National Institute for Health and Care Excellence

Final

Pneumonia (community-acquired): antimicrobial prescribing guideline

Evidence review

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1 Context

1.1 Background

Pneumonia is an infection of the lung tissue. It affects the air sacs (alveoli) of the lungs, which fill with microorganisms, fluid and inflammatory cells, impacting their normal function (NICE guideline on pneumonia in adults: diagnosis and management 2014).

Community-acquired pneumonia is pneumonia that is acquired outside hospital and is most commonly caused by bacterial infection (British Thoracic Society [BTS] guideline on management of community-acquired pneumonia in adults, 2009). *Streptococcus pneumoniae* is the main cause of community-acquired pneumonia worldwide, independent of age (clinical knowledge summaries [CKS] – chest infections, 2015), however *Mycoplasma pneumoniae* occurs in outbreaks approximately every 4 years in the UK and is much more common in school-aged children and young adults (BTS, management of community acquired-pneumonia in adults, 2009). Other pathogens isolated in people with community-acquired pneumonia treated in the community in the UK include *Haemophilus influenzae, Staphlococcus aureus* and *Legionella pneumophila*. While bacterial infection is the most common cause of community-acquired pneumonia, viral infection causes approximately 13% of cases in adults (BTS, management of community-acquired pneumonia in adults, 2009) and approximately 66% of cases in children and young people (Jain et al. 2015).

Community-acquired pneumonia is a common condition, with an annual incidence of 5-10 per 1000 adults. Five to 12% of lower respiratory tract infections managed by GPs in the community are caused by community-acquired pneumonia, and there is a significant rate of hospital admission of 22-42% (NICE guideline on pneumonia in adults: diagnosis and management [2014]); between 1.2 and 10% of adults admitted to hospital with community-acquired pneumonia are managed in an intensive care unit. The incidence varies markedly with age, being much higher in the very young and the elderly (BTS guideline on management of community-acquired pneumonia in adults, 2009). Mortality ranges from 1% in people managed in primary care to 5 to 14% in people requiring hospital admission, and is more than 30% in people requiring intensive care (CKS – chest infections, 2015).

In general practice, signs and symptoms are often used to diagnose community-acquired pneumonia, which may be followed up by a chest x-ray. People presenting at hospital (for example people attending accident and emergency departments) with suspected pneumonia are usually diagnosed by chest x-ray showing new radiographic shadowing for which there is no other explanation. Clinical signs of pneumonia used in diagnosis include cough with at least one of sputum, wheeze, dyspnoea or pleuritic pain; the presence of focal chest signs such as dullness to percussion, course crepitation or vocal fremitus and at least one systemic feature present with or without temperature above 38°C, including sweat, fever or myalgia (CKS – chest infections, 2015).

The severity of pneumonia (low, moderate or high) is used to guide treatment decisions. A judgement is made by the managing clinician as to the likelihood of adverse outcomes, 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 (NICE guideline on pneumonia in adults: diagnosis and management 2014).

CRB65 (confusion, respiratory rate ≥ 30/min, low systolic [< 90 mm Hg] or diastolic [≤ 60 mm Hg] blood pressure, age ≥65) is a commonly used scoring system which specifies

less than 1% mortality risk with a score of 0 (low risk); 1-10% mortality risk with a score of 1-2 (intermediate risk) and more than 10% mortality risk with a score of 3 or 4 (high risk) (NICE guideline on pneumonia in adults: diagnosis and management 2014; Lim et al. 2003). A CURB65 test includes the measurement of urea concentration added to the CRB65 test (usually when diagnosis is made in hospital; an additional point is given for urea > 7 mmol/l). The CURB65 test specifies less than 3% mortality risk with a score of 0 or 1 (low risk); 3-15% mortality risk with a score of 2 (moderate risk) and more than 15% mortality risk with a score of 3 to 5 (high risk). People with a CURB65 score of 1 and particularly 2 are at increased risk of death and should be considered for hospital referral; people with a score of 3 or more are at high risk of death and require urgent hospital admission (NICE guideline on pneumonia: diagnosis and management 2014; BTS guideline on management of community-acquired pneumonia in adults, 2009).

Pneumonia severity index (PSI) is also a well-studied predictive model used in the management of community-acquired pneumonia. The PSI is based on 20 variables which are used to provide a score between I to V based on the risk of 30-day mortality. It was developed to identify people at low risk of mortality who might be suitable for out-patient treatment. People in classes I to III are usually considered to be at low risk of mortality, although the importance of clinical judgement is emphasised (BTS guideline on management of community-acquired pneumonia in adults, 2009).

1.2 Managing infections that require antibiotics

Community-acquired pneumonia is a chest infection needing treatment with an antibiotic. Depending on the severity of pneumonia, different antibiotic regimens may be necessary. Antibiotics should be started as soon as possible, and for people hospitalised, within 4 hours of diagnosis (NICE guideline on pneumonia in adults: diagnosis and management).

