluoroquinolone					
Torres 2008[193]	Sequential IV and oral moxifloxacin (400 mg once per day). After 3 days of IV therapy patients could be switched to oral therapy at the discretion of the investigator **Duration** 7 to 14 days (N = 368).	Ceftriaxone (IV 2 g once per day) plus sequential IV and oral levofloxacin (500 mg twice per day). After 3 days of IV therapy with levofloxacin, patients could be switched to oral therapy at the discretion of the investigator. **Duration** 7 to 14 days (N = 365).	Moderate- to high-severity CAP (PSI score III-V) managed in hospital and required intravenous treatment.	• Mortality • clinical cure at end of treatment • maintaining cure at end of follow-up • *C. difficile*-associated diarrhoea	• Included subgroup analysis for different PSI classes. • Previous systemic antimicrobial treatment received in 39%; had failed in 35% of these cases.
Respiratory fluoroquinolone compared with cephalosporin plus non-respiratory fluoroquinolone					
Leroy 2005[115]	Levofloxacin 500 mg by IV infusion over 60 min bid. Thereafter, levofloxacin could be given as a 500-mg tablet bid. **Duration:** 10 to 14 days (up to 21 days if Legionella or purulent pleurisy). (N = 191).	Cefotaxime 1g by IV infusion over 20 to 60 min tid and 200 mg ofloxacin by IV infusion over 60 min bid. Oral ofloxacin was administered as a 200-mg tablet bid. **Duration:** 10 to14 days (up to 21 days if Legionella or purulent pleurisy). (N = 198).	High-severity CAP requiring ITU admission.	• Mortality • clinical cure at test-of-cure visit • clinical cure at end of follow-up • withdrawal due to adverse events • length of hospital stay	• Switch to oral therapy permitted once indicated for fluoroquinolones. • Out-patients who had been treated for > 48 hours with antibiotics and admitted to ITU due to lack of response were included (17.5% had failed a prior antibiotic).

Table 92: Summaries of cohort studies with multivariate analysis comparing beta-lactam and beta-lactam plus macrolide

Ref	PICO	Study design	Setting	N
Bratzler 2008[28]	Population: Hospitalised CAP (CXR-confirmed) Medicare fee-for service hospital claims ≥ 65 years Immunocompetent 63.6% PSI IV-V Intervention and comparison: Ref: 3rd generation cephalosporin (IV) Exp: cephalosporin (IV) plus macrolide (IV or PO) Exp: beta-lactam/beta-lactamase (IV) inhibitor plus macrolide (IV or PO) Outcome(s): Mortality (in-hospital, 14-day and 30-day)	Combined from 2 retrospective cohorts (July to March 1998-1999 and 2000-2001) Multivariate logistic regression Covariates: age, sex, neoplastic disease, cardiovascular disease, altered mental status, respiratory rate ≥ 30 breaths/min, systolic blood pressure < 90 mm Hg, temperature < 35°C or ≥ 40°C, pulse ≥ 125 beats/min, arterial pH < 7.35, blood urea nitrogen level > 11 mmol/L, sodium level < 130 mEq/L, haematocrit < 30%, partial pressure of oxygen < 60 mm Hg, and presence of pleural effusion.	USA	12836 taking interventions of interest.
Gleason 1999[86]	Population: Inpatient pneumonia (CAP and HCAP; CXR-confirmed) Medicare ≥ 65 years 68.3% PSI IV-V Intervention and comparison: Ref: non-pseudomonal 3rd gen cephalosporin alone Exp: cephalosporin + macrolide Exp: beta-lactam/beta-lactamase inhibitor plus macrolide Outcome(s): 30-day mortality	Retrospective review Cox proportional hazards model (HR) – MVA Oct 1994 – Sept 1995 Covariates: antibiotics before hospitalisation, pneumonia severity, admitted from LCF, initiation of antibiotic therapy within 8 h, blood culture within 24 hours, location, ITU treatment on day 1, change in antibiotics after first 48 hours, high risk pneumonia aetiology.	USA	8725 taking interventions of interest.
Houck 2001[98]	Population: Hospitalised CAP (CXR confirmed) Medicare ≥ 65 years ➢ 65% PSI IV-V	3 separate cohort studies (1993, 1995 and 1997) Note: 1995 cohort may overlap with Gleason cohort Regression model (multivariate analysis)	USA	7223 taking interventions of interest.

Ref	PICO	Study design	Setting	N
	Intervention and comparison: Many antibiotic regimens but stratified results (beta-lactam vs. beta-lactam + macrolide) Outcome(s): 30-day mortality	Covariates: pre-hospital antibiotic therapy, antibiotics initiated > 24 hours after hospital admission, isolated of pathogen from blood, ITU admission in first 24 hours, severity		
Rodrigo 2012[168]	Population: Hospitalised CAP (stratified for severity; CXR confirmed) ➢ 16 years Intervention and comparison: Single-agent therapy with beta-lactam (any penicillin or cephalosporin antibiotic) Combination therapy with beta-lactam penicillin and macrolide (defined as erythromycin, clarithromycin or azithromycin) Outcome(s): 30-day inpatient death rate. ITU admission Need for MV Need for inotropic support	Cohort – prospective data collection; retrospective analysis 2009-2011 Logistic regression analysis (multivariate analysis) Covariates: age, sex, binary variables within the CURB65 pneumonia severity score excluding age (confusion, urea > 7 mmol/litre, respiratory rate ≥ 30/min, blood pressure < 90 mm Hg systolic or ≤ 60 mm Hg diastolic), individual comorbidities, intravenous antibiotic use, nursing home residency and ITU admission	England and Wales (72 trusts)	5240.
Dudas 2000[64]	Population: Hospitalised CAP Intervention and comparison: Ref: 2nd or 3rd generation cephalosporin or beta-lactam/beta-lactamase stable Exp: 2nd or 3rd generation cephalosporin or beta-lactam/beta-lactamase stable penicillin plus macrolide Outcome(s): Mortality (in hospital)	Cohort Nov 1996 – March 1997 Multiple regression analysis (multivariate analysis) Covariates: severity, congestive heart failure, chronic renal failure, ITU admission > 8 hours to first antibiotic, age, heart rate, respiratory rate, WBC count and serum creatinine.	US 72 centres	2963 (including 210 under 18 years and 2643 using interventions of interest).
Tessmer 2009[192]	Population: Hospitalised CAP (CXR confirmed) Intervention and comparison:	Cohort – prospective data collection July 2002 to Dec 2006 Multiple regression analysis	Germany	1854.

Ref	PICO	Study design	Setting	N
	Single-agent therapy with beta-lactam or combination therapy with beta-lactam and macrolide (IV) Outcome(s): Mortality and treatment failure (death during treatment or change of treatment due to lack of effect/resistance) (14 and 30-day)	Covariates: PSI score, chronic respiratory disease, vaccination status and prior antimicrobial therapy		
Paul 2007[157]	Population: CAP (excluding those in ITU) Intervention and comparison: Single-agent therapy with beta-lactam or combination therapy with beta-lactam plus macrolide Outcome(s): 30-day mortality Length of hospital stay	Cohort study (with propensity analysis) June to December 2002 (Israel and Germany), March to September 2003 (Italy) Summary of propensity analysis findings: Patients treated with monotherapy (n = 169) were older (mean: 70.6 ± 17.3 vs 65.0 ± 19.6), had a higher chronic diseases score and a different clinical presentation compared with patients treated with combination therapy (n = 282). 27 patients in the monotherapy group could be matched to 27 patients in the combination group using the propensity score. The mortality in these groups was identical, with 3 deaths (11%) each. Author's conclusion: "The benefit of combination therapy compared with monotherapy cannot be reliably assessed in observational studies, since the propensity to prescribe these regimens differs markedly."	Israel, Germany, Italy	451.

Table 93: Clinical evidence profile: Macrolide compared with macrolide plus cephalosporin for moderate- to high-severity community-acquired pneumonia in hospital

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Macrolide	Macrolide plus cephalosporin	Relative (95% CI)	Absolute	Quality
All-cause mortality (follow-up up to 6 weeks after treatment in 1 study and unclear in 1 study) [Vergis 2000; Vetter 1997]											
2	randomised trials	very serious[1]	no serious	no serious	very serious[2]	none	8/201 (4%)	5/203 (2.5%)	RR 1.61 (0.54 to 4.81)	14 more per 1000 (from 11 fewer to 88 more)	Very low
Clinical cure at end of treatment (7 to 14 days) [Vergis 2000; Vetter 1997]											
2	randomised trials	very serious[1]	serious[3]	no serious	no serious	none	128/201 (63.7%)	129/203 (63.5%)	RR 0.99 (0.79 to 1.25)	7 fewer per 1000 (from 139 fewer to 165 more)	Very low
Clinical cure at end of follow-up (4 to 6 weeks after treatment) [Vetter 1997]											
1	randomised trial	very serious[4]	no serious	no serious	serious[5]	none	73/118 (61.9%)	66/117 (56.4%)	RR 1.1 (0.89 to 1.36)	56 more per 1000 (from 62 fewer to 203 more)	Very low
Withdrawal due to adverse events (follow-up 11 to 14 days) [Vetter 1997]											
1	randomised trial	very serious[4]	no serious	no serious	serious[5]	none	8/118 (6.8%)	16/117 (13.7%)	RR 0.5 (0.22 to 1.11)	68 fewer per 1000 (from 107 fewer to 15 more)	Very low
ITU admission (follow-up up to 6 weeks after treatment) [Vergis 2000]											
1	randomised trial	very serious[6]	no serious	no serious	very serious[2]	none	5/83 (6%)	8/86 (9.3%)	RR 0.65 (0.22 to 1.9)	33 fewer per 1000 (from 73 fewer to 84 more)	Very low
Length of hospital stay											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Health-related quality-of-life											

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Macrolide	Macrolide plus cephalosporin	Relative (95% CI)	Absolute	Quality
0	no evidence available	-	-	-	-	none	-	-	-	-	
Complications											
0	no evidence available	-	-	-	-	none	-	-	-	-	
***C. difficile*-associated diarrhoea**											
	no evidence available	-	-	-	-	none	-	-	-	-	

[1] *Both studies were of high risk of selection bias and the largest study was also of high risk attrition bias*
[2] *95% CI crosses both default MIDs*
[3] *Significant heterogeneity (I^2 = 61%). A random-effect model was applied.*
[4] *High risk of selection bias*
[5] *95% CI crosses 1 default MID*
[6] *High risk of selection and attrition bias*

Table 94: Clinical evidence profile: Respiratory fluoroquinolone compared with cephalosporin plus macrolide for moderate- to high-severity community-acquired pneumonia in hospital

Quality assessment							No of patients		Effect		
No studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Respiratory fluoroquinolone	Macrolide plus cephalosporin	Relative (95% CI)	Absolute	Quality
All-cause mortality (up to 6 weeks after treatment) (follow-up 35 days in one study and 30 days after treatment in the other) [Fogarty 2004; Zervos 2004]											
2	randomised trials	serious[1]	no serious	serious[2]	serious[3]	none	20/234 (8.5%)	12/247 (4.9%)	RR 1.75 (0.88 to 3.48)	35 more per 1000 (from 6 fewer to 117 more)	Very low
Clinical cure or improvement at end of treatment (follow-up 14 days) [Zervos 2004]											
1	randomised trial	serious[1]	no serious	no serious	serious[3]	none	44/93 (47.3%)	58/97 (59.8%)	RR 0.79 (0.60 to 1.04)	126 fewer per 1000 (from 239 fewer to 24 more)	Very low
Clinical cure or improvement at end of follow-up [Fogarty 2004; Frank 2002; Zervos 2004]											
3	randomised trials	serious[1]	no serious	serious[2]	no serious	none	273/339 (80.5%)	266/352 (75.6%)	RR 1.07 (0.99 to 1.15)	53 more per 1000 (from 8 fewer to 113 more)	Very low
Withdrawal due to adverse events [Fogarty 2004; Frank 2002; Zervos 2004]											
3	randomised trials	serious[1]	serious[4]	serious[2]	serious[3]	none	11/344 (3.2%)	27/361 (7.5%)	RR 0.43 (0.22 to 0.85)	50 fewer per 1000 (from 13 fewer to 69 fewer)	Very low
Hospital admission											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Length of hospital stay (follow-up unclear in one study; 1 month after treatment in the other; Better indicated by lower values) [Zervos 2004]											
1	randomised trial	serious[1]	no serious	no serious	no serious	none	8.4 (6.9)	7.7 (4.7)	-	MD 0.7 higher (1.16 lower to 2.56 higher)	Low

Quality assessment							No of patients		Effect		
No studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Respiratory fluoroquinolone	Macrolide plus cephalosporin	Relative (95% CI)	Absolute	Quality
***C. difficile*-associated diarrhoea**											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Complications											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Health-related quality-of-life											
0	no evidence available	-	-	-	-	none	-	-	-	-	

[1] *High risk of selection bias as studies unblinded and not clear details on randomisation and allocation concealment*
[2] *Studies changed antibiotic agents in comparator arm from cephalosporin to beta-lactamase stable penicillin when transitioned from IV to oral therapy, outcome definition not similar across studies*
[3] *95% CI crosses 1 default MID*
[4] *Effect estimates suggesting different directions of effect with no explanation based on pre-defined subgroups*

Table 95: Clinical evidence profile: Respiratory fluoroquinolone compared with beta-lactamase stable penicillin plus macrolide for moderate- to high-severity community-acquired pneumonia in hospital

Quality assessment							No of patients		Effect		
No studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Respiratory fluoroquinolone	Macrolide plus beta-lactamase stable penicillin	Relative (95% CI)	Absolute	Quality
All-cause mortality											
0	no evidence available	-	-	-	-	-	-	--	-	-	-
Clinical cure or improvement at end of treatment (follow-up 5 to 7 days) [Lin 2007]											
1	randomised trial	serious[1]	no serious	no serious	serious[2]	none	18/23 (78.3%)	17/22 (77.3%)	RR 1.01 (0.74 to 1.38)	8 fewer per 1000 (from 224 fewer to 294 more)	Very low
Clinical cure or improvement at end of follow-up (follow-up 21 to 28 days) [Lin 2007]											
1	randomised trial	serious[1]	no serious	no serious	no serious	none	16/18 (88.9%)	15/17 (88.2%)	RR 1.01 (0.79 to 1.28)	9 more per 1000 (from 185 fewer to 247 more)	Low
Withdrawal due to adverse events											
0	no evidence available	-	-	-	-	-	-	--	-	-	-
Hospital admission											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Length of hospital stay (follow-up 21 to 28 days; Better indicated by lower values) [Lin 2007]											
1	randomised trial	serious[1]	no serious	no serious	no serious	none	7.4 (3.1)	6.8 (2.1)	-	MD 0.6 higher (1.15 lower to 2.35 higher)	Low
***C. difficile*-associated diarrhoea**											

Quality assessment							No of patients		Effect		
No studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Respiratory fluoroquinolone	Macrolide plus beta-lactamase stable penicillin	Relative (95% CI)	Absolute	Quality
0	no evidence available	-	-	-	-	none	-	-	-	-	
Complications											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Health-related quality-of-life											
0	no evidence available	-	-	-	-	none	-	-	-	-	

[1] *High risk of selection bias as studies unblinded and not clear details on randomisation and allocation concealment*
[2] *95% CI crosses 1 default MID*

Table 96: Clinical evidence profile: Respiratory fluoroquinolone compared with cephalosporin plus respiratory fluoroquinolone for moderate- to high-severity community-acquired pneumonia managed in hospital

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Respiratory fluoroquinolone	Cephalosporin plus respiratory fluoroquinolone	Relative (95% CI)	Absolute	Quality
All-cause mortality (follow-up 30 days) [Torres 2008]											
1	randomised trial	serious[1]	no serious	no serious	very serious[2]	none	18/364 (4.9%)	12/357 (3.4%	RR 1.5 (0.74 to 3.04)	15 more per 1000 (from 8 fewer to 61 more)	Very low
Clinical cure or improvement at end of treatment (4 to 14 days after therapy) [Torres 2008]											
1	randomised trial	serious[1]	no serious	no serious	no serious	none	253/291 (86.9%)	250/278 (89.9%)	RR 0.97 (0.91 to 1.02)	27 fewer per 1000 (from 82 fewer to 18 more)	Moderate
Maintaining success at end of follow-up (21 to 28 days after therapy) [Torres 2008]											
1	randomised trial	serious[1]	no serious	no serious	no serious	none	243/253 (96%)	243/250 (97.2%)	RR 0.99 (0.96 to 1.02)	10 fewer per 1000 (from 39 fewer to 19 more)	Moderate
Withdrawal due to adverse events											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Hospital admission											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Length of hospital stay											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Health-related quality-of-life											

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Respiratory fluoroquinolone	Cephalosporin plus respiratory fluoroquinolone	Relative (95% CI)	Absolute	Quality
0	no evidence available	-	-	-	-	none	-	-	-	-	
Complications											
0	no evidence available	-	-	-	-	none	-	-	-	-	
***C. difficile*-associated diarrhoea (follow-up unclear) [Torres 2008]**											
1	randomised trial	very serious[3]	no serious	no serious	very serious[2]	none	0/368 (0%)	1/365 (0.3%)	PETO OR 0.13 (0.00 to 6.76)	3 fewer per 1000 (from 10 fewer to 5 more)	Very low

[1] *High risk of attrition bias and unclear allocation concealment*
[2] *95% CI crosses both default MIDs*
[3] *High risk of attrition and outcome reporting bias (not pre-specified and stool cultures for C. difficile not performed routinely)*

Table 97: Clinical evidence profile: Respiratory fluoroquinolone compared with cephalosporin plus non-respiratory fluoroquinolone for high-severity community-acquired pneumonia managed in hospital

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Respiratory fluoroquinolone	Cephalosporin plus non-respiratory fluoroquinolone	Relative (95% CI)	Absolute	Quality
All-cause mortality (follow-up 28 days) [Leroy 2005]											
1	randomised trial	serious[1]	no serious	no serious	very serious[2]	none	18/149 (12.1%)	20/159 (12.6%)	RR 0.96 (0.53 to 1.74)	5 fewer per 1000 (from 59 fewer to 93 more)	Very low
Clinical cure at end of treatment (8 to 11 days) [Leroy 2005]											
1	randomised trial	serious[1]	no serious	no serious	no serious	none	112/149 (75.2%)	123/159 (77.4%)	RR 0.97 (0.86 to 1.1)	23 fewer per 1000 (from 108 fewer to 77 more)	Moderate
Clinical cure at end of follow-up (21 to 45 days after treatment) [Leroy 2005]											
1	randomised trial	serious[1]	no serious	no serious	no serious	none	88/149 (59.1%)	99/159 (62.3%)	RR 0.95 (0.79 to 1.14)	31 fewer per 1000 (from 131 fewer to 87 more)	Moderate
Withdrawal due to adverse events (follow-up 7 to 21 days) [Leroy 2005]											
1	randomised trial	serious[1]	no serious	no serious	very serious[2]	none	5/194 (2.6%)	4/201 (2%)	RR 1.3 (0.35 to 4.75)	6 more per 1000 (from 13 fewer to 75 more)	Very low
Hospital admission											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Length of hospital stay (Better indicated by lower values) [Leroy 2005]											
1	randomised trial	serious[1]	no serious	no serious	no serious	none	11.9 (9.4)	12 (9.7)	-	MD 0.1 lower (2.23 lower to 2.03 higher)	Low
Health-related quality-of-life											

Quality assessment							No of patients		Effect		
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Respiratory fluoroquinolone**	**Cephalosporin plus non-respiratory fluoroquinolone**	**Relative (95% CI)**	**Absolute**	**Quality**
0	no evidence available	-	-	-	-	none	-	-	-	-	
Complications											
0	no evidence available	-	-	-	-	none	-	-	-	-	
***C. difficile*-associated diarrhoea**											
0	no evidence available	-	-	-	-	none	-	-	-	-	

[1] *Unclear allocation concealment (unblinded study)*
[2] *95% CI crosses both default MIDs*

Table 98: Results from cohort studies with multivariate analysis for the comparison of beta-lactam and beta-lactam plus macrolide

No of studies	Design	Outcomes	Relative effect (95% CI)	Quality
Cephalosporin compared with cephalosporin and macrolide				
Bratzler 2008	Combined from 2 retrospective cohorts	30-day mortality	ITU: 0.70 (0.47 to 1.04)	Very low
			PSI IV/V: 0.71 (0.61 to 0.81)	
Gleason 1999	Retrospective review	30-day mortality	0.71 (0.52 to 0.96)[1] 0.74 (0.60 to 0.92)[2]	Very low
Cephalosporin compared with beta-lactamase stable penicillin and macrolide				
Bratzler 2008	Combined from 2 retrospective cohorts	30-day mortality	ITU: 1.00 (0.28, 3.61 PSI IV/V: 0.80 (0.41 to 1.55)	Very low
Cephalosporin compared with beta-lactamase stable penicillin and macrolide				
Gleason 1999	Retrospective review	30-day mortality	1.77 (1.28 to 2.45)	Very low
Beta-lactam compared with beta-lactam and macrolide				
Houck 1993, 1995, 1997, Paul 2007, Rodrigo 2012, Tessmer 2009	Majority prospective studies	Mortality	Range of RRs: 0.42 (0.25 to 0.70) to 1.04 (0.66 to 1.63)	Low
		ITU admission	0.94 (0.72 to 1.22)	

[1] *The comparison was between non-pseudomonal 3rd generation cephalosporin and 2nd generation cephalosporin plus macrolide*
[2] *The comparison was between non-pseudomonal 3rd generation cephalosporin and non-pseudomonal 3rd generation cephalosporin plus macrolide*

10.8.2 Economic evidence

Published literature

Two economic evaluations were identified with the relevant comparison in moderate to high-severity CAP and have been included in this review.[82,123] These are summarised in the economic evidence profiles below (Table 99 and Table 100) and economic study evidence tables in Appendix H:. See also the study selection flow chart in Appendix E:.

One study that met the inclusion criteria for moderate- to high-severity CAP was selectively excluded due to the availability of more applicable evidence[136] – this is reported in Appendix K: with reasons for exclusion given.

Table 99: Economic evidence profile: Respiratory fluoroquinolone compared with cephalosporin and macrolide

Study	Applicability	Limitations	Other comments	Incremental cost[c]	Incremental effects (QALYs)[d]	Cost effectiveness (£ per QALY gained)[d]	Uncertainty
Frei2005[82] (USA)	Partially applicable[a]	Very serious limitations[b]	High-severity CAP. This study compared 4 strategies. Only the dual vs single comparison of the non-dominated strategies is shown here. The respiratory fluoroquinolone is levofloxacin and the cephalosporin is ceftriaxone.	£580	0.252	£2,307	Mortality rate was varied by ± 5% according to a normal distribution, and the total hospital cost was fit to a log-normal distribution and varied over the entire interval. No overall conclusion can be drawn from the analysis.

(f) Study conducted in the US with no quality-of-life considerations

(g) Clinical data based on a cohort study, information on drug doses not given, billing data used as proxy for costs, only conducted in a single hospital

(c) 2005 US$ converted into GBP using the purchasing power parities[155]

(d) QALYs gained and incremental analyses calculated by the NCGC as a complete incremental analysis was not performed in the study. QALYs were estimated based on the survival reported in the study, the average EQ-5D scores for general UK population (70 to 80 years) from Kind et al (1998)[107], and the life expectancy for the general population reported in the England and Wales Life Tables.[150] QALYs have been discounted by 3.5% per year

Table 100: Economic evidence profile: Respiratory fluoroquinolone compared with respiratory fluoroquinolone and cephalosporin

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects (clinical cure per patient)	Cost effectiveness	Uncertainty
Lloyd 2008[123] [Germany]	Partially applicable[a]	Very serious limitations[b]	Fluoroquinolone when used as monotherapy was moxifloxacin, when used in combination was levofloxacin. Economic analysis based on the intention to treat analysis of the RCT MOTIV, included in our clinical review (see 10.8.1).[193]	£321[c]	0.042	£7,642 per additional clinical cure	95% CI: dual therapy more effective and less costly - £78,721 per additional cure. The difference in cost is statistically significant (95% CI: £103 to £554). When the perspective adopted was that of the insurer, dual therapy was cost saving but this was not significant.

(a) Study conducted in Germany from a hospital/insurer perspective. QALYs not estimated. Patients were classified as having high-severity CAP however mortality in the study was low, suggesting that the severity may have been lower than how it was classified

(b) Outcomes obtained from 1 RCT only and the study was sponsored by the manufacturer of the drug given as monotherapy. The study did not assess adverse events which could be an important outcome for fluoroquinolone

(c) 2006 Euro converted into GBP using the purchasing power parities.[155] Cost components incorporated were: medication, diagnostics, therapeutic procedures, hospitalisation

Both studies reported in the tables above show that dual-antibiotic therapy with respiratory fluoroquinolone and macrolide or respiratory fluoroquinolone and cephalosporin is more costly than single-antibiotic therapy with respiratory fluoroquinolone only. Dual therapy could be more effective than single therapy at reducing mortality and increasing clinical cure rates, however results from the economic studies did not show any significant difference. The same inconclusive results were reported in our clinical review which could not show with certainty whether dual therapy decreased mortality or increased clinical cure.

Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided in Appendix O: to aid consideration of cost effectiveness.

10.8.3 Evidence statements for patients with moderate-to high-severity community-acquired pneumonia

10.8.3.1 Clinical

10.8.3.1.1 Macrolide compared with macrolide plus cephalosporin

- Very low quality evidence from 2 randomised trials of over 400 patients with moderate- to high-severity CAP found that macrolide may have a clinical benefit on improving clinical cure at follow-up and reducing withdrawals due to adverse events compared with macrolide plus cephalosporin. However, there is a serious imprecision about the estimate of this effect.

10.8.3.1.2 Respiratory fluoroquinolone compared with macrolide plus cephalosporin

- Very low quality evidence from 3 trials including over 500 patients with moderate- to high-severity CAP showed there might be a survival benefit associated with the combination of macrolide plus cephalosporin in patients with moderate-to high-severity CAP compared with respiratory fluoroquinolone, but the risk of withdrawal due to adverse events was higher in the dual-antibiotic group.

10.8.3.1.3 Respiratory fluoroquinolone compared with macrolide plus beta-lactamase stable penicillin

- Low to very low quality evidence from 1 study of 50 patients with moderate- to high-severity CAP reported a slightly increased length of hospital stay with single respiratory fluoroquinolone treatment compared with the combination of macrolide plus beta-lactamase stable penicillin, but there was no clinically significant difference between the 2 groups for the outcome of clinical cure.

10.8.3.1.4 Respiratory fluoroquinolone compared with cephalosporin plus respiratory fluoroquinolone

- When respiratory fluoroquinolone was compared with cephalosporin plus respiratory fluoroquinolone in patients with moderate- to high-severity CAP, no clinically significant difference was found in any of the outcomes (mortality, clinical cure, length of hospital stay). This evidence was rated moderate to very low quality from a large randomised trial.

10.8.3.1.5 Respiratory fluoroquinolone compared with cephalosporin plus non-respiratory fluoroquinolone

- No difference was found in any outcome reported for the comparison of respiratory fluoroquinolone compared with the combination of cephalosporin plus non-respiratory fluoroquinolone in patients with moderate- to high-severity CAP, as noted by moderate to very low quality randomised evidence from 1 trial of good sample size (around 400 participants).

10.8.3.1.6 Cohort studies comparing beta-lactam with beta-lactam plus macrolide

- Results from low to very low quality evidence from observational studies with multivariate analysis comparing beta-lactam with beta-lactam plus macrolide in patients with moderate- to high-severity CAP showed that there may be a benefit for both outcomes of 30-day mortality and ITU admission from dual therapy of beta-lactam plus macrolide however there was much uncertainty around this effect. Very low quality evidence from 1 retrospective study showed that there may be a 30-day mortality benefit (with less uncertainty compared with the other comparisons in this section) for patients who received beta-lactamase stable penicillin plus macrolide compared with those treated with cephalosporin.

10.8.3.2 Economic

- One cost-utility analysis found that dual therapy (cephalosporin plus macrolide) was cost effective compared with monotherapy (respiratory fluoroquinolone) for treating high-severity CAP (ICER: £2307 per QALY gained). This analysis was assessed as partially applicable with very serious limitations.
- One cost-effectiveness analysis found that dual therapy (respiratory fluoroquinolone plus cephalosporin) was more costly and more effective (with considerable uncertainty around the direction and magnitude of effectiveness) than single therapy (respiratory fluoroquinolone) for treating high-severity CAP (ICER: £7,642 per additional clinical cure). This analysis was assessed as partially applicable with very serious limitations.

10.8.4 Recommendations and link to evidence

Table 101: Linking evidence to recommendations– single- compared with dual-antibiotic therapy for moderate- and high-severity community-acquired pneumonia

Recommendations	**Consider dual antibiotic therapy with amoxicillin and a macrolide for patients with moderate-severity community-acquired pneumonia.** **Consider dual antibiotic therapy with a beta-lactamase stable beta-lactam[b] and a macrolide for patients with high-severity community-acquired pneumonia.**
Relative values of different outcomes	The GDG considered mortality the most important outcome in any severity grouping (although the baseline risk is clearly greater with increasing severity) with clinical cure, length of hospital stay and adverse events as other important outcomes.
Trade-off between clinical benefits and harms	No RCT data comparing beta-lactamase stable beta-lactam with beta-lactam plus macrolide were available. The GDG considered data from several cohort studies with multivariate analysis to address this comparison. The majority of the data demonstrated a direction of effect favouring patients treated with beta-lactam plus macrolide combination compared with beta-lactam alone for reduced mortality and reduced treatment failure. However, there was a degree of uncertainty in most cases. The only exception was 1 study showing that a non-pseudomonal third-generation cephalosporin alone was favoured over beta-lactam/beta-lactamase stable penicillin plus macrolide combination and in this comparison there were nearly 20-times more patients in the monotherapy group. RCT data were available comparing other single- and dual-antibiotic combinations - the majority of which (6 of the 8 included studies) indicated that mortality may be reduced by using dual therapy compared with a single antibiotic agent alone.

[b] Available beta-lactamase stable beta-lactams include: co-amoxiclav, cefotaxime, ceftaroline fosamil, ceftriaxone, cefuroxime and piperacillin-tazobactam.

	Four studies compared levofloxacin with beta-lactam plus macrolide combinations in high-severity CAP. In these studies there was a clinically meaningful reduction in mortality and increase in clinical cure at the end of treatment in the dual-antibiotic groups, although the direction of effect for clinical cure was reversed (marginally favouring the single therapy) for clinical cure at the end of follow-up. There was also a clinically significantly increased number of withdrawals due to adverse events in the dual-antibiotic groups in these studies. Four further studies compared various other single- and dual-antibiotic combinations for moderate- and high-severity CAP. The results were not consistent enough to strongly influence the GDG's deliberations. However, 1 retrospective study showed that there may be a 30-day mortality benefit for patients who received beta-lactamase stable penicillin plus macrolide compared with those treated with cephalosporin (very low quality evidence). There was very little evidence on specific harms of dual-antibiotic therapy across any of the studies.
Trade-off between net health benefits and resource use	A cost-utility analysis showed that dual therapy with cephalosporin plus macrolide was more costly but also more effective than single therapy with respiratory fluoroquinolone in patients with high-severity CAP. The ICER was £2307 per QALY gained, which is below the NICE threshold for considering an intervention to be cost effective. Another cost-effectiveness analysis found that dual therapy (respiratory fluoroquinolone plus cephalosporin) was more costly and more effective (with considerable uncertainty around the direction and magnitude of effectiveness) than single therapy (respiratory fluoroquinolone) for treating high-severity CAP (ICER: £7,642 per additional clinical cure). No economic evidence was found on the combination of beta-lactamase stable penicillin plus a macrolide for high-severity pneumonia plus a macrolide for high-severity pneumonia, and no RCT data were found in the clinical review; however non-RCT data favoured treatment with a beta-lactam plus macrolide combination compared with a beta-lactam alone. This evidence was considered together with the unit costs of antibiotics. The GDG noted that there were considerable price differences between intravenous and oral antibiotics; however this difference was less between antibiotic classes. The GDG agreed that the increased cost of either intravenous or oral dual antibiotic therapy, or the possible adverse events would be outweighed by any demonstrable clinical benefit in mortality, hospital admission or length of stay, clinical cure or health-related quality-of-life in high-severity pneumonia. No economic evidence or clinical evidence was found for the combination of amoxicillin plus a macrolide for moderate-severity CAP. Therefore the GDG did not have enough information to decide whether alternative treatments are more cost-effective than standard treatment and made their recommendation on consensus.
Quality of evidence	There were no RCT data directly comparing beta-lactam to the beta-lactam plus macrolide combination. The combination is well established in the UK, and so data from large cohort studies comparing beta-lactam with beta-lactam plus macrolide were considered even though the GDG recognised that this evidence is open to greater bias than a well-conducted RCT. However, the data obtained covered many thousands of patients and convey a degree of robustness. The GDG noted that older patients appeared more likely to receive single- than dual-antibiotic therapy in some studies, independent of severity of their pneumonia, which could bias outcomes. Studies comparing levofloxacin to beta-lactam plus macrolide were generally of low

	or very low quality by GRADE criteria. All were industry-sponsored, open-label studies and were powered to demonstrate non-inferiority rather than superiority. Studies comparing other combinations of antibiotics were of variable quality. For all of the RCTs there was a lack of consistency in findings between 2 of the critical outcomes – mortality and clinical cure – as well as uncertainty around the mortality estimates, all of which reduced the confidence of the GDG in the evidence. The economic evidence was assessed as partially applicable and with very serious limitations.
Other considerations	The GDG noted that the RCT evidence from comparison of the beta-lactam plus macrolide combination with levofloxacin weakly favoured dual-antibiotic therapy; and that the comparison of the same combination with beta-lactam alone in the intrinsically weaker cohort studies also favoured dual-antibiotic therapy. In view of the lack of high-quality evidence, the GDG also debated the merits of dual-antibiotic therapy based on consideration of spectra of antibiotic cover, likely pathogens in community-acquired pneumonia, and the benefits and harms of single-and dual-antibiotic therapy. The main theoretical benefit of dual-antibiotic therapy over single-antibiotic therapy (beta-lactam or macrolide alone) is a broader spectrum of antibacterial cover which should result in a lower treatment failure rate. Although evidence is lacking to confirm this assumption the GDG considered this to be important in high-severity community-acquired pneumonia, where treatment failure is more likely to result in complications and increased mortality, and given that the available evidence weakly supports (or at least does not contradict) this strategy, decided to recommend dual-antibiotic therapy for moderate- to high-severity community-acquired pneumonia. However, they were concerned that this extremely important question has not been definitively answered, and phrased the recommendation in terms of considering dual therapy rather than mandating this, so as not to preclude further research. They also noted that, according to the Clinical Trials Database, there are 2 on-going RCTs of dual- compared with single-antibiotic therapy, which may provide further clarity. For patients with high-severity community-acquired pneumonia, a recommendation for a beta-lactamase stable beta-lactam plus macrolide was agreed by GDG consensus. The GDG felt the mortality rate associated with high-severity community-acquired pneumonia to be sufficiently high to justify using broad-spectrum empirical therapy despite the potential adverse effects associated with antibiotic therapy such as beta-lactamase stable beta-lactams. The GDG debated how specific the recommendation relating to beta-lactam and macrolide should be. For patients with high-severity community-acquired pneumonia, the GDG noted that some hospitals currently use intravenous second generation cephalosporins or antipseudomonal penicillins (such as piperacillin-tazobactam) as the “beta-lactam” component of dual therapy. The GDG felt that co-amoxiclav was likely to be the most reasonable first-line choice on the basis of antimicrobial spectrum, cost, oral step-down availability and *C. difficile* rates. However, the GDG acknowledged that there was little robust evidence to suggest that alternative beta-lactamase stable beta-lactams were inferior, and that some local policies will specify alternative agents. Whilst the GDG agreed that a beta-lactamase stable beta-lactam was indicated in high-severity community-acquired pneumonia as part of dual-antibiotic therapy, they acknowledged that some antibiotics that fit this description would be less suitable. For example, the carbapenems were felt to be unnecessarily broad-spectrum, and some cephalosporins have poor activity against *S. pneumoniae*. The GDG's opinion was that co-amoxiclav was the most suitable choice, but a list including other available

	beta-lactamase stable beta-lactams that could potentially be used is included in a footnote to the recommendation. For the macrolide component, clarithromycin is by far the most commonly used macrolide for CAP in the UK, and the GDG felt that wide clinical experience of its use was an advantage over other macrolide antibiotics. Azithromycin was considered, but experience in the UK is not as wide as with clarithromycin for the treatment of pneumonia. For patients with moderate-severity CAP, the risk-benefit ratio of very broad-spectrum empirical antibiotic therapy is less favourable – mortality is lower in this group than in patients with high-severity CAP and therefore the possibility of adverse effects outweighing clinical benefit is of greater concern. The GDG therefore felt that a slightly less broad-spectrum regime such as amoxicillin plus a macrolide would be a reasonable empirical combination for patients with moderate-severity CAP. The GDG acknowledged that levofloxacin gives a similar spectrum of antibacterial cover to the beta-lactam plus macrolide combination, and that studies had suggested non-inferiority. However, the licence for levofloxacin for treatment of CAP in the UK is limited to situations where other options cannot be prescribed or are ineffective. This relates to concerns regarding its safety profile, specifically hepatotoxicity, skin reactions, cardiac arrhythmias and tendon rupture. The GDG therefore concluded that levofloxacin should not be routinely offered rather than dual antibiotic therapy in high-severity CAP unless there is a compelling reason to do so (for example, allergy). In contrast to low-severity CAP, the GDG felt that there were numerous alternative antibiotic regimes that would be reasonable to use in patients with high-severity CAP who are unable to receive a component of empirical dual-antibiotic therapy (for example, due to allergy). Given the number of factors requiring consideration when individuals with high-severity pneumonia have a drug allergy, the GDG did not conclude that a specific recommendation should be made for this group. The GDG agreed it would be appropriate for clinicians to liaise with local microbiology services to ensure adequate empirical cover for common pathogens for patients with moderate-severity community-acquired pneumonia who are allergic to penicillin when an alternative treatment regimen is not clear.