In line with the Public Health England guidance (Start Smart Then Focus) and the NICE guideline on antimicrobial stewardship consider reviewing intravenous antibiotic prescriptions at 48 to 72 hours, documenting response to treatment and any available microbiology results to determine if the antibiotic should be continued or switched to a narrower spectrum or an oral antibiotic.

1.2.1 Antibiotic prescribing strategies

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

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

1.3 Safety information

1.3.1 Safety netting

All people with community acquired pneumonia should be offered an antibiotic, as it is not a self-limiting infection and is associated with risk of mortality.

The NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population (2017) recommends that safety netting advice should be given to everyone who has an infection (regardless of whether or not they are prescribed or supplied with antimicrobials). This should include:

- How long symptoms are likely to last with and without antimicrobials
- What to do if symptoms get worse
- What to do if they experience adverse effects from the treatment
- When they should ask again for medical advice
- See your GP if you feel unwell and you have typical symptoms of pneumonia.
- Seek urgent medical attention if you're experiencing severe symptoms, such as rapid breathing, chest pain or confusion.

People who feel unwell and have the following typical symptoms of pneumonia should see their GP:

- cough (which may be dry, or produce thick yellow, green, brown or blood-stained mucus
- difficulty breathing (which may be rapid and shallow and include breathlessness when resting)
- rapid heartbeat
- fever
- sweating and shivering
- loss of appetite
- chest pain which gets worse when breathing or coughing.

Urgent medical attention should be sought in people experiencing severe symptoms such as rapid breathing, chest pain or confusion (NHS – pneumonia).

People with a severe systemic infection should be assessed and managed as outlined in the NICE guideline on sepsis.

Children aged under 5 who present with fever should be assessed and managed as outlined in the NICE guideline on fever in under 5s: assessment and initial management.

1.4 Antimicrobial resistance

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

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

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

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

The ESPAUR report 2018 reported that antimicrobial prescribing declined significantly between 2013 and 2017, with the total consumption of antibiotics in primary and secondary care declining by 4.5%. This reflected a 13.2% decrease in primary care and a 7.7% increase in secondary care. The peak of antibiotic consumption over the last 20 years occurred in 2014, with levels falling since then. The most commonly used antibiotics in England remained stable between 2013 and 2017 and were: penicillins (44.6% in 2017), tetracyclines (22.2% in 2017) and macrolides (14.7% in 2017).

Over the 5-year period, significant declining trends of use were seen for penicillins (inhibitor combinations only), first and second-generation cephalosporins, sulfonamides and trimethoprim, and anti-*C. difficile* agents. In contrast, use of third, fourth and fifth-generation cephalosporins and other antibacterials (including nitrofurantoin) have significantly increased.

In the 5-year period from 2013 to 2017, primary care use of penicillins declined by 10.9%, with use of penicillins in the dental setting remaining largely the same. In the hospital setting, prescribing of penicillins was higher in 2017 for both inpatients (2.4%) and outpatients (14.7%) compared to 2013. Prescribing of co-amoxiclav and amoxicillin between 2013 and 2017 decreased by 11.3% and 7.4%, respectively.

Overall use of tetracyclines was unchanged between 2013 and 2017, with doxycycline (49.7% in 2017) and lymecycline (36.3% in 2017) most commonly used. Macrolide use declined by 5.8% from 2013 to 2017. Azithromycin use continued to increase in 2017, with overall use rising by 31.3% since 2013. In contrast, erythromycin use has declined over the same period by 40.7%.

During a 5-year surveillance period, the proportion of bloodstream isolated of *Streptococcus pneumoniae* non-susceptible to penicillin and macrolides remained stable at 3 to 4% and 5 to 8%, respectively. The proportion of *Staphylococcus aureus* that were methicillin-resistant *S. aureus* (MRSA) continued to decline year-on-year from 9.5% in 2012/13 to 6.6% in 2017/18.

In bacterial community-acquired pneumonia, the most common causative pathogens are *Streptococcus pneumoniae*, *Haemophilus influenza, Staphylococcus aureus, Legionella pneumophila and Mycoplasma pneumoniae* (British Thoracic Society [BTS] guideline on management of community-acquired pneumonia in adults, 2009).

1.5 Other considerations

1.5.1 Medicines adherence

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

1.5.2 Resource impact

Antibiotics for community-acquired pneumonia

Recommended antibiotics are available as generic formulations, see Drug Tariff for costs.