10.9 Dual- compared with other dual-antibiotic therapy for moderate- to high-severity community-acquired pneumonia

For full details see review protocol in Appendix C:.

10.9.1 Clinical evidence

We searched for systematic reviews and randomised trials (RCTs) comparing the effectiveness and safety of empirical treatment with different combinations of antibiotics from 2 different classes for the treatment of moderate-to high-severity pneumonia acquired in the community. Data from studies comparing the same classes of antibiotics were pooled into a single analysis (see Appendix N: for classifications). Data were accepted for antibiotic therapy administered by the oral, intravenous or intramuscular routes.

A matrix of included comparisons is presented to facilitate navigation of the evidence (Figure 11). Two RCTs were included in the review.[84,189] Table 102 summarises the study details.

Evidence from the included studies is summarised in the clinical GRADE evidence profiles below (Table 103 and Table 104). No data were reported for the following outcomes: hospital admission; health-related quality-of-life; or *C. difficile*-associated diarrhoea.

See also the study selection flow chart in Appendix D:, forest plots in Appendix I:, study evidence tables in Appendix G: and exclusion list in Appendix J:.

Figure 11: Dual- compared with other dual-antibiotic therapy for moderate- to high-severity community-acquired pneumonia (click on hyperlinks or refer to page numbers)

	Cephalosporin plus macrolide	Beta-lactamase stable penicillin plus macrolide
Narrow spectrum beta-lactam plus non-respiratory fluoroquinolone		Table 103, 272
Cephalosporin plus macrolide	Table 104, 274	

Table 102: Summary of studies included in the dual compared with other dual antibiotic therapy review for moderate- to high-severity community-acquired pneumonia

Study	Intervention	Comparison	Severity definition	Outcomes	Comments
CAP					
Narrow spectrum beta-lactam plus non-respiratory fluoroquinolone compared with beta-lactamase stable penicillin plus macrolide					
Gaillat 1994[84]	Penicillin G 3 x 10^6 U/6 h plus ofloxacin 200 mg twice daily IV, followed by oral amoxicillin 1 g/8 h plus ofloxacin 200 mg/12 h **Route of administration:** IV then oral **Duration:** at least 10 days. (N = 52).	Amoxicillin-clavulanate 1 g/6 h plus erythromycin 1 g/8 h IV, followed by oral amoxicillin-clavulanate 500 mg/8 h plus erythromycin 1 g/12 h **Route of administration:** IV then oral **Duration:** at least 10 days. (N = 50)	Formal assessment (based on PaO_2 or SAPS and comorbidities).	• Mortality • clinical cure at end of treatment • complications – superinfection	• Treatment with a single antibiotic from the assigned regimen was allowed after 72 hours, provided the micro-organism isolated was sensitive to the drug. • Dose IV co-amoxiclav unclear, but the 1 g may relate to the amoxicillin content – meaning a 1.2 g dose of co-amoxiclav more frequently than recommended. • Number mechanically ventilated - Penicillin/ofloxacin: 27%; amoxiclav/erythromycin: 22%.
Cephalosporin plus macrolide (azithromycin) compared with cephalosporin plus other macrolide					
Tamm 2007[189]	Ceftriaxone 1-2 g once daily IV, plus azithromycin 500 mg once-daily IV for 2 to 5 days followed by step-down to oral	Ceftriaxone 1-2 g once daily IV, plus either clarithromycin 500 mg twice daily IV or erythromycin 1 g 3 times a day for 2 to 5 days	Formal assessment: mean PSI score = 92.	• Mortality • clinical cure at end of treatment • clinical cure at end of	• Rationalised to macrolide monotherapy when transitioned to oral therapy. • Study funded by industry.

Study	Intervention	Comparison	Severity definition	Outcomes	Comments
	azithromycin 500 mg once-daily **Route of administration:** IV then oral **Duration:** 7 to 10 days. (N = 135).	followed by step-down to either oral clarithromycin 500 mg twice daily or erythromycin 1 g 3-times a day **Route of administration:** IV then oral **Duration:** 7 to 14 days. (N = 143).		follow-up • withdrawal due to adverse events • length of hospital stay	

Table 103: Clinical evidence profile: Non-respiratory fluoroquinolone plus narrow-spectrum beta-lactam (class 1) compared with macrolide plus beta-lactamase stable penicillin

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Non-respiratory fluoroquinolone plus narrow spectrum beta-lactam (class 1)	Macrolide plus beta-lactamase stable penicillin	Relative (95% CI)	Absolute	Quality
Mortality [Gaillat 1994]											
1	randomised trial	very serious[1]	no serious	no serious[2]	very serious[3]	none	6/52 (11.5%)	6/50 (12%)	RR 0.96 (0.33 to 2.78)	5 fewer per 1000 (from 80 fewer to 214 more)	Very low
Clinical cure at end of treatment (follow-up at least 10 days) [Gaillat 1994]											
1	randomised trial	very serious[4]	no serious	no serious[2]	serious[5]	none	40/52 (76.9%)	38/50 (76%)	RR 1.01 (0.82 to 1.26)	8 more per 1000 (from 137 fewer to 198 more)	Very low
Withdrawal due to adverse events											
0	no evidence available					none	-	-	-	-	
Hospital admission											
0	no evidence available					none	-	-	-	-	
Length of hospital stay											
0	no evidence available					none	-	-	-	-	
Health-related quality-of-life											
0	no evidence available					none	-	-	-	-	

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Non-respiratory fluoroquinolone plus narrow spectrum beta-lactam (class 1)	Macrolide plus beta-lactamase stable penicillin	Relative (95% CI)	Absolute	Quality
Complications - superinfection (follow-up 30 days) [Gaillat 1994]											
1	randomised trial	very serious[6]	no serious	no serious[2]	very serious[3]	none	1/32 (3.1%)	0/36 (0%)	PETO OR 8.37 (0.17 to 424.85)	31 more per 1000 (from 49 fewer to 112 more)	Very low
***C. difficile*-associated diarrhoea**											
0	no evidence available					none	-	-	-	-	

[1] *High risk of selection and attrition bias*
[2] *Note: Intervention in experimental arm switched when transition to oral*
[3] *95% CI crosses both default MIDs*
[4] *High risk of selection bias and unblinded*
[5] *95% CI crosses 1 default MID*
[6] *High risk of selection, attrition, and measurement bias*

Table 104: Clinical evidence profile: Azithromycin plus cephalosporin compared with other macrolide plus cephalosporin

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azithromycin plus cephalosporin	Other macrolide plus cephalosporin	Relative (95% CI)	Absolute	Quality
Mortality (follow-up 28 to 35 days) [Tamm 2007]											
1	randomised trial	serious[1]	no serious	no serious	very serious[2]	None	7/135 (5.2%)	5/143 (3.5%)	RR 1.48 (0.48 to 4.56)	17 more per 1000 (from 18 fewer to 125 more)	Very low
Clinical cure at end of treatment (follow-up 12 to 16 days) [Tamm 2007]											
1	randomised trial	very serious[3]	no serious	no serious	no serious	None	102/121 (84.3%)	104/126 (82.5%)	RR 1.02 (0.91 to 1.14)	16 more per 1000 (from 74 fewer to 115 more)	Low
Clinical cure at end of follow-up (follow-up 28 to 35 days) [Tamm 2007]											
1	randomised trial	very serious[4]	no serious	no serious	serious[5]	None	81.7%	75%	-	-	Very low
Withdrawal due to adverse events (follow-up 12 to 16 days) [Tamm 2007]											
1	randomised trial	serious[1]	no serious	no serious	very serious[2]	None	1/135 (0.74%)	4/143 (2.8%)	RR 0.26 (0.03 to 2.34)	21 fewer per 1000 (from 27 fewer to 38 more)	Very low
Hospital admission											
0	no evidence available					None	-	-	-	-	
Length of hospital stay (follow-up 28 to 35 days; Better indicated by lower values) [Tamm 2007]											
1	randomised trials	serious[1]	no serious	no serious	serious[6]	None	10.7 (6.8)	12.6 (10.8)	-	MD 1.9 lower (4.01 lower to 0.21 higher)	Low
Health-related quality-of-life											

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azithromycin plus cephalosporin	Other macrolide plus cephalosporin	Relative (95% CI)	Absolute	Quality
0	no evidence available					None	-	-	-	-	
										-	
Complications											
0	no evidence available					None	-	-	-	-	
										-	
***C. difficile*-associated diarrhoea**											
0	no evidence available					None	-	-	-	-	
										-	

[1] *High risk of selection bias and unclear attrition*
[2] *95% CI crosses both default MIDs*
[3] *High risk of selection bias and unblinded*
[4] *High risk of selection bias and unblinded, plus outcome reporting bias*
[5] *Unable to assess imprecision. Frequencies not reported, only percentages of patients cured at end of follow-up in the evaluable population. Therefore RR and absolute effect could not be calculated*
[6] *95% CI crosses 1 default MID*

10.9.2 Economic evidence

One study was identified with the relevant comparison for high-severity CAP and was included in this review.[82] This is summarised in the economic evidence profile below (Table 105). See also the study selection flow chart in Appendix E: and study evidence tables in Appendix H:.

Table 105: Economic evidence profile: Cephalosporin and respiratory fluoroquinolone compared with cephalosporin and macrolide

Study	Applicability	Limitations	Other comments	Incremental cost[c]	Incremental effects (QALYs)[d]	Cost effectiveness[d]	Uncertainty
Frei2005[82] (USA)	Partially applicable[a]	Very serious limitations[b]	High-severity CAP. This study compared 4 strategies. Only the dual comparison is shown here. The respiratory fluoroquinolone is levofloxacin and the cephalosporin is ceftriaxone.	£527	- 0.189	Ceftriaxone plus levofloxacin is dominated by ceftriaxone plus macrolide.	Mortality rate was varied by ± 5% according to a normal distribution, and the total hospital cost was fit to a log-normal distribution and varied over the entire interval. No overall conclusion can be drawn from the analysis.

(h) Study conducted in the US with no quality-of-life considerations

(i) Clinical data based on a cohort study, information on drug doses not given, billing data used as proxy for costs, only conducted in a single hospital

(j) 2005 US$ converted into GBP using the purchasing power parities[155]

(k) QALYs gained and incremental analyses calculated by the NCGC as a complete incremental analysis was not performed in the study. QALYs were estimated based on the survival reported in the study, the average EQ-5D scores for general UK population (70 to 80 years) from Kind et al (1998)[107], and the life expectancy for the general population reported in the England and Wales Life Tables.[150] QALYs have been discounted by 3.5% per year

Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided in Appendix O: to aid consideration of cost effectiveness.

10.9.3 Evidence statements for patients with moderate- to high- severity community-acquired pneumonia

10.9.3.1 Clinical

10.9.3.1.1 Non-respiratory fluoroquinolone plus narrow spectrum beta-lactam (class 1) compared with macrolide plus beta-lactamase stable penicillin

- Very low quality evidence from 1 randomised trial with 100 patients with moderate- to high-severity CAP showed that there may be no clinical differences between groups in the estimate of effects for any outcomes investigated (mortality, clinical cure and complications).

10.9.3.1.2 Cephalosporin combined with azithromycin compared with a different macrolide plus cephalosporin

- Low to very low quality evidence from 1 randomised trial with almost 300 patients with moderate- to high-severity CAP showed that there may be no clinical differences between the 2 antibiotic combinations in the estimate of effects for any outcomes (mortality, clinical cure, withdrawal due to adverse events and length of hospital stay).

10.9.3.2 Economic

- One cost-effectiveness analysis found that cephalosporin plus macrolide was dominant (less costly and more effective) compared with cephalosporin plus respiratory fluoroquinolone for treating moderate-to high-severity CAP. This study was assessed as partially applicable with very serious limitations.

10.9.4 Recommendations and link to evidence

Table 106: Linking evidence to recommendations – dual-compared with other dual-antibiotic therapy for moderate- to high-severity community-acquired pneumonia

Recommendations	No recommendation made.
Relative values of different outcomes	The GDG considered mortality the most important outcome, with clinical cure, length of hospital stay and adverse events as other important outcomes.
Trade-off between clinical benefits and harms	Two RCTs were considered. One compared penicillin G/amoxicillin plus ofloxacin with co-amoxiclav plus erythromycin. There was no consistent or reliable evidence for a difference in any of the reported outcomes (mortality, clinical cure and withdrawal due to adverse events) between the groups. The other study compared ceftriaxone plus azithromycin with ceftriaxone plus erythromycin or clarithromycin. The data suggested that although not clinically significant, there may be a benefit of a cephalosporin combined with azithromycin compared with a different macrolide plus cephalosporin in terms of reduced length of hospital stay and fewer withdrawals due to adverse events. However, there was no difference between the trial arms in the most important outcome, mortality, nor in clinical cure.
Trade-off between net health benefits	A cost-utility analysis showed that dual therapy with cephalosporin plus macrolide was less costly and more effective than dual therapy with respiratory

and resource use	fluoroquinolone plus cephalosporin in patients with high-severity CAP. As no economic evidence was found on the current standard antibiotic treatment for moderate-to high-severity CAP which is a combination of beta-lactam plus macrolide, the GDG did not have enough information to decide whether alternative therapies such as those assessed in the studies are more cost effective than standard treatment. The GDG noted that there were considerable price differences between intravenous and oral antibiotic therapy; however this difference was less between antibiotic classes. The GDG agreed that the increased cost of either intravenous or oral dual-antibiotic therapy and the possible adverse events would be outweighed by any demonstrable clinical benefit in mortality, hospital admission or length of stay, clinical cure or health-related quality-of-life in high-severity pneumonia.
Quality of evidence	Studies were of low or very low quality by GRADE criteria, with large uncertainty around the effect estimates. Both included studies included relatively small numbers of patients, were conducted outside the UK and did not report a number of the important outcomes. The GDG also noted the low mortality rates seen in both studies, and questioned how comparable these populations were with the UK high-severity CAP population. The economic evidence was assessed as partially applicable with very serious limitations.
Other considerations	Both clinical studies contained beta-lactamase stable beta-lactam plus macrolide arms, which reflects current practice in the UK for high-severity CAP. As such, comparisons between beta-lactam plus macrolide and other combinations were of particular interest to the GDG to see whether any other combination of antibiotic therapy is superior to that currently used. However, the evidence did not show any combination to be clearly superior to any other. The recommendation for beta-lactam plus macrolide was therefore made by GDG consensus, based on wide clinical experience supporting this combination.

10.10 Review question: In adults with community-acquired pneumonia what is the clinical and cost effectiveness of short- compared with longer-course antibiotics?

For full details see review protocol in Appendix C:.

Data were stratified for low- and moderate- to high-severity CAP (defined by formal assessment tools or site of care).

10.11 Low-severity community-acquired pneumonia

10.11.1 Clinical evidence

We searched for systematic reviews and randomised trials (RCTs) comparing the effectiveness and safety of different durations of antibiotic therapy. Data from studies comparing the same classes of antibiotics were pooled into a single analysis (see Appendix N: for classifications). Data were accepted for antibiotic therapy administered by the oral or intravenous routes or when a combination of oral and IV, and IM routes were used.

Four[65,67,114,182] RCTs were included in the review.

Table 107 includes a summary of the studies included in the review. Evidence from the included studies is summarised in the GRADE profiles below (Table 108 and Table 109). None of the available studies for any comparison reported re-admission, relapse, health-related quality-of-life or hospital admission.

See also the study selection flow chart in Appendix D:, forest plots in Appendix I:, study evidence tables in Appendix G:and exclusion list in Appendix J:.

Table 107: Summary of studies included in the review of low-severity community-acquired pneumonia duration of antibiotic therapy

Study	Intervention	Comparison	Severity definition[(a)]	Outcomes	Comments
Higher dose and shorter duration of treatment compared with lower dose and longer duration of treatment					
Dunbar 2003[65]	Levofloxacin **750 mg** once daily **Duration:** 5 days **Route:** IV or oral. (N = 256).	Levofloxacin **500 mg** once daily **Duration:** 10 days **Route:** IV or oral. (N = 272).	Majority in the study were assessed as having low-severity CAP. Stratified by PSI scores. PSI class I and II (mild) – can be treated in the community. PSI class III to IV – treated in hospital for at least 24 hours.	• clinical cure (measured as resolution of pre-treatment syndrome) or improvement at end of treatment (by severity) • withdrawal due to adverse events • all-cause 30-day mortality	• Different doses used for intervention compared with comparison arm (high dose, short duration/low dose, long duration comparison).
Shorter compared with longer duration of treatment					
Elmoussaoui 2006[67]	Amoxicillin 3 days IV (dose unspecified), followed by placebo for 5 days **Duration:** 3 days **Route:** IV and oral. (N = 63).	Amoxicillin 3 days IV (dose unspecified), followed by 750 mg 3 times daily for 5 days **Duration:** 8 days **Route:** IV and oral. (N = 56).	Low- to moderate-severity.	• clinical cure at end of follow-up • withdrawal due to adverse events	• Randomisation after 3 days of IV therapy, among patients who had improved 2 points or more on a scale to measure symptom improvement. • Intravenous amoxicillin dose not stated. • Shorter duration group higher percentage smokers and more severe symptoms at baseline.
Leophonte 2002[114]	Ceftriaxone 1 g 24 hourly, followed by placebo **Duration:** 5 days **Route:** IV 5 days, and IM placebo for 5 days. (N = 125).	Ceftriaxone 1 g 24 hourly **Duration:** 10 days **Route:** IV 5 days, and IM 5 days. (N = 119).	Not specified by the authors.	• Mortality • clinical cure at end of treatment • withdrawal due to adverse events • *C. difficile*-associated diarrhoea	• About 30% of patients had received prior antibiotic therapy before randomisation.

Siegel 1999[182]	Cefuroxime 750 mg IV 8 hourly for 2 days, followed by 500 mg bd orally for 5 days, and placebo for 3 days **Duration:** 7 days **Route:** IV 2 days, and orally 5 days. (N = 24).	Cefuroxime 750 mg IV 8 hourly for 2 days, followed by 500 mg bd orally for 8 days **Duration:** 10 days **Route:** IV 2 days, and orally 8 days. (N = 22).	Moderate-severity.	• Mortality • clinical success at end of treatment • withdrawal due to adverse events	• Blinding unclear. • Unclear how patients were classified as treatment failure as opposed to withdrawal.

(a) All studies used some method of excluding high-severity pneumonia, although these varied between the studies (e.g. requiring parenteral therapy or hospital admission)

Table 108: Clinical evidence profile: Higher dose with shorter duration compared with lower dose and longer duration of antibiotic therapy

Quality assessment							No of patients		Effect		
No studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher dose and shorter duration	Lower dose and longer duration	Relative (95% CI)	Absolute	Quality
All-cause mortality – fluoroquinolone [Dunbar 2003]											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	5/256 (2%)	9/265 (3.4%)	RR 0.58 (0.2 to 1.69)	14 fewer per 1000 (from 27 fewer to 23 more)	Low
Clinical cure (at 7 to 14 days after therapy)(all patients) [Dunbar 2003]											
1	RCT	serious[1]	no serious	no serious	no serious	none	183/198 (92.4%)	175/192 (90.6%)	RR 1.01 (0.91 to 1.12)	9 more per 1000 (from 82 fewer to 109 more)	Moderate
Clinical cure – low-severity subgroup [Dunbar 2003]											
1	RCT	very serious[3]	no serious	no serious	no serious	none	114/122 (93.4%)	102/106 (96.2%)	RR 0.97 (0.91 to 1.03)	29 fewer per 1000 (from 87 fewer to 29 more)	Moderate
Withdrawal due to treatment-related adverse event [Dunbar 2003]											
1	RCT	serious[1]	no serious	no serious	serious[2]	none	18/256 (7%)	22/265 (5.7%)	RR 0.85(0.47 to 1.54)	12 more per 1000 (from 44 fewer to 45 more)	Low
Hospital re-admission											
	no evidence available										
Length of hospital stay											
0	no evidence available										
Health-related quality-of-life											
0	no evidence available										
Complications (composite of empyema, effusion, abscess, metastatic infection, superinfection, MODS)											
0	no										

Quality assessment							No of patients		Effect		
No studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher dose and shorter duration	Lower dose and longer duration	Relative (95% CI)	Absolute	Quality
	evidence available										
Relapse rate											
0	no evidence available										
***C. difficile*-associated diarrhoea**											
0	no evidence available										

[1] *Patient comorbidities at baseline were not reported. Another associated paper reported that patients were stratified by centre and PSI severity, there were about 20% more patients with PSI Class III to V in the longer duration group. Method of randomisation, allocation concealment and blinding was not reported*
[2] *95% CI crosses 1 default MID*
[3] *Post hoc subgroup analysis. Patient comorbidities at baseline were not reported. Method of randomisation, allocation concealment and blinding was not reported*

Table 109: Clinical evidence profile: Shorter duration compared with longer duration of antibiotic therapy

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Shorter	Longer	Relative (95% CI)	Absolute	Quality
All-cause 30-day mortality [El Moussaoui 2006, Siegel 1999, Leophonte 2002]											
3	RCT	serious[1]	no serious	no serious	very serious[2]	none	6/206 (2.9%)	5.9%	RR 0.58 (0.22 to 1.56)	25 fewer per 1000 (from 46 fewer to 33 more)	Very low
All-cause 30-day mortality - (sensitivity analysis for patients with low- to moderate-severity CAP (PSI ≤ 110)) [El Moussaoui 2006]											
1	RCT	serious[1]	no serious	no serious	very serious[2]	none	1/57 (1.8%)	1.6%	RR 1.12 (0.07 to 17.54)	2 more per 1000 (from 15 fewer to 258 more)	Very low
All-cause 30-day mortality [Siegel 1999, Leophonte 2002]											
2	RCT	serious[1]	no serious	no serious	very serious[2]	none	5/149 (3.4%)	7.5%	RR 0.52 (0.18 to 1.53)	36 fewer per 1000 (from 62 fewer to 40 more)	Very low
Clinical cure (at day 28) [El Moussaoui 2006, Siegel 1999, Leophonte 2002]											
3	RCT	serious[1]	no serious	serious[3]	no serious	none	150/174 (86.2%)	88%	RR 1.01 (0.93 to 1.1)	9 more per 1000 (from 62 fewer to 88 more)	Low
Clinical cure (at day 28) – amoxicillin (low- to moderate-severity, PSI ≤ 110) [El Moussaoui 2006]											
1	RCT	serious[1]	no serious	no serious	serious[4]	none	47/56 (83.9%)	77.8%	RR 1.08 (0.91 to 1.29)	62 more per 1000 (from 70 fewer to 226 more)	Low
Clinical cure – (at day 28) – cephalosporin [Siegel 1999, Leophonte 2002]											
2	RCT	serious[1]	no serious	serious[3]	no serious	none	103/118 (87.3%)	89.5%	RR 0.99 (0.9 to 1.08)	9 fewer per 1000 (from 90 fewer to 72 more)	Low
Withdrawal due to adverse events [Siegel 1999, Leophonte 2002]											
2	RCT	serious[1]	no serious	no serious	no serious	none	0/81 (0%)	0%	not pooled	not pooled	Moderate
Withdrawal due to adverse events – amoxicillin (low- to moderate-severity, PSI ≤ 110) [El Moussaoui2006]											
1	RCT	serious[1]	no serious	no serious	no serious	none	0/57 (0%)	0%	not pooled	not pooled	Moderate
Withdrawal due to adverse events – cephalosporin [Siegel 1999]											
1	RCT	serious[1]	no serious	no serious	no serious	none	0/24 (0%)	0%	not pooled	not pooled	Moderate

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Shorter	Longer	Relative (95% CI)	Absolute	Quality
Complication (worsening infections, abscess, metastatic infection, MODS) [El Moussaoui 2006, Siegel 1999]											
2	RCT	serious[1]	no serious	no serious	very serious[2]	none	5/81 (6.2%)	6.9%	RR 1.01 (0.3 to 3.38)	1 more per 1000 (from 48 fewer to 164 more)	Very low
Complication (worsening infections, abscess, metastatic infection, MODS) – amoxicillin (low- to moderate-severity, PSI ≤ 110) [El Moussaoui 2006]											
1	RCT	serious[1]	no serious	no serious	very serious[2]	none	2/57 (3.5%)	4.7%	RR 0.75 (0.13 to 4.32)	12 fewer per 1000 (from 41 fewer to 156 more)	Very low
Complication (worsening infections, abscess, metastatic infection, MODS) – cephalosporin [Siegel 1999]											
1	RCT	serious[1]	no serious	no serious	very serious[2]	none	3/24 (12.5%)	2/22 (9.1%)	RR 1.38 (0.25 to 7.47)	35 more per 1000 (from 68 fewer to 588 more)	Low
***C. difficile*-associated diarrhoea – cephalosporin [Leophonte 2002]**											
1	RCT	serious[1]	no serious	no serious	very serious[2]	none	0/125 (0%)	1/119 (0.8%)	RR 0.32 (0.01 to 7.72)	5 fewer per 1000 (from 8 fewer to 54 more)	Very low
Hospital re-admission											
0	no evidence available										
Length of hospital stay											
0	no evidence available										
Health-related quality-of-life											
0	no evidence available										
Relapse rate											
0	no evidence available										

[1] *High risk of bias as method of randomisation, allocation concealment and blinding was unclear. Differences in baseline characteristics – more severe symptoms and higher percentage of smokers in the shorter duration group*
[2] *95% confidence interval crosses 2 default MIDs*
[3] *About 30% of patients had received antibiotic therapy prior to enrolment. Study only included patients who had responded to 3 days of IV amoxicillin therapy before randomisation*
[4] *95% confidence interval crosses 1 default MID*

10.11.2 Economic evidence

Published literature

One study was included with the relevant comparison for low-severity CAP.[153] This is summarised in the economic evidence profile below (Table 110). See also the study selection flow chart in Appendix E: and study evidence tables in Appendix H:.

Two studies that met the inclusion criteria were selectively excluded due to methodological limitations[182,191] – these are reported in Appendix K:, with reasons for exclusion given.

Table 110: Economic evidence profile: 3-day amoxicillin compared with 8-day amoxicillin

Study	Applicability	Limitations	Other comments	Incremental cost	Incremental effects	Cost effectiveness	Uncertainty[e]
Opmeer 2007[153] [Netherlands]	Partially applicable[a]	Very serious limitations[b]	This is a cost analysis that is performed alongside the RCT included in the clinical review by el Moussaoui.[67] Study used societal perspective but results here have been recalculated to only include health care system costs in line with the NICE reference case. Study follow-up time was for 28 days.	Saves £147[c]	NA[d]	NA	When undertaken from the societal perspective, short course amoxicillin is cost saving compared with standard course. 500 repeated bootstrap samples were used to create a 95% CI around the mean difference between short- and standard-course antibiotic therapy. This runs from -£548 to £847. Sensitivity analysis was conducted by varying unit costs per day of hospital stay by ± 20%. The difference in costs varied between 1.7% and 4.9% in favour of short-course therapy. When costs were adjusted to account for increased costs in academic centres, there was a 4.9% increase in mean difference costs in favour of short course antibiotics and total costs substantially decreased.

(l) Study performed from a Dutch societal perspective. Results here have been recalculated to only include health care system costs in line with the NICE reference case

(m) No ICER is presented or can be calculated from the data; only a comparative costing is performed, and as such, no health effects or health-related quality-of-life outcomes are reported; only patients who significantly improve after 3 days of therapy were randomised into the study; no sensitivity analysis was undertaken on follow-up costs; costs of medication for the placebo group were included after 3 days, and authors unsure if costs were attributed to placebo; length of follow-up may be inadequate to account for all costs and outcomes

(e) Converted from 2002 Euros using purchasing power parities.[155] See economic evidence table for full list of cost components

(f) The RCT found no difference between short and standard courses of antibiotic therapy across all outcomes

(g) The 95% CI and sensitivity analysis could not be recalculated from a health care system perspective. As such, these results are only applicable to the societal perspective

Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided in Appendix O: to aid consideration of cost effectiveness.

10.11.3 Evidence statements for patients with low-severity community-acquired pneumonia

10.11.3.1 Clinical

- For patients with low-severity CAP, low and moderate quality evidence from the majority of the outcomes across the different antibiotic classes compared for longer and shorter durations showed no clinical difference.

10.11.3.2 Economic

- One cost analysis found that 3-day amoxicillin was less costly than 8-day amoxicillin for treating low-severity CAP (cost difference: -£147 per patient). This analysis was assessed as partially applicable with very serious limitations.

10.11.4 Recommendations and link to evidence

Table 111: Linking evidence to recommendations – duration of antibiotic therapy for low-severity community-acquired pneumonia

Recommendations	**Offer a 5-day course of antibiotic therapy to patients with low-severity community-acquired pneumonia.** **Consider extending the course of the antibiotic for longer than 5 days as a possible management strategy for patients with low-severity community-acquired pneumonia whose symptoms do not improve as expected after 3 days.** **Explain to patients with low-severity community-acquired pneumonia treated in the community, and when appropriate their families or carers, that they should seek further medical advice if their symptoms do not begin to improve within 3 days of starting the antibiotic, or earlier if their symptoms are worsening.**
Relative values of different outcomes	The GDG considered mortality the most important outcome, though acknowledged that this was likely to be a rare event in patients with low-severity CAP. Clinical cure and adverse events were considered to be other important outcomes.
Trade-off between clinical benefits and harms	Four RCTs comparing different durations of antibiotic therapy for low-severity CAP were considered. One study (Leophonte 2002) did not provide clear information on the severity status of its sample but the GDG considered it most likely to be of low-severity CAP and its evidence was considered together with the other studies of low-severity CAP. One study compared 3 days of intravenous amoxicillin followed by 5 days of oral amoxicillin or placebo. One study compared 5 days of intravenous ceftriaxone followed by 5 days of intramuscular ceftriaxone or placebo. One study compared 2 days of intravenous cefuroxime followed by 8 days oral cefuroxime or 5 days oral cefuroxime and 3 days placebo. The final study compared 5 or 10 days of intravenous or oral levofloxacin, with a higher dose used in the shorter duration group. Across all reported outcomes (mortality, clinical cure, withdrawal due to adverse events, and complications including *C. difficile*-associated diarrhoea), there was no evidence to suggest that a shorter duration of antibiotic therapy resulted in a worse

	clinical outcome compared with a longer duration. The direction of effect favoured the shorter course for all outcomes, although the size of the effect did not reach the clinically significant threshold except for mortality. Despite uncertainty in the results owing to imprecision and poor quality of evidence, the consistent findings across a number of studies suggested at worst no clinically significant difference between shorter and longer courses, and at best a favourable outcome with shorter courses.
Trade-off between net health benefits and resource use	One economic study compared 3 days of intravenous amoxicillin followed by 5 days of oral amoxicillin or placebo. The study was conducted from a societal perspective but the results were recalculated by the NCGC to only consider healthcare system costs in line with the NICE reference case. The study suggested that the shorter antibiotic course (3 days intravenous amoxicillin) saved £147 per patient compared with the longer antibiotic course (3 days IV amoxicillin followed by 5 days oral amoxicillin). This was primarily due to reduction in hospital length of stay, but partially offset by an increase in costs for subsequent outpatient and primary care reviews. The GDG considered that the cost savings generated by a reduction in duration of hospital stay were unlikely to be realised in a UK setting, as the majority of patients with low-severity CAP are managed in the community on oral antibiotics. It was noted that there was no economic evidence for the current standard-treatment duration of 7 days but that the cost of antibiotic therapy is low for first-line antibiotics in low-severity CAP. The GDG agreed that short courses of antibiotic therapy may potentially be cost-saving if outcomes are equivalent to those in longer courses, but that unless there is a reduction in hospitalisation cost savings were likely to be minimal. However, given the volume of prescriptions for CAP in the UK, it was considered that treatment for 5 days was likely to be cost-saving compared with treatment for 7 days. The GDG also noted that shorter durations of antibiotic therapy, which may be unnecessary for some patients, may lead to the reduction of antimicrobial resistance and produce long-term economic benefits.
Quality of evidence	Studies were of moderate to very low quality by GRADE criteria, with serious or very serious imprecision noted for the outcomes. None of the studies included a UK population. The studies used different classes, doses or routes of antibiotic therapy from those routinely used for low-severity CAP in the UK. The studies either did not report harmful effects, or gave little detail. The GDG commented that this was surprising, since reduction in adverse effects is one of the main hypothetical advantages of shortening the antibiotic course. Despite the differences between studies in various parameters, including the durations and doses compared, the GDG noted that they were consistent in showing near equivalence between shorter and longer courses. The economic evidence was considered partially applicable with very serious limitations.
Other considerations	The GDG discussed whether underpowered studies may lead to false reassurance regarding the relative safety of short courses of antibiotic therapy. Smaller studies will have wider error margins, increasing the chances of there being no significant difference between outcomes. However, in the absence of any evidence to suggest inferiority of shorter courses, coupled with the desirability of improved antibiotic stewardship associated with shorter courses, the GDG concluded it was reasonable to make a recommendation favouring shorter courses of antibiotic therapy than the 7 days which has been traditional in the UK. The available studies used different durations to define a “short” course of

	treatment. The recommendation for 5 days was reached by GDG consensus. The GDG considered it appropriate to recommend an early assessment of the effectiveness of an antibiotic course, partly as a safety measure given that they recommend shortening the standard length of an antibiotic course, and partly as good practice which is already applied in some other countries. It was considered that 3 days of treatment should be sufficient to see improvement in the majority of patients on appropriate antibiotic therapy, and that this was a suitable time for such an assessment. For patients treated in the community, a subjective patient or carer assessment was considered to be adequate, resulting in a recommendation that the patient or carer should be told at the time of antibiotic prescription to seek further advice if improvement had not occurred by 3 days. For patients treated in hospital, improvement would be assessed by the clinical team caring for the patient. The GDG emphasised the benefit of referring to medication charts in hospital including the DH initiative Start Smart then Focus – reviewing antibiotic prescription after 48 hours. The GDG agreed that patients not improving after 3 days of treatment may warrant a longer course of antibiotic therapy to reduce the risk of treatment failure, but that other strategies such as changing antibiotic therapy and assessment for complications (for example, empyema) should also be considered.