2 Evidence selection

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

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

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

2.1 Literature search

A literature search was developed to identify evidence for the effectiveness and safety of interventions for managing pneumonia (including hospital-acquired pneumonia; see appendix C: literature search strategy for full details). The literature search identified 15,691 references. These references were screened using their titles and abstracts and 457 full text references were obtained and assessed for relevance, including studies of both community- and hospital-acquired pneumonia. Ninety-seven full text references of systematic reviews and randomised controlled trials (RCTs) were assessed as relevant to the guideline review question (see appendix B: review protocol). Ten percent of studies were screened to establish inter-rater reliability, and this was within the required threshold of 90%.

The methods for identifying, selecting and prioritising the best available evidence are described in the interim process guide. Thirty-two of the 97 references were prioritised by the committee as the best available evidence and were included in this evidence review (see appendix F: included studies).

The 64 references that were not prioritised for inclusion are listed in appendix I: not prioritised studies, with reasons for not prioritising the studies. Only studies which included antibiotics available in the UK were prioritised. Also see appendix E: evidence prioritisation for more information on study selection.

The remaining 360 references were excluded. These are listed in appendix J: excluded studies with reasons for their exclusion.

See also appendix D: study flow diagram.

2.2 Summary of included studies

A summary of the included studies is shown in Table 1 to Table 10. Details of the study citation can be found in appendix F: included studies. An overview of the quality assessment of each included study is shown in appendix G: quality assessment of included studies.

Table 1: Summary of included studies: antibiotic prescribing strategies in adults

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Moderate- to high-severity					
Falguera et al. 2009 RCT Spain	N=177	Adults with CAP admitted from the emergency department; PSI IV or V and clinical stability reached between day 2 and 6	Empirical treatment (antibiotic switch after clinical stability was reached, to complete either 5 days or 10 days of empirical antibiotic treatment)	Targeted antibiotic treatment using pneumococcal and *L. pneumophilae* urine antigen tests to guide treatment decisions; if both urine antigen tests were negative, empirical treatment was given	Mortality, clinical relapse, admission to intensive care, length of hospital stay, readmission and adverse events
Mixed-severity					
Uranga et al. 2016 Non-inferiority RCT Spain	N=312	Adults hospitalised with CAP; PSI score I to V	Antibiotic stopping based on guidelines (antibiotics given for a minimum of 5 days, with antibiotic treatment stopped if body temperature was 37.8°C or below for 48 hours, with no more than 1 CAP associated sign of clinical instability)	Physician-guided stopping (duration of treatment was determined by physicians in clinical practice)	Clinical success at day 10 and day 30 (no need for further antibiotics); CAP related symptoms
Aliberti et al. 2017 Non-inferiority RCT Italy	N=260	Adults hospitalised with CAP; PSI score I to V; including healthcare associated pneumonia	Standard CAP treatment (duration of antibiotics determined by physician)	Individualised treatment (treatment according to clinical response with antibiotic discontinued at 48 hours clinical stability after 5 days treatment)	Early failure, including: complications, clinical failure, relapse, re-admission or death

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Garin et al. 2014 Non-inferiority RCT Switzerland	N=580	Adults hospitalised with CAP; PSI score I to IV	Upfront dual therapy (beta-lactam plus macrolide)	Test-dependant dual therapy (beta-lactam plus clarithromycin with postivie *Legionaella pneumophilla* test)	Number of people not reaching clinical stability by day 7
Abbreviations: RCT, randomised controlled trial; CAP, community-acquired pneumonia; PSI, pneumonia severity score					

Table 2: Summary of included studies: antibiotic prescribing strategies in children

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Severe					
In-iw et al. 2015 Non-inferiority RCT Thailand	N=57	Children aged 1 month to 5 years hospitalised with CAP	Switch from intravenous to oral antibiotics based on core body temperature dropping below 37.8°C for at least 8 hours and clinical signs becoming stable	Standard medical procedure (switching to oral antibiotics after at least 48 hours after dissipation of fever)	Length of hospital stay; readmission rate
Abbreviations: RCT, randomised controlled trial; CAP, community-acquired pneumonia					

Table 3: Summary of included studies: antibiotic choice in adults

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Low-severity					
Pakhale et al. 2014 Systematic review Worldwide	11 RCTs N=3,352	Adult outpatients with CAP over the age of 12 (1 RCT included young people aged 12 to 16, others 18 years and over)	Single or dual antibiotics	Single or dual antibiotics	Clinical response at test of clinical cure, defined as improvement of