10.12 Moderate- and high-severity community-acquired pneumonia

10.12.1 Clinical Evidence

One *post-hoc* subgroup analysis on moderate-and high-severity CAP from 1 study (Dunbar 2003) which was included in the low-severity section (10.11) was the only evidence identified for this review question.

Table 112: Summary of studies included in the review of duration of antibiotic therapy in moderate- and high-severity community-acquired pneumonia

Study	Intervention/N randomised	Comparison/N randomised	Severity definition	Outcomes	Comments
Higher dose and shorter duration of treatment compared with lower dose and longer duration of treatment					
Dunbar 2003[65]	Levofloxacin **750 mg** once daily **Duration:** 5 days **Route:** IV or oral. (N = 76).	Levofloxacin **500 mg** once daily **Duration:** 10 days **Route:** IV or oral. (N = 86).	*Post hoc* subgroup analysis on patients with moderate- and high-severity CAP. (PSI class III to IV – treated in hospital for at least 24 hours).	• clinical cure (measured as resolution of pre-treatment syndrome) or improvement at end of treatment (by severity)	• Different doses used for intervention compared with comparison arm (high dose, short duration/low dose, long duration comparison).

Table 113: Clinical evidence profile: Higher dose with shorter duration compared with lower dose and longer duration of antibiotic therapy

Quality assessment							No of patients		Effect		
No studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher dose and shorter duration	Lower dose and longer duration	Relative (95% CI)	Absolute	Quality
All-cause mortality											
0	no evidence available										
Clinical cure – moderate-to high-severity subgroup [Dunbar 2003]											
1	RCT	very serious[1]	no serious	no serious	no serious	none	69/76 (90.8%)	73/86 (84.9%)	RR 1.07 (0.95 to 1.2)	59 more per 1000 (from 42 fewer to 170 more)	Low
Withdrawal due to treatment-related adverse event											
0	no evidence available										
Hospital re-admission											
0	no evidence available										
Length of hospital stay											
0	no evidence available										
Health-related quality-of-life											
0	no evidence available										
Complications (composite of empyema, effusion, abscess, metastatic infection, superinfection, MODS)											
0	no evidence										

Quality assessment							No of patients		Effect		
No studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Higher dose and shorter duration	Lower dose and longer duration	Relative (95% CI)	Absolute	Quality
	available										
Relapse rate											
0	no evidence available										
***C. difficile*-associated diarrhoea**											
0	no evidence available										

[1] *Post hoc subgroup analysis. Patient comorbidities at baseline were not reported. Another associated paper reported that patients were stratified by centre and PSI severity, there were about 20% more patients with PSI Class III to V in the longer duration group. Method of randomisation, allocation concealment and blinding was not reported*

10.12.2 Economic evidence

Published literature

No relevant economic evaluations comparing shorter with longer duration antibiotic therapy in patients with moderate- to high-severity CAP were identified.

Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided in Appendix O: to aid consideration of cost effectiveness.

10.12.3 Evidence statements for patients with moderate-and high-severity community-acquired pneumonia

10.12.3.1 Clinical

- Low quality evidence from a *post hoc* subgroup analysis of patients with moderate- and high-severity CAP showed that there may be no clinical difference in the outcome of clinical cure between the groups of patients who received longer and shorter durations.

10.12.3.2 Economic

- No relevant economic evaluations were identified.

10.12.4 Recommendations and link to evidence

Table 114: Linking evidence to recommendations – duration of antibiotic therapy for high-severity community-acquired pneumonia

Recommendations	Consider a 7- to 10-day course of antibiotic therapy for patients with moderate- or high-severity community-acquired pneumonia.
Relative values of different outcomes	The GDG considered mortality the most important outcome, with clinical cure and adverse events considered other important outcomes.
Trade-off between clinical benefits and harms	One *post hoc* subgroup analysis examining the optimal duration of antibiotic therapy in moderate- or high-severity CAP was available and showed no clinically important difference in the outcome of cure. No data were found on other outcomes including harms.
Trade-off between net health benefits and resource use	No economic evidence was found on this question. A longer duration of antibiotic therapy would be more costly than a shorter duration in terms of antibiotic costs. However, the GDG commented that a longer duration than the standard 7 days of treatment may be more effective for high-severity pneumonia and therefore may be cost effective in some patients, as drug costs are low compared with the cost of treatment failure and serious consequences from ineffective treatment of high-severity CAP.
Quality of evidence	Evidence was of low quality by GRADE criteria.
Other considerations	The GDG recommended 7 to 10 days of antibiotic therapy for high-severity CAP based on consensus opinion. This is current clinical practice in the UK. The GDG felt that the evidence examining duration of antibiotic therapy in moderate- or high-severity CAP was very limited. The GDG discussed whether a shorter course (5 days) may be appropriate, in line with the recommendation for low-severity CAP but concluded that both the risk of treatment failure was higher, and the consequences

	of treatment failure more serious in high-severity CAP, and that the possible reduced risk of treatment failure of a longer course would be more likely to outweigh the risk of antibiotic-related complications in this group. The recommendation of 7 to 10 days is for empirical treatment of an unknown pathogen. The GDG acknowledged that specific causative pathogens would subsequently be identified in some patients and might require a longer course of treatment.

10.13 Recommendation summary

Timely diagnosis and treatment

9. Put in place processes to allow diagnosis (including X-rays) and treatment of community-acquired pneumonia within 4 hours of presentation to hospital.

10. Offer antibiotic therapy as soon as possible after diagnosis, and certainly within 4 hours to all patients with community-acquired pneumonia who are admitted to hospital.

Antibiotic therapy

Low-severity community-acquired pneumonia

11. Offer a 5-day course of a single antibiotic to patients with low-severity community-acquired pneumonia.

12. Consider amoxicillin in preference to a macrolide or a tetracycline for patients with low-severity community-acquired pneumonia. Consider a macrolide or a tetracycline for patients who are allergic to penicillin.

13. Consider extending the course of the antibiotic for longer than 5 days as a possible management strategy for patients with low-severity community-acquired pneumonia whose symptoms do not improve as expected after 3 days.

14. Explain to patients with low-severity community-acquired pneumonia treated in the community, and when appropriate their families and carers, that they should seek further medical advice if their symptoms do not begin to improve within 3 days of starting the antibiotic, or earlier if their symptoms are worsening.

15. Do not routinely offer patients with low-severity community-acquired pneumonia:

- **a fluoroquinolone**
- **dual antibiotic therapy.**

Moderate- and high-severity community-acquired pneumonia

16. Consider a 7- to 10-day course of antibiotic therapy for patients with moderate- or high-severity community-acquired pneumonia.

17. Consider dual antibiotic therapy with amoxicillin and a macrolide for patients with moderate-severity community-acquired pneumonia.

18. Consider dual antibiotic therapy with a beta-lactamase stable beta-lactam[c] and a macrolide for patients with high-severity community-acquired pneumonia.

[c] Available beta-lactamase stable beta-lactams include: co-amoxiclav, cefotaxime, ceftaroline fosamil, ceftriaxone, cefuroxime and piperacillin-tazobactam.

11 Glucocorticosteroid treatment

Inflammation, or inflammatory response, is the cellular and immune response of the body to infection which aims to kill infecting organisms. It has long been recognised that many of the symptoms experienced and illness features that are measured in pneumonia are caused by inflammation rather than the causative agents. It is also recognised that even when appropriate antibiotic therapy is administered and the causative bacteria killed, not only can the illness and its symptoms continue for some time, but in severe cases death may yet ensue. The concept of altering symptoms, illness duration and outcome through suppression of the inflammatory response has thus evolved.

Glucocorticosteroids are a group of medications whose principal mechanism of action is through suppression of inflammation and these drugs are widely and effectively used in other non-infective disease areas. Unfortunately it is also recognised that such suppression of inflammation can increase susceptibility to infection and make on-going infections worse. For this reason there has been a reluctance to use glucocorticosteroid treatment widely in the treatment of infection. However in some serious conditions with an infective cause (for example, meningitis), and in *Pneumocystis carinii* pneumonia in people who are immunocompromised, the addition of a glucocorticosteroid has been found to improve outcome. It is therefore pertinent to ask whether the addition of a glucocorticosteroid to standard antibiotic therapy at the initiation of treatment might offer a similar benefit to patients with pneumonia. Note that the outcome of this analysis does not inform the question about whether glucocorticosteroid treatment should be offered at a later stage or if sepsis develops.

11.1 Review question: In adults with community-acquired pneumonia or hospital-acquired pneumonia requiring management in hospital, what is the clinical and cost effectiveness of initial glucocorticosteroid treatment in addition to antibiotic treatment compared with antibiotic treatment alone?

For full details see review protocol in Appendix C:.

No data were found for hospital-acquired pneumonia.

11.2 Clinical evidence

We searched for systematic reviews and randomised controlled trials (RCTs) comparing the effectiveness and safety of a glucocorticosteroid plus antibiotic treatment with antibiotic treatment alone for treating community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP). Data for all antibiotics were pooled as long as they were considered appropriate by the treating physician, were prescribed according to national guidelines and were consistent in a given study. Data for all glucocorticosteroids were also pooled into a single analysis. This decision was based on the assumption that the mechanism of action of different types of glucocorticosteroids against systemic and pulmonary inflammation in the early phase of CAP is similar (down-regulation of pro-inflammatory cytokine transcription which prevents an extended cytokine response). No studies were excluded based on the route of administration, for either antibiotic therapy (oral or intravenous) or for glucocorticosteroid treatment (oral, intravenous or nasal routes).

Eight RCTs (5 of which were of small sample size) of patients with CAP were included in the review.[54,76,127,129,131,139,172,186] No relevant studies were found for patients with HAP.

A Cochrane review was found[49] but was excluded due to the inclusion of children in their population.

There was heterogeneity of the included studies in terms of:

- Population: 3 studies were limited to people managed in ITU[54,127,172] and in 2 studies not all patients had CXR-confirmed pneumonia.[127,139] A subgroup analysis was conducted for the studies in the ITU setting, since it is theoretically possible that glucocorticosteroid therapy may have greater benefit in a more severe patient group.
- Intervention: 3 main types of glucocorticosteroids were included in the selected RCTs; intravenous hydrocortisone, prednisolone and dexamethasone. The dosages and durations of glucocorticosteroids used in the studies varied widely. In 4 studies[54,129,172,186] , the duration of glucocorticosteroid treatment was 7 days whereas in 1 study[127] hydrocortisone was given as a single dose. Six studies used exclusively intravenous administration of a glucocorticosteroid[54,76,127,131,139,172], 1 used the oral route[129], and 1 administered the glucocorticosteroid by the same route as the antibiotic, which was likely to be intravenous in the majority of patients.[186] All studies were pooled together when appropriate.
- Comparison: a variety of antibiotics were used in the included studies (see Table 115). All studies were pooled together when appropriate.

Details of the included studies are presented in Table 113. Evidence from the included studies is summarised in the clinical GRADE evidence profile below (Table 114). See also the study selection flow chart in Appendix D:, forest plots in Appendix I:, study evidence tables in Appendix G:and exclusion list in Appendix J:.

Table 115: Summary of studies included in the review

Study	Comparison/interventions	Population/diagnosis	Outcomes	Comments
Confalonieri 2005[54]	*Antibiotic (according to guidelines) plus hydrocortisone compared with antibiotic (according to guidelines) plus placebo.* **Antibiotic:** Initial choice followed ATS 1993 guidelines **Glucocorticosteroid:** hydrocortisone IV as 200 mg loading bolus followed by an infusion (hydrocortisone 240 mg in 500 cc 0.9% saline) at a rate of 10 mg/hour. Total glucocorticosteroid duration 7 days. **Placebo:** saline administered as for glucocorticosteroid.	N = 48; CAP High-severity CAP as defined by meeting 2 minor or 1 major 1993 ATS criterion for severe pneumonia. Clinical and CXR evidence of pneumonia. Unclear how CAP differentiated from HAP.	• mortality (8 and 60 days) • mechanical ventilation • length of hospital stay • complications (Multiple Organ Dysfunction Syndrome (MODS))	• ITU setting – Italy. • After an interim analysis, enrolment was suspended because a significant difference was identified for improvement of $Pa0_2$:FIO_2 and mortality.
Fernandez-Serrano 2011[76]	*Cephalosporin plus fluoroquinolone plus methylprednisolone compared with cephalosporin plus fluoroquinolone plus to placebo.* **Empirical antibiotics:** 1 g/day IV ceftriaxone (9 days) and 500 mg/day levofloxacin (5 days then oral for at least 20 days). **Glucocorticosteroid:** Bolus of 200 mg methylprednisolone 30 minutes before starting antibiotic followed by titrated IV dose of 20 mg every 6 hours for 3 days, then 20 mg per 12 hours for 3 days then 20 mg/day for 3 days. **Placebo:** administered as for glucocorticosteroid.	N = 56; CAP Pneumonia diagnosed by CXR and at least 2 from: fever, purulent expectoration, pleuritic chest pain, or leukocytosis (white blood cell count of > 10,000/mm^3) HAP excluded: defined as pneumonia that developed within 8 days of hospital discharge.	• mortality (less than 9 days, over 9 days) • length of hospital stay • mechanical ventilation	• Excluded those aged over 75 years. • Concurrent omeprazole to minimise glucocorticosteroid side effects and insulin to control blood glucose levels permitted if necessary. • Glucocorticosteroid dose at top of licensed range.
Marik 1993[127]	*Antibiotic (according to guidelines) plus hydrocortisone compared with antibiotic (according to guidelines) plus placebo* **Antibiotics:** All initially received ceftriaxone 1 g IV every 6 hours. The first dose was given 30 minutes after study drug. Additional antibiotics were added according to microbiological results - amikacin, cloxacillin or erythromycin.	N = 30; CAP Diagnosis of high severity pneumonia included CXR confirmation but this was not a requirement for all cases. Unclear how CAP	• mortality (up to death or discharge) • length of ITU stay • mechanical ventilation	• ITU setting – South Africa. • Excluded those aged over 75 years. • Duration of follow-up unclear.

Study	Comparison/interventions	Population/diagnosis	Outcomes	Comments
	Glucocorticosteroid: Hydrocortisone was given as a single 10 mg/kg bolus (low dose). **Placebo:** Saline solution administered as for glucocorticosteroid.	differentiated from HAP.		• Appropriate supportive treatment permitted, including mechanical ventilation and inotropic support. • Unclear if CXR confirmed.
McHardy 1972[129]	*Beta-lactam (1 g or 2 g) plus prednisolone compared with beta-lactam (1 g or 2 g).* **Antibiotics:** Ampicillin 1 g or 2 g (in 4 divided doses) – oral for at least 7 days plus an additional 7 days if satisfactory response not achieved **Steroid:** Prednisolone 20 mg daily (in 4 divided doses) – oral for up to 7 days **Control:** No placebo used.	N = 126; CAP Admitted as emergencies to the respiratory wards with a diagnosis of pneumonia (CXR evidence of pneumonia or clinical evidence of pneumonia). Unclear how CAP differentiated from HAP.	• mortality	• Duration of follow-up unclear. • Oral administration throughout. • Two-step randomisation: first to ampicillin dose, then for with or without glucocorticosteroid. • 52% were current smokers and 15% ex-smokers. • Diabetic patients were excluded from randomisation to glucocorticosteroid.
Meijvis 2011[131]	*Antibiotic (according to guidelines) plus dexamethasone compared with antibiotic (according to guidelines) plus placebo.* **Antibiotics**: choice, duration and administration were at the discretion of the medical team and in accordance with national guidelines. All patients received antibiotic therapy within 4 hours of hospital admission and treatment was modified based on outcome of microbiological tests	N = 304; CAP New pulmonary infiltrate on CXR plus at least 2 clinical signs/symptoms. HAP excluded: defined as pneumonia diagnosed > 24 hours after admission.	• 30-day mortality • length of hospital stay • hyperglycaemia • complications(empyema or pleural effusion) • RAND-36 quality-of-	• Only 37% of those screened were enrolled in the study; 53% of those excluded were currently on/needed glucocorticosteroids (limits

Study	Comparison/interventions	Population/diagnosis	Outcomes	Comments
	Glucocorticosteroid: dexamethasone (5 mg) intravenously once-daily for 4 days. Initial dose given within a maximum of 12 hours of admission; all received antibiotic therapy before the glucocorticosteroid was given. **Placebo:** administered as for glucocorticosteroid.		life measure	generalisability).
Mikami 2007[139]	*Antibiotic (according to guidelines) plus prednisolone compared with antibiotic (according to guidelines) alone.* **Antibiotics:** IV within 8 hours of hospital arrival and modified based on culture results. Selection and duration of antibiotics was decided by the treating physician. **Glucocorticosteroid:** Prednisolone 40 mg in 100 ml saline IV for 3 days **Control:** no placebo.	N = 31; CAP Diagnosis of CAP was based on clinical signs and symptoms of LRTI. CXR abnormalities consistent with infection were neither pre-existing nor caused by any other previous conditions (unclear if all had new consolidations on X-ray). HAP excluded: none admitted to hospital within prior 3 months.	• length of hospital stay	• *Post-hoc* subgroup analysis for high-severity CAP. • Very strict exclusion criteria. • Of 60 eligible patients only 31 were randomised; 6 declined to participate but 23 (38%) were not invited to participate for undisclosed 'logistical' reasons. • Unclear if CXR-confirmed.
Sabry 2011[172]	*Antibiotic (according to guidelines) plus hydrocortisone compared with antibiotic (according to guidelines) plus placebo.* **Antibiotics:** Maximal conventional therapy **Glucocorticosteroid:** Hydrocortisone, loading dose of 200 mg over 30 minutes, followed by 300 mg in 500 ml 0.9% saline at a rate of 12.5 mg/h for 7 days. **Placebo:** saline solution administered as for glucocorticosteroid.	N = 80; CAP CXR showing bilateral involvement or multilobar involvement plus clinical symptoms suggestive of CAP. HAP excluded: Discharge from hospital within the previous 14 days or transferred from another hospital.	• ITU mortality • mechanical ventilation • complications (MODS)	• ITU setting Egypt. • High proportion receiving mechanical ventilation at baseline.
Snijders 2010[186]	*Antibiotic (according to guidelines) plus prednisolone compared with antibiotic (according to guidelines) plus*	N = 123; CAP New consolidations on CXR	• 30-day mortality • clinical cure	• Excluded those who had used macrolides

Study	Comparison/interventions	Population/diagnosis	Outcomes	Comments
	placebo. **Antibiotic:** According to national guidance; IV or oral at the discretion of the medical team. **Glucocorticosteroid:** 40 mg prednisolone once daily for 7 days by the same mode of administration as the antibiotic (likely to be IV in > 50%) **Placebo:** administered as for glucocorticosteroid.	plus clinical symptoms suggestive of CAP. HAP excluded: defined as pneumonia that developed within 8 days of hospital discharge.	• length of hospital stay • hyperglycaemia • complications (pleural effusion or empyema)	for > 24 hours. • *Post-hoc* subgroup analysis for high-severity CAP.

Table 116: Clinical evidence profile: Antibiotic plus glucocorticosteroid compared with antibiotic (with or without placebo) for community-acquired pneumonia managed in hospital

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic plus glucocorticosteroid	Antibiotic (with or without placebo)	Relative (95% CI)	Absolute	Quality
Mortality (all settings) [Confalonieri 2005, Marik 1993, Sabry 2011, Fernandez-Serrano 2011, Meijvis 2011, Snijders 2010, McHardy 1972]											
7	randomised trials	very serious[1]	no serious	serious[2]	serious[3]	none	22/400 (5.5%)	38/455 (8.4%)	RR 0.69 (0.41 to 1.14)	26 fewer per 1000 (from 49 fewer to 12 more)	Very low
Mortality up to 8 days (ITU setting) [Confalonieri 2005, Marik 1993, Sabry 2011] (sensitivity analysis)											
3	randomised trials	very serious	no serious	no serious	serious[3]	none	3/77 (3.9%)	11/79 (13.9%)	RR 0.32 (0.1 to 1)	102 fewer per 1000 (from 135 fewer to 0 more)	Very low
Mortality at 60 days (ITU setting) [Confalonieri 2005]											
1	randomised trials	serious[5]	no serious	no serious	serious[3]	none	0/23 (0%)	8/23 (34.8%)	RR 0.06 (0 to 0.96)	327 fewer per 1000 (from 14 fewer to 348 fewer)	Very low
Mechanical ventilation (all settings) [Confalonieri 2005, Marik 1993, Sabry 2011, Fernandez-Serrano 2011]											
4	randomised trials	very serious[1]	no serious	serious[2]	no serious	none	19/105 (18.1%)	50/107 (46.7%)	RR 0.38 (0.25 to 0.59)	290 fewer per 1000 (from 192 fewer to 350 fewer)	Very low
Mechanical ventilation (ITU setting) [Confalonieri 2005, Marik 1993, Sabry 2011] (sensitivity analysis)											
3	randomised trials	very serious[4]	no serious	no serious	no serious	none	18/77 (23.4%)	45/79 (57%)	RR 0.41 (0.26 to 0.63)	336 fewer per 1000 (from 211 fewer to 422 fewer)	Low
Clinical cure (time to clinical stability; up to 40 days) [Snijders 2010]											
1	randomised trial	no serious	no serious	no serious	serious[3]	none		77%	HR 1.14 (0.82 to 1.59)	43 more per 1000 (from 70 fewer to 133 more)	Moderate
Length of hospital stay (in days) (all settings) (Better indicated by lower values) [Mikami 2007, Meijvis 2011, Confalonieri 2005, Fernandez-Serrano											

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic plus glucocorticosteroid	Antibiotic (with or without placebo)	Relative (95% CI)	Absolute	Quality
2011]											
1	randomised trial	very serious[6]	no serious	no serious	serious[3]		11.3 (5.5)	15.5 (10.7)		MD 1.46 lower (4.37 lower to 1.44 higher)	Very low
3	randomised trials	very serious[7]	no serious	serious[8]	N/A	none	median 6.5 (5.0 to 6.0) (N = 151) 13 (3 to 53) (N = 24) 10 (9 to 13) (N = 28)	median 7.5 (5.3 to 11.5) (N = 153) 21 (3 to 72) (N = 24) 12 (9 to 18) (N = 28)	N/A	range of median difference (within studies) from 8 to 1 lower days	Very low
Hyperglycaemia (hospital setting) (follow-up up to 30 days) [Meijvis 2011, Snijders 2010]											
2	randomised trials	serious[9]	no serious	no serious	no serious	none	72/255 (28.2%)	37/262 (14.1%)	RR 1.98 (1.41 to 2.76)	122 more per 1000 (from 51 more to 218 more)	Moderate
Complications - empyema, pleural effusion and superinfection (hospital setting) (follow-up up to 30 days) [Meijvis 2011, Snijders 2010]											
2	randomised trials	serious[9]	no serious	no serious	serious[3]	none	30/255 (11.8%)	15/262 (5.7%)	RR 2.06 (1.13 to 3.73)	59 more per 1000 (from 7 more to 153 more)	LOW
Complications- MODS (ITU setting) (follow-up 8 days) [Confalonieri 2005, Sabry 2011]											
2	randomised trials	serious[10]	no serious	no serious	no serious	none	20/63 (31.7%)	44/63 (69.8%)	RR 0.45 (0.31 to 0.68)	384 fewer per 1000 (from 223 fewer to 482 fewer)	Moderate
Withdrawal due to adverse events											
0	no evidence available	-	-	-	-	none	-	-	-	-	-
Health-related quality-of-life (HQoL)											

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic plus glucocorticosteroid	Antibiotic (with or without placebo)	Relative (95% CI)	Absolute	Quality
1	see narrative summary below	-	-	-	-	none	-	-	-	-	-

[1] *The majority of studies were at high to very high risk of bias as intervention and control groups were not comparable at baseline with regards to severity of pneumonia and proportions on mechanical ventilation*

[2] *Three studies included only ITU population*

[3] *95% CI crosses 1 default MID*

[4] *Very high risk of selection bias as intervention and control groups were not comparable at baseline with regards to severity of pneumonia (control group had more severe disease compared with intervention) and all studies had unclear allocation concealment and 1 study stopped early for observed benefit in experimental arm*

[5] *High risk of selection bias: Unclear allocation concealment and sequence generation; stopped early for observed benefit in experimental arm*

[6] *Single blinded study with no details on randomisation method and allocation concealment. 23/60 of eligible patients were not offered participation in the study and no justification was given*

[7] *High risk of selection bias as intervention and control groups were not comparable at baseline in terms of severity of disease*

[8] *One study was conducted in ITU setting*

[9] *At baseline, the intervention group in both studies had a higher proportion of participants in PSI IV/V compared with control group*

[10] *One study was at high risk of selection bias due to unclear allocation concealment and sequence generation and was also stopped early for observed benefit in experimental arm; baseline imbalance of characteristics in the 2 groups in the other study with a higher proportion of participants in the control group on mechanical ventilation compared with the intervention group*

Narrative summary

One study (Meijvis 2011) reported a HQoL measurement (RAND-36 survey) on days 3 and 30 after the beginning of the trial. This HQoL tool assesses physical and social functioning, physical and emotional role restriction, mental health, vitality, pain, general health and change in health in the 30 days preceding the assessment. Although only 69% and 52% of the sample completed this survey at 3 and 30 days of the trial respectively, patients in the intervention arm (dexamethasone plus antibiotic group) had significant improvements in social functioning by day 30 compared with controls (p = 0.0091). No difference was found on day 3 between the 2 groups in any HQoL domain.

11.3 Economic evidence

Published literature

No relevant economic evaluations comparing glucocorticosteroid plus antibiotic therapy with antibiotic therapy alone were identified.

Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided in Appendix O: to aid consideration of cost effectiveness.

11.4 Evidence statements

11.4.1 Clinical

- Very low quality heterogeneous evidence from 7 randomised trials (the majority of small sample size) of several hundred patients with community-acquired pneumonia showed that the addition of glucocorticosteroid treatment to antibiotic treatment did not add any significant clinical benefit in terms of improving mortality rates compared with those who received antibiotic treatment alone. However, when the analysis was restricted only to 3 randomised studies in the ITU setting there was very low quality evidence that mortality at 8 days follow-up may be significantly improved in patients with CAP who received glucocorticosteroid treatment plus antibiotic treatment compared with the group of patients on antibiotic treatment alone.
- The addition of glucocorticosteroid treatment to standard antibiotic therapy may have a clinically significant benefit for the outcomes of mechanical ventilation (very low quality evidence) and MODS (moderate quality evidence). There was very low quality evidence indicating no clinically significant differences in length of hospital stay and occurrence of complications (empyema, pleural effusion and superinfection) between the groups of patients with and without glucocorticosteroid treatment in addition to antibiotic treatment.
- In relation to adverse events, moderate quality evidence from 2 randomised studies of 500 patients in hospital found that a higher proportion of patients with CAP who received glucocorticosteroid treatment in addition to antibiotic therapy experienced hyperglycaemia compared with those who had antibiotic therapy alone.

11.4.2 Economic

- No relevant economic evaluations were identified.

11.5 Recommendations and link to evidence

Table 117: Linking evidence to recommendations –glucocorticosteroid treatment

Recommendations	**19. Do not routinely offer a glucocorticosteroid to patients with community-acquired pneumonia unless they have other conditions for which glucocorticosteroid treatment is indicated.**
Relative values of different outcomes	The GDG considered mortality the most important outcome, with clinical cure and adverse events as other critical outcomes. Length of hospital stay, need for ventilatory support and other complications were also considered.
Trade-off between clinical benefits and harms	In all settings, the evidence from 7 randomised trials showed no clinical benefit in mortality rates for the group of patients on glucocorticosteroid treatment plus antibiotic therapy compared with those on antibiotic treatment alone. In an ITU setting, the evidence suggested reduced mortality in patients treated with a glucocorticosteroid. There also appeared to be a reduced dependence on mechanical ventilation and a reduced incidence of some complications (MODS). Other outcomes, including clinical cure, length of hospital stay and other complications, were not reported in ITU-based studies and showed no difference between the 2 intervention arms for patients treated outside an ITU setting. Although there was a large, clinically important increase in hyperglycaemia with glucocorticosteroid treatment, the GDG commented that this was a predictable complication that could be managed adequately, and agreed that this effect would be outweighed by any benefit in mortality or clinical cure. The results for the quality-of-life outcome as reported by 1 randomised trial were insufficient to accurately estimate the effect of the addition of a glucocorticosteroid to antibiotic therapy compared with antibiotic therapy alone.
Trade-off between net health benefits and resource use	No health economic studies were available on this topic. The GDG noted that glucocorticosteroids are inexpensive, and that if there are significant clinical benefits then they are likely to be cost effective. However, the clinical evidence showed no significant clinical benefit in mortality or clinical cure when a glucocorticosteroid was added to standard antibiotic therapy in patients treated outside an ITU setting.
Quality of evidence	The GDG noted that much of the evidence was of low or very low quality by GRADE criteria due to methodological flaws of the included studies, and that the quality of evidence was lowest for the most critical outcomes, including mortality. Moderate quality evidence was found only for the outcome of clinical cure which was reported by 1 trial and for the adverse outcomes of hyperglycaemia and MODS. The GDG expressed concern regarding the reliability of the evidence of mortality benefit in the ITU setting. Only 3 studies, together including a small number of patients, conducted in different countries at different times, and using different glucocorticosteroid doses and regimes, contributed to the mortality evidence in an ITU setting. One of these studies stopped enrolment early due to apparent benefit in an interim analysis. The GDG noted that the different treatment groups in the studies were not well matched; for example, a larger proportion of the placebo groups required ventilatory support prior to randomisation, suggesting that the placebo groups may have had more severe disease at baseline. The studies were conducted in ITUs in Egypt, South Africa and Italy, and the GDG reflected that differences in admission criteria might result in substantially different ITU populations to that seen in the UK, limiting the applicability of the evidence to UK clinical practice.

	No economic studies were found on this question.
Other considerations	The GDG acknowledged the apparent benefits of glucocorticosteroid treatment seen in the studies conducted in the ITU setting. However, after extensive debate, the GDG members concluded that they could not make a specific positive recommendation for the use of glucocorticosteroid treatment in this setting. This was primarily due to reservations regarding the quality of the evidence. The majority of the size of effect on mortality was due to a large difference seen in a single small study, in which the groups were not well-matched at randomisation, and the mortality rate in the intervention arm was considered to be remarkably low and unlikely to be representative of what would be seen in usual clinical practice. Routine glucocorticosteroid treatment for patients with CAP treated in ITU is not current UK practice, and it was agreed that the evidence was not sufficiently robust to recommend a change in current practice. Although routine glucocorticosteroid treatment was not being recommended, there was concern that a significant proportion of patients with CAP may have other indications for this treatment, such as a co-existent severe sepsis or an exacerbation of chronic obstructive pulmonary disease. The GDG wished to make clear that there was no significant evidence of harm with glucocorticosteroid treatment, and that whilst glucocorticosteroid treatment could not be recommended for pneumonia *per se*, it should be given when there are other indications for glucocorticosteroid use. The GDG noted that there are 3 on-going trials examining the use of glucocorticosteroid treatment in CAP. These studies are aiming to include a large number of patients in comparison with the currently available evidence, and may hopefully contribute to strengthening the evidence base in this topic.

12 Gas exchange

Gas exchange management is an important aspect of the management of a patient in hospital with pneumonia. Supplementary oxygen is sufficient for most in order to avoid hypoxemia and the risk of organ damage. Historically (since the advent of ventilatory support in the 1950s), when oxygen therapy alone had failed, or was insufficient to maintain adequate gas exchange, the only additional course of action involved sedation of the patient, intubation and ventilation.

Two newer forms of gas exchange augmentation are now available which avoid the need for either sedation or intubation and their associated complications. These newer therapies can be delivered in higher dependency areas on wards or in specialist areas. Both involve the use of a bedside piece of equipment to deliver air (or oxygen-enriched air), usually via a tight-fitting face mask or hood. Continuous positive airway pressure (CPAP) delivers this at a constant pressure; and bi-level positive airway pressure at 2 different levels - a higher pressure on inspiration and a lower pressure on expiration. This latter technique is commonly referred to as non-invasive ventilation (NIV). NIV is of proven benefit in the treatment of respiratory failure complicating exacerbations of chronic obstructive pulmonary disease.

These 2 questions in this chapter set out to assess the relative benefits and harms of these new approaches compared with conventional supplemental oxygen support (usual care) and elective intubation.

12.1 Review question: In adults with community-acquired pneumonia or hospital-acquired pneumonia managed in hospital, what is the clinical and cost effectiveness of non-invasive ventilation compared with continuous positive airways pressure or usual care?

For full details see review protocol in Appendix C:.

No data were found for hospital-acquired pneumonia.

12.2 Clinical evidence

We searched for systematic reviews, randomised controlled trials (RCTs) and comparative observational studies to assess the clinical effectiveness of NIV compared with CPAP or usual care in adults with pneumonia (CAP or HAP) managed in hospital. Two RCTs were included in the review[53,55] comparing CPAP (either delivered with a full-face mask or a helmet) with standard care and summarised in Table 118 below. One study (Confalonieri 1999) reported subgroup analyses (although not pre-specified) of patients with and without COPD, and these results are presented separately.

No relevant studies were found for adults with HAP.

Evidence from these studies is summarised in the GRADE clinical evidence profile below (Table 119). See also the study selection flow chart in Appendix D:, study evidence tables in Appendix G:, forest plots in Appendix I:, and excluded studies list in Appendix J:.

None of the studies compared NIV with CPAP or usual care. In our search, we also found a Cochrane systematic review[209] which included the studies identified by this review, but was excluded as it had included a third study that did not meet our inclusion criteria.

Table 118: Summary of studies included in the review

Study	Intervention/comparison/ N randomised	Population	Outcomes	Comments
CPAP compared with usual care				
Confalonieri 1999[53]	CPAP full-face mask/ standard care (clinical management and oxygen supplementation) (N = 56).	Adults with moderate- and high-severity CAP and acute respiratory failure treated in ITU.	• hospital mortality • need for mechanical ventilation/ intubation • length of stay (hospital/ITU)	• Patients with severe illness were included (e.g. patients with a respiratory rate of over 30 and patients with respiratory acidosis). • In the full sample, patients with concomitant COPD were equally distributed in both treatment groups. • Patients requiring emergency intubation were excluded. • A *post-hoc* subgroup analysis of patients with and without COPD was conducted.
Cosentini 2010[55]	CPAP delivered by helmet/ standard oxygen therapy (N = 47).	Adults with CAP and early acute respiratory failure treated outside ITU.	• clinical improvement (patients who reached $PaO_2/FiO_2 \geq 315$ as a surrogate of clinical cure)	• Short follow-up of 48 hours. • Recruitment was stopped early due to "clear benefit of CPAP".

Table 119: Clinical evidence profile: CPAP compared with standard therapy with oxygen supplementation for patients with community-acquired pneumonia

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CPAP	Usual care	Relative (95% CI)	Absolute/Mean difference	Quality
Hospital mortality - All patients (follow-up 2 months) [Confalonieri 1999]											
1	RCT	no serious	no serious	no serious	very serious[2]	none	7/28 (25%)	6/28 (21.4%)	RR 1.17 (0.45 to 3.04)	36 more per 1000 (from 118 fewer to 437 more)	Low
Hospital mortality - Without COPD (follow-up 2 months) (subgroup analysis) [Confalonieri 1999]											
1	RCT	very serious[3]	no serious	no serious	very serious[2]	none	6/16 (37.5%)	4/17 (23.5%)	RR 1.59 (0.55 to 4.62)	139 more per 1000 (from 106 fewer to 852 more)	Very low
Hospital mortality - With COPD (follow-up 2 months) (subgroup analysis) [Confalonieri 1999]											
1	RCT	very serious[4]	no serious	no serious	very serious[2]	None	1/12 (8.3%)	2/11 (18.2%)	RR 0.46 (0.05 to 4.38)	98 fewer per 1000 (from 173 fewer to 615 more)	Very low
Need for intubation - All patients (follow-up 2 months) [Confalonieri 1999]											
1	RCT	no serious	no serious	no serious	serious[1]	None	6/28 (21.4%)	17/28 (60.7%)	RR 0.35 (0.16 to 0.76)	395 fewer per 1000 (from 146 fewer to 510 fewer)	Moderate
Need for intubation - Without COPD (follow-up 2 months) (subgroup analysis) [Confalonieri 1999]											
1	RCT	very serious[3]	no serious	no serious	very serious[2]	None	6/16 (37.5%)	8/17 (47.1%)	RR 0.8 (0.35 to 1.79)	94 fewer per 1000 (from 306 fewer to 372 more)	Very low
Need for intubation - With COPD (follow-up 2 months) (subgroup analysis) [Confalonieri 1999]											
1	RCT	very	no serious	no serious	very	none	0/12 (0%)	6/11	RR 0.07	507 fewer per 1000 (from	Very

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CPAP	Usual care	Relative (95% CI)	Absolute/Mean difference	Quality
		serious[4]			serious[2]			(54.5%)	(0 to 1.13)	545 fewer to 71 more)	low
Duration of intubation - All patients (follow-up 2 months; Better indicated by lower values) [Confalonieri 1999]											
1	RCT	no serious	no serious	no serious	serious[1]	None	7 (3)	10 (3)	-	MD 3 lower (4.57 to 1.43 lower)	Moderate
Duration of intubation - Without COPD (follow-up 2 months; Better indicated by lower values) (subgroup analysis) [Confalonieri 1999]											
1	RCT	very serious[3]	no serious	no serious	serious[1]	None	6.8 (4.2)	8.0 (3.4)	-	MD 1.2 lower (3.82 lower to 1.42 higher)	Low
Duration of intubation - With COPD (follow-up 2 months; Better indicated by lower values) (subgroup analysis) [Confalonieri 1999]											
1	RCT	very serious[3]	no serious	no serious	no serious	none	0 (0.1)	12.3 (3.9)	-	MD 12.3 lower (14.61 to 9.99 lower)	Low
Duration of hospital stay - All patients (Better indicated by lower values) [Confalonieri 1999]											
1	RCT	no serious	no serious	no serious	serious[1]	none	17.0 (2.0)	18.0 (2.0)	-	MD 1 lower (2.05 lower to 0.05 higher)	Low
Duration of hospital stay - Without COPD (follow-up 2 months; Better indicated by lower values) (subgroup analysis) [Confalonieri 1999]											
1	RCT	very serious[3]	no serious	no serious	serious[1]	none	17.9 (2.9)	15.1 (2.8)	-	MD 2.8 higher (0.85 to 4.75 higher)	Low
Duration of hospital stay - With COPD (follow-up 2 months; Better indicated by lower values) (subgroup analysis) [Confalonieri 1999]											
1	RCT	very serious[3]	no serious	no serious	no serious	none	14.9 (3.4)	22.5 (3.5)	-	MD 7.6 lower (10.42 to 4.78 lower)	Low
Duration of ITU stay - All patients (follow-up 2 months; Better indicated by lower values) [Confalonieri 1999]											
1	RCT	no serious	no serious	no serious	no serious	none	1.8 (0.7)	6.0 (2.0)	-	MD 4.2 lower (4.98 to 3.42 lower)	Moderate
Duration of ITU stay - Without COPD (follow-up 2 months; Better indicated by lower values) (subgroup analysis) [Confalonieri 1999]											

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CPAP	Usual care	Relative (95% CI)	Absolute/Mean difference	Quality
1	RCT	very serious[3]	no serious	no serious	no serious	none	2.9 (1.8)	4.8 (1.7)	-	MD 7.35 lower (8.82 to 5.88 lower)	Low
Duration of ITU stay - With COPD (follow-up 2 months; Better indicated by lower values) (subgroup analysis) [Confalonieri 1999]											
1	RCT	very serious[3]	no serious	no serious	serious[1]	none	0.25 (2.1)	7.6 (2.2)	-	MD 1.9 lower (3.33 to 0.47 lower)	Very low
Clinical improvement (reach $PaO_2/FiO_2 \geq 315$) (follow-up 48 hours)[Cosentini 2010]											
1	RCT	very serious[5]	no serious	no serious	no serious	none	19/20 (95%)	8/27 (29.6%)	RR 3.21 (1.78 to 5.78)	655 more per 1000 (from 231 more to 1000 more)	Low
Health-related quality-of-life											
0	no evidence available	-	-	-	-	-	-	-	-	-	-
Composite of complications											
0	no evidence available	-	-	-	-	-	-	-	-	-	-

[1] *Confidence interval crossed 1 default MID*
[2] *Confidence interval crossed 2 default MIDs*
[3] *Post-hoc subgroup analysis. Difference in baseline characteristics between the 2 groups (patients treated with CPAP were older than those on standard care)*
[4] *Post-hoc subgroup analysis*
[5] *Study was underpowered, recruitment was stopped early due to "clear benefit of CPAP"*

Narrative summary

In the study by Cosentini[55] a multivariate analysis (Cox survival analysis) was conducted to investigate the impact of CPAP on time to achieve an outcome of clinical cure (reached $PaO_2/FiO_2 \geq 315$) adjusted for the effect of centre, age, and baseline PaO_2/FiO_2 ratio. CPAP was the only predictor for reaching the endpoint of $PaO_2/FiO_2 \geq 315$ at 48 hours; patients in the CPAP group were 11.3 times more likely to reach this endpoint than patients in the control group (HR 11.3, 95% CI 3.51 to 36.32).[55]

12.3 Review question: In adults with pneumonia managed in hospital, what is the clinical and cost effectiveness of NIV, CPAP or usual care compared with elective intubation?

For full details see review protocol in Appendix C:.

12.4 Clinical evidence

No data were found for community-acquired or hospital-acquired pneumonia.

12.5 Economic evidence

Published literature

No relevant economic evaluations were identified. See also the economic article selection flow diagram in Appendix E:.

Unit costs

Due to the limited cost data pertaining to NIV and CPAP usage in pneumonia, HRGs for COPD with and without NIV use are detailed below. Cost data on usual care (oxygen) could not be found. However, all these procedures require oxygen and as such, there is unlikely to be a significant incremental difference within this cost component.

Table 120 represents the costs of adult critical care.

Table 121 represents the costs of NIV in COPD. It should be noted that this may be more expensive in CAP due to an expected longer length of stay in hospital. There are no specific HRGs for CPAP. However, the equipment costs (flow generator and masks) for CPAP tend to be slightly less expensive than NIV and therefore the costs may be marginally lower. In practice, NIV is used in sicker patients and/or those patients who have more comorbidities.

Table 122 represents the costs of the initial act of intubation. On-going costs such as higher staffing levels, various anaesthetics and other procedures will be captured by the HRGs for adult critical care.

Table 120: ITU/HDU costs

HRG code	Description	National average unit cost	Lower quartile unit cost	Upper quartile unit cost	Critical care periods
XC05Z	Adult Critical Care, 2 Organs Supported	£1,223	£1,010	£1,395	93,060
XC06Z	Adult Critical Care, 1 Organ Supported	£868	£666	£998	156,930

(a) Critical Care Services - Adult: Critical Care Unit. NHS Reference Costs, 2011-2012[61]

Table 121: Chronic obstructive pulmonary disease with and without non-invasive ventilation costs

HRG	HRG codes[a]	National average unit cost	Lower quartile unit cost	Upper quartile unit cost
Chronic Obstructive Pulmonary Disease or Bronchitis, with NIV, without Intubation	DZ21E, DZ21F, DZ21G[b]	£2,282	£1,680	£2,688
Chronic Obstructive Pulmonary Disease or Bronchitis, without NIV, without Intubation	DZ21H, DZ21J, DZ21H[c]	£1,763	£1,422	£2,008
Difference[d]		**£519**	**£258**	**£681**

(a) HRG codes for all levels of complications have been included and a weighted average calculated
(b) Total activity – 6,285 FCE's
(c) Total activity – 108, 596 FCE's
(d) Difference for CAP likely to be higher due to the higher length of NIV use
Source: NHS Reference Costs, 2011-2012[61]

Table 122: Initial act of intubation costs

Resource	Mean cost	Range of costs	Notes/source
Total cost of single use laryngoscope per patient	**£13.50**		NHS Supply Chain Catalogue
Endotracheal tubes	£3.88	< £1 to £58	NHS Supply Chain Catalogue
Fentanyl (100 micrograms)	£0.30		GDG Expert Opinion. MIMS Nov 2013[1]
Propofol (200 mg)	£3.07		GDG Expert Opinion. MIMS Nov 2013[1]
Suxamethonium (100 mg)	£0.71		GDG Expert Opinion. MIMS Nov 2013[1]
Atracurium (50 mg)	£3.00		GDG Expert Opinion. MIMS Nov 2013[1]
Consumables cost per patient	**£10.97**		
STR3+ Doctor for 0.5 hours	£35.50		GDG Expert Opinion - PSSRU 2012
Band 7 nurse for 0.5 hours	£29.00		GDG Expert Opinion - PSSRU 2012
Staff costs	**£64.50**		
Total cost of initial intubation per patient	**£88.97**		

12.6 Evidence statements

12.6.1 Clinical

12.6.1.1 CPAP compared with usual care

- Low to very low quality evidence from 1 RCT of almost 60 participants suggested that there may be no clinical benefit of CPAP compared with usual care in reducing hospital mortality. However, very low quality evidence from the *post hoc* subgroup analysis of the same RCT showed that patients without COPD who received CPAP may have increased risk of hospital mortality compared with those in usual care, whereas patients with COPD seem to benefit from CPAP compared with usual care for the same outcome. However, results should be interpreted with caution as both subgroup analyses included very low numbers of events in each group for the outcome of hospital mortality.
- Moderate to low quality evidence from 1 RCT of almost 60 participants found that there may be a clinically significant benefit for patients with CAP who received CPAP compared with those on usual care for the following outcomes:

- need for intubation
- duration of intubation
- duration of hospital stay.

The clinical benefit for all these outcomes was found to be larger in the subgroup of patients with COPD although the evidence was of very low quality (*post hoc* subgroup analysis).

- Low-quality evidence from 1 randomised trial of almost 50 participants with CAP suggested there may be a clinical benefit of CPAP compared with usual care in clinical improvement (as assessed by the proportion of patients who reached $PaO_2/FiO_2 \geq 315$ in 48 hours).

12.6.2 Economic

- No relevant economic evaluations were identified.

12.7 Recommendations and link to evidence

Table 123: Linking evidence to recommendations – NIV and CPAP compared with usual care

Recommendations	No recommendation made.
Relative values of different outcomes	The GDG considered mortality the most important outcome. Need for intubation and invasive ventilation, length of stay (in ITU and total hospital stay), clinical cure, quality-of-life and complications (both of CPAP/NIV themselves and of any subsequent invasive ventilation) were considered other important outcomes.
Trade-off between clinical benefits and harms	No studies were found comparing NIV (Bi-level CPAP) to CPAP or usual care. Two RCTs comparing CPAP to usual care were identified. The first study randomised patients with CAP and indicators of a more severe illness (including patients with a respiratory rate of over 30, and patients with respiratory acidosis) who were treated in ITU to receive either CPAP or usual care. The population included patients with and without COPD who were analysed by *post-hoc* subgroup analysis. There was no overall difference in mortality between treatment groups. There was an apparent reduction in need for intubation, duration of intubation and length of stay in ITU in patients treated with CPAP, though this effect was heavily weighted by a large effect seen in the COPD subgroup, with little difference seen in those without COPD. Duration of hospital stay was shorter with CPAP in patients with CAP with COPD, but longer in patients with CAP without COPD. The second study randomised patients with CAP who were less sick (respiratory rate < 35, excluded patients with respiratory acidosis) who were treated outside ITU with CPAP or usual care. Follow-up was for 48 hours only, with no deaths or intubations reported. Patients achieved a PaO_2/FiO_2 ratio of ≥ 315 (a surrogate for clinical improvement) more quickly with CPAP than with usual care.
Trade-off between net health benefits and resource use	No suitable economic studies were available. The GDG noted that the cost effectiveness of CPAP or NIV would depend on the cost of equipment, but also on the costs of monitoring the patient and location of care (critical care/ITU/HDU or medical ward) and the downstream effects on outcomes such as mortality and length of stay. However, since no evidence was available on the clinical effectiveness of NIV in CAP, the GDG could not conclude if this intervention is cost effective.
Quality of evidence	Evidence was of moderate to very low quality by GRADE criteria, with the majority of evidence being of low or very low quality. The GDG noted that the number of patients included in the available studies was small, with a degree of imprecision around many of the results. The evidence from the *post hoc* subgroup analysis of

	patients with CAP with and without COPD should be interpreted with caution as it included a very small sample size.
Other considerations	The GDG acknowledged the paucity of applicable evidence in this area. The GDG discussed whether additional studies that included patients with respiratory failure due to a mixture of causes including CAP might help inform deliberations. However, it was agreed that the mechanism of CPAP and NIV in treating other conditions (for example the hydrostatic effects of positive pressure in pulmonary oedema) would not necessarily translate well to treating CAP. The authors of 2 large studies in acute respiratory failure were approached to obtain data. There was no reply from one and the other no longer had the data from what is now an old study. In the absence of any evidence regarding NIV in CAP the GDG could not make a recommendation regarding its use, either positive or negative, and prioritised a research recommendation in this area. The GDG then discussed the apparent benefit of CPAP in patients with CAP and co-existent COPD. The benefit of NIV in treating acute respiratory failure associated with exacerbations of COPD is now well established, but was not at the time of the study showing benefit of CPAP in patients with CAP and COPD. However, because of the small numbers included in the study, the GDG concluded that a specific recommendation should not be made for CPAP in patients with COPD and CAP despite some evidence suggestive of benefit.

Table 124: Linking evidence to recommendations – NIV, CPAP and usual care compared with elective intubation

Recommendations	**No recommendation made.**
Relative values of different outcomes	The GDG considered mortality the most important outcome. Need for intubation and invasive ventilation, length of stay (in ITU and total hospital stay), clinical cure, quality-of-life and complications (of CPAP/NIV) and of intubation with invasive ventilation) were considered other important outcomes.
Trade-off between clinical benefits and harms	No suitable studies were identified.
Trade-off between net health benefits and resource use	No suitable economic studies were available. The GDG noted that the cost effectiveness of CPAP or NIV would depend on the cost of equipment, but more so on the costs of monitoring the patient and location of care (critical care/ITU/HDU or medical ward) and the downstream effects on outcomes such as mortality and length of stay.
Quality of evidence	No suitable evidence was available.
Other considerations	The GDG noted the lack of evidence in this area. However, it was recognised that conducting randomised controlled trials on this question would be difficult. In the absence of suitable evidence, the GDG discussed the potential benefits and harms of the CPAP or NIV compared with elective intubation. It was noted that intubation and invasive ventilation are associated with risks, such as ventilator-associated pneumonia, which are largely avoided with CPAP/NIV. However, non-invasive mechanisms of delivering CPAP or ventilation can cause significant discomfort for the patient, and have their own associated risks, including that of treatment failure and subsequent delayed intubation. Persistence with CPAP or NIV when treatment is failing could lead to a delay in intubation and invasive ventilation, which may be associated with worse outcomes. These considerations did not allow the GDG to make a firm recommendation for either course of action. The GDG discussed whether a recommendation for location of care for patients

	treated with CPAP or NIV should be made. Treatment outside a critical care setting could amplify delays in intubation in the event of treatment failure, but treatment in critical care areas is significantly more costly. In the absence of evidence for or against CPAP or NIV, the GDG concluded that a recommendation on location of care for the small group of patients who would receive these treatments could not confidently be made.

12.8 Research recommendation

2. What is the clinical effectiveness of continuous positive pressure ventilation compared with usual care in patients with community-acquired pneumonia and type I respiratory failure without a history of chronic obstructive pulmonary disease?

Why this is important

Type I respiratory failure is a common feature of pneumonia. Mild type I respiratory failure is easily corrected with low levels of supplemental oxygen, whereas severe life-threatening hypoxemia needs immediate intubation and invasive ventilation. Research into whether continuous positive pressure ventilation improves gas exchange and subsequent outcomes, such as mortality, could help improve care for patients with respiratory failure between these extremes.

13 Monitoring

Patients with community-acquired pneumonia (CAP) and hospital-acquired pneumonia (HAP) who are admitted to hospital are currently monitored by routine physiological observations, repeat clinical assessments and blood tests. Evidence of improvement in the patient's condition informs decisions about when to stop antibiotic therapy and when to discharge from hospital. Absence of improvement or deterioration guides change in empirical antibiotic therapy. Currently this approach is unstructured, with the potential for over or under treatment with antibiotics and inappropriate discharge decisions. The guideline development group (GDG) wished to investigate the evidence to determine whether more objective assessment using repeated C-reactive protein and/or procalcitonin measurement is better than or adds to subjective clinical judgement alone in regard to these decision points when managing patients with pneumonia in hospital.

13.1 Review question: In adults with community-acquired pneumonia or hospital-acquired pneumonia managed in hospital, what is the clinical and cost effectiveness of C-reactive protein or procalcitonin monitoring in addition to clinical observation in helping to determine when to stop or change treatment and when to discharge?

For full details see review protocol in Appendix C:.

No data were found for hospital-acquired pneumonia.

13.2 Clinical evidence

We searched for studies investigating the value of using C-reactive protein (CRP) and procalcitonin (PCT) in addition to clinical judgement to monitor people with CAP or HAP in hospital. Systematic reviews, test-and-treat randomised trials (RCTs) and prognostic studies reporting the prognostic value of these monitoring assessments in terms of risk of outcome assessed by multivariate analysis were included as a first preference. Derivation and validation studies of the accuracy of these measures to predict outcomes were not included as they cannot control for the effect of confounders on outcomes. We searched for prognostic studies which reported the risk of specific outcomes given a particular value of PCT or CRP, to assess whether PCT or CRP are useful in aiding clinical decisions on when to stop or change treatment, and/or when to discharge patients with pneumonia.

Eight studies were included in the review for CAP: 1 systematic review (using an individual patient data [IPD] meta-analysis) of 14 RCTs reported in 2 papers[175,177] (of which 1 was a Cochrane systematic review); a subgroup analysis of unpublished data of 1 RCT[51]; and 6 observational studies with multivariate analyses.[25,32,44,52,133,134] No relevant studies were found for patients with HAP.

The details of these studies are summarised in Table 125.

The available data were subject to the following analysis:

- Randomised data:
  - The studies included in the IPD meta-analysis used PCT not only as a monitoring intervention but also to determine whether to initiate antibiotic therapy, making unclear the independent impact of monitoring PCT on outcome. However, the results are presented from a multivariate analysis which controlled for the effect of important confounders such as patient age, acute

respiratory infections (ARI) diagnosis and trial effect. In addition, the population for this IPD meta-analysis was patients (in all settings) with ARI; patients with CAP constituted over 50% of the whole sample. Although no difference was found in the direction of results for the whole sample and the CAP subgroup, for the purposes of our review we present the results of the sensitivity analysis for patients with CAP below. The GDG identified 1 RCT[51] included in the IPD meta-analysis that they thought could provide further information regarding this review. The GDG noted that in this RCT, 15% of the intervention group (PCT-guided treatment) and 1% of the control group (usual care) did not receive antibiotic therapy. A *post hoc* subgroup analysis was performed by excluding the subgroup of patients who did not receive antibiotic therapy in both groups as this would give a more discriminatory estimate of the effect of PCT monitoring on the outcomes. For consistency, all the included RCTs in the IPD meta-analysis were checked for similar information. No other studies reported such details. The authors of this RCT[51] were contacted and they agreed to submit the anonymised individual patient data of the subgroup of patients in the study who had received antibiotic therapy based on PCT measurement or on usual care. The unpublished data from the Christ Crain 2006 study are presented separately to the IPD meta-analysis (Schuetz 2012) to avoid double counting the estimate of effects.

- Observational data:
  - These studies were designed as purely prognostic investigations without an interventional element, meaning that the values of PCT or CRP were not used to influence management decisions.
  - None of the studies controlled for the management strategy used.
  - Insufficient data were available to calculate absolute risk differences for most outcomes.
  - The analyses in the observational studies were conducted to establish whether a particular prognostic factor, as defined in the study, was a risk factor or a protective factor for a specific future outcome. The prognostic factor definitions varied; most studies defined the predictive variable as a risk factor (reduction in biomarker value *below* a threshold or absolute biomarker value at a given time *above* a threshold), so that an odds ratio (OR) greater than 1 indicates an increased risk of the outcome. However, in some cases the predictive variable is a protective factor (increase in biomarker value *above* a threshold or absolute biomarker value at a given time *below* a threshold), so that an OR less than 1 indicates a decreased risk of the outcome. Where the threshold defines a protective factor, this is highlighted in the results table to avoid confusion about the direction of effect. Studies that reported CRP or PCT measurements only at day 1 were excluded because this review question requires data on repeated biomarker measurements over time to guide change in management.

Evidence from these studies is summarised in the clinical GRADE evidence profiles below (Table 126, Table 127, Table 128, Table 129 and Table 130). See also the study selection flow chart in Appendix D:, forest plots in Appendix I:, study evidence tables in Appendix G: and exclusion list in Appendix J:.

1 **Table 125: Summary of studies included in the review**

Study	Prognostic factor or intervention/N randomised	Control/N randomised	Population and setting	Number of patients	Outcomes	Comments
Randomised data for CAP						
Schuetz 2012[175,177]	PCT-guided antibiotic therapy Similar PCT algorithms used among included studies Variability: • Single PCT measurement on admission to guide initiation of antibiotic therapy or repeated measurements for guiding the duration of treatment. • Thresholds for recommending antibiotic therapy differed; majority suggested discontinuation of antibiotics when PCT < 0.25 µg/l and strongly recommended discontinuation when PCT < 0.1 µg/l.	Clinical assessment alone.	• Initial suspicion of ARI ○ 3 studies LRTI (n = 2820) ○ 3 studies CAP (n = 585) ○ 1 study VAP (n = 101) ○ 4 studies sepsis or bacterial infection (n = 497) ○ 1 study COPD (n = 208) • All settings ○ 2 in primary care (n = 1008) ○ 7 in ED/hospital (n = 2605) ○ 5 in ITU (n = 598).	14 trials, 4211 participants (2027 with CAP – unclear how many trials these were drawn from)	• mortality • treatment failure • duration of antibiotics: total days of antibiotic therapy in patients in whom antibiotic therapy was initiated. • total exposure to antibiotics: total days of antibiotic therapy in all randomised patients	• Physicians were allowed to deviate from the proposed PCT-based prescribing. • PCT concentrations on admission were highest in patients from the ITU setting and lowest in primary care patients. • No statistically significant differences in PCT concentrations between PCT and control groups overall and for individual settings.
Christ-Crain 2006[51]	PCT to guide antibiotic therapy (N = 151).	Clinical assessment alone (N = 151).	• Patients with CAP admitted to hospital. • 60.2% PSI IV/V.	302 (275 received antibiotic therapy at the beginning of the trial based on PCT concentrations)	• mortality • length of hospital stay • duration of antibiotics • ITU admission • treatment failure	• Cohort of older patients with a high rate of comorbidities. • Decisions on antibiotic initiation or continuation on the basis of PCT cut-off concentrations: ○ 0.1 to 0.25µg/l:

Study	Prognostic factor or intervention/N randomised	Control/N randomised	Population and setting	Number of patients	Outcomes	Comments
						strongly discouraged ○ 0.25 to 0.5 µg/l: encouraged ○ > 0.5 µg/l: strongly encouraged.
Observational data (with multivariate analysis) of PCT and CRP for CAP						
Boussekey 2006[25]	• CRP and PCT increase day 1 to day 3.	NA.	• CAP in ITU. • Mean age 62.9 (15.1).	120	• mortality (at ITU discharge)	• Indirect population – limited to ITU (but pathogen spectrum matches that expected in high-severity CAP in UK). • Did not report non-significant AORs.
Bruns 2008[32]	CRP: • Day 0 to 3 decline < 60% • Day 0 to 7 decline < 90%	NA	• CAP in hospital • 86.5% PSI class IV-V • Mean age 69.7 (13.8)	289	• inappropriate use of antibiotics • 28-day mortality • Early (within 3 days) treatment failure (clinical instability, ITU admission or mortality) • Late (within 28 days) treatment failure (clinical deterioration or complications, mortality, need for mechanical ventilation, re-admission for intravenous antibiotic therapy, re-admission (for pulmonary infection), increase in body temperature)	• Retrospective analysis of RCT data: more selective population • Adjusted results for patient characteristics, pneumonia severity, symptoms and signs of pneumonia on admission.

Study	Prognostic factor or intervention/N randomised	Control/N randomised	Population and setting	Number of patients	Outcomes	Comments
Chalmers 2008A[44]	CRP measured on admission and on day 4 • failure of CRP to fall by 50% at day 4 • discharge CRP < 100 mg/l vs ≥ 100 mg/l.	NA	• CAP in hospital • Median age 62 (44 to 76)	570	• 30-day mortality • need for invasive ventilation or ionotropic support • complicated pneumonia (lung abscess, empyema, or complicated pneumonic effusion)	• Only 268 (52%) had repeat measurement at day 4 (but baseline characteristics similar to full sample). • Adjusted results for age, sex, pneumonia severity, co-morbidity, smoking status.
Coelho 2012[52]	CRP measured during first week of ITU stay on days (D) 1, 3, 5 and 7 • Day 5 CRP ratio > 0.5.	NA.	• CAP in ITU. • Median age 70 (54 to 81). • Median CURB65: 3 (3 to 4).	191	• ITU mortality	• Indirect population – limited to ITU (causative pathogen only found in a small proportion). • Adjusted results for age, sex, APACHE II, day 1 PaO_2/FiO_2, mechanical ventilation, ITU-acquired infection, septic shock and day 1 SOFA score. • Did not report non-significant AORs.
Menendez 2008[133]	CRP and PCT measured on day 1 and 3 • Above 75th percentile.	NA.	• CAP in hospital. • 52.3% PSI IV/V. • Mean age 67.3 (17.1).	453	• overall treatment failure • early treatment failure (clinical deterioration-need for mechanical ventilation and/or shock or death- within 72 hours of treatment)	• Non-significant results not reported for: ○ any outcome for PCT ○ early treatment

Study	Prognostic factor or intervention/N randomised	Control/N randomised	Population and setting	Number of patients	Outcomes	Comments
					• Late treatment failure (persistence or reappearance of fever, CXR progression, pleural effusion and/or empyema, nosocomial infection, impairment of respiratory failure and need for mechanical ventilation or shock after 72 hours)	failure for CRP. • Thresholds chosen based on study results. • Adjusted results for severity, comorbid condition, cytokine levels and markers. • Cohort overlaps with Menendez 2009B.
Menendez 2009B[135]	CRP and PCT measured on day 1 and 3 • CRP < 3 mg/dL day 3 • PCT < 0.25 ng/mL day 3.	NA	• CAP in hospital. • Mean age 66.5 (17.2) years. • 47.9% PSI IV/V.	394.	• Severe complications after 72 hours (death within 30 days of admission, shock or need for mechanical ventilation (invasive or non-invasive), or admission to the ITU)	• Thresholds chosen based on study results (highest specificity and PPV). • Cohort overlaps with Menendez 2008. • Adjusted results for clinical stability (Halm's criteria) within the first 72 hours of treatment.