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
					signs and symptoms, usually at a pre-defined test-of-cure (TOC) visit
Maimon et al. 2008 Systematic review Worldwide	13 RCTs N=4,314	Adult outpatients with CAP; mean age 49	Antibiotics with atypical coverage	Antibiotics with non-atypical coverage	Clinical response at test of cure and 28 day all-cause mortality
Raz-Pasteur et al. 2015 Systematic review Worldwide	16 RCTs N=4,809	Adults with CAP treated in hospital (ICU or non-ICU) or in the community (subgroup analysis of population treated in community included for low-severity)	Fluoroquinolone or macrolide as single antibiotic	Dual therapy of a fluoroquinolone or macrolide plus beta-lactam	30 day all-cause mortality
Llor et al. 2017 Non-inferiority RCT Spain	N=43	Adults with CAP, treated as outpatients; aged 18-75	Phenoxymethyl-penicillin	Amoxicillin	Clinical cure at 14 days (absence of fever, resolution or improvement of cough, improvement of general well-being and resolution or reduction of crackles)
Paris et al. 2008 Non-inferiority RCT Italy	N=267	Adults and young people (aged 14 to 76) with low-severity CAP (PSI I or II)	3 day azithromycin	7 day co-amoxiclav	Clinical response at the end of therapy (no need for further antibiotics)
Ige et al. 2015 RCT Nigeria	N=73	Adults with CAP treated as outpatients, with PSI score of I or II	Cefixime	Ciprofloxacin	Clinical response
Moderate- to high-severity					
Eliakim-Raz et al. 2012	28 RCTs N=5,939	Adult patients hospitalised due to suspected CAP	Antibiotics with atypical coverage	Antibiotics with non-atypical coverage	End of study and 30 day mortality

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Systematic review Worldwide					
Nemeth et al. 2015 Systematic review Worldwide	33 RCTs, N=9,597	Adults with serious bacterial infections, including CAP; hospitalised or severe infection	Bacteriostatic antibiotics (levofloxacin included in the evidence review)	Bactericidal antibiotics (tigecycline and doxycycline included in the evidence review)	Clinical outcome, as defined by study authors
Skalsky et al. 2013 Systematic review Worldwide	16 RCTs N=4,989	Adults with CAP treated in hospital or as outpatients; mean or median age 45 to 64	Macrolides (erythromycin included in the evidence review)	Fluoroquinolones (ofloxacin included in the evidence review)	30 day all-cause mortality and clinical failure
El Hajj et al. 2017 Systematic review Worldwide	6 RCTs N=3,393	People with high-severity CAP or skin and skin structure infections (subgroup analysis of CAP included)	Ceftaroline fosamil	Other antibiotics (ceftriaxone included in the evidence review)	Clinical cure (resolution of all signs and symptoms so that no need for further antibiotics)
Yuan et al. 2012 Systematic review Worldwide	14 RCTs N=6,923	Adults with low- to moderate-severity CAP, either hospitalised or treated as outpatients	Moxifloxacin	Other antibiotics (levofloxacin included in the evidence review)	Treatment success at test of cure (resolution of 2 or more baseline symptoms)
Bai Nan et al. 2014 Systematic review	8 RCTs N=2,883	Adults and children with CAP requiring parenteral treatment, complicated urinary tract infection or intra-abdominal infection (subgroup analysis of CAP included)	Ertapenem	Ceftriaxone	Clinical treatment success (no need for further antibiotics)
Raz-Pasteur et al. 2015 Systematic review Worldwide	16 RCTs N=4,809	Adults with CAP treated in hospital (ICU or non-ICU) or in the community (subgroup analysis of hospitalised	Fluoroquinolone or macrolide as single antibiotic	Dual therapy of a fluoroquinolone or macrolide plus beta-lactam	30 day all-cause mortality

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
		population included for moderate- to high-severity)			
Nicholson et al. 2012 Non-inferiority RCT	N=706	Adults with high-severity CAP, requiring hospitalisation and intravenous treatment	Ceftobiprole	Ceftriaxone ± linezolid if MRSA infection suspected	Clinical cure at test of cure visit (no need for further antibiotics)
Tamm et al. 2007 Non-inferiority RCT Europe and South Africa	N=278	Adults with moderate- to high-severity CAP requiring hospitalisation	Ceftriaxone plus azithromycin	Ceftriaxone plus macrolides	Clinical cure based on symptoms and radiological findings at end of treatment
Abbreviations: RCT, Randomised controlled trial; CAP, community acquired pneumonia; PSI, pneumonia severity index; ICU, intensive care unit					

Table 4: Summary of included studies: antibiotic choice in children

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Non-severe					
Lodha et al. 2013 Systematic review Worldwide	29 RCTs N=14,188	Children and young people under 18 with non-severe or severe pneumonia, treated in hospital or in the community (subgroup analysis of non-severre or community treated included in non-severe CAP)	Antibiotic	Other antibiotic	Clinical cure; treatment failure rates (including loss to follow-up or withdrawal)
Severe					
Lodha et al. 2013 Systematic review Worldwide	29 RCTs N=14,188	Children and young people under 18 with non-severe or severe pneumonia, treated in hospital or in the	Antibiotic	Other antibiotic	Clinical cure; treatment failure rates (including loss to follow-up or withdrawal)