Table 126: Clinical evidence profile: IPD meta-analysis of RCTs comparing PCT to guide antibiotic administration plus monitoring decisions compared with standard care alone for community-acquired pneumonia

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCT	Standard care	Relative (95% CI)	Absolute	Quality
Mortality (follow-up 2 weeks to 30 days) [Schuetz 2012]											
12	randomised trials	serious[1]	no serious[2]	serious[3]	serious[4]	none	92/999 (9.2%)	111/1028 (10.8%)	AOR 0.89 (0.64 to 1.24)	11 fewer per 1000 (from 36 fewer to 23 more)	Very low
Treatment failure (follow-up 2 weeks to 30 days) [Schuetz 2012]											
12	randomised trials	serious[1]	no serious[2]	serious[2]	serious[3]	none	190/999 (19%)	240/1028 (23.3%)	AOR 0.77 (0.62 to 0.96)	43 fewer per 1000 (from 7 fewer to 75 fewer)	Very low
Hospital re-admission											
0	no evidence available	-	-	-	-	none	-	-	-	-	-
Length of hospital stay											
0	no evidence available	-	-	-	-	none	-	-	-	-	-
Duration of antibiotics (in days) (follow-up 2 weeks to 30 days; Better indicated by lower values) [Schuetz 2012]											
12	randomised trials	serious[1]	no serious	serious[2]	no serious	none	7 (5 to 10)	10 (8 to 14)	-	3.34 lower (3.79 to 2.89 lower)	Low
Exposure to antibiotics (in days) (follow-up 2 weeks to 30 days; Better indicated by lower values) [Schuetz 2012]											
12	randomised trials	serious[1]	no serious[2]	serious[2]	no serious	none	6 (4 to 10)	10 (8 to 14)	-	3.98 lower (4.44 to 3.52 lower)	Low

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCT	Standard care	Relative (95% CI)	Absolute	Quality
Quality-of-life											
0	no evidence available	-	-	-	-	none	-	-	-	-	-
Complications											
0	no evidence available	-	-	-	-	none	-	-	-	-	-

[1] Sensitivity analysis on the subgroup of patients with CAP. Unclear from which trials CAP population is derived. Risk of bias was extrapolated from all studies in the IPD meta-analysis; more that 50% of the included studies were at high risk of bias due to allocation concealment and detection bias. No information regarding performance bias.
[2] Could not be assessed because the IPD meta-analysis gave a summary estimate of effect with no assessment of inconsistency (forest plots were not provided)
[3] PCT was used for guiding initiation of antibiotic therapy, not just for monitoring
[4] 95% CI crosses 1 default MID

Table 127: Clinical evidence profile: *Post-hoc* analysis of a RCT [Christ-Crain 2006] comparing PCT to guide antibiotic administration plus monitoring decisions compared with standard care for the subgroup of patients with community-acquired pneumonia who received antibiotic therapy

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCT	Usual care	Relative (95% CI)	Absolute	Quality
Mortality [Christ-Crain 2006 unpublished data]											
1	randomised trials	very serious[1]	no serious	no serious	very serious[2]	none	18/126 (14.3%)	20/149 (13.4%)	RR 1.06 (0.59 to 1.92)	8 more per 1000 (from 55 fewer to 123 more)	Very low
Length of hospital stay (Better indicated by lower values) [Christ-Crain 2006 unpublished data]											
1	randomised trials	very serious[1]	no serious	no serious	no serious	none	12.54 (9.46)	13.06 (8.94)	-	MD 0.52 lower (2.71 lower to 1.67 higher)	Low
Duration of antibiotics (Better indicated by lower values) [Christ-Crain 2006 unpublished data]											
1	randomised trials	very serious[1]	no serious	no serious	no serious	none	6.86 (5.09)	13.11 (6.4)	-	MD 6.25 lower (7.61 to 4.89 lower)	Low
ITU admission [Christ-Crain 2006 unpublished data]											
1	randomised trials	very serious[1]	no serious	no serious	very serious[2]	none	20/126 (15.9%)	21/149 (14.1%)	RR 1.13 (0.64 to 1.98)	18 more per 1000 (from 51 fewer to 138 more)	Very low
Treatment failure [Christ-Crain 2006 unpublished data]											
1	randomised trials	very serious[1]	no serious	no serious	very serious[2]	none	23/126 (18.3%)	27/149 (18.1%)	RR 1.01 (0.61 to 1.67)	2 more per 1000 (from 71 fewer to 121 more)	Very low

[1] *Post hoc subgroup analysis on group of patients who received antibiotic therapy. High risk of bias study (unblinded study, inadequate sequence generation (unnumbered envelopes) and unclear allocation concealment)*

[2] *95% CI crosses both default MIDs*

Table 128: Clinical evidence profile: Observational studies investigating the role of CRP to guide monitoring decisions for community-acquired pneumonia

Outcome	Study design	Quality Assessment					Results				Quality
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Study ID	N*	Cut-off points	Adjusted OR (95% CI)	
Mortality											
Overall 28- or 30-day mortality	2 cohorts: 1 retrospective and 1 prospective	Very Serious[1]	None	None	Very serious[3]	None	Bruns 2008	210	Day 0 to 7 decline < 90%	1.23 (0.45 to 2.99)	Very low
								264	Day 0 to 3 decline < 60%	1.09 (0.32 to 3.73)	
		Very serious[2]	None	None	None	None	Chalmers 2008A	268	Day 0 to 4 decline < 50%	24.5 (6.4 to 93.4)	Low
ITU mortality	1 prospective cohort	Very Serious[4]	None	Serious[5]	None	None	Coelho 2012	175	Day 5 CRP ratio > 0.5	4.47 (1.64 to 12.20)	Very low
Inappropriate use of antibiotic therapy or treatment failure											
Inappropriate use of antibiotic therapy	1 retrospective cohort	Very serious[6]	None	None	Serious[7]	None	Bruns 2008	137	Day 0 to 7 decline < 90%	3.74 (1.12 to 13.77)	Low
					None				Day 0 to 3 decline < 60%	6.98 (1.56 to 31.33)	
Treatment failure	1 prospective cohort	Very serious[4]	None	None	None	None	Menendez 2008	453	Day 3 CRP above 75th percentile	3.4 (1.7 to 6.7)	Low
Early treatment failure (within 3 days)	1 retrospective cohort	very serious[6]	None	None	Serious[7]	None	Bruns 2008	264	Day 0 to 3 decline < 60	1.57 (0.85 to 2.92)	Very low
Late treatment failure (after 72 hours)	1 prospective cohort	Very serious[4]	None	None	None	None	Menendez 2008	453	Day 3 CRP above 75th percentile	4.8 (2.1 to 11.2)	Low
Late treatment failure (within	1 retrospective cohort	Very serious[6]	None	None	Very serious[3]	None	Bruns 2008	210	Day 0 to 7 decline < 90%	0.87 (0.39 to 1.94)	Very low

Outcome	Study design	Quality Assessment					Results				Quality
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Study ID	N*	Cut-off points	Adjusted OR (95% CI)	
28 days)									Day 0 to 3 decline < 60%	1.29 (0.62 to 2.68)	
Complications											
Severe complications after 72 hours	1 prospective cohort	Very serious[8]	None	None	None	None	Menendez 2009B	394	Protective factor: Day 3 CRP < 3 mg/dl	0.86 (0.77 to 0.97)	Low
Need for invasive ventilation or ionotropic support	1 prospective cohort	Very serious[2]	None	None	None	None	Chalmers 2008A	268	Day 0 to 4 CRP decline < 50%	7.1 (2.8 to 17.8)	Low
Complicated pneumonia	1 prospective cohort	Very Serious[4]	None	None	None	None	Chalmers 2008A	268	Day 0 to 4 CRP decline < 50%	15.4 (6.32 to 37.6)	Low

[1] *Retrospective analysis. Multivariate model did not adjust for all key confounders (including prior antibiotic therapy and glucocorticosteroid use)*
[2] *Multivariate model did not adjust for all key confounders (including prior antibiotic therapy and glucocorticosteroid use); had significant missing data*
[3] *95% CI crosses both default MIDs*
[4] *Reporting bias (non-significant results not reported and thresholds chosen based on study findings); did not adjust for all key confounders*
[5] *ITU setting*
[6] *Retrospective analysis. Multivariate analysis did not adjust for all key confounders and significant missing data at 7-day follow-up*
[7] *95% CI crosses 1 default MID*
[8] *Prognostic factor cut-off chosen based on study results and did not adjust for all key confounders*

**Available for analysis*

Table 129: Clinical evidence profile: Observational studies investigating the role of PCT to guide monitoring decisions for community-acquired pneumonia

Outcome	Study design	Results					Study ID	N*	Cut-off points	Adjusted OR (95% CI)	Quality
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other					
ITU mortality	1 prospective cohort	Very serious[1]	None	Serious[2]	None	None	Bousseke y 2006	100	PCT increase day 1 to day 3	4.54 (1.31 to 15.75)	Very low
Treatment failure (overall or late treatment failure (after 72 hours))	1 prospective cohort	Very serious[3]	None	None	None	None	Menende z 2008	453	Day 3 PCT above 75th percentile	Not reported – non-significant	Low
Severe complications after 72 hours	1 prospective cohort	Very serious[4]	None	None	Serious[5]	None	Menende z 2009B	394	Protective factor: Day 3 PCT < 0.25 ng/ml	1.17 (0.78 to 1.76)	Very low

[1] *Reporting bias (non-significant results not reported and thresholds chosen based on study findings); did not adjust for all key confounders*
[2] *ITU setting*
[3] *Reporting bias (non-significant results not reported and thresholds chosen based on study findings); did not adjust for all key confounders*
[4] *Prognostic factor cut-off chosen based on study results and did not adjust for all key confounders*
[5] *95% CI crosses 1 default MID*

**Available for analysis*

Table 130: Clinical evidence profile of observational studies investigating the role of clinical stability to guide monitoring decisions

Outcome	Study design	Quality Assessment						Results				Quality
		Total N	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	Study ID	n*	Cut-off points	Adjusted OR (95% CI)	
Complications												
Severe complications after 72 hours	1 prospective cohort	394	Serious[1]	None	None	Serious[2]	None	Menendez 2009B	394	Protective factor: Meeting all criteria for clinical stability[3]	0.78 (0.71 to 0.86)	Low

[1] *Did not adjust for all key confounders*
[2] *95% CI crosses 1 default MID*
[3] *Based on achieving the following threshold values for all parameters: temperature ≤ 37.2 °C, heart rate ≤ 100 beats/min, respiratory rate ≤ 24 breaths/min, systolic blood pressure ≥ 90 mm Hg and oxygen saturation ≥ 90% or arterial oxygen tension ≥ 60 mm Hg when the patient was not receiving supplemental oxygen.*

**Available for analysis*

13.3 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow diagram in Appendix E:.

Unit costs

No economic evaluations were identified. Relevant unit costs are provided below to aid consideration of cost effectiveness.

Table 131: Cost of diagnostic tests

Test	Cost	Source
Point of care PCT	£25 to £35	GDG estimate
Point of care CRP	£12 to £15	GDG estimate

13.4 Evidence statements

Clinical

- Low to very low quality individual patient data sensitivity analysis of 12 randomised trials on 2000 patients with CAP showed that an overall strategy of using PCT to guide antibiotic administration had a beneficial effect on significantly reducing duration and total exposure to antibiotics. No difference was found between the groups of patients who received the PCT strategy and usual care group for the outcomes of mortality and treatment failure.
- Low to very low quality analysis of unpublished randomised data from a subgroup of almost 300 patients with CAP in whom antibiotic administration was based on PCT measurement showed a clinically significant benefit on reducing the duration of antibiotic therapy compared with those in the usual care group. No difference was found for the other outcomes (mortality, duration of antibiotic therapy, length of hospital stay, treatment failure, or ITU admission) between the 2 groups.
- Findings from 5 observational studies for the association between change in CRP or PCT and the risk of other adverse outcomes (such as mortality and treatment failure) were inconsistent, but some studies indicated an association between slow reduction in CRP or PCT and adverse outcomes.

Economic

- No relevant economic evaluations were identified.

13.5 Recommendations and link to evidence

Table 132: Linking evidence to recommendations – biological marker monitoring

Recommendations	**20. Consider measuring a baseline C-reactive protein concentration in patients with community-acquired pneumonia on admission to hospital, and repeat the test if clinical progress is uncertain after 48 to 72 hours.**
Relative values of different outcomes	The GDG considered mortality, clinical cure, duration of antibiotic therapy and complications to be the most important outcomes for this question, though noted that duration of antibiotic therapy and length of stay were likely to be the most directly relevant outcomes.
Trade-off between clinical benefits and harms	One systematic review of 14 RCTs examined the use of PCT in addition to usual care in a wide variety of LRTIs, both as an measurement to guide antibiotic initiation, and a repeat measurement to help guide on-going management. A variety of thresholds of PCT for stopping antibiotic therapy were used, and physicians were allowed to deviate from the recommended prescribing protocol. In patients with CAP use of PCT was associated with a reduced total duration of antibiotic treatment (average 3.34 days). However, the GDG noted that it was unclear whether this was primarily due to monitoring of PCT or the initial measurement. In addition, the median duration of antibiotic therapy used in the usual care group was longer than that recommended in the present guideline. The PCT group had fewer cases of treatment failure and a trend towards reduced mortality, though there was a large amount of imprecision around this result. In order to clarify whether the reduction in antibiotic exposure seen in the systematic review was primarily due to a reduction in initiation of antibiotic therapy, unpublished anonymised individual patient data were obtained from one of the included studies for the subgroup of patients with confirmed CAP who received antibiotic therapy, to see whether PCT monitoring (as opposed to initial measurement) conferred any benefit. A reduction in duration of antibiotic therapy of over 6 days was seen with PCT monitoring compared with usual care. However, the length of antibiotic duration in the control group was 13 days, which is considerably longer than that in usual UK practice. No difference was seen in other outcomes between the 2 groups. One observational study examined the addition of PCT monitoring to usual care in patients with CAP treated in ITU. There was a higher risk of mortality in patients whose PCT level increased between day 1 and day 3. However, in a separate study outside the ITU concentrations of PCT did not predict treatment failure and there was no association between a low PCT and complication rates. Four observational studies examined the addition of CRP monitoring to usual care in patients with CAP treated in hospital (including 1 study in ITU). A reduction in CRP concentration over time was associated with reduced mortality, though there was imprecision around the results. One study reported a very large effect size for reduction in mortality contrasting with the majority of other evidence. A reduction in CRP was associated with reduced ITU mortality and a lower rate of treatment failure in the majority of studies, though there was imprecision around these results. Failure of CRP to fall was associated with a higher rate of complications and need for invasive ventilation. A CRP concentration of more than 100 mg/l at discharge was associated with a higher re-admission rate, though this was reported as an unadjusted relative risk ratio which may be open to considerable bias.
Trade-off between net health benefits and resource use	No suitable economic studies were identified. The potential cost savings due to monitoring should be considered against the additional cost. PCT and CRP tests are unlikely to prove cost effective unless they reduce antibiotic prescribing, reduce

	length of hospital stay, improve early recognition of potential complications, reduce relapse, or reduce re-admission to hospital. The GDG noted that PCT testing is more expensive than CRP testing. In addition, PCT testing is not widely available in the UK, and therefore introduction of PCT testing would be associated with additional implementation costs. The GDG acknowledged that if CRP testing conferred benefit to the individual (such as reduced antibiotic exposure or better identification of complications of CAP) or population (such as reduced antimicrobial resistance due to reduced overall antibiotic use) then it would be likely to be cost effective.
Quality of evidence	The systematic review examining addition of PCT testing to usual care was well-conducted, but included studies of moderate to low quality by GRADE criteria. The review included patients with various types of respiratory tract infection, including patients with CAP for whom individual patient data were utilised. The studies were conducted in a variety of settings (primary care, emergency departments and hospital inpatients) which limits their applicability. The GDG noted that the studies were powered to detect a difference in use of antibiotics but were likely to be underpowered to detect differences in other outcomes such as mortality. The additional unpublished data (Christ-Crain 2006) was of low to very low quality by GRADE criteria as we used these data for a *post hoc* subgroup analysis. The observational study examining addition of PCT monitoring to usual care contained evidence of low to very low quality by GRADE criteria. The observational studies examining addition of CRP monitoring to usual care contained evidence of moderate to very low quality by GRADE criteria, with the majority being of low to very low quality. The GDG noted that the observational studies did not include an intervention and therefore could not examine the impact of PCT or CRP monitoring. The studies used various percentage changes or absolute cut-off values for PCT and CRP at various time points. Only 1 study included a comparison of PCT with CRP. There was also wide variation in the populations included in the studies. This inconsistency resulted in the GDG being reluctant to recommend specific cut-offs on which management decisions should be based.
Other considerations	The GDG noted that there was limited evidence of benefit for monitoring PCT or CRP in hospitalised patients with CAP. There did not appear to be any major advantage for either of the tests. However, PCT is less widely available in the UK than CRP and has a much higher cost. It was also noted that CRP is recommended in this guidance (see section 7.5) as the initial test and it would be practical to repeat the same test to monitor clinical progress. The GDG therefore did not feel able to make a recommendation for PCT for monitoring purposes. The GDG discussed the potential benefits of CRP monitoring. The GDG agreed that the majority of the evidence indicated that persistent elevation of CRP was associated with adverse outcomes. Therefore, failure of CRP to improve may identify patients whose management should be reassessed. This is likely to be most useful in patients whose clinical progress is equivocal, as those who are clearly deteriorating are likely to need their management reconsidered regardless of change in CRP. Similarly, rechecking CRP in patients with clear evidence of clinical improvement may not alter management, although it could potentially increase the clinician's confidence in using a shorter course of antibiotic therapy and discharging the patient. However, an improving CRP in patients whose clinical progress is equivocal may reassure clinicians that escalating antibiotic therapy is unnecessary, which may benefit the patient and the wider population in terms of antimicrobial stewardship. It was concluded that capturing these broader benefits in clinical studies was difficult, and the GDG therefore agreed a recommendation to consider monitoring CRP in patients with CAP in hospital.

	The data did not clearly support an optimal frequency or timing for CRP monitoring. The GDG wished to emphasise from their clinical experience that daily monitoring of CRP is likely to be less helpful than establishing a baseline value on admission and then repeating this measurement to confirm progress (if necessary) when the clinician considers that the patient should be improving. The GDG agreed that the evidence base for CRP to guide duration of antibiotic therapy could be strengthened and therefore prioritised a research recommendation in this area.

13.6 Research recommendation

3. **In patients hospitalised with moderate- to high-severity community-acquired pneumonia, does using C-reactive protein monitoring in addition to clinical observation to guide antibiotic duration safely reduce the total duration of antibiotic therapy compared with a fixed empirical antibiotic course?**

Why this is important

The recommended duration of antibiotic therapy for adults hospitalised with moderate- to high-severity community-acquired pneumonia is based on evidence of very low quality; no relevant clinical trials were identified by NICE. The burden of community-acquired pneumonia is large, and its treatment accounts for a high proportion of antibiotic use in hospitals. Overuse of antibiotics is associated with antimicrobial resistance, which is a national and global priority.

14 Safe discharge

14.1 Introduction

Inpatient stay remains appropriate for patients with pneumonia only as long as hospital care is delivering management that cannot safely be delivered at home. When making the decision to discharge a patient from hospital, often inadequately quantified benefits and harms of hospital stay must be considered. The benefits of on-site clinical expertise, observation and timely intervention must be balanced with the risks of nosocomial infection and premature discharge (for example, relapse or re-admission) as well as the patient's quality-of-life and social circumstances.

The aim of this review is to assess to what degree specifically defined objective measures can assist clinicians in determining when it is safe to discharge a patient who has had pneumonia from hospital.

14.2 Review question: What is the prognostic value, clinical and cost effectiveness of various factors for assessing whether it is safe to discharge adults with community-acquired pneumonia or hospital-acquired pneumonia requiring management in hospital?

For full details see review protocol in Appendix C:.

No data were found for hospital-acquired pneumonia.

14.3 Clinical evidence

We searched for systematic reviews, RCTs (test-and-treat studies) and prognostic cohort studies investigating the prognostic value of various factors measured before hospital discharge to assess whether it is safe to discharge adults with pneumonia managed in hospital. We identified only prognostic cohort studies for CAP. No relevant studies were found for the HAP population.

Six cohort studies were included in the review[3,5,40,41,58,90]; these are summarised in Table 133 below. Evidence from these studies is summarised in the clinical evidence profiles below (Table 134, Table 135 and Table 136). See also the study selection flow chart in Appendix D:, study evidence tables in Appendix G:, forest plots in Appendix I:, and excluded studies list in Appendix J:.

Four of the studies were prospective in design[40,41,58,90], one[5] was retrospective and one[3]was a secondary analysis of a prospective study of consecutive unselected patients.

The evidence base for this review question was heterogeneous. It included:

- One derivation study[90] of clinical instability measures based on temperature, heart rate, blood pressure, respiratory rate, oxygenation, mental status, and ability to maintain oral intake during the 24 hours prior hospital discharge. These clinical variables were used to assess the relationship between clinical instability at discharge and 30-day patient outcomes.
- Prognostic studies which evaluated the impact of all or some of Halm's clinical instability measures on patient outcomes.[40,41,58] The 2 studies by Capelastegui et al.[40,41] followed up part of the same cohort of patients, which included patients with normal mental status and able to ingest food and oral medication. They assessed the prognostic ability of the same instability factors derived in the Halm study but the temperature threshold differed (37.2 C and 37.5 C, respectively, instead of the 37.8 C cut-off in the Halm study).

- One cohort study[5] did not directly answer the review question as it compared the predictive ability of 2 sets of criteria of clinical stability and did not compare the outcomes of patients who were clinically stable at discharge with those presenting one or more instabilities.
- One study[3] compared the discriminatory ability of Halm's criteria with severity assessment tools (CURB and ATS 2001 criteria) during the first 7 days of hospitalisation.

Table 133: Summary of studies included in the review

Study	Prognostic factors	Population/Severity	Outcomes (after discharge)	Comments
Halm 2002 [90] Derivation study of clinical stability criteria	Number of clinical instabilities (unstable factors) 24 hours prior to hospital discharge: • Temperature > 37.8 C • Respiratory rate > 24/min • Heart rate > 100/min • Systolic blood pressure ≤ 90 mmHg • Oxygen saturation < 90% • Altered mental status • Inability to maintain oral intake.	• Patients with CAP (N = 680) • PSI ≥ IV: 194 (28.5%).	• 30-day mortality • 30-day hospital re-admission • failure to return to usual activities 30 days	• Patients were part of the PORT cohort study, but they were younger and had lower predicted 30-day mortality than the overall PORT cohort.
Aliberti 2013[5] Retrospective study	Criteria for clinical stability ATS 2001: • Improved symptoms of pneumonia (cough and shortness of breath) • Lack of fever for at least 8 hours • Improving leucocytosis (decrease at least 10% from the previous day) ATS/IDSA 2007: • Temperature ≤ 37.8 C • Heart rate ≤ 100 beats/min • Respiratory rate ≤ 24 breaths/min • Systolic blood pressure ≥ 90 mmHg • Arterial oxygen saturation ≥ 90% if a partial pressure of oxygen ≥ 60 mmHg on room air • Normal mental status.	• Patients with CAP (N = 487) • CURB65 ≥ 3: 49 (10.1%) • PSI ≥ IV: 282 (57.9%).	• 30-day mortality • 30-day hospital re-admission	• All the participants were male (97.9%). • 17% were immunocompromised. • Patients had a high burden of comorbidity.
Capelastegui 2008[41] Prospective study	Criteria for clinical instability in the 24 hours prior to hospital discharge: • Temperature > 37.5 C • Respiratory rate > 24 breaths/min • Heart rate > 100 beats/min • Systolic blood pressure < 90 mmHg and/or diastolic BP < 60 mmHg • Oxygen saturation < 90%.	• Patients with CAP (N = 870) • PSI ≥ IV: 447 (51.4%) • CURB65 ≥ 3: 195 (22.4%).	• 30-day mortality • 30-day hospital re-admission	• The same data set was used to derive the prediction model and test it, therefore performance of the model may be overestimated. • Mental condition was not included as a stability criterion.
Capelastegui	Criteria for clinical instability in the	• Patients	• 30-day	• Some patients

Study	Prognostic factors	Population/Severity	Outcomes (after discharge)	Comments
2009[40] Prospective study	24 hours prior to hospital discharge: • Temperature > 37.2 C • Respiratory rate > 24 breaths/min • Heart rate > 100 beats/min • Systolic blood pressure < 90 mmHg • Oxygen saturation < 90% or PO_2 < 60 mmHg • Patient receiving mechanical ventilation or supplemental oxygen by face mask or nasal prongs.	with CAP (N = 1117) • PSI ≥ IV: 543 (48.6%).	hospital re-admission	from the same cohort as Capelastegui 2008.
Dagan 2006[58] Prospective study	Number of clinical instabilities (unstable factors) 24 hours prior to hospital discharge: • Temperature > 37.8 C • Respiratory rate > 24/min • Heart rate > 100/min • Systolic blood pressure ≤ 90 mmHg • Oxygen saturation < 90% • Altered mental status • Inability to maintain oral intake.	• Patients with CAP (N = 373) • PSI ≥ IV: 206 (55.2%).	• 30-day mortality • 30-day hospital re-admission	• Functional status of the population was not assessed, which could influence the outcome of CAP.
Akram 2013[3] Secondary analysis of the Edinburgh pneumonia study database	Criteria for clinical stability across the first 7 days of hospitalisation: Halm's stability criteria • Temperature ≤ 37.8 C • Respiratory rate ≤ 24/min • Heart rate ≤ 100/min • Systolic blood pressure ≥ 90 mmHg • Oxygen saturation ≥ 90% • Normal mental status • Normal oral intake. ATS 2001 stability criteria • Improvement in cough and shortness of breath • Afebrile status < 37.8 C for ≥ 8 hours • Normalising leukocyte count by 10% from previous day • Adequate oral intake. CURB severity assessment tool: • Confusion • Urea > 7 mM/L • Respiratory rate ≥ 30 breaths/min • Blood pressure: Diastolic blood pressure ≤ 60 mmHg or systolic blood pressure < 90.	• Patients with CAP (N = 1079) • CURB65 ≥ 3: 32.5%.	• 30-day mortality • complicated pneumonia (development of a complicated parapneumonic effusion, empyema or pulmonary abscess)	• Secondary analysis of the Edinburgh pneumonia study database of consecutive unselected patients admitted to NHS Lothian hospitals.

The majority of included cohort studies provided results from multivariate analyses presenting the risk of patient outcomes for individual or for number of instability factors (Table 136). Two studies provided information on the frequency of outcomes per set or number of stability criteria and results are presented in GRADE tables (Table 134 and Table 135). Another study reported only discriminatory analysis of different sets of stability criteria and these results are reported separately (Table 137).

Table 134: Clinical evidence profile: ATS 2001 compared with ATS/IDSA 2007 criteria for assessing clinical stability of patients with community-acquired pneumonia

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	ATS 2001 criteria	ATD/IDSA 2007 criteria	Relative (95% CI)	Absolute	Quality
30-day hospital re-admission [Aliberti 2013]											
1	observational study	serious[1]	no serious	no serious	very serious[2]	none	62/429 (14.5%)	59/410 (14.4%)	RR 1 (0.72 to 1.4)	0 fewer per 1000 (from 40 fewer to 58 more)	Very low
30-day mortality [Aliberti 2013]											
1	observational study	serious[1]	no serious	no serious	very serious[2]	none	14/429 (3.3%)	14/410 (3.4%)	RR 0.96 (0.46 to 1.98)	1 fewer per 1000 (from 18 fewer to 33 more)	Very low

[1] *Retrospective study design*
[2] *Confidence interval crosses both default MIDs*

Table 135: Clinical evidence profile: ≥ 1 clinical instabilities (Halm's criteria) compared with no instabilities as assessed 24 hours prior to hospital discharge of patients with community-acquired pneumonia

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	≥ 1 instability	No instabilities	Relative (95% CI)	Absolute	Quality
30-day hospital re-admission [Dagan 2006]											
1	observational study	no serious	no serious	no serious	serious[1]	none	9/82 (11%)	19/291 (6.5%)	RR 1.68 (0.79 to 3.57)	44 more per 1000 (from 14 fewer to 168 more)	Low
30-day mortality [Dagan 2006]											
1	observational study	no serious	no serious	no serious	no serious	none	7/82 (8.5%)	4/291 (1.4%)	RR 6.21 (1.86 to 20.7)	72 more per 1000 (from 12 more to 271 more)	Moderate

[1] *Confidence interval crosses 1 default MID*

Table 136: Results of multivariate analyses: predictive ability of number of and individual instability criteria for outcomes in patients with community-acquired pneumonia after hospital discharge

Prognostic factors	Adjusted OR/HRs	Included studies	Quality of included studies	Notes
30-day mortality				
Any instability (≥ 1)	AOR: 2.1 (0.8 to 5.4)	1 Halm 2002	Low risk of bias	Clinical instability factors • Temperature > 37.8 C • Respiratory rate > 24/min • Heart rate > 100/min • Systolic blood pressure ≤ 90 mmHg • Oxygen saturation < 90% • Altered mental status • Inability to maintain oral intake Multivariate analysis was adjusted for PSI index (age, sex, nursing home residence, comorbidities, initial laboratory values, and vital signs) and do-not-resuscitate status
1 instability	AOR: 1.1 (0.3 to 3.5)			
≥ 2 instabilities	AOR: 14.1 (3.1 to 69.0)			
Temperature > 37.5 C	AHR: 4.5 (1 to 19.2)	1 Capelastegui 2008	Low risk of bias	HRs adjusted for all the individual instability criteria Criteria for clinical instability in the 24 hours prior to hospital discharge: • Temperature > 37.5 C • Respiratory rate > 24 breaths/min • Heart rate > 100 beats/min • Systolic blood pressure < 90 mmHg and/or diastolic BP < 60 mmHg • Oxygen saturation < 90% Multivariate analysis in model 1 was adjusted for PSI and COPD. Multivariate analysis in model 2 was adjusted for CURB65, Katz index, Charlson comorbidity index,
SBP < 90 mmHg and/or DBP < 60 mmHg	AHR: 2.6 (1.2 to 5.8)			
Respiratory rate > 24 breaths/min	AHR: 2.4 (1.1 to 5.2)			
Oxygen saturation < 90%	AHR: 2.4 (1.1 to5.2)			
Heart rate > 100 beats/min	AHR: 0.9 (0.2 to3.6)			
Instability score ≥ 2* (model 1)	AHR: 4.2 (2.0 to9.0)			
Number of instability factors ≥ 1 (model 1)	AHR: 2.3 (1.0 to4.9)			
Instability score ≥ 2* (model 2)	AHR: 5.8 (2.5 to 13.1)			
Number of instability factors ≥ 1 (model 2)	AHR: 2.4 (1.0 to 5.9)			

Prognostic factors	Adjusted OR/HRs	Included studies	Quality of included studies	Notes
				and length of stay. Patients with a score ≥ 2 were considered unstable.
30-day hospital re-admission				
Any instability (≥ 1)	AOR: 1.5 (0.8 to 2.7)	1 Halm 2002	Low risk of bias	Clinical instability factors • Temperature > 37.8 C • Respiratory rate > 24/min • Heart rate > 100/min • Systolic blood pressure ≤ 90 mmHg • Oxygen saturation < 90% • Altered mental status • Inability to maintain oral intake OR adjusted for PSI index, age, sex, nursing home residence, comorbidities, initial laboratory values, and vital signs
1 instability	AOR: 1.3 (0.7 to 2.5)			
≥ 2 instabilities	AOR: 3.5 (1.0 to 12.4)			
Temperature > 37.5 C	AHR: 0.9 (0.1 to 6.2)	1 Capelastegui 2008	Low risk of bias	HRs adjusted for all the individual instability criteria
SBP < 90 mmHg and/or DBP < 60 mmHg	AHR: 0.7 (0.3 to 1.4)			
Respiratory rate > 24 breaths/min	AHR: 1.4 (0.8 to 2.4)			
Oxygen saturation < 90%	AHR: 1.8 (1.1 to 3.2)			
Heart rate > 100 beats/min	AHR: 0.3 (0.1 to 1.4)			
Instability factors ≥ 1	AHR: 2.8 (1.3 to 6.2)	1 Capelastegui 2009	Low risk of bias	The study did not provide information on the confounders in the multivariate model.
30-day failure to return to usual activities				
Any instability (≥ 1)	AOR: 1.5 (1.0–2.4)	1 Halm 2002	Low risk of bias	Clinical instability factors: • Temperature > 37.8 C • Respiratory rate > 24/min • Heart rate > 100/min • Systolic blood pressure ≤ 90 mmHg

Prognostic factors	Adjusted OR/HRs	Included studies	Quality of included studies	Notes
				• Oxygen saturation < 90% • Altered mental status • Inability to maintain oral intake Multivariate analysis was adjusted for PSI index, age, sex, nursing home residence, comorbidities, initial laboratory values, and vital signs. Data on return to usual activities 30 days after discharge were available in 641 out of the 680 patients.

**Score of instability at discharge: variables were grouped into major (temperature > 37.5°C, 2 points) and minor (systolic BP < 90 mm Hg and/or diastolic BP < 60 mm Hg, respiratory rate > 24 breaths/min, and oxygen saturation < 90%, 1 point respectively). The points assigned to each variable were totalled and a score was determined for each patient. Patients with a score ≥ 2 are considered unstable*

Table 137: Results of a discriminatory analysis of stability criteria and severity assessment tools for predicting 30-day mortality and complicated pneumonia

	AUC (95% CI)				
Prognostic factors	**30-day mortality**	**Complicated pneumonia[1]**	**Included studies**	**Quality of included studies**	**Notes**
Halm's criteria of clinical stability	0.95 (0.94 to 0.96)	0.92 (0.91 to 0.93)	1 Akram 2013	High risk of bias as a secondary analysis of a prospective study	Measurements on criteria/severity assessment tools were taken over each 24-hour period and the most abnormal result was taken during the first 7 days of hospitalisation.
ATS 2001 stability criteria	0.94 (0.93 to 0.95)	0.87 (0.86 to 0.88)			
CURB	0.82 (0.81 to 0.84)	0.74 (0.72 to 0.75)			

[1] *Defined as development of a complication: parapneumonic effusion, empyema or pulmonary abscesses*

14.4 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix E:.

Unit costs

On the one hand, discharging people with CAP prematurely could lead to further GP and/or Accident & Emergency attendances; on the other hand unnecessarily prolonging the hospital stay of patients with CAP could lead to increased cost. Unit costs relevant to both circumstances (cost of Accident & Emergency attendances and cost of extra bed days) are provided below to aid consideration of cost effectiveness.

- The average cost of a GP consultation is £43 for 11.7 minute consultation in a surgery (PSSRU 2012).[56,57]
- The costs of Accident & Emergency attendances are reported in Table 138.
- The costs of excess bed days are reported in Table 139.

Table 138: Accident & Emergency costs

Currency code	Currency description	FCEs (million)	National average unit cost	Lower quartile unit cost	Upper quartile unit cost
Accident & Emergency - Leading to admission					
VB08Z	Emergency Medicine, Category 2 Investigation with Category 1 Treatment[a]	1.45	£155	£130	£175
Accident & Emergency - Not leading to admission					
VB08Z	Emergency Medicine, Category 2 Investigation with Category 1 Treatment[a]	2.76	£131	£113	£146

(a) A category 2 investigation with category 1 treatment is equivalent to the cost of a plain film x-ray or a blood culture, followed by reviewing results or prescribing medicines
Source: NHS Reference Costs 2011-2012[61]

Table 139: Excess bed days

Currency code	Currency description	FCEs (million)	National average unit cost	Lower quartile unit cost	Upper quartile unit cost
Elective Inpatient Excess Bed Days					
DZ11A	Lobar, Atypical or Viral Pneumonia, with Major CC	2,609	£259	£187	£291
DZ11B	Lobar, Atypical or Viral Pneumonia, with Intermediate CC	1,468	£324	£262	£311
DZ11C	Lobar, Atypical or Viral Pneumonia, without CC	292	£341	£289	£289
Non-elective long stay excess bed days					
DZ11A	Lobar, Atypical or Viral Pneumonia, with Major CC	192,208	£228	£180	£254
DZ11B	Lobar, Atypical or Viral Pneumonia, with Intermediate CC	47,545	£227	£185	£259
DZ11C	Lobar, Atypical or Viral Pneumonia, without CC	2,865	£242	£185	£298
Pooled Average			**£229**	**£182**	**£256**

Source: NHS Reference Costs 2011-2012[61]

14.5 Evidence statements

14.5.1 Clinical

- Very low quality evidence from 1 retrospective study of over 800 patients with CAP showed no difference in the outcomes of hospital re-admission and 30-day mortality for those achieving clinical stability according to the ATS 2001 and the ATS/IDSA 2007 criteria.
- Results from the low risk of bias derivation study of Halm's clinical instability criteria (temperature, respiratory rate, heart rate, systolic blood pressure, oxygen saturation, altered mental status and ability to maintain oral intake) showed that patients with CAP who were discharged with 2 or more instabilities had a significantly higher risk of 30-day mortality and hospital re-admission than patients who had no instabilities at discharge when other factors were also accounted for (demographic and comorbidities). However, no significant difference was found between the 2 groups for the outcome of failure to return to usual activities.
- Another prospective study (at low risk of bias) of almost 900 patients with CAP found that those who were considered unstable at hospital discharge by any (except heart rate) of the individual Halm clinical instability criteria were more likely to experience a higher risk of 30-day mortality but not hospital re-admission after discharge. Of the individual clinical criteria, temperature higher than 37.5 C was associated with the highest mortality risk 30 days after discharge.
- Evidence from a secondary analysis of a large pneumonia database (over 1000 CAP patients, but at high risk of bias) showed that Halm's clinical stability criteria may be better able to predict 30-day mortality and complicated pneumonia for patients with CAP than severity assessment tools (namely CURB, ATS 2001).

14.5.2 Economic

- No relevant economic evaluations were identified.

14.6 Recommendations and link to evidence

Table 140: Linking evidence to recommendations – safe discharge

Recommendations	**21. Do not routinely discharge patients with community-acquired pneumonia if in the past 24 hours they have had 2 or more of the following findings:** • **temperature higher than 37.5°C** • **respiratory rate 24 breaths per minute or more** • **heart rate over 100 beats per minute** • **systolic blood pressure 90 mmHg or less** • **oxygen saturation under 90% on room air** • **abnormal mental status** • **inability to eat without assistance.** **22. Consider delaying discharge for patients with community-acquired pneumonia if their temperature is higher than 37.5°C.**
Relative values of different outcomes	The GDG considered mortality and hospital re-admission up to 30 days after hospital discharge to be the most important outcomes for this question. They were also interested in symptoms and quality-of-life after discharge, and any data linking the incidence of later complications to discharge timing.
Trade-off between clinical benefits and harms	The included evidence evaluated the predictive ability of routinely measured physiological parameters of clinical instability to predict safe discharge in patients hospitalised with CAP. Four prospective observational studies (including the derivation study by Halm et al (2002) reported the ability of 7 physiological factors of clinical instability (temperature, respiratory rate, heart rate, systolic blood pressure, oxygen saturation, altered mental status and ability to maintain oral intake) to predict safe discharge. The evidence from these studies showed that patients who were discharged with 1 or more of the above instability factors were at significantly increased risk of 30-day mortality than patients considered stable at discharge. The risk of 30-day mortality was found to be much higher when 2 or more instability factors were present at discharge. The GDG members confirmed that their current clinical experience corroborated these results and agreed that these physiological parameters should be used to assess inpatient suitability for hospital discharge. The risk of 30-day hospital re-admission was also higher in patients with more instability factors; patients discharged with 2 or more instability parameters had a higher risk of re-admission, but the effect was smaller in those with one or more instabilities. The GDG commented that hospital re-admission risk in patients discharged with 1 or more instability parameters was lower than expected, but it was noted that comorbidities may be a key influence on re-admission rates. One retrospective study comparing the ATS/IDSA 2007 criteria (which were the same as the above clinical instability factors except the ability to maintain oral intake) with ATS 2001 criteria (improved symptoms of pneumonia, lack of fever for at least 8 hours, and improving leucocytosis – at least 10% decrease from the previous day) was also available. The GDG noted that the ATS 2001 criteria included soft variables which are difficult to measure accurately and routinely in clinical practice, and were therefore less suitable for assessing safe discharge. The members of the GDG could not adequately use the results of this study to inform their recommendation as it did

	not evaluate outcomes of patients who were stable at discharge compared with those considered clinically unstable. Adverse outcomes were more likely with raised temperature than other physiological parameters although some of the studies did not allow comparison between the variables. There was a variation in the selected temperature threshold for hospital discharge between the included studies. Two of the studies used a temperature threshold of 37.2 and 37.5 C, and the other two used a threshold of 37.8 C. The GDG agreed to use the 37.5C threshold, following a more conservative approach due to the potential harm of further adverse outcomes arising from high temperature (> 37.5 C). In addition, the only evidence on the independent prognostic ability of temperature used a threshold of 37.5 C and this was found to be strongly associated with 30-day mortality risk (Capelastegui 2008).
Trade-off between net health benefits and resource use	No suitable economic studies were identified. The GDG noted that no further costs will be incurred as a result of measuring these physiological parameters as these data are routinely collected. Discharging patients earlier than safe to do so, will reduce hospital costs initially but must be weighed against increased re-consultation rates to the GP and Accident & Emergency.
Quality of evidence	The majority of the included studies had a prospective observational design, which adequately addresses this review question. No relevant RCTs (test and treat) were found. The majority of the evidence from the prospective studies was at low risk of bias. These studies employed a multivariate type of analysis which adjusted for the effect of severity status and comorbidities. The retrospective Aliberti 2013 study which compared 2 sets of criteria for clinical stability (ATS 2001 and ATS/IDSA 2007) and the secondary analysis of a large pneumonia database (Akram 2013) were considered to be at high risk of bias.
Other considerations	The GDG noted that the clinical instability parameters recommended in this review are closely aligned to those in the widely used Early Warning Score (EWS), but acknowledged the lack of evidence regarding the use of EWS for safe discharge in patients with pneumonia specifically. It was highlighted that hospital doctors currently use EWS to assess appropriateness for discharge, but this tool has not been validated in patients with CAP. Across the studies, these 7 physiological parameters were measured within 24 hours of discharge. In routine UK hospital practice, measurements would be made within 8 hours, but it is very unlikely that this difference would affect the conclusion that these are useful measures for predicting safe discharge. It was therefore agreed that the recommendations should advocate the use of the 7 physiological parameters, and discourage discharge if 2 or more values are abnormal. The evidence that temperature is the most important variable was weaker, but after discussion the GDG agreed that in a patient with CAP it is the one that most specifically suggests that the infection has not fully resolved. A separate, more cautious, recommendation was therefore developed singling out temperature. The GDG agreed that there are other important factors determining when discharge can take place. In particular, the elderly were one group discussed in detail. The higher prevalence of frailty and comorbidities in elderly patients means that improvement in the condition leading to admission is often not the factor on which the timing of discharge is dependent. Deconditioning, loss of mobility and need for

	additional assistance with activities of daily living may all occur and require a more global assessment involving healthcare professionals such as physiotherapists and occupational therapists, as well as family members and carers. However, these issues are not particular to community-acquired pneumonia, are familiar to healthcare professionals looking after hospitalised patients, and an evidence search on these specific points had not been undertaken within the community-acquired pneumonia scope. As such, the GDG did not feel that addressing these more general issues in a recommendation was appropriate, although they noted that the evidence based purely on those admitted with community-acquired pneumonia included features which reflect frailty (in particular the inability to feed oneself). They felt that a list of criteria identifying those features specific to CAP which render a person not medically fit for discharge would be the best form for a recommendation to take. The GDG discussed whether a recommendation relating to safe discharge of patients with HAP could be made. Since by definition HAP occurs in patients who are in hospital for another reason, their suitability for discharge is more likely to be determined by factors other than those specific to pneumonia. Whilst the GDG felt that it may be reasonable to assume that the same factors apply in patients where HAP is the only issue preventing their discharge, there was no evidence to support this and the GDG agreed that a specific recommendation for hospital-acquired pneumonia could not be made.

15 Patient information

Components of good patient experience in general are set out in 'Patient experience in adult NHS services'. Questions relating specifically to patients with pneumonia including patient information on self-care and self-medication, condition-specific information, support and communication needs of patients (and carers and families as appropriate) fall within the scope of this guideline.

Within this remit, the GDG considered that many patients are unaware of what to expect when recovering from pneumonia. The group was keen to explore the evidence base underpinning the natural history of symptoms experienced during the recovery phase of the illness and the time people take to return to "feeling themselves again". It is hoped that knowledge of the likely symptoms and their probable duration will reduce unnecessary anxiety, while simultaneously promoting re-consultation to a healthcare professional when appropriate.

The aim of this review is to establish the most common symptoms and their standard duration in people recovering from pneumonia in order to communicate information that facilitates appropriate self-management.

15.1 Review question: What advice should be given to adults about what symptoms and duration of symptoms can be expected following treatment for community-acquired or hospital-acquired pneumonia, and when should patients be advised to consult or re-consult a GP?

For full details see review protocol in Appendix C:.

No data were found for hospital-acquired pneumonia.

15.2 Clinical evidence

We searched for systematic reviews and observational studies including qualitative studies assessing the symptoms, along with resolution of symptoms and re-consultation of patients with pneumonia after they received antibiotic therapy in order to provide relevant advice to patients. We considered that randomised clinical trials (RCTs) would be less applicable as they use highly selected populations. We considered for inclusion follow-up studies of RCTs only if they provided information for the whole sample and were not stratified by treatment arm.

One systematic review[77] and 9 observational studies[27,33,68,74,110,128,137,138,181] were included in the review; these are summarised in Table 141 below. The systematic review[77] was old and at very high risk of bias as the literature searches were not sufficiently rigorous and no individual quality assessment was incorporated on its findings. All observational studies except 3 (Bruns 2010[33], El Moussaoui 2006[68], Fernandez 2010[74]) were multicentre studies. Only 1 of the included observational studies employed a retrospective study design (Sicras-Mainar 2012[181]).

We stratified results according to severity when possible. All studies except Brandenburg 2000[27] included patients with low- to moderate-severity CAP with the majority reported to be outpatients.

No studies were found to answer the second part of the review question - when patients should be advised to consult or re-consult a GP. No relevant studies were found for patients with HAP.

See also the study selection flow chart in Appendix D:, study evidence tables in Appendix G:, and excluded studies list in Appendix J:.

Evidence from these studies is summarised in a narrative way below. The presentation of this review is divided by outcomes.

Table 141: Summary of studies included in the review

Study	Type of study/Number of patients	• Population	Outcomes	Comments
Brandenburg 2000[27]	Prospective cohort study (part of PORT cohort study) (N = 156).	• 50% of the sample > 65 years old. • 89.2% were inpatients with 13.3% admitted to ITU.	• symptoms at 30 days • return to daily household activities • return to work	• The GDG considered this population to have high-severity CAP.
El Moussaoui 2006[68]	Prospective cohort (from a RCT) (N = 102).	• Low- to moderate-severity CAP. • Median age: 65 (48-72). • Mean PSI (SD): 71 (23). • Comorbidities: COPD: 27%, diabetes mellitus: 17%, cardiovascular disease: 24%.	• time to return to pre-pneumonia levels for: ○ respiratory CAP score (dyspnoea, cough, sputum) ○ wellbeing CAP score (fitness, general health) • SF-36 score	• 8 item self-administered validated score (CAP) was completed at study entry (day 0) and at days 3, 7, 10, 14, 28, and at 6 and 18 months after the beginning of treatment. • Average response rate (66%)
Bruns 2010[33]	Prospective cohort study linked to study by El Moussaoui et al, 2006 (N = 119).	• Low- to moderate-severity CAP. • Mean age: 56.6 (17.8). • Mean PSI (SD): 65.5 (22.1). • At least 1 comorbidity: 66.4%.	• normalisation of the CAP score (defined as a CAP score equal to or greater than the initial pre-pneumonia score) at day 10 and 28 after the beginning of treatment	• The aim of the study was to compare the CXR resolution of low- to moderate-severity CAP to resolution of clinical symptoms as assessed by the physician or the patient.
Fine 1996[77]	Systematic review and meta-analysis of 127 studies representing 33148 patients.	• Mainly hospitalised patients (66.1%).	• return to work • return to usual activities • assessment of	• No information was given on which studies

Study	Type of study/Number of patients	• Population	Outcomes	Comments
		• No reference to the severity of CAP. • Mean age: 61 years (SD 13). • Comorbidities; cigarette smoking (48.6%) pulmonary disease (32.7%), congestive heart failure (26.2%).	functional status after hospital discharge	reported which outcomes. • No quality assessment of individual studies.
Fernandez 2010[74]	Community based study (CAPIS) of older adults (> 60 years) with pneumonia (N = 195).	• No information regarding the CAP severity. • 65.2% were older than 70 years old (mean 72.8% (SD 6.8)). • Heart disease: 18.9%. • 100% women.	• symptoms 4 weeks after diagnosis • decline in health status	• Part of the CAPIS study (community mixed methods study to identify the impact of CAP. • Unclear how many participants invited to the study. • Clinical diagnosis of CAP.
Labarere 2007[110]	Prospective multicentre follow up from a RCT (N = 1493).	• Low- to moderate-risk CAP patients (PSI I to III) without contraindications to outpatient treatment. • Outpatients: 63% Inpatients: 37%.	• return to work (days) • return to usual activities (days) for workers • return to usual activities (days) for non-workers	• Cohort of a cluster trial (assessed role of PSI to guide site of treatment for patients with CAP). • Only 43% of the sample were workers. • The authors also conducted multivariate analysis adjusting by the effect of patient, provider

Study	Type of study/Number of patients	• Population	Outcomes	Comments
				and department.
Marrie 2000[128]	Prospective multicentre cohort from a RCT (N = 535).	• Mean age: 61.6 (19.1). • Mean PSI: 76.2 (32.8). • Antibiotic monotherapy: 75.1%. • Inpatients: 53.8%.	• prevalence of symptoms (fatigue, cough, shortness of breath, sputum production, chest pain on breathing) at 2, 6 weeks post treatment	• Low response rate (30%). • Cohort of a trial assessing levofloxacin (CAPITAL study).
Metlay 1997[138]	Prospective multicentre study (N = 576).	• Low-severity patients with CAP. • Age < 40 years:46%, ≥ 60 years 22%. • Outpatients: 65%. • Comorbidities: • 0: 51% • 1: 32% • ≥ 2: 17%.	• prevalence of symptoms (fatigue, cough, dyspnoea, sputum production, pleuritic chest pain) at day 7, 30, 90 from the CXR diagnosis • pneumonia-related re-consultations at day 30 and 90.	• Response rate: 75%. • Available data on follow-ups: 61.1%. • The authors also specified the severity of symptoms.
Metlay 1998[137]	Prospective multicentre study (N = 166) (76% response rate).	• Low-severity CAP. • Mean age: 52.7 years. • Outpatients: 55.6%. • COPD: 11.1%.	• time to resolution (defined as symptomatic cure) of symptoms (fever, myalgia, fatigue, cough, dyspnoea) • proportion of patients with unresolved symptoms by day 28 (from the time of diagnosis)	• 5 item self-administered questionnaire was developed based on the results of study Metlay 1997 and was completed at days 0, 7, 14, 21 and 28 from diagnosis.
Sicras-Mainar 2012[181]	Retrospective multicentre study in Spain (N = 581).	• Mean age: 57.5 (19.1). • PSI: ○ I or II: 58.9% ○ III: 18.4% ○ IV/ V: 22.7%. • Mean comorbidities: 6.8 (4.8).	• change of initial treatment • time to recovery (in days)	• The authors also reported subgroup analysis by site of care for time to recovery.

15.2.1 Re-consultation

One prospective cohort study (Metlay 1997) reported that 49% of patients with low-severity CAP had a pneumonia-related re-consultation 30 days after diagnosis and 13.9% re-consulted at day 90. However, the quality of evidence was low as the response rate of this cohort study was 61%; the majority of included patients were younger than 59 years old (78%) and had no comorbidities (51%) so the generalisability of the results is limited.

15.2.2 Resolution of symptoms

Two main themes arose from the studies investigating the resolution of symptoms after pneumonia diagnosis; the prevalence of symptoms (pneumonia-related) at different points in time and the timing to complete resolution of symptoms.

Three studies included resolution of symptoms (Bruns 2010, Metlay 1998 and Sicras-Mainar 2012). The Sicras-Mainar 2012 study included a general outcome of time-to-recovery which was self-reported and recorded as 29.9 days for the whole sample and 27.3 and 33.8 for the outpatients and inpatients respectively. The follow-up of this retrospective study was 6 months.

Metlay 1998 also reported the proportion of patients with unresolved symptoms by day 28; almost one third of the sample (35%) still experienced at least 1 symptom, 26% felt fatigue and only 4% experienced fever.

Bruns 2010 reported that 32% of patients with mild-to-moderate severity pneumonia had achieved normalisation of the CAP score (defined as equal to or greater than the initial pre-pneumonia score as a proof of patient's perception of clinical cure) at day 10 and 41.7% at day 28.

Results for the other studies are summarised in the following table.

Table 142: Resolution of pneumonia-related symptoms (timing to resolution and prevalence of different symptoms at different points in time)

No. of studies	Design	Sample	Themes	Quality assessment
Sub theme: Median time (range) to resolution* of individual symptoms in days [Metlay 1998]				
1	1:1 telephone interviews or self-administered questionnaires (in both studies)	N = 126 [Metlay 1998]	• Fever: 3 (2 to 4) • Myalgia: 5 (4 to 6) • Dyspnoea: 6 (5 to 14) • Cough: 14 (7 to 21) • Fatigue: 14 (6 to 21)	• Moderate quality. • Transferable to population addressed.
Sub-theme: Median time to resolution* (range) of multiple symptoms in days [Metlay 1998, El Moussaoui 2006]				
2	1:1 telephone interviews or self-administered questionnaires (in both studies)	N = 126 [Metlay 1998] N = 102 [El Moussaoui 2006]	• All symptoms (fever, myalgia, dyspnoea, cough and fatigue): 21 (21 to 28) • Respiratory section of CAP score (cough, sputum, dyspnoea): 14 • Well-being section of CAP score (fitness, general state of health): 6 months	• Moderate quality. • Transferable to population addressed.
Sub-theme: Prevalence (%) of fatigue (range of % if more than 1 study for the same time point) [Metlay 1997, Metlay 1998, Marrie 2000]				
3	1:1 interviews (by person or telephone)	N = 576 [Metlay 1997] N = 126 [Metlay 1998] N = 535 [Marrie 2000]	• Day 0 (time of diagnosis): 93% • Day 7 (after diagnosis): 80% • 2 weeks (after completion of treatment): 66.7% • Day 28 or 30 (since diagnosis): 25.7 to 65% • 6 weeks (after completion of treatment): 45% • Day 90 (after diagnosis): 51%	• Moderate quality. • Transferable to population addressed.
Sub-theme: Prevalence (%) of cough (range of % if more than 1 study for the same time point) [Metlay 1997, Metlay 1998, Marrie 2000]				
3	1:1 interviews (by person or telephone)	N = 576 [Metlay 1997] N = 126 [Metlay 1998] N = 535 [Marrie 2000]	• Day 0 (time of diagnosis): 90 to 93.4% • Day 7 (after diagnosis): 82% • 2 weeks (after completion of treatment): 55.5% • Day 28-30 (since diagnosis): 19.9 to 53% • 6 weeks (after completion of treatment): 35.3% • Day 90 (after diagnosis): 32%	• Moderate to low quality. • Transferable to population addressed.

Sub-theme: Prevalence (%) of dyspnoea/shortness of breath (range of % if more than 1 study for the same time point) [Metlay 1997, Fernandez 2010, Metlay 1998, Marrie 2000, Fernandez 2010]				
4	1:1 interviews (by person or telephone)	N = 576 [Metlay 1997] N = 126 [Metlay 1998] N = 535 [Marrie 2000] N = 195 [Fernandez 2010]	• Day 0 (time of diagnosis): 68 to 78.7% • Day 7 (after diagnosis): 50% • 2 weeks (after completion of treatment): 58% • Day 28- 30 (since diagnosis): 16.8 to 64.5% • 6 weeks (after completion of treatment): 34% • Day 90 (after diagnosis): 28%	• Moderate to very low quality. • Results from younger and older patients with CAP.
Sub-theme: Prevalence (%) of sputum production (range of % if more than 1 study for the same time point) [Metlay 1997, Marrie 2000]				
2	1:1 interviews (by person or telephone)	N = 576 [Metlay 1997] N = 535 [Marrie 2000]	• Day 0 (time of diagnosis):63 to 69.2% • Day 7 (after diagnosis): 59% • 2 weeks (after completion of treatment): 46% • Day 30 (since diagnosis): 40% • 6 weeks (after completion of treatment): 26% • Day 90 (after diagnosis): 27%	• Moderate to low quality. • Transferable to population addressed.
Sub-theme: Prevalence (%) of pleuritic chest pain (range of % if more than 1 study for the same time point) [Metlay 1997, Marrie 2000]				
2	1:1 interviews (by person or telephone)	N = 576 [Metlay 1997] N = 535 [Marrie 2000]	• Day 0 (time of diagnosis): 47 to 51.1% • Day 7 (after diagnosis): 22% • 2 weeks (after completion of treatment): 18% • Day 30 (since diagnosis): 12% • 6 weeks (after completion of treatment): 12% • Day 90 (after diagnosis): 8%	• Moderate to low quality. • Transferable to population addressed.
Sub-theme: Prevalence (%) of fever [Metlay 1997, Marrie 2000]				
1	1:1 interviews (by person or telephone)	N = 535 [Marrie 2000] N = 126 [Metlay 1998]	• Day 0 (time of diagnosis): 41.3% • 2 weeks (after completion of treatment): 9% • 6 weeks (after completion of treatment): 6.6% • 28 days (after diagnosis): 3.5%	• Low quality. • Transferable to population addressed (low to moderate severity).
Sub-theme: Prevalence (%) of sweats [Fernandez 2010]				

1	1:1 telephone interviews	N = 195 [Fernandez 2010]	• 4 weeks (after diagnosis): 52%	• Very low quality. • Older patients with no CXR-confirmed CAP - restricts the generalisability of findings.
Sub-theme: Prevalence (%) of sore throat [Fernandez 2010]				
1	1:1 telephone interviews	N = 195 [Fernandez 2010]	• 4 weeks (after diagnosis): 39%	• Very low quality. • Older patients with no CXR-confirmed CAP - restricts the generalisability of findings.
Sub-theme: Prevalence (%) of no energy [Fernandez 2010]				
1	1:1 telephone interviews	N = 195 [Fernandez 2010]	• 4 weeks (after diagnosis): 74.5%	• Very low quality. • Older patients with no CXR-confirmed CAP - restricts the generalisability of findings.
Sub-theme: Prevalence (%) of headache [Fernandez 2010]				
1	1:1 telephone interviews	N = 195 [Fernandez 2010]	• 4 weeks (after diagnosis): 31.8%	• Very low quality. • Older patients with no CXR-confirmed CAP - restricts the generalisability of findings.
Sub-theme: Prevalence (%) of any symptom [Marrie 2000]				
1	1:1 interviews (by person or telephone)	N = 535 [Marrie 2000]	• Day 0 (time of diagnosis): no information • 2 weeks (after completion of treatment): 86% • 6 weeks (after completion of treatment): 66%	• Low quality. • Transferable to population addressed (low to moderate severity).

* Time to resolution defined as the time for the score to return to pre-pneumonia levels.

At 28 days, a lower proportion of patients in the study by Metlay 1998 experienced fatigue, cough, dyspnoea, fever and any symptom compared with the other 2 studies of patients with low-severity CAP at the same time point (Metlay 1997, Fernandez 2010). The authors discussed this difference in the prevalence of outcomes as a potential difference in the assessment of pneumonia severity in their study.

Table 143: Types of symptoms after diagnosis reported by patients with high-severity community-acquired pneumonia

Studies	Design	Sample	Themes	Quality assessment
Prevalence of symptoms at 30 days after diagnosis [Brandenburg 2000]				
1	1:1 interviews	N = 156	• Fatigue: 37.1% • Cough: 50% • Shortness of breath: 47.5% • Sputum production: 52% • Pleuritic chest pain: 86.8%	• Very low quality. • Mixed population of bacteraemic and non-bacteraemic patients makes the results difficult to be transferable to general population with pneumonia.

15.2.3 Return to usual activities including work

One systematic review (Fine 1996) of mixed population and 2 cohort studies (Labarere 2007, Brandendurg 2000) provided information regarding the amount of time patients with pneumonia took to return to their normal activities and/or work through personal interviews. The GDG considered the participants in the Brandenburg 2000 study to have high-severity CAP and their results are presented separately. Labarere 2007 included both inpatients and outpatients with low-severity CAP and only 43% of the sample were workers.

Table 144: Return to usual activities after presentation of pneumonia for patients with high-severity community-acquired pneumonia (as assessed by the GDG)

Studies	Outcomes	Quality assessment
Brandenburg 2000	Return to normal activities: 17 days	Very low quality. Mixed population of bacteraemic and non-bacteraemic patients makes the results difficult to transfer to the general pneumonia population.
	Return to work: 12 days	
	Return to usual activities for workers: 9 days	

Table 145: Return to usual activities after presentation for patients with low- to moderate-severity community-acquired pneumonia

Outcomes	Studies	Median time (days or weeks) to return to usual activities (population)	Quality assessment
Return to normal activities	Fine 1996	- 8 weeks (for ambulatory and hospitalised patients)	Very low quality
Return to work	Fine 1996	- 30 days (for 78.2% of ambulatory and hospitalised patients)	Very low quality
	Labarere 2007	- 7 days (4 to 14) for outpatients/ 14 (8 to 29+) for inpatients	Low quality
Return to usual activities for workers	Labarere 2007	- 13 days (6 to 23) for outpatients/ 22 (11 to 29+) for inpatients	Very low quality
Return to usual activities for non-workers	Labarere 2007	- 14 days (6 to 28) for outpatients/ 20 (9 to 29+) for inpatients	Low quality

15.2.4 Alteration of initial treatment or additional course of antibiotic therapy

One retrospective multicentre study (Sicras-Mainar 2012) reported that 7.1% of the sample of patients required a change of their initial treatment due to lack of response. However, no further information is provided regarding the definition of lack of response or the alternative treatment. The majority of patients in the sample had low-severity CAP (PSI I or II: 58.9%).

15.2.5 Quality-of-life changes

Four studies provided information related to quality-of-life change for patients with pneumonia (Fine 1996, El Moussaoui 2006, Metlay 1997, Fernandez 2010).

Metlay 1997 reported the mean scores of all 8 domains of SF-36 (physical and physical role functioning, bodily pain, vitality, social functioning, mental health, and emotional role functioning, general perception) prior to the presentation of pneumonia and at days 7, 30 and 90 from the time of diagnosis. At days 7 and 30, all the domains of SF-36 scored lower than the pre-pneumonia levels but almost returned to pre-pneumonia levels by day 90 (Table 146).

Table 146: Mean scores[1] SF-36 by different time intervals pre-pneumonia and at days 7, 30 and 90 after antibiotic therapy

Mean scores SF-36	Pre-pneumonia	Day 7	Day 30	Day 90
Physical functioning	86.8	59.5	75.0	81.2
Physical role functioning	81.7	25.2	63.2	77.5
Bodily pain	89.1	73.9	84.7	86.6
Vitality	68.3	38.3	56.2	63.2
Social functioning	89.1	53.3	80.1	86.8
Mental health	80.3	74.9	78.1	79.5
Emotional role functioning	87.3	71.6	80.5	86.0
General health perception	74.5	64.2	65.6	67.2

[1] *The higher the scores the better outcomes in terms of quality-of-life*

The El Moussaoui study found that patients with low-to moderate-severity CAP had significantly lower scores in 2 of the 8 domains of SF-36 (physical functioning and general health) compared with the reference population without pneumonia. The same study also reported that all domains of SF-36 (except emotional functions and mental health) were significantly higher for patients who scored higher in CAP symptom domains (indicating high recovery from pneumonia-related symptoms) at 18 months after the beginning of antibiotic therapy compared with those with lower CAP scores (indicating low recovery from pneumonia-related symptoms).

The Fernandez 2010 study looked at predictors of quality-of-life (as assessed by SF-8) in older patients 4 weeks after diagnosis of pneumonia. In a multivariate analysis, they found that the only symptoms related to patients' quality-of-life affected by pneumonia were lack of energy and sweats.

The systematic review by Fine 1996 included 1 study that showed that 43.3% of patients who were discharged from the ITU returned to their baseline physical health by 6 months after hospital admission. However, these results should be interpreted with caution as this systematic review was at high risk of bias due to lack of quality assessment and lack of clear information of included studies.

15.3 Economic evidence

Published literature

No relevant economic evaluations were identified.

See also the economic article selection flow chart in Appendix E:.

Unit costs

Providing patients with information on what symptoms and duration of symptoms can be expected following treatment for community-acquired or hospital-acquired pneumonia, and advising patients on when they should consult or re-consult a GP could reduce unnecessary cost of GP consultations and Accident & Emergency attendances. Relevant unit costs are provided below to aid consideration of cost effectiveness.

The average cost of a GP consultation is £43 for 11.7 minute consultation in a surgery (PSSRU 2012).[56,57]

Table 147: Accident & Emergency costs

Currency code	Currency description	FCEs (million)	National average unit cost	Lower quartile unit cost	Upper quartile unit cost
Accident & Emergency- Leading to admission					
VB08Z	Emergency Medicine, Category 2 Investigation with Category 1 Treatment[a]	1.45	£155	£130	£175
Accident & Emergency- Not leading to admission					
VB08Z	Emergency Medicine, Category 2 Investigation with Category 1 Treatment[a]	2.76	£131	£113	£146

(a) A category 2 investigation with category 1 treatment is equivalent to the cost of a plain film x-ray or a blood culture, followed by reviewing results or prescribing medicines

Source: NHS Reference Costs 2011-2012[61]

15.4 Evidence statements

Based on moderate to very low quality evidence of observational studies (mainly prospective cohort studies), patients with low-to moderate-severity CAP:

- at 2 weeks after diagnosis, may have returned to normal activities
- between 1 and 2 weeks outpatients may have returned to work whereas for inpatients this can take longer
- at 30 days after diagnosis:
  - less than 5% still had fever
  - almost 50% re-consulted for a reason related to their pneumonia
  - the majority of patients still experienced cough, dyspnoea, fatigue, sputum production
  - all the quality-of-life domains were lower than their pre-pneumonia levels.
- between 3 and 6 months patients returned to their pre-pneumonia quality-of-life and general wellbeing.

The results from the only cohort study of patients with high-severity CAP were not appropriate for generalisability.

Economic

- No relevant economic evaluations were identified.

15.5 Recommendations and link to evidence

Table 148: Linking evidence to recommendations – what clinicians can inform patients to expect when recovering from pneumonia

Recommendations	**23. Explain to patients with community-acquired pneumonia that after starting treatment their symptoms should steadily improve, although the rate of improvement will vary with the severity of the pneumonia, and most people can expect that by:** • **1 week: fever should have resolved** • **4 weeks: chest pain and sputum production should have substantially reduced** • **6 weeks: cough and breathlessness should have substantially reduced** • **3 months: most symptoms should have resolved but fatigue may still be present** • **6 months: most people will feel back to normal.** **24. Advise patients with community-acquired pneumonia to consult their healthcare professional if they feel that their condition is deteriorating or not improving as expected.**
Relative values of different outcomes	The purpose of this question was to allow formulation of advice on when and/or in what circumstances a person with a diagnosis of pneumonia should re-present to a healthcare professional after initially commencing treatment. There is a perception that many people receive second courses of antibiotic therapy for persistent symptoms that would resolve spontaneously given sufficient time. This incurs re-consultation and prescription costs and exposes patients to unnecessary treatment risks. Ideally the GDG would have liked to see papers directly addressing the question of appropriate re-consultation, but anticipated that these would be hard to find. The search was therefore also directed at finding papers reporting the rate of change in symptoms with time. The GDG considered complete resolution of specific symptoms to be the most important outcome, since this would allow recommendations to be produced in terms that people with pneumonia would readily understand. Information on change in quality-of-life and activities of daily living was also sought.
Trade-off between clinical benefits and harms	The aim of this review was to establish the most common symptoms and their standard duration in patients with pneumonia and to use this to judge when patients should be advised to consult or re-consult a health professional. The studies showed that the first symptom to be resolved was fever (within 1 week after starting treatment), followed by chest pain and sputum production (within 4 weeks after starting treatment) and resolution of cough (within 6 weeks). Fatigue was the symptom that was slowest to resolve, taking up to 6 months after treatment. Around 2 weeks after pneumonia diagnosis, outpatients with CAP have returned to normal activities (including work) whereas for inpatients this could be longer. However, the GDG recognised that this may be influenced by personal socio-economic circumstances.

	Although the included studies varied in terms of patient characteristics and settings, the GDG considered that the trend of symptom prevalence and duration matched their clinical experience. Only 1 prospective cohort study reported the outcome of re-consultation (Metlay 1997), but the patient population tended to be younger and had fewer comorbidities than in other studies. The GDG noted that assessing the appropriateness of re-consultation in a non-UK setting is difficult as unknown social and economic factors might influence re-consultation, and declined to generate a recommendation based on consensus about when or in what circumstances to advise patients to re-consult their healthcare professional.
Trade-off between net health benefits and resource use	No suitable economic studies were identified. Apart from the very modest amount of time this takes, there is no cost incurred in offering advice. There is a potential gain from the reduction in unnecessary prescriptions of antibiotic and unnecessary re-consultations.
Quality of evidence	According to the NICE checklist for quality assessment of observational studies, the evidence was of moderate to very low quality. All included studies were observational with the majority of prospective design. However, there is a possibility of recall bias across the included studies as patients were asked retrospectively about their symptoms and quality-of-life before developing pneumonia. Low response rate was a limitation for some of the included studies. Most of the included studies focused on patients with low- to moderate-severity CAP, except for 1 study (Brandenburg 2000) which focused on those with more severe illness.
Other considerations	It was noted that in a community setting, where chest X-ray evidence of pneumonia may not be obtained, there was the potential for these recommendations to be applied to those suffering from non-pneumonic LRTI. However, there was reasonable consensus among the GDG that the resolution of symptoms in LRTI, particularly in relation to fever, cough and sputum production, is very similar to that found in these pneumonia studies and that if the same advice was issued to people with LRTI it would do no harm. There was some variation in time of symptom resolution for some symptoms. The GDG favoured suggesting that such symptoms should have “substantially reduced” rather than resolved, based on a combination of the evidence available and GDG experience. The GDG suggested it would be valuable to develop a patient information leaflet from these recommendations. **Key priority for implementation** The GDG prioritised this recommendation because it would have a high impact on outcomes that are important to patients by reducing anxiety and improving understanding of the natural history of recovery from pneumonia, and lead to more efficient use of NHS resources.

Hospital-acquired pneumonia

The evidence base was sparse. Studies of ventilator-associated pneumonia, or cohorts that were dominated by ventilator-associated pneumonia made up virtually all the evidence for HAP. Since the scope included only HAP that was NOT ventilator-associated this was not relevant and could not be used. The only data identified for review pertained to choice of empirical antibiotic therapy and these results are detailed in the following section. Questions relevant to HAP are detailed in section 5.1 and all ancillary information on protocols are available in Appendix C:, search strategies in Appendix F:, clinical evidence tables in Appendix G:, excluded clinical studies in Appendix J:, forest plots in Appendix I:, excluded economic studies in Appendix K: and research recommendations in Appendix M:.

16 Severity assessment

16.1 Review question: In adults with hospital-acquired pneumonia what is the most accurate and cost-effective severity assessment tool to stratify patients at first presentation according to who would benefit from ITU assessment?

See review protocol in Appendix C:.

No data were found for this review.

17 Microbiological tests

17.1 In adults with community-acquired pneumonia or hospital-acquired pneumonia in a hospital setting, what microbiological test or combination of tests at presentation (including urinary pneumococcal and urinary legionella antigen, blood culture and sputum culture) is most likely to be clinically and cost effective?

Please see section 9 for clinical introduction.

Please see Appendix C: for review protocol.

No relevant evidence was identified.

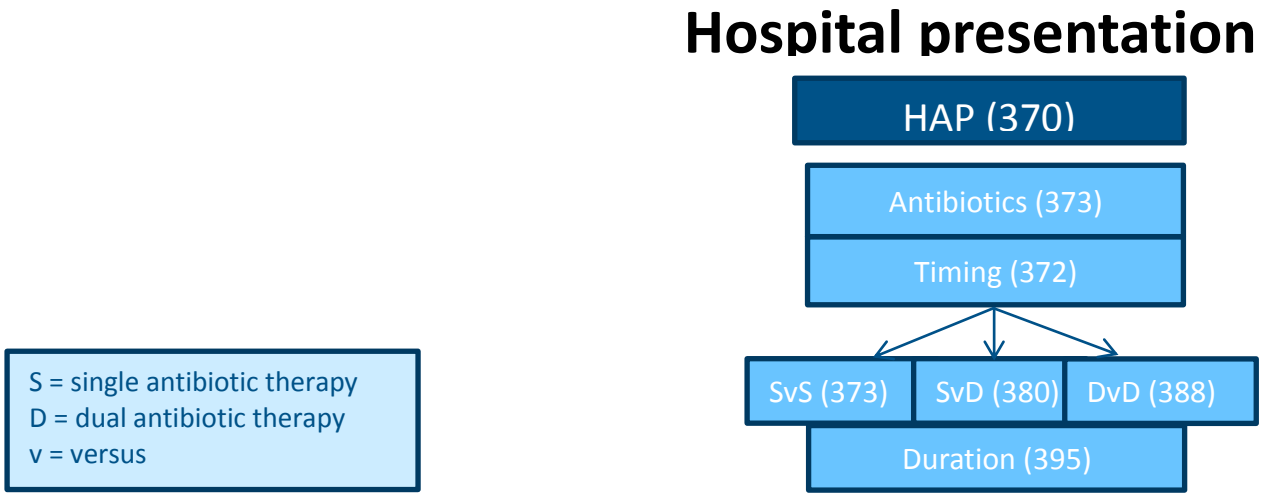
18 Antibiotic therapy

Please see section 10 for an introduction.

Please see Appendix C: for review protocol.

Please see Figure 12 for assistance in navigating this chapter.