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
		community (subgroup analysis of severe or hospitalised included in severe CAP)			
Cannavino et al. 2016 RCT Worldwide	N=161	Children and young people aged 2 months to 18 years with bacterial CAP requiring hospitalisation and intravenous therapy	Ceftaroline fosamil for a minimum of 3 days, before switch to co-amoxiclav	Ceftriaxone for a minimum of 3 days, before switch to co-amoxiclav	Clinical response (improvement in at least 2 of 7 symptoms of pneumonia at end of intravenous treatment (day 4); adverse events
Blumer et al. 2016 RCT Worldwide	N=40	Children aged between 2 months and 17 years with complicated bacterial CAP requiring 3 days initial hospitalisation	Ceftaroline fosamil	Ceftriaxone plus vancomycin	Clinical response (improvement in at least 2 of 7 symptoms of pneumonia at end of intravenous treatment (day 4); adverse events
Abbreviations: RCT, Randomised controlled trial; CAP, community acquired pneumonia					

Table 5: Summary of included studies: antibiotic dose in adults

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Low-severity					
Zhao et al. 2016 Non-inferiority RCT China	N=457	Adults with low-severity CAP (CURB65 score 0-2)	Low-dose levofloxacin for 7 to 14 days	High-dose levofloxacin for 5 days	Cure or improved (no need for further antibiotics)
Siquier et al. 2006 Non-inferiority RCT	N=566	Adults with CAP of suspected pneumococcal origin based on clinical criteria for typical bacterial pneumonia;	Low-dose co-amoxiclav	High-dose co-amoxiclav	Clinical response at test of cure

		PSI score I to V, 88% PSI I to III			
Abbreviations: RCT, randomised controlled trial; CAP, community acquired pneumonia; PSI, pneumonia severity index; CURB65, confusion, urea, respiratory rate, blood pressure, age >65					

Table 6: Summary of included studies: antibiotic dose in children

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Non-severe					
Hazir et al. 2007 Non-inferiority RCT Pakistan	N=876	Children aged 2 to 59 months with non-severe CAP, treated as outpatients	Low-dose amoxicillin	High-dose amoxicillin	Treatment failure by day 5
Severe					
Amarilyo et al. 2014 RCT Israel	N=35	Children aged 3 months to 18 years with CAP; hospitalised but stable	Low-dose benzylpenicillin	High-dose benzylpenicillin	Length of hospital stay
Abbreviations: RCT, randomised controlled trial; CAP, community acquired pneumonia					

Table 7: Summary of included studies: antibiotic course length in adults

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Mixed-severity					
Li et al. 2007 Systematic review	15 RCTs N=2,796	Adults and young people (aged 12 or over) with CAP; mean age 40 to 64 (unreported mean age in 2 RCTs)	Short course (7 days or less) antibiotic	Long course (>7 days) antibiotic	Failure to achieve clinical improvement or cure, as defined by individual studies
El Moussaoui et al. 2006 Non-inferiority RCT Netherlands	N=119	Adults with mild to moderate-severity CAP; PSI score 110 or less; causative	Short course amoxicillin	Long course amoxicillin	Clinical cure rate at test of cure (no need for further antibiotics)

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
		pathogens susceptible to amoxicillin			
Abbreviations: RCT, randomised controlled trial; CAP, community acquired pneumonia; PSI, pneumonia severity index					

Table 8: Summary of included studies: antibiotic course length in children

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Non-severe					
Haider et al. 2008 Systematic review Asia	4 RCTs N=6,177	Children aged 2 to 59 months with non-severe CAP	Short course antibiotic treatment	Long course antibiotic treatment (with the same antibiotic)	Clinical cure rate (return of respiratory rate to normal age-specific range)
Greenberg et al. 2014 Non-inferiority RCT Israel	N=66	Children aged 6 to 59 months with CAP, treated in the community	3 or 5 day course of amoxicillin	10 day course of amoxicillin	Absence of treatment failure by day 30 (need for study drug to be replaced, hospitalisation, no response to treatment or relapse)
Abbreviations: RCT, randomised controlled trial; CAP, community acquired pneumonia					

Table 9: Summary of included studies: antibiotic route of administration in adults

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Moderate- to high-severity					
Athanassa et al. 2008 Systematic review	6 RCTs N=1,219	Adults hospitalised with moderate- to high-severity CAP; PSI IV or V, or CURB65 score III-V	Switch to oral antibiotics for people showing clinical improvement	Continuous intravenous treatment	Treatment success (cure or improvement); all-cause mortality

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Abbreviations: CAP, community acquired pneumonia; PSI, pneumonia severity index; CURB65, confusion, urea, respiratory rate, blood pressure, age >65					

Table 10: Summary of included studies: antibiotic dose frequency in children

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Non-severe					
Vilas-Boas et al. 2014 Non-inferiority RCT Brazil	N=820	Children with non-severe CAP aged 2 to 59 months	Amoxicillin 2 times daily, plus placebo	Amoxicillin three times daily	Treatment failure, including withdrawal, serious adverse reactions and death
Abbreviations: RCT, randomised controlled trial; CAP, community acquired pneumonia					

3 Evidence summary

Full details of the evidence are shown in appendix H: GRADE profiles.