Figure 12: Map of hospital-acquired pneumonia antibiotic therapy chapter (numbers in brackets are page numbers and hyperlink to the relevant section)



18.1 Timing of antibiotic therapy for hospital-acquired pneumonia

18.2 Review question: In adults with hospital-acquired pneumonia is earlier rather than later antibiotic administration more clinically and cost effective?

18.2.1 Clinical and economic evidence

No relevant data were identified to inform this review but the GDG considered whether the evidence for patients with community-acquired pneumonia could be transferable when reflecting upon a recommendation for this different patient population.

18.2.2 Recommendations and link to evidence

Table 149: Linking evidence to recommendations – timing of antibiotic therapy for hospital-acquired pneumonia

Recommendations	**25. Offer antibiotic therapy as soon as possible after diagnosis, and certainly within 4 hours, to patients with hospital-acquired pneumonia.**
Relative values of different outcomes	The GDG considered mortality the most important outcome. Clinical cure, length of hospital stay and adverse events were considered other important outcomes.
Trade-off between clinical benefits and harms	No suitable studies examining the timing of antibiotic administration in HAP were available.
Trade-off between net health benefits and resource use	The GDG felt that the cost of adverse events and inappropriate prescribing were likely to be outweighed by the additional risk of mortality by waiting to prescribe antibiotic therapy.
Quality of evidence	No suitable evidence was available. No economic evidence was found on this question.
Other considerations	The GDG debated whether, in the absence of any evidence regarding timing of antibiotic administration of HAP, any recommendation should be made. The GDG was in agreement that in patients with HAP early antibiotic administration was likely to be desirable resulting in the recommendation by consensus opinion. The GDG acknowledged that a drive for very early antibiotic administration could lead to inappropriate antibiotic administration in patients who do not have HAP, and emphasised the importance of rapid and accurate assessment and diagnosis.

18.3 Review question: In adults with hospital-acquired pneumonia what is the most clinically- and cost-effective empirical antibiotic choice?

18.4 Single-compared with other single-antibiotic therapy for hospital-acquired pneumonia

For full details see review protocol in Appendix C:.

18.4.1 Clinical evidence

We searched for systematic reviews of randomised controlled trials (RCTs), and RCTs comparing the effectiveness and safety of empirical therapy with single antibiotics from different classes for the treatment of pneumonia acquired in hospital. Data from studies comparing the same classes of antibiotics were pooled into a single analysis (see Appendix N: for classifications). Data were accepted for antibiotics administered by oral or intravenous routes.

Two RCTs were included in the review. Both studies terminated early due to low recruitment.[94,174] Table 150 summarises the study details. A matrix of included comparisons is presented to facilitate navigation of the evidence (Figure 13).

Evidence from the included studies is summarised in the clinical GRADE evidence profiles below (Table 151 and Table 152). Only the 3 critical outcomes were reported.

See also the study selection flow chart in Appendix D:, forest plots in Appendix I:, study evidence tables in Appendix G:and exclusion list in Appendix J:.

Figure 13: Single- compared with other single-antibiotic therapy for hospital-acquired pneumonia (click on hyperlinks or refer to page numbers)

	Cephalosporin	Carbapenem
Respiratory fluoroquinolone	• Moxifloxacin vs. ceftriaxone followed by cefuroxime Table 151, page 376	
Beta-lactamase stable penicillin		• Piperacillin-tazobactam vs. imipenem-cilastatin Table 152, page 378

Table 150: Summary of studies included in the review of single- compared with other single-antibiotic therapy for hospital-acquired pneumonia

Study	Intervention N randomised	Comparison N randomised	Time of onset	Outcomes	Comments
Respiratory fluoroquinolone compared with cephalosporin					
Hoffken 2007[94]	Moxifloxacin 400 mg IV once daily followed by moxifloxacin 400 mg oral once daily **Route of administration:** IV then oral **Duration:** 7 to 14 days. (N = 78).	Ceftriaxone 2 g IV once daily followed by cefuroxime axetil 500 mg oral twice daily. **Route of administration:** IV then oral **Duration:** 7 to 14 days. (N = 83).	• New onset HAP ≥ 48 hours after hospitalisation. • Median time between hospitalisation and diagnosis of HAP = 7 days.	• mortality • clinical cure at end of follow-up; defined as resolution • withdrawal due to adverse events	• Trial enrolment terminated early due to low recruitment • Excluded those with high-severity HAP (according to revised ATS criteria and with APACHE score > 20) • Switch to oral therapy could be made from day 4 onwards (after receiving the first 3 doses) at the investigator's discretion. • 8.8% on mechanical ventilation at baseline. • 41% had received prior antibiotic therapy.
Beta-lactamase stable penicillin compared with carbapenem					
Schmitt 2006[174]	Piperacillin-tazobactam 4 g/0.5 g IV q8h. **Route of administration:** IV **Duration:** 5 to 21 days. (N = 110).	Imipenem-cilastatin 1 g/1 g IV q8h. **Route of administration:** IV **Duration:** 5 to 21 days. (N = 111).	• HAP onset ≥ 48 hours after hospitalisation.	• mortality • clinical cure at end of treatment • clinical cure at end of follow-up • withdrawal due to adverse events	• Trial enrolment terminated early due to low recruitment. • Excluded patients infected with drug-resistant pathogens. • 23.5% needed mechanical ventilation at baseline. • If *P. aeruginosa* was present additional aminoglycoside therapy was mandatory (this was the case in 4%).

Table 151: Clinical evidence profile: Respiratory fluoroquinolone compared with cephalosporin for patients with hospital-acquired pneumonia

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Respiratory fluoroquinolone	Cephalosporin	Relative (95% CI)	Absolute	Quality
Mortality (follow-up 21 to 31 days after treatment) [Hoffken 2007]											
1	randomised trial	very serious[1]	no serious	serious[2]	very serious[3]	none	8/77 (10.4%)	11/82 (13.4%)	RR 0.77 (0.33 to 1.82)	31 fewer per 1000 (from 90 fewer to 110 more)	Very low
Clinical cure at end of follow-up (follow-up 7 to 10 days after treatment) [Hoffken 2007]											
1	randomised trial	very serious[4]	no serious	serious[2]	serious[5]	none	56/77 (72.7%)	56/82 (68.3%)	RR 1.06 (0.87 to 1.3)	41 more per 1000 (from 89 fewer to 205 more)	Very low
Withdrawal due to adverse events (follow-up 7 to 14 days) [Hoffken 2007]											
1	randomised trial	very serious[1]	no serious	serious[2]	very serious[3]	none	4/78 (5.1%)	2/83 (2.4%)	RR 2.13 (0.4 to 11.29)	27 more per 1000 (from 14 fewer to 247 more)	Very low
Length of hospital stay											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Health-related quality-of-life											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Complications											
0	no evidence available	-	-	-	-	none	-	-	-	-	

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Respiratory fluoroquinolone	Cephalosporin	Relative (95% CI)	Absolute	Quality
***C. difficile*-associated diarrhoea**											
0	no evidence available	-	-	-	-	none	-	-	-	-	

[1] *High risk of selection bias and attrition bias*
[2] *Indirect population: excluded severe HAP (APACHE II > 20 or based on modified ATS criteria)*
[3] *95% CI crosses both default MIDs*
[4] *High risk of selection and measurement bias (outcome not defined) and unblinded*
[5] *95% CI crosses 1 default MID*

Table 152: Clinical evidence profile: Beta-lactamase stable penicillin compared with carbapenem for patients with hospital-acquired pneumonia

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Beta-lactamase stable penicillin	Carbapenem	Relative (95% CI)	Absolute	Quality
Mortality (follow-up 21 days after treatment) [Schmitt 2006]											
1	randomised trial	serious[1]	no serious	serious[2]	serious[3]	none	17/110 (15.5%)	11/111 (9.9%)	RR 1.56 (0.77 to 3.18)	55 more per 1000 (from 23 fewer to 216 more)	Very low
Clinical cure at end of treatment (follow-up 5 to 21 days) [Schmitt 2006]											
1	randomised trial	serious[1]	no serious	serious[4]	no serious	none	76/107 (71%)	85/110 (77.3%)	RR 0.92 (0.78 to 1.08)	62 fewer per 1000 (from 170 fewer to 62 more)	Low
Clinical cure at end of follow-up (follow-up 10 to 18 days after treatment) [Schmitt 2006]											
1	randomised trial	serious[1]	no serious	serious[4]	serious[3]	none	64/107 (59.8%)	73/110 (66.4%)	RR 0.9 (0.73 to 1.11)	66 fewer per 1000 (from 179 fewer to 73 more)	Very low
Withdrawal due to adverse events (follow-up 5 to 21 days) [Schmitt 2006]											
1	randomised trial	serious[1]	no serious	serious[2]	very serious[4]	none	13/110 (11.8%)	9/111 (8.1%)	RR 1.46 (0.65 to 3.27)	37 more per 1000 (from 28 fewer to 184 more)	Very low
Length of hospital stay											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Health-related quality-of-life											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Complications											
0	no	-	-	-	-	none	-	-	-	-	

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Beta-lactamase stable penicillin	Carbapenem	Relative (95% CI)	Absolute	Quality
	evidence available										
***C. difficile*-associated diarrhoea**											
0	no evidence available	-	-	-	-	none	-	-	-	-	

[1] *High risk of bias; unblinded, unclear sequence generation and not comparable at baseline for requiring mechanical ventilation (more in the piperacillin group [28 vs 19%])*
[2] *23.5% may have had VAP*
[3] *95% CI crosses 1 default MID*
[4] *95% CI crosses both default MIDs*

18.4.2 Economic evidence

Published literature

No relevant economic evaluations comparing single- with other single-antibiotic therapy were identified for HAP.

Unit costs

Unit costs are provided for reference in Appendix O:.

18.4.3 Evidence statements

18.4.3.1 Clinical

18.4.3.1.1 Respiratory fluoroquinolone compared with cephalosporin

- Very low quality evidence from 1 randomised study of 159 patients with HAP suggested a clinical benefit for respiratory fluoroquinolone compared with cephalosporin for the outcomes of mortality and clinical cure at end of follow-up, but not for the outcome of withdrawal due to adverse events.

18.4.3.1.2 Beta-lactamase stable penicillin compared with carbapenem

- Low to very low quality evidence from 1 randomised study of over 200 patients with HAP showed that there may be a clinical benefit for those on carbapenem compared with those treated with beta-lactamase stable penicillin for the outcomes of mortality and clinical cure at the end of treatment. No clinical difference was found between the 2 treatment groups for the outcome of withdrawal due to adverse events.

18.4.3.2 Economic

- No relevant economic evaluations were identified.

18.5 Single-compared with dual-antibiotic therapy for hospital-acquired pneumonia

Please see Appendix C: for review protocol.

18.5.1 Clinical evidence

We searched for systematic reviews of randomised controlled trials (RCTs), and RCTs comparing the effectiveness and safety of single- and dual-antibiotic therapy for the treatment of pneumonia acquired in hospital. Dual therapy was defined as the administration of 2 antibiotics from different classes. Since the use of more than 2 antibiotics as empirical therapy would be unusual in the UK, a search for triple therapy was not conducted. Data from studies comparing the same classes of antibiotics were pooled into a single analysis (see Appendix N: for classifications). Data were accepted and stratified for administration of antibiotics by oral and intravenous routes.

Three studies were identified for patients with HAP.[75,100,171]

A variety of antibiotics were used and population characteristics varied (see Table 153).

All studies were multicentre, non-inferiority and unblinded trials. Two studies included a wider pneumonia population, and conducted *post-hoc* subgroup analyses of patients with HAP.

Evidence from the included studies is summarised in the clinical GRADE evidence profiles below (Table 154 and Table 155).

See also the study selection flow chart in Appendix D:, forest plots in Appendix I:, study evidence tables in Appendix G:and exclusion list in Appendix J: A matrix of included comparisons is presented to facilitate navigation of the evidence (Figure 14).

Figure 14: Single- compared with dual-antibiotic therapy for hospital-acquired pneumonia (click on hyperlinks or refer to page numbers)

	Cephalosporin plus aminoglycoside
Cephalosporin	• Ceftazidime vs. ceftriaxone + tobramycin • Cefotaxime vs. cefotaxime or other cephalosporins[1] + aminoglycoside Table 154, page 384
Carbapenem	• Meropenem vs. cefuroxime + gentamicin Table 155, page 386

1.Other antibiotics were used in combination with aminoglycoside in the comparison arm, but the majority (60%) compared cefotaxime with cefotaxime or other cephalosporins plus aminoglycoside

Table 153: Summary of studies included in the review

Study	Intervention N randomised	Comparison N randomised	Time of onset	Outcomes	Comments
Cephalosporin compared with cephalosporin plus aminoglycoside					
Fernandez-Guerrero 1991[75]	Cefotaxime IV, starting dose 2 g q8 h, reduced to 2 g q12 h after improvement **Duration:** Continued until at least 3 days after clinical remission, X-ray normalisation and microbiological test negativity (N = 280).	Broad-spectrum beta-lactam in addition to aminoglycoside, but the majority of patients (60%) were treated with a combination of cephalosporin and aminoglycoside. Combinations included cephalosporin plus aminoglycoside, broad-spectrum penicillin plus aminoglycoside, narrow-spectrum penicillin plus aminoglycoside, clindamycin plus aminoglycoside. The cephalosporins were only specified as 'cefotaxime, cephalosporins with action against Gram-positive organisms, cephalosporins with action against Gram-negative organisms, cephalosporins active against pseudomonas, and cephalosporins active against anaerobes.' (N = 308). **Duration**: Continued until at least 3 days after clinical remission, X-ray normalisation and microbiological test negativity.	Onset of symptoms more than 72 hours after hospital admission.	• mortality • clinical cure at end of treatment; definition of clinical cure not reported	• For the outcome of mortality, the comparator group was comprised of different antibiotic combinations (although the comparator group was broad-spectrum beta-lactam in addition to aminoglycoside in 70% of patients). The mortality data for different combinations were not provided. • Patients receiving antibiotics within 7 days of disease onset and those in ITU were excluded from the study.
Rubinstein 1995[171]	Ceftazidime IV, 2 g twice daily (infusion or short-bolus injection). (N = 159).	Ceftriaxone IV, 2 g once daily plus tobramycin, loading dose 2 mg/kg then 3-5 mg/kg daily IV or IM. (N = 138).	Onset of symptoms more than 48 hours after hospital	• clinical cure at end of treatment; defined as	• *Post-hoc* subgroup analysis in patients with pneumonia. The full population included nosocomial bacterial pneumonia, sepsis or

	Duration Mean 9 days (range: 0 to 25).	**Duration** Mean 9 days (range: 0 to 25).	admission	complete resolution of signs and symptoms	severe upper urinary tract infection. • Across all groups, 43% required intensive care, and of these 65% were mechanically ventilated. • 39% of total population had received prior antibiotic therapy. • Metronidazole 500 mg 3-times daily could be added to both treatment groups.
Carbapenem compared with cephalosporin plus aminoglycoside					
Jaspers 1998[100]	Meropenem IV 1 g q8 h **Duration** up to 28 days (mean 7.5 days; range 3 to 21). (N = 20).	Cefuroxime IV 1.5 g q8 h in addition to gentamicin 4 mg/kg of body weight (dissolved in 100 ml of sterile isotonic saline) once daily or in 2 or 3 divided doses **Duration** up to 28 days (mean 7.4 days; range 3 to 17). (N = 21).	Onset of symptoms more than 48 hours after hospital admission	• clinical cure or improvement at end of treatment; defined as resolution or improvement of all signs and symptoms	• *Post-hoc* subgroup analysis in patients with pneumonia. The full population included patients with sepsis syndrome, intra-abdominal infection, LRTI, complicated urinary tract infection, and/or bacteraemia. • Patients were aged ≥ 65 years.

Table 154: Clinical evidence profile: Cephalosporin compared with cephalosporin plus aminoglycoside for patients with hospital-acquired pneumonia

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cephalosporin	Cephalosporin plus aminoglycoside	Relative (95% CI)	Absolute	Quality
Mortality (follow-up unclear) [Fernandez-Guerrero 1991]											
1	randomised trial	very serious[1]	no serious	very serious[2]	serious[3]	none	36/275 (13.1%)	52/273 (19%)	RR 0.69 (0.47 to 1.02)	59 fewer per 1000 (from 101 fewer to 4 more)	Very low
Clinical cure at end of treatment (follow-up unclear in one study, mean 9 days in the other) [Fernandez-Guerrero 1991; Rubinstein 1995]											
2	randomised trials	very serious[1]	no serious	no serious	serious[3]	none	309/434 (71.2%)	177/300 (59%)	RR 1.17 (1.05 to 1.3)	100 more per 1000 (from 29 more to 177 more)	Very low
Withdrawal due to adverse events											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Length of hospital stay											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Health-related quality-of-life											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Complications											
0	no evidence available	-	-	-	-	none	-	-	-	-	
***C. difficile*-associated diarrhoea**											

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cephalosporin	Cephalosporin plus aminoglycoside	Relative (95% CI)	Absolute	Quality
0	no evidence available	-	-	-	-	none	-	-	-	-	

[1] *Very high risk of bias; selection bias and unblinded*
[2] *Indirect comparison: comparator group comprised of different combination strategies (in 60% of patients, the comparator group was cephalosporin plus aminoglycoside)*
[3] *95% CI crosses 1 default MID*

Table 155: Clinical evidence profile: Carbapenem compared with cephalosporin plus aminoglycoside for patients with hospital-acquired pneumonia

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Carbapenem	Cephalosporin plus aminoglycoside	Relative (95% CI)	Absolute	Quality
Mortality											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Clinical cure or improvement at end of treatment (follow-up 28 days) [Jaspers 1998]											
1	randomised trial	very serious[1]	no serious	serious[2]	serious[3]	none	17/20 (85%)	16/21 (76.2%)	RR 1.12 (0.83 to 1.51)	91 more per 1000 (from 130 fewer to 389 more)	Very low
Withdrawal due to adverse events											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Length of hospital stay											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Health-related quality-of-life											
0	no evidence available	-	-	-	-	none	-	-	-	-	
Complications											
0	no evidence available	-	-	-	-	none	-	-	-	-	

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Carbapenem	Cephalosporin plus aminoglycoside	Relative (95% CI)	Absolute	Quality
***C. difficile*-associated diarrhoea**											
0	no evidence available	-	-	-	-	none	-	-	-	-	

[1] *Very high risk of bias; post-hoc analysis of pneumonia patients, attrition bias, and unblinded*
[2] *Indirect population; only included those aged ≥ 65 and may not all have CXR-confirmed diagnosis of pneumonia*
[3] *95% CI crosses 1 default MID*

18.5.2 Economic evidence

Published literature

No relevant economic evaluations comparing single with dual antibiotic therapy were identified for HAP.

Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided in Appendix O: to aid consideration of cost effectiveness.

18.5.3 Evidence statements

18.5.3.1 Clinical

18.5.3.1.1 Cephalosporin compared with cephalosporin plus aminoglycoside

- Very low quality evidence from 1 randomised trial of less than 600 patients with HAP suggested that there may be a survival benefit of single antibiotic therapy with a cephalosporin compared with dual antibiotic therapy with different antibiotic combinations (although the majority of patients were given the combination of a cephalosporin plus an aminoglycoside).
- Very low quality evidence from 2 randomised trials of more than 800 patients with HAP suggested that there may be a clinical benefit of single-antibiotic therapy with a cephalosporin compared with dual-antibiotic therapy with different antibiotic combinations (although the majority of patients were given the combination of a cephalosporin plus an aminoglycoside) for the outcome of clinical cure.

18.5.3.1.2 Carbapenem compared with cephalosporin plus aminoglycoside

- Very low quality evidence from 1 randomised trial indicated an increase in the rate of clinical cure or improvement with a carbapenem compared with dual-antibiotic therapy with cephalosporin plus aminoglycoside in patients with HAP.

18.5.3.2 Economic

- No relevant economic evaluations were identified.

18.6 Dual- compared with other dual-antibiotic therapy for hospital-acquired pneumonia

For full details see review protocol in Appendix C:.

18.6.1 Clinical evidence

We searched for systematic reviews of randomised controlled trials (RCTs), and RCTs comparing the effectiveness and safety of empirical therapy with 2 different classes of antibiotics for the treatment of pneumonia acquired in hospital. (see Appendix N: for classifications). Data were accepted for antibiotic therapy administered by the oral, intravenous or intramuscular routes.

One RCT was included in the review. In particular, this study was limited to patients with lower respiratory tract infection (LRTI), although more than 70% were diagnosed with pneumonia caused by bacteria suspected to be susceptible to study drugs.[104] Table 156 summarises the study details.

Evidence from the included study is summarised in the clinical GRADE evidence profile below (Table 157). No data were reported for the following outcomes: hospital admission, length of hospital stay, health-related quality-of-life, or complications.

See also the study selection flow chart in Appendix D:, forest plots in Appendix I:, study evidence tables in Appendix G:and exclusion list in Appendix J:.

Figure 15: Dual- compared with dual-antibiotic therapy for hospital-acquired pneumonia (click on hyperlinks or refer to page numbers)

	Cephalosporin plus aminoglycoside
Beta-lactamase stable penicillin plus aminoglycoside	• Piperacillin-tazobactam + tobramycin vs. ceftazidime + tobramycin Table 157, page 391

Table 156: Summary of studies included in the dual- compared with other dual-antibiotic therapy for patients with hospital-acquired pneumonia review

Study	Intervention N randomised	Comparison N randomised	Time of onset	Outcomes	Comments
Beta-lactamase stable penicillin plus aminoglycoside compared with cephalosporin plus aminoglycoside					
Joshi 1999[104]	Piperacillin-tazobactam 3 g/375 mg every 4 hours plus tobramycin IV 5 mg/kg/day given in divided doses every 8 hours. **Route of administration:** intravenous **Duration:** at least 5 days (mean 9 days). Mean duration of aminoglycoside therapy: 5.1 days (N = 155) (87% diagnosed with pneumonia).	Ceftazidime 2 g administered every 8 hours plus intravenous tobramycin 5 mg/kg/day given in divided doses every 8 hours. **Route of administration:** intravenous **Duration:** at least 5 days (mean 9 days). Mean duration of aminoglycoside therapy: 5.4 days. (N = 145) (72% diagnosed with pneumonia).	• Nosocomial LRTI onset ≥ 72 hours after hospitalisation.	• Mortality • clinical cure at end of follow-up; defined as completion of full course of therapy and complete recovery from acute infection • withdrawal due to adverse events • *C. difficile*–associated diarrhoea	• Limited to those with LRTI caused by bacteria suspected to be susceptible to study drugs. • Mixed population: 79% pneumonia and 21% bronchitis. • 36% of the sample had received antibiotic therapy within 72 hours of hospital admission. • In those with *P. aeruginosa* isolated from sputum at baseline, tobramycin was to be continued for the duration of the study. When a baseline isolate of *P. aeruginosa* was resistant to tobramycin, amikacin at a dose of 15 mg/kg/day could be substituted. Tobramycin could be discontinued in other patients after the baseline culture results were known.

Table 157: Clinical evidence profile: Beta-lactamase stable penicillin plus aminoglycoside compared with cephalosporin plus aminoglycoside for patients with hospital-acquired pneumonia

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Beta-lactamase stable penicillin plus aminoglycoside	Cephalosporin plus aminoglycoside	Relative (95% CI)	Absolute	Quality
Mortality (30 days after treatment) [Joshi 1999]											
1	randomised trial	serious[1]	no serious	serious[2]	serious[3]	none	12/155 (7.7%)	24/145 (16.6%)	RR 0.47 (0.24 to 0.9)	88 fewer per 1000 (from 17 fewer to 126 fewer)	Very low
Clinical cure at end of follow-up (follow-up 1 to 14 days after end of treatment) [Joshi 1999]											
1	randomised trial	very serious[4]	no serious	no serious	serious[3]	none	51/70 (72.9%)	22/42 (52.4%)	RR 1.39 (1.01 to 1.92)	204 more per 1000 (from 5 more to 482 more)	Very low
Withdrawal due to adverse events (follow-up up to 14 days after treatment) [Joshi 1999]											
1	randomised trial	serious[1]	no serious	serious[2]	very serious[5]	none	4/155 (2.6%)	7/145 (4.8%)	RR 0.53 (0.16 to 1.79)	23 fewer per 1000 (from 40 fewer to 38 more)	Very low
Hospital admission											
0	no evidence available					none	-	-	-		
Length of hospital stay											
0	no evidence available					none	-	-	-		
Health-related quality-of-life											
0	no					none	-	-	-		

Quality assessment							No of patients		Effect		
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Beta-lactamase stable penicillin plus aminoglycoside	Cephalosporin plus aminoglycoside	Relative (95% CI)	Absolute	Quality
	evidence available										
Complications											
0	no evidence available					none	-	-	-		
***C. difficile*-associated diarrhoea (follow-up up to 14 days after treatment) [Joshi 1999]**											
1	randomised trial	very serious[4]	no serious	no serious	no serious	none	0/70 (0%)	0/42 (0%)	not pooled	not pooled	Very low

[1] *Unclear allocation concealment and higher proportion with pneumonia in the piperacillin group (87% compared with 72%)*
[2] *Mixed population 79% pneumonia and 21% bronchitis, population may have been limited to those with bacteria susceptible to the study drugs*
[3] *95% CI crosses 1 default MID*
[4] *Post-hoc subgroup analysis in patients with pneumonia, unclear allocation concealment and unblinded*
[5] *95% CI crosses 2 default MIDs*

18.6.2 Economic evidence

Published literature

No relevant economic evaluations comparing dual with dual-antibiotic therapy were identified for patients with HAP.

Unit costs

In the absence of recent UK cost-effectiveness analysis, relevant unit costs are provided in Appendix O: to aid consideration of cost effectiveness.

18.6.3 Evidence statements

18.6.3.1 Clinical

18.6.3.1.1 Beta-lactamase stable penicillin plus aminoglycoside compared with cephalosporin plus aminoglycoside

- Very low quality evidence from 1 study of 300 patients with hospital-acquired lower respiratory tract infections (79% pneumonia) suggested that the combination of beta-lactamase stable penicillin plus aminoglycoside was clinically beneficial compared with cephalosporin plus aminoglycoside for reducing mortality but not for withdrawal due to adverse events.
- Very low quality evidence from a *post-hoc* subgroup analysis of patients with HAP showed that the combination of beta-lactamase stable penicillin plus aminoglycoside was beneficial for clinical cure compared with cephalosporin plus aminoglycoside.

18.6.3.2 Economic

- No relevant economic evaluations were identified.

18.7 Recommendations and link to the evidence

Table 158: Linking evidence to recommendations –combined antibiotic therapy data for hospital-acquired pneumonia

Recommendations	**26. Choose antibiotic therapy in accordance with local hospital policy (which should take into account knowledge of local microbial pathogens) and clinical circumstances for patients with hospital-acquired pneumonia.**
Relative values of different outcomes	The GDG considered mortality the most important outcome, with clinical cure, length of hospital stay and adverse events as other important outcomes.
Trade-off between clinical benefits and harms	Two RCTs compared different single-antibiotic therapy for HAP. One study suggested reduced mortality but increased adverse events with moxifloxacin compared with ceftriaxone. The other study suggested reduced mortality, and reduced withdrawal due to adverse events, as well as a clinically significant increase in cure with imipenem-cilastatin compared with piperacillin-tazobactam. Three RCTs compared single- and dual-antibiotic therapy for treatment of HAP were considered. One study showed reduced mortality with cephalosporin compared with broad-spectrum beta-lactam plus aminoglycoside, and results from 2 studies suggested an increase in clinical cure at end of treatment for the

	cephalosporin group. A further study suggested that single-antibiotic therapy with carbapenem may increase cure rate compared with broad-spectrum beta-lactam plus aminoglycoside. One RCT compared dual-antibiotic therapies; piperacillin-tazobactam plus tobramycin compared with ceftazidime plus tobramycin. The study found reduced mortality and improved clinical cure rates in the piperacillin-tazobactam and tobramycin arm, with no clear difference in withdrawal due to adverse events.
Trade-off between net health benefits and resource use	No economic studies were identified for this review. Due to the high mortality rate, the GDG acknowledged that if an antibiotic or combination of antibiotics is more effective at reducing mortality, without causing other adverse events, this is likely to be cost effective.
Quality of evidence	The evidence examining different single-antibiotic comparisons was of low or very low quality by GRADE criteria. Both studies were designed to detect non-inferiority rather than superiority, and as pooling of data was not possible the data remained underpowered to detect a difference between interventions in statistical terms. Neither study included a UK patient population. The studies comparing single- with dual-antibiotic therapy were of very low quality by GRADE criteria. Two of the 3 studies had conducted *post-hoc* subgroup analyses in patients with HAP. The GDG noted that the studies were published during or prior to 1998, when the profile of HAP pathogens may have differed substantially from those currently seen in clinical practice. The study comparing different dual-antibiotic combinations was of very low quality by GRADE criteria. The GDG noted numerous problems with the study. Only patients with pathogens suspected to be susceptible to treatment were included. The study was conducted in North America, and included patients with hospital-acquired lower respiratory tract infections as well as patients with pneumonia. Perhaps because of the inclusion of these patients, who did not have CXR evidence of pneumonia, the spectrum of pathogens was not representative of those expected in UK patients with HAP, with *H. influenzae* and *S. pneumoniae* frequently identified. A *post-hoc* subgroup analysis (which increases the risk of bias) in patients with pneumonia was conducted to assess the outcome of clinical cure. In addition, half of the patients were deemed “not evaluable” for the main outcomes. Overall, the GDG agreed that the methodology of the study was sufficiently flawed for the findings not to influence to the GDG’s considerations. No economic evidence was found for this question.
Other considerations	The GDG noted that many antibiotic regimens currently used for HAP in the UK had not been considered, and that resistance profiles in pathogens in HAP may be significantly different now to when the included studies had been performed. The GDG expressed concerns regarding the quality and relevance of the evidence. In the absence of any clear benefit of any one single- or dual-antibiotic strategy in the published evidence, the GDG agreed that hospital practitioners should prescribe in accordance with local guidance based on local resistance patterns and patient characteristics, and that a national recommendation would not be helpful. The GDG agreed that a research recommendation in this area is high priority.

18.8 Research recommendation

4. Can rapid microbiological diagnosis of hospital-acquired pneumonia reduce the use of extended-spectrum antibiotic therapy, without adversely affecting outcomes?

Why this is important:

Data are limited on the microbiology of hospital-acquired pneumonia to guide antibiotic therapy. Hospital-acquired infections can be caused by highly resistant pathogens that need treatment with extended-spectrum antibiotics (for example extended-spectrum penicillins, third-generation cephalosporins, aminoglycosides, carbapenems, linezolid, vancomycin, or teicoplanin), as recommended by British Society of Antimicrobial Chemotherapy guidance. Because routine microbial tests lack sensitivity and take 24-48 hours to identify a causative pathogen, patient characteristics are used to guide antibiotic choice. However, this may lead to unnecessary use of extended-spectrum antibiotics in patients infected with non-resistant organisms, and inappropriate use of first-line antibiotics (such as beta-lactam stable penicillins, macrolides or doxycycline) in patients infected with resistant organisms.

Rapid diagnostic tests to identify causative bacterial pathogens and determine whether they are resistant to antibiotics may have a role in guiding antibiotic choice for postoperative hospital-acquired pneumonia.

To limit population variability and include high-risk patients spending time in intensive care, studies should include postoperative patients from different surgical specialties.

18.9 Duration of antibiotic therapy for hospital-acquired pneumonia

18.10 In adults with hospital-acquired pneumonia what is the clinical and cost effectiveness of short- compared with longer-course antibiotics?

No data were identified to inform this review, but the GDG considered whether the evidence for patients with low-severity community-acquired pneumonia (CAP) could be helpful in informing a recommendation for this different patient population.

18.10.1 Recommendations and link to evidence

Table 159: Linking evidence to recommendations – duration of antibiotic therapy for hospital-acquired pneumonia

Recommendations	27. Consider a 5- to 10-day course of antibiotic therapy for patients with hospital-acquired pneumonia.
Relative values of different outcomes	The GDG considered mortality the most important outcome, with clinical cure and adverse events considered other important outcomes.
Trade-off between clinical benefits and harms	No suitable studies examining the optimal duration of antibiotic therapy in HAP were available.
Economic considerations	Whilst drug costs in HAP are generally higher than in CAP, the GDG agreed that the most clinically effective duration was still likely to be the most cost effective due to the serious consequences of ineffective treatment.
Quality of evidence	No suitable clinical evidence was available. No economic evidence was found on this question.
Other considerations	The recommendation for 5- to-10 days of antibiotic therapy for HAP was reached by consensus opinion. The GDG agreed that the optimal course duration of antibiotic therapy is likely to vary. Decisions should primarily be based on response to

	treatment, though disease severity, co-morbidity and risk of antibiotic-related complications should also be considered.

19 Glucocorticosteroid treatment

19.1 In adults with community-acquired pneumonia or hospital-acquired pneumonia requiring management in hospital, what is the clinical and cost effectiveness of initial glucocorticosteroid treatment in addition to antibiotic treatment compared with antibiotic treatment alone?

Please see section 11 for an introduction.

Please see Appendix C: for review protocol.

No relevant evidence was identified.