The main results are summarised below for adults, young people and children with community-acquired pneumonia.

See the summaries of product characteristics, British National Formulary (BNF) and BNF for children (BNF-C) for information on drug interactions, contraindications, cautions and adverse effects of individual medicines, and for appropriate use and dosing in specific populations, for example, hepatic impairment, renal impairment, pregnancy and breastfeeding.

Although many studies included in the review were non-inferiority trials, the committee considered that the reasons for the choice of non- inferiority margin were poorly reported in the studies. Therefore the committee decided to treat non-inferiority trials as superior head to head trials. Clinical effectivess was assessed using a minimal important difference of 1.0 and imprecision was assessed using the standard GRADE minimal important difference of a relative risk (RR) of 0.75 and 1.25 for all outcomes except mortality, for which a RR of 1.0 was used to assess both effectiveness and imprecision.

3.1 Antibiotics in adults

The evidence for antibiotics in adults has been divided pragmatically into 2 groups relevant to primary care and hospital physicians: low-severity community-acquired pneumonia and moderate- to high-severity community-acquired pneumonia respectively. Stratification was based on formal severity assessment scores (such as Pneumonia Severity Index [PSI] and CURB-65), treatment setting (community or hospital) or the description of severity by study authors when this detail was not available. This is consistent with the approach taken in the NICE guideline on pneumonia in adults: diagnosis and management 2014.

3.1.1 Antibiotic prescribing strategies in moderate- to high-severity community-acquired pneumonia

The evidence for antibiotic prescribing strategies in adults with moderate- to high-severity community-acquired pneumonia comes from 1 randomised controlled trial (RCT; Falguera et al. 2009, n=177). Community-acquired pneumonia was diagnosed using chest x-ray in combination with at least 2 symptoms compatible with pneumonia, including fever, chills, cough, sputum production or chest pain. Twenty percent of the study population also had chronic obstructive pulmonary disease (COPD), although it is unclear if pneumonia was associated with an exacerbation of COPD. Exclusion criteria included immunosuppression and infection caused by tuberculosis or empyema.

The evidence for antibiotic treatment strategies in people with moderate- to high-severity community-acquired pneumonia is presented here, including people with Pneumonia Severity Index (PSI) score of IV or V.

Broad-specturm antibiotics versus targeted antibiotics

An RCT (Falguera et al. 2009) compared broad-specturm antibiotics with targeted antibiotics using urine antigen test results. All participants initially received either co-amoxiclav, ceftriaxone plus azithromycin, or levofloxacin. If stable after 2 to 6 days

treatment, participants were randomised to either broad-spectrum antibiotics (people who initially received co-amoxiclav or ceftriaxone plus azithromycin were switched to co-amoxiclav [875/125 mg three times daily] or cefditoren [400 mg twice daily] to complete 10 days treatment, plus azithromycin (500 mg daily) for 5 days; participants who initially received levofloxacin were continued on levofloxacin [750 mg daily] to complete 10 days treatment) or targeted treatment (if a pneumococcal urine antigen test was positive, participants were switched to oral amoxicillin [1g three times daily] to complete a 10 day course; if a *L. pneumophilae* urine antigen test was positive, participants were switched to oral azithromycin [500mg daily] to complete a 5 day course; participants with a negative urine antigen test were given the same treatment as the broad-spectrum group).

Broad-spectrum antibiotic treatment was not significantly different to targeted antibiotic treatment in adults with high-severity community-acquired pneumonia for mortality (1 RCT, n=177, 0.0% versus 1.1%, relative risk [RR] 0.33, 95% confidence interval [CI] 0.01 to 7.98 [NICE analysis]; low quality evidence), clinical relapse (1 RCT, n=177, 2.2% versus 4.5%, RR 0.49, 95% CI 0.09 to 2.63 [NICE analysis]; very low quality evidence), admission to intensive care or readmission. There was also no significant difference between the treatment groups in length of hospital stay (1 RCT, n=177, mean difference 0 days, 95% CI −1.15 to 1.15; moderate quality evidence), length of antimicrobial treatment or length of intravenous treatment.

Broad-spectrum antibiotic treatment was not significantly different to targeted treatment in adults with high-severity community-acquired pneumonia for the number of adverse events (1 RCT, n=177, 18.0% versus 9.1%, RR 1.98, 95% CI 0.89 to 4.38 [NICE analysis]; very low quality evidence).

When analysis was stratified by the treatment received (people randomised to the targeted antibiotics arm with a negative urine antigen test [therefore treated as the broad-spectrum arm] were analysed as broad-spectrum treatment), broad-spectrum antibiotic treatment was not significantly different to targeted antibiotics in adults with high-severity community-acquired pneumonia for mortality (1 RCT, n=177, 0.66% versus 0.0%, RR 0.51, 95% CI 0.02 to 12.18 [NICE analysis]; low quality evidence) or admission to intensive care. There was also no significant difference between the treatment groups in length of hospital stay (1 RCT, n=177, mean difference 0.2 days, 95% CI −1.95 to 1.55 days; low quality evidence), length of antimicrobial treatment or length of intravenous treatment. However, braod-spectrum treatment significantly decreased the incidence of clinical relapse (1 RCT, n=177, 2.0% versus 12.0%, RR 0.16, 95% CI 0.04 to 0.77 [NICE analysis]; low quality evidence) and the incidence of readmission (1 RCT, n=177; 2.6% versus 12.0%, RR 0.22, 95% CI 0.05 to 0.92, number needed to harm [NNT] 11 [95% CI not estimable; NICE analysis]; low quality evidence) compared with targeted antibiotics.

In the same stratified analysis, broad-spectrum treatment was not significantly different to targeted antibiotics in adults with high-severity community-acquired pneumonia for the number of adverse events (1 RCT, n=177, 14.5% versus 8.0%, RR 1.81, 95% CI 0.45 to 7.22 [NICE analysis]; very low quality evidence).

See GRADE profiles: Table 24 and Table 25

3.1.2 Antibiotic prescribing strategies in a mixed-severity population with community-acquired pneumonia

The evidence for antibiotic prescribing strategies in a mixed severity population of adults with community-acquired pneumonia comes from 3 non-inferiority randomised

controlled trials (RCTs; Uranga et al. 2016, n=312; Aliberti et al. 2017, n=260 and Garin et al. 2014, n=580).

Community-acquired pneumonia was diagnosed using chest x-ray in combination with at least 1 or 2 symptoms compatible with pneumonia, including fever, chills, cough, sputum production or chest pain in most participants, however Aliberti et al. 2017 did not specify the definition of community-acquired pneumonia. Fifteen to 22 percent of the study population also had chronic obstructive pulmonary disease (COPD), although it is unclear if pneumonia was associated with an exacerbation of COPD. Exclusion criteria included immunosuppression, requiring a chest tube or having concomitant infection on hospital admission requiring antibiotic therapy. Aliberti et al. 2017 also included people with healthcare associated pneumonia.

Stopping antibiotics: guideline-based compared with physician-guided

A non-inferiority study (Uranga et al. 2016) compared antibiotics given for a minimum of 5 days, with antibiotic treatment stopped if body temperature was 37.8°C or less for 48 hours, with no more than one community-acquired pneumonia associated sign of clinical instability (stopping antibiotics based on guidelines) with duration determined by physicians in clinical practice (physician-guided stopping); approximately 80% of participants received a fluoroquinolone. People with a pneumonia severity index (PSI) score between I to V were included.

Stopping antibiotics based on guidelines was not significantly different to physician-guided stopping in adults with PSI score of I to V for mortality (1 RCT, n=283, 2.2% versus 2.1%, relative risk [RR] 1.07, 95% confidence interval [CI] 0.22 to 5.19; low quality evidence), recurrence rates at day 30 (1 RCT, n=283, 2.7% versus 4.4%, RR 0.63, 95% CI 0.18 to 2.17; very low quality evidence), community-acquired pneumonia symptom questionnaire score at day 5 or day 10 (1 RCT, n=312, mean difference 0.7, 95% CI −2.56 to 1.16; moderate quality evidence) or length of hospital stay (1 RCT, n=283, mean difference 0.2 days, 95% CI −0.40 to 0.80; moderate quality evidence). Antibiotic stopping based on guidelines was associated with longer time taking antibiotics (1 RCT, n=283, median 5 days, interquartile range [IQR] 5 to 6.5 versus 10 days IQR 10 to 11; low quality evidence), and longer time to returning to normal activity (1 RCT, n=283, median 15 days IQR 10 to 21 versus 18 days IQR 9 to 25; low quality evidence), but with shorter time on intravenous antibiotics (1 RCT, n=283, median 3 days IQR 2 to 4 versus 2 days IQR 1 to 4; low quality evidence) compared with physician-guided stopping.