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21 Acronyms and abbreviations

AHR	Adjusted hazard ratio
AMI	Acute myocardial infarction
AOR	Adjusted odds ratio
APACHE II	Acute Physiology and Chronic Health Evaluation II
ARF	Acute respiratory failure
ARI	Acute respiratory infection
ATS	American Thoracic Society
BID	Twice a day
BP	Blood pressure
CAP	Community-acquired pneumonia
CHF	Chronic heart failure
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CPAP	Continuous positive airway pressure
CRP	C-reactive protein
CVA	Cerebrovascular accident
CXR	Chest X-ray
DBP	Diastolic blood pressure
ED	Emergency department
EWS	Early warning score
GDG	Guideline development group
HAP	Hospital-acquired pneumonia
HIV	Human immunodeficiency virus
HQoL	Health-related quality-of-life
HR	Hazard ratio
ICER	Incremental cost-effectiveness ratio
ITU	Intensive care unit
IDSA	Infectious Disease Society of America

IGF-1	Insulin-like growth factor-1
IL-6	Interleukin 6
IM	Intramuscular
IPD	Individual patient data
IRVS	Intensive respiratory or vasopressor support
ITU	Intensive treatment unit
IV	Intravenous
LFC	Long-term care facilities
LgAG	Legionella antigen
LOS	Length of stay
LRTI	Lower respiratory tract infection
MEWS	Modified early warning score
MID	Minimal important difference
MODS	Multiple Organ Dysfunction Syndrome
NA	Not applicable
NIV	Non-invasive ventilation
NMA	Network meta-analysis
NMB	Net monetary benefit
NR	Not reported
OR	Odds ratio
PCT	Procalcitonin
PnAG	Pneumoccocal antigen
PO	Oral
PSA	Probabilistic sensitivity analysis
PSI	Pneumonia severity index
QALY	Quality-adjusted life year
QOL	Quality-of-life
RCT	Randomised controlled trial
RR	Relative risk
SA	Sensitivity analysis

SBP	Systolic blood pressure
SCAP	Severe community-acquired pneumonia
SE	Standard error
SEWS	Standardised early warning score
SIRS	Systemic inflammatory response syndrome
SOFA	Sepsis-Related/Sequential Organ Failure Assessment Score.
Strem-1	Serum soluble triggering receptor expressed on myeloid cells-1
TFAD	Time to first antibiotic dose
TNFα	Tumour necrosis factor alpha
URTI	Upper respiratory tract infection
VAP	Ventilatory-acquired pneumonia
WBC	White blood cell
SEWS	Adjusted hazard ratio

22 Glossary

Abstract	Summary of a study, which may be published alone or as an introduction to a full scientific paper.
A-DROP score	Severity scoring system developed by the Japanese respiratory society that includes the following parameters: Age (male ≥ 70 years, female ≥ 75 years) Dehydration (blood urea nitrogen (BUN) ≥ 210 mg/l) Respiratory failure (SaO2 ≤ 90% or PaO2 ≤ 60 mm Hg) Orientation disturbance (confusion) Low blood Pressure (SBP ≤ 90 mm Hg).
American Thoracic Society (ATS) severity criteria	Severity assessment tool including major criteria (invasive ventilation, septic shock) and minor criteria (low systolic blood pressure ≤ 90 mmHg, multilobar disease, PaO2/FiO2 ratio ≤ 250).
American Thoracic Society (ATS) 2001 criteria of clinical stability	Criteria of clinical stability including the following variables: improved symptoms of pneumonia (cough and shortness of breath), lack of fever for at least 8 h, improving leucocytosis (decrease at least 10% from the previous day).
APACHE II	Severity assessment tool developed to predict ITU mortality.
Attrition bias	Systematic differences between comparison groups in withdrawals or exclusions of participants from a study.
Atypical organisms/pathogens:	Organisms that may be regarded as unusual causes of pneumonia including *Mycoplasma pneumoniae, Coxiella burnetii, Chlamydophila pneumoniae, Chlamydophila psittaci*.
AUC	Area under the curve of a receiver operating characteristics (ROC) curve. See 'ROC'.
Allocation concealment	The process used to prevent advance knowledge of group assignment in an RCT. The allocation process should be impervious to any influence by the individual making the allocation, by being administered by someone who is not responsible for recruiting participants.
Applicability	How well the results of a study or NICE evidence review can answer a clinical question or be applied to the population being considered.
Arm (of a clinical study)	Subsection of individuals within a study who receive one particular intervention, for example placebo arm
Association	Statistical relationship between 2 or more events, characteristics or other variables. The relationship may or may not be causal.
Available case analysis (ACA)	Analysis of data that is available for participants at the end of follow-up.
Baseline	The initial set of measurements at the beginning of a study (after run-in period where applicable), with which subsequent results are compared.
Before-and-after study	A study that investigates the effects of an intervention by measuring particular characteristics of a population both before and after taking the intervention, and assessing any change that occurs.
Bias	Influences on a study that can make the results look better or worse than they really are. (Bias can even make it look as if a treatment works when it does not.) Bias can occur by chance, deliberately or as a result of systematic

	errors in the design and execution of a study. It can also occur at different stages in the research process, for example, during the collection, analysis, interpretation, publication or review of research data. For examples see selection bias, performance bias, information bias, confounding factor, and publication bias.
Blinding	A way to prevent researchers, doctors and patients in a clinical trial from knowing which study group each patient is in so they cannot influence the results. The best way to do this is by sorting patients into study groups randomly. The purpose of 'blinding' or 'masking' is to protect against bias. A single-blinded study is one in which patients do not know which study group they are in (for example whether they are taking the experimental drug or a placebo). A double-blinded study is one in which neither patients nor the researchers/doctors know which study group the patients are in. A triple blind study is one in which neither the patients, clinicians or the people carrying out the statistical analysis know which treatment patients received.
Carer (caregiver)	Someone who looks after family, partners or friends in need of help because they are ill, frail or have a disability.
Case–control study	A study to find out the cause(s) of a disease or condition. This is done by comparing a group of patients who have the disease or condition (cases) with a group of people who do not have it (controls) but who are otherwise as similar as possible (in characteristics thought to be unrelated to the causes of the disease or condition). This means the researcher can look for aspects of their lives that differ to see if they may cause the condition. For example, a group of people with lung cancer might be compared with a group of people the same age that do not have lung cancer. The researcher could compare how long both groups had been exposed to tobacco smoke. Such studies are retrospective because they look back in time from the outcome to the possible causes of a disease or condition.
Case series	Report of a number of cases of a given disease, usually covering the course of the disease and the response to treatment. There is no comparison (control) group of patients.
Chest X-ray (CXR)	Chest X-ray. Chest radiograph used to diagnose pneumonia.
Clinical efficacy	The extent to which an intervention is active when studied under controlled research conditions.
Clinical effectiveness	How well a specific test or treatment works when used in the 'real world' (for example, when used by a doctor with a patient at home), rather than in a carefully controlled clinical trial. Trials that assess clinical effectiveness are sometimes called management trials. Clinical effectiveness is not the same as efficacy.
Clinician	A healthcare professional who provides patient care. For example, a doctor, nurse or physiotherapist.
Cochrane Review	The Cochrane Library consists of a regularly updated collection of evidence-based medicine databases including the Cochrane Database of Systematic Reviews (reviews of randomised controlled trials prepared by the Cochrane Collaboration).
Cohort study	A study with 2 or more groups of people – cohorts – with similar characteristics. One group receives a treatment, is exposed to a risk factor or has a particular symptom and the other group does not. The study follows their progress over time and records what happens. See also

	observational study.
Community-acquired pneumonia (CAP)	CAP is defined as pneumonia not acquired in a hospital or a long-term care facility.
Comorbidity	A disease or condition that someone has in addition to the health problem being studied or treated.
Comparability	Similarity of the groups in characteristics likely to affect the study results (such as health status or age).
Concealment of allocation	The process used to ensure that the person deciding to enter a participant into a randomised controlled trial does not know the comparison group into which that individual will be allocated. This is distinct from blinding, and is aimed at preventing selection bias. Some attempts at concealing allocation are more prone to manipulation than others, and the method of allocation concealment is used as an assessment of the quality of a trial.
Confidence interval (CI)	There is always some uncertainty in research. This is because a small group of patients is studied to predict the effects of a treatment on the wider population. The confidence interval is a way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. The CI is usually stated as '95% CI', which means that the range of values has a 95 in a 100 chance of including the 'true' value. For example, a study may state that 'based on our sample findings, we are 95% certain that the 'true' population blood pressure is not higher than 150 and not lower than 110'. In such a case the 95% CI would be 110 to 150. A wide confidence interval indicates a lack of certainty about the true effect of the test or treatment - often because a small group of patients has been studied. A narrow confidence interval indicates a more precise estimate (for example, if a large number of patients have been studied).
Confounding factor	Something that influences a study and can result in misleading findings if it is not understood or appropriately dealt with. For example, a study of heart disease may look at a group of people that exercises regularly and a group that does not exercise. If the ages of the people in the 2 groups are different, then any difference in heart disease rates between the 2 groups could be because of age rather than exercise. Therefore age is a confounding factor.
Consensus methods	Techniques used to reach agreement on a particular issue. Consensus methods may be used to develop NICE guidance if there is not enough good quality research evidence to give a clear answer to a question. Formal consensus methods include Delphi and nominal group techniques.
Continuous outcome	Data with a potentially infinite number of possible values within a given range. Height, weight and blood pressure are examples of continuous variables.
Continuous positive airway pressure (CPAP)	Gas exchange augmentation technique that delivers air (or oxygen-enriched air) at a constant pressure.
Control group	A group of people in a study who do not receive the treatment or test being studied. Instead, they may receive the standard treatment (sometimes called 'usual care') or a dummy treatment (placebo). The results for the control group are compared with those for a group receiving the treatment being tested. The aim is to check for any differences. Ideally, the people in the control group should be as similar as possible to those in the treatment group, to make it as easy as possible to detect any

	effects due to the treatment.
CORB	Severity assessment tool including: confusional state (acute), oxygen saturation < 90% in room air, respiratory rate ≥ 30/min, systolic blood pressure (SBP) < 90mmHg or diastolic blood pressure (DBP) < 60mmHg.
Cost–benefit analysis (CBA)	Cost-benefit analysis is one of the tools used to carry out an economic evaluation. The costs and benefits are measured using the same monetary units (for example, pounds sterling) to see whether the benefits exceed the costs.
Cost–consequences analysis (CCA)	Cost-consequence analysis is one of the tools used to carry out an economic evaluation. This compares the costs (such as treatment and hospital care) and the consequences (such as health outcomes) of a test or treatment with a suitable alternative. Unlike cost-benefit analysis or cost-effectiveness analysis, it does not attempt to summarise outcomes in a single measure (like the quality-adjusted life year) or in financial terms. Instead, outcomes are shown in their natural units (some of which may be monetary) and it is left to decision-makers to determine whether, overall, the treatment is worth carrying out.
Cost-effectiveness analysis (CEA)	Cost-effectiveness analysis is one of the tools used to carry out an economic evaluation. The benefits are expressed in non-monetary terms related to health, such as symptom-free days, heart attacks avoided, deaths avoided or life years gained (that is, the number of years by which life is extended as a result of the intervention).
Cost-effectiveness model	An explicit mathematical framework, which is used to represent clinical decision problems and incorporate evidence from a variety of sources in order to estimate the costs and health outcomes.
Cost–utility analysis (CUA)	Cost-utility analysis is one of the tools used to carry out an economic evaluation. The benefits are assessed in terms of both quality and duration of life, and expressed as quality-adjusted life years (QALYs). See also utility.
COX proportional hazard model	In survival analysis, a statistical model that asserts that the effect of the study factors (for example the intervention of interest) on the hazard rate (the risk of occurrence of an event) in the study population is multiplicative and does not change over time.
Credible interval (CrI)	The Bayesian equivalent of a confidence interval.
CURB	Severity assessment tool including: confusion, urea, respiratory rate, blood pressure
CURB65	Severity assessment tool including: confusion, urea, respiratory rate, blood pressure, age over 65 years.
Decision analysis	An explicit quantitative approach to decision-making under uncertainty, based on evidence from research. This evidence is translated into probabilities, and then into diagrams or decision trees which direct the clinician through a succession of possible scenarios, actions and outcomes.
Dichotomous outcomes	Outcome that can take one of two possible values, such as dead/alive, smoker/non-smoker, present/not present (also called binary data).
Discounting	Costs and perhaps benefits incurred today have a higher value than costs and benefits occurring in the future. Discounting health benefits reflects individual preference for benefits to be experienced in the present rather than the future. Discounting costs reflects individual preference for costs to be experienced in the future rather than the present.
Dominance	A health economics term. When comparing tests or treatments, an option

	that is both less effective and costs more is said to be 'dominated' by the alternative.
Drop-out	A participant who withdraws from a trial before the end.
Economic evaluation	An economic evaluation is used to assess the cost effectiveness of healthcare interventions (that is, to compare the costs and benefits of a healthcare intervention to assess whether it is worth doing). The aim of an economic evaluation is to maximise the level of benefits - health effects - relative to the resources available. It should be used to inform and support the decision-making process; it is not supposed to replace the judgement of healthcare professionals. There are several types of economic evaluation: cost-benefit analysis, cost-consequence analysis, cost-effectiveness analysis, cost-minimisation analysis and cost-utility analysis. They use similar methods to define and evaluate costs, but differ in the way they estimate the benefits of a particular drug, programme or intervention.
Effect (as in effect measure, treatment effect, estimate of effect, effect size)	A measure that shows the magnitude of the outcome in one group compared with that in a control group. For example, if the absolute risk reduction is shown to be 5% and it is the outcome of interest, the effect size is 5%. The effect size is usually tested, using statistics, to find out how likely it is that the effect is a result of the treatment and has not just happened by chance (that is, to see if it is statistically significant).
Effectiveness	How beneficial a test or treatment is under usual or everyday conditions, compared with doing nothing or opting for another type of care.
Efficacy	How beneficial a test, treatment or public health intervention is under ideal conditions (for example, in a laboratory), compared with doing nothing or opting for another type of care.
Epidemiological study	The study of a disease within a population, defining its incidence and prevalence and examining the roles of external influences (for example, infection, diet) and interventions.
EQ-5D (EuroQol 5 dimensions)	A standardised instrument used to measure health-related quality-of-life. It provides a single index value for health status.
Equivalence study	A trial designed to determine whether the response to two or more treatments differs by an amount that is clinically unimportant. This is usually demonstrated by showing that the true treatment difference is likely to lie between a lower and an upper equivalence level of clinically acceptable differences.
Evidence	Information on which a decision or guidance is based. Evidence is obtained from a range of sources including randomised controlled trials, observational studies, expert opinion (of clinical professionals or patients).
Exclusion criteria (literature review)	Explicit standards used to decide which studies should be excluded from consideration as potential sources of evidence.
Exclusion criteria (clinical study)	Criteria that define who is not eligible to participate in a clinical study.
Extended dominance	If Option A is both more clinically effective than Option B and has a lower cost per unit of effect, when both are compared with a do-nothing alternative then Option A is said to have extended dominance over Option B. Option A is therefore more cost effective and should be preferred, other things remaining equal.

Extrapolation	An assumption that the results of studies of a specific population will also hold true for another population with similar characteristics.
Fixed-effect model	In meta-analysis, a model that calculates a pooled effect estimate using the assumption that all observed variation between studies is caused by the play of chance. Studies are assumed to be measuring the same overall effect.
Follow-up	Observation over a period of time of an individual, group or initially defined population whose appropriate characteristics have been assessed in order to observe changes in health status or health-related variables.
Forest plot	A graphical representation of the individual results of each study included in a meta-analysis together with the combined meta-analysis result. The plot also allows readers to see the heterogeneity among the results of the studies. The results of individual studies are shown as squares centred on each study's point estimate. A horizontal line runs through each square to show each study's confidence interval. The overall estimate from the meta-analysis and its confidence interval are shown at the bottom, represented as a diamond. The centre of the diamond represents the pooled point estimate, and its horizontal tips represent the confidence interval.
Generalisability	The extent to which the results of a study hold true for groups that did not participate in the research. See also external validity.
Gold standard	A method, procedure or measurement that is widely accepted as being the best available to test for or treat a disease.
GRADE, GRADE profile	A system developed by the GRADE Working Group to address the shortcomings of present grading systems in healthcare. The GRADE system uses a common, sensible and transparent approach to grading the quality of evidence. The results of applying the GRADE system to clinical trial data are displayed in a table known as a GRADE profile.
Halm criteria of clinical stability	A measure of effect produced by a survival analysis. This represents the increased risk with which one group is likely to experience the outcome of interest.
Harms	Adverse effects of an intervention.
Hazard ratio	A graphical representation of the individual results of each study included in a meta-analysis together with the combined meta-analysis result. The plot also allows readers to see the heterogeneity among the results of the studies. The results of individual studies are shown as squares centred on each study's point estimate. A horizontal line runs through each square to show each study's confidence interval. The overall estimate from the meta-analysis and its confidence interval are shown at the bottom, represented as a diamond. The centre of the diamond represents the pooled point estimate, and its horizontal tips represent the confidence interval.
Healthcare-associated pneumonia (HCAP)	HCAP includes patients who have recently been hospitalised within 90 days of the infection, resided in a nursing home or long-term care facility, or received parenteral antimicrobial therapy, chemotherapy, or wound care within 30 days of pneumonia
Health economics	Study or analysis of the cost of using and distributing healthcare resources.
Health-related quality-of-life (HRQoL)	A measure of the effects of an illness to see how it affects someone's day-to-day life.
Heterogeneity or Lack of homogeneity	The term is used in meta-analyses and systematic reviews to describe when the results of a test or treatment (or estimates of its effect) differ

	significantly in different studies. Such differences may occur as a result of differences in the populations studied, the outcome measures used or because of different definitions of the variables involved. It is the opposite of homogeneity.
Hospital acquired pneumonia (HAP)	HAP is defined as pneumonia that occurs 48 hours or more after hospital admission and that was not present at the time of admission.
Imprecision	Results are imprecise when studies include relatively few patients and few events and thus have wide confidence intervals around the estimate of effect.
Inclusion criteria (literature review)	Explicit criteria used to decide which studies should be considered as potential sources of evidence.
Incremental analysis	The analysis of additional costs and additional clinical outcomes with different interventions.
Incremental cost	The extra cost linked to using one test or treatment rather than another. Or the additional cost of doing a test or providing a treatment more frequently.
Incremental cost-effectiveness ratio (ICER)	The difference in the mean costs in the population of interest divided by the differences in the mean outcomes in the population of interest for one treatment compared with another.
Incremental net benefit (INB)	The value (usually in monetary terms) of an intervention net of its cost compared with a comparator intervention. The INB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the INB is calculated as: (£20,000 x QALYs gained) – Incremental cost.
Indirectness	The available evidence is different to the review question being addressed, in terms of PICO (population, intervention, comparison and outcome).
Individual patient data (IPD)	In meta-analysis, the availability of raw data for each study participant in each included study, as opposed to aggregate data (summary data for the comparison groups in each study).
Infectious Diseases Society of America (IDSA)/ American Thoracic Society (ATS)	Severity assessment tool including: major criteria (invasive ventilation, septic shock) and minor criteria (raised respiratory rate (≥ 30 per min), PaO_2/FiO_2 ratio ≤ 250, multilobar radiographic shadowing, confusion or disorientation, uraemia (blood urea nitrogen ≥ 20 mg/dL), leukopenia (< 4000 WBCs/mm3), thrombocytopenia (< 100,000 platelets/mm^3), hypothermia (temperature < 36°C), hypotension requiring resuscitation).
Intention-to-treat analysis (ITT)	An assessment of the people taking part in a clinical trial, based on the group they were initially (and randomly) allocated to. This is regardless of whether or not they dropped out, fully complied with the treatment or switched to an alternative treatment. Intention-to-treat analyses are often used to assess clinical effectiveness because they mirror actual practice: that is, not everyone complies with treatment and the treatment people receive may be changed according to how they respond to it.
Intervention	In medical terms this could be a drug treatment, surgical procedure, diagnostic or psychological therapy. Examples of public health interventions could include action to help someone to be physically active or to eat a more healthy diet.
Intraoperative	The period of time during a surgical procedure.
Kappa statistic	A statistical measure of inter-rater agreement that takes into account the agreement occurring by chance.

Length of stay	The total number of days a participant stays in hospital.
Licence	See 'Product licence'.
Life years gained	Mean average years of life gained per person as a result of the intervention compared with an alternative intervention.
Likelihood ratio	The likelihood ratio combines information about the sensitivity and specificity. It tells you how much a positive or negative result changes the likelihood that a patient would have the disease. The likelihood ratio of a positive test result (LR+) is sensitivity divided by (1 minus specificity).
Long-term care	Residential care in a home that may include skilled nursing care and help with everyday activities. This includes nursing homes and residential homes.
Loss to follow-up	Patients who have withdrawn from the clinical trial at the point of follow-up.
Markov model	A method for estimating long-term costs and effects for recurrent or chronic conditions, based on health states and the probability of transition between them within a given time period (cycle).
Mean	An average value, calculated by adding all the observations and dividing by the number of observations.
Mean difference	In meta-analysis, a method used to combine measures on continuous scales (such as weight), where the mean, standard deviation and sample size in each group are known. The weight given to the difference in means from each study (e.g. how much influence each study has on the overall results of the meta-analysis) is determined by the precision of its estimate of effect.
Median	The value of the observation that comes half way when the observations are ranked in order.
Meta-analysis	A method often used in systematic reviews. Results from several studies of the same test or treatment are combined to estimate the overall effect of the treatment.
Minimal important difference (MID)	Thresholds for clinical importance, which represent minimal important differences for benefit or for harm; e.g. the threshold at which drug A is less effective than drug B by an amount that is clinically important to patients.
Multivariate model	A statistical model for analysis of the relationship between 2 or more predictor (independent) variables and the outcome (dependent) variable.
Negative predictive value (NPV)	In screening or diagnostic tests: A measure of the usefulness of a screening or diagnostic test. It is the proportion of those with a negative test result who do not have the disease, and can be interpreted as the probability that a negative test result is correct. It is calculated as follows:
Net monetary benefit (NMB)	The value (usually in monetary terms) of an intervention net of its cost. The NMB can be calculated for a given cost-effectiveness (willingness to pay) threshold. If the threshold is £20,000 per QALY gained then the NMB is calculated as: (£20,000 x QALYs gained) – cost.
Network meta-analysis	Meta-analysis in which multiple treatments (that is, three or more) are being compared using both direct comparisons of interventions within randomised controlled trials and indirect comparisons across trials based on a common comparator.
Non-inferiority trial	A trial designed to determine whether the effect of a new treatment is not worse than a standard treatment by more than a pre-specified amount. A one-sided version of an equivalence trial.

Non-invasive ventilation (NIV)	Gas exchange augmentation technique that delivers air (or oxygen-enriched air) at bi-level positive airway pressure at 2 different levels - a higher pressure on inspiration and a lower pressure on expiration.
Number needed to treat (NNT)	The average number of patients who need to be treated to get a positive outcome. For example, if the NNT is 4, then 4 patients would have to be treated to ensure 1 of them gets better. The closer the NNT is to 1, the better the treatment. For example, if you give a stroke prevention drug to 20 people before 1 stroke is prevented, the number needed to treat is 20. See also number needed to harm, absolute risk reduction.
Nursing home-associated pneumonia (NHAP)	Pneumonia acquired during a patient stay at nursing home facilities.
Observational study	Individuals or groups are observed or certain factors are measured. No attempt is made to affect the outcome. For example, an observational study of a disease or treatment would allow 'nature' or usual medical care to take its course. Changes or differences in one characteristic (for example, whether or not people received a specific treatment or intervention) are studied without intervening. There is a greater risk of selection bias than in experimental studies.
Odds ratio	Odds are a way to represent how likely it is that something will happen (the probability). An odds ratio compares the probability of something in one group with the probability of the same thing in another. An odds ratio of 1 between 2 groups would show that the probability of the event (for example a person developing a disease, or a treatment working) is the same for both. An odds ratio greater than 1 means the event is more likely in the first group. An odds ratio less than 1 means that the event is less likely in the first group. Sometimes probability can be compared across more than 2 groups - in this case, one of the groups is chosen as the 'reference category', and the odds ratio is calculated for each group compared with the reference category. For example, to compare the risk of dying from lung cancer for non-smokers, occasional smokers and regular smokers, non-smokers could be used as the reference category. Odds ratios would be worked out for occasional smokers compared with non-smokers and for regular smokers compared with non-smokers. See also confidence interval, relative risk, risk ratio.
Opportunity cost	The loss of other health care programmes displaced by investment in or introduction of another intervention. This may be best measured by the health benefits that could have been achieved had the money been spent on the next best alternative healthcare intervention.
Outcome	The impact that a test, treatment, policy, programme or other intervention has on a person, group or population. Outcomes from interventions to improve the public's health could include changes in knowledge and behaviour related to health, societal changes (for example, a reduction in crime rates) and a change in people's health and wellbeing or health status. In clinical terms, outcomes could include the number of patients who fully recover from an illness or the number of hospital admissions, and an improvement or deterioration in someone's health, functional ability, symptoms or situation. Researchers should decide what outcomes to measure before a study begins.
P value	The p value is a statistical measure that indicates whether or not an effect is statistically significant.

	For example, if a study comparing 2 treatments found that one seems more effective than the other, the p value is the probability of obtaining these results by chance. By convention, if the p value is below 0.05 (that is, there is less than a 5% probability that the results occurred by chance) it is considered that there probably is a real difference between treatments. If the p value is 0.001 or less (less than a 1% probability that the results occurred by chance), the result is seen as highly significant. If the p value shows that there is likely to be a difference between treatments, the confidence interval describes how big the difference in effect might be.
PaO_2/FiO_2 ratio	The ratio of partial pressure arterial oxygen and fraction of inspired oxygen measures the oxygen level in the blood compared with the oxygen concentration that is breathed, and it is used to identify respiratory failure.
Performance bias	Systematic differences between intervention groups in care provided apart from the intervention being evaluated. Blinding of study participants (both the recipients and providers of care) is used to protect against performance bias.
Perioperative	The period from admission through surgery until discharge, encompassing the pre-operative and post-operative periods.
Peto odds ratio	A way of combining odds ratios in meta-analysis when either intervention or control groups have no experience of events.
Placebo	A fake (or dummy) treatment given to participants in the control group of a clinical trial. It is indistinguishable from the actual treatment (which is given to participants in the experimental group). The aim is to determine what effect the experimental treatment has had - over and above any placebo effect caused because someone has received (or thinks they have received) care or attention.
Pneumonia severity index (PSI)	A scoring system used to determine mortality risk associated with pneumonia in hospital that includes the following variables: Demographics – age, sex, nursing home resident Comorbidities – neoplastic disease, liver disease, congestive heart failure, cerebrovascular disease, renal disease Examination findings – altered mental status, respiratory rate ≥ 30 per minute, systolic blood pressure < 90 mmHg, temperature < 35oC or ≥ 40oC, pulse ≥ 125 beats per minute Laboratory findings – pH < 7.35 (do ABG only if hypoxic), blood urea ≥ 10.7 mmol/L, sodium < 130 mEq/L, glucose ≥ 13.9 mmol/L, haematocrit < 0.30, PaO_2 < 60 mmHg or oxygen saturation < 90%, pleural effusion.
Polypharmacy	The use or prescription of multiple medications.
Positive predictive value (PPV)	In screening or diagnostic tests: A measure of the usefulness of a screening or diagnostic test. It is the proportion of those with a positive test result who have the disease, and can be interpreted as the probability that a positive test result is correct. It is calculated as follows:
Post-hoc analysis	Statistical analyses that are not specified in the trial protocol, and are generally suggested by the data.
Post-operative	Pertaining to the period after patients leave the operating theatre, following surgery.
Post-test probability	In diagnostic tests: The proportion of patients with that particular test result

	who have the target disorder (post-test odds/[1 plus post-test odds]).
Power (statistical)	The ability to demonstrate an association when one exists. Power is related to sample size; the larger the sample size, the greater the power and the lower the risk that a possible association could be missed.
Preoperative	The period before surgery commences.
Pre-test probability	In diagnostic tests: The proportion of people with the target disorder in the population at risk at a specific time point or time interval. Prevalence may depend on how a disorder is diagnosed.
Primary care	Healthcare delivered outside hospitals. It includes a range of services provided by GPs, nurses, health visitors, midwives and other healthcare professionals and allied health professionals such as dentists, pharmacists and opticians.
Primary outcome	The outcome of greatest importance, usually the one in a study that the power calculation is based on.
Product licence	An authorisation from the MHRA to market a medicinal product.
Prognosis	A probable course or outcome of a disease. Prognostic factors are patient or disease characteristics that influence the course. Good prognosis is associated with low rate of undesirable outcomes; poor prognosis is associated with a high rate of undesirable outcomes.
Prospective study	A research study in which the health or other characteristic of participants is monitored (or 'followed up') for a period of time, with events recorded as they happen. This contrasts with retrospective studies.
Publication bias	Publication bias occurs when researchers publish the results of studies showing that a treatment works well and don't publish those showing it did not have any effect. If this happens, analysis of the published results will not give an accurate idea of how well the treatment works. This type of bias can be assessed by a funnel plot.
Quality-of-life	See ‘Health-related quality-of-life’.
Quality-adjusted life year (QALY)	A measure of the state of health of a person or group in which the benefits, in terms of length of life, are adjusted to reflect the quality-of-life. One QALY is equal to 1 year of life in perfect health. QALYS are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a scale of 0 to 1). It is often measured in terms of the person's ability to perform the activities of daily life, freedom from pain and mental disturbance.
RAND-36	Survey instrument used to measure health-related quality-of-life, comprised of 36 items that assess eight health concepts: physical functioning, role limitations caused by physical health problems, role limitations caused by emotional problems, social functioning, emotional well-being, energy/fatigue, pain, and general health perceptions.
Randomisation	Assigning participants in a research study to different groups without taking any similarities or differences between them into account. For example, it could involve using a random numbers table or a computer-generated random sequence. It means that each individual (or each group in the case of cluster randomisation) has the same chance of receiving each intervention.
Randomised controlled trial (RCT)	A study in which a number of similar people are randomly assigned to 2 (or

	more) groups to test a specific drug or treatment. One group (the experimental group) receives the treatment being tested, the other (the comparison or control group) receives an alternative treatment, a dummy treatment (placebo) or no treatment at all. The groups are followed up to see how effective the experimental treatment was. Outcomes are measured at specific times and any difference in response between the groups is assessed statistically. This method is also used to reduce bias.
RCT	See 'Randomised controlled trial'.
Receiver operated characteristic (ROC) curve	A graphical method of assessing the accuracy of a diagnostic test. Sensitivity is plotted against 1 minus specificity. A perfect test will have a positive, vertical linear slope starting at the origin. A good test will be somewhere close to this ideal.
Reference standard	The test that is considered to be the best available method to establish the presence or absence of the outcome – this may not be the one that is routinely used in practice.
Relative risk (RR)	The ratio of the risk of disease or death among those exposed to certain conditions compared with the risk for those who are not exposed to the same conditions (for example, the risk of people who smoke getting lung cancer compared with the risk for people who do not smoke). If both groups face the same level of risk, the relative risk is 1. If the first group had a relative risk of 2, subjects in that group would be twice as likely to have the event happen. A relative risk of less than one means the outcome is less likely in the first group. Relative risk is sometimes referred to as risk ratio.
Reporting bias	See 'Publication bias'.
Resource implication	The likely impact in terms of finance, workforce or other NHS resources.
Retrospective study	A research study that focuses on the past and present. The study examines past exposure to suspected risk factors for the disease or condition. Unlike prospective studies, it does not cover events that occur after the study group is selected.
Review question	In guideline development, this term refers to the questions about treatment and care that are formulated to guide the development of evidence-based recommendations.
Review protocol	The plan or set of steps to be followed in a study. A protocol for a systematic review describes the rationale for the review, the objectives, and the methods that will be used to locate, select, and critically appraise studies, and to collect and analyse data from the included studies.
Secondary outcome	An outcome used to evaluate additional effects of the intervention deemed a priori as being less important than the primary outcomes.
Selection bias	Selection bias occurs if: a) The characteristics of the people selected for a study differ from the wider population from which they have been drawn, or b) There are differences between groups of participants in a study in terms of how likely they are to get better.
Sensitivity	How well a test detects the thing it is testing for. If a diagnostic test for a disease has high sensitivity, it is likely to pick up all cases of the disease in people who have it (that is, give a 'true positive' result). But if a test is too sensitive it will sometimes also give a positive

	result in people who don't have the disease (that is, give a 'false positive'). For example, if a test were developed to detect if a woman is 6 months pregnant, a very sensitive test would detect everyone who was 6 months pregnant, but would probably also include those who are 5 and 7 months pregnant. If the same test were more specific (sometimes referred to as having higher specificity), it would detect only those who are 6 months pregnant, and someone who was 5 months pregnant would get a negative result (a 'true negative'). But it would probably also miss some people who were 6 months pregnant (that is, give a 'false negative'). Breast screening is a 'real-life' example. The number of women who are recalled for a second breast screening test is relatively high because the test is very sensitive. If it were made more specific, people who don't have the disease would be less likely to be called back for a second test but more women who have the disease would be missed.
Sensitivity analysis	A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other settings. The analysis is repeated using different assumptions to examine the effect on the results. One-way simple sensitivity analysis (univariate analysis): each parameter is varied individually in order to isolate the consequences of each parameter on the results of the study. Multi-way simple sensitivity analysis (scenario analysis): 2 or more parameters are varied at the same time and the overall effect on the results is evaluated. Threshold sensitivity analysis: the critical value of parameters above or below which the conclusions of the study will change are identified. Probabilistic sensitivity analysis: probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (for example, Monte Carlo simulation).
SF-36	36-Item Short Form Health Survey, a survey instrument to measure patient-reported health-related quality-of-life through eight health concepts: physical functioning, role limitations due to physical health problems, bodily pain, general health, vitality (energy/fatigue), social functioning, role limitations due to emotional problems and mental health (psychological distress and psychological wellbeing).
Significance (statistical)	A result is deemed statistically significant if the probability of the result occurring by chance is less than 1 in 20 ($p<0.05$).
SIRS criteria	Severity assessment tool to predict sepsis and septic shock including: Temperature > 38°C or < 36°C, Heart rate of > 90 beats per minute, Respiratory rate > 20 breaths per minute or $PaCO_2$ < 32mm Hg, Abnormal white blood cell count (>12,000/µL or < 4000/µL or > 10% immature [band] forms).
SMART-COP	Severity assessment tool including: low systolic blood pressure < 90 mmHg, multilobar CXR involvement, albumin level < 35 g/l, raised respiratory rate (≥ 30 per min), tachycardia ≥ 125 beats per min, confusion (new onset), low oxygen, pH < 7.35.
Specificity	The proportion of true negatives that are correctly identified as such. For example in diagnostic testing the specificity is the proportion of non-cases correctly diagnosed as non-cases.

	See related term ‘Sensitivity’. In terms of literature searching a highly specific search is generally narrow and aimed at picking up the key papers in a field and avoiding a wide range of papers.
Stakeholder	An organisation with an interest in a topic that NICE is developing a clinical guideline or piece of public health guidance on. Organisations that register as stakeholders can comment on the draft scope and the draft guidance. Stakeholders may be: • manufacturers of drugs or equipment • national patient and carer organisations • NHS organisations • organisations representing healthcare professionals.
Standard deviation	A measure of the spread or dispersion of a set of observations, calculated as the average difference from the mean value in the sample.
Subgroup analysis	An analysis in which the intervention effect is evaluated in a defined subset of the participants in a trial, or in complementary subsets.
Systematic review	A review in which evidence from scientific studies has been identified, appraised and synthesised in a methodical way according to predetermined criteria. It may include a meta-analysis.
Time horizon	The time span over which costs and health outcomes are considered in a decision analysis or economic evaluation.
Treatment allocation	Assigning a participant to a particular arm of a trial.
Univariate	Analysis which separately explores each variable in a data set.
Utility	In health economics, a 'utility' is the measure of the preference or value that an individual or society places upon a particular health state. It is generally a number between 0 (representing death) and 1 (perfect health). The most widely used measure of benefit in cost-utility analysis is the quality-adjusted life year, but other measures include disability-adjusted life years (DALYs) and healthy year equivalents (HYEs).
Ventilator-associated pneumonia (VAP)	VAP refers to pneumonia that occurs 48 hours or more after endotracheal intubation.

Appendices

Appendix A: Scope

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Appendix B: Declarations of interest

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Appendix C: Review protocols

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Appendix D: Clinical article selection

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Appendix E: Economic article selection

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Appendix F: Literature search strategies

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Appendix G: Clinical evidence tables

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Appendix H: Economic evidence tables

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Appendix I: Forest plots

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Appendix J: Excluded clinical studies

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Appendix K: Excluded economic studies

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Appendix L: Cost-effectiveness analysis: microbiological investigations

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Appendix M: Research recommendations

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Appendix N: Antibiotic classification

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Appendix O: Unit costs

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Appendix P: Supplementary evidence

See separate document.