Stopping antibiotics based on guidelines was not significantly different to physician-guided stopping in adults with PSI score of I to III for clinical success at day 10 or at day 30 (1 RCT, n=177, 93.7% versus 97.6%, relative risk [RR] 0.96, 95% confidence interval [CI] 0.90 to 1.02 [NICE analysis]; moderate quality evidence).

Stopping antibiotics based on guidelines was not significantly different to physician-guided stopping in adults with PSI score of IV or V for clinical success at day 10 (intention to treat analysis; 1 RCT, n=119, 54.2% versus 50.0%, RR 1.08, 95% CI 0.77 to 1.53; low quality evidence). However, stopping antibiotics based on guidelines was significantly more effective than physician-guided stopping for clinical success at day 30 in intention to treat analysis in adults with PSI score of IV or V (1 RCT, n=119, 93.1% versus 80.3%, RR 1.16, 95% CI 1.01 to 1.34, number needed to treat [NNT] 8 [4 to 117]; low quality evidence), but not in per protocol analysis (1 RCT, n=103, 95.9% versus 85.2%, RR 1.13, 95% CI 0.99 to 1.28; low quality evidence).

Stopping antibiotics based on guidelines was not significantly different to physician-guided stopping in adults with PSI score of I to V for the number of adverse events (1

RCT, n=283, 11.6% versus 13.1%, RR 0.89, 95% CI 0.48 to 1.65; very low quality evidence).

A second non-inferiority trial (Aliberti et al. 2017) compared physician-guided stopping with stopping antibiotics based on guidelines (antibiotics given for a minimum of 5 days, with antibiotic treatment stopped after 48 hours of clinical stability). PSI score ranged from I to V and the majority of people were given either macrolides, cephalosporins or fluoroquinolones.

Physician-guided stopping was not significantly different to stopping antibiotics based on guidelines in adults hospitalised with community-acquired pneumonia for deaths due to pneumonia (1 RCT, n=260, 0.0% versus 0.0%, RR not estimable; very low quality evidence), total mortality (1 RCT, n=260, 0.74% versus 3.2%, RR 0.23, 95% CI 0.03 to 2.04 [NICE analysis]; very low quality evidence) or failure rates (1 RCT, n=260, 2.2% versus 3.2%, RR 0.69, 95% CI 0.16 to 3.04 [NICE analysis]; very low quality evidence).

Physician-guided stopping was also not significantly different stopping antibiotics based on guidelines in adults hospitalised with community-acquired pneumonia for adverse events including diarrhoea (1 RCT, n=260, 3.0% versus 3.2%, RR 0.93, 95% CI 0.24 to 3.62 [NICE analysis]; very low quality evidence), vomiting (1 RCT, n=260, 0.74% versus 0%, RR not estimable; very low quality evidence), abdominal pain (1 RCT, n=260, RR 2.78, 95% CI 0.11 to 67.6; very low quality evidence) and nausea (1 RCT, n=260, 0.74% versus 0.0%, RR 2.78, 95% CI 0.11 to 67.6 [NICE analysis]; very low quality evidence).

See GRADE profiles: Table 26 to Table 29

Upfront dual therapy versus test-dependant dual therapy

A non-inferiority trial (Garin et al. 2014) compared a beta-lactam (cefuroxime [intravenous 1.5g, three times a day] or co-amoxiclav [intravenous 1.2g, four times a day]) plus upfront clarithromycin (intravenous or oral 500 mg, 2 times a day; upfront dual therapy) with a beta-lactam (same as dual therapy) plus clarithromycin only when a positive *Legionella pneumophila* urine sample was confirmed (test-dependant dual therapy); urine antigen testing was regularly performed in the test-dependant group. Median antibiotic treatment length was 10 days.

Test-dependant dual therapy was not significantly different to upfront dual therapy in adults with moderate-severity community-acquired pneumonia for 90-day mortality rate (1 RCTs, n=580, 8.2% versus 6.9%, RR 1.19, 95% CI 0.67 to 2.11 [NICE analysis]; low quality evidence) or the number of people not reaching clinical stability by day 7 (1 RCT, n=580, 41.2% versus 33.6%, RR 1.23, 95% CI 0.99 to 1.52 [NICE analysis]; low quality evidence), including when adjusted for age and PSI score (1 RCT, n=580, hazard ratio [HR] 0.92, 95% CI 0.76 to 1.12; moderate quality evidence).

Upfront dual therapy was significantly better for achieving clinical stability in people with an atypical infection compared with test-dependant dual therapy (1 RCT, n=31, HR 0.33, 95% CI 0.13 to 0.85 [raw data not available]; moderate quality evidence), however there was no difference between the treatment arms for people with a non-atypical infection. There was also no significant difference between test-dependant dual therapy and upfront dual therapy for admission to intensive care, incidence of complicated pleural effusion or length of hospital stay (1 RCT, n=580, 8 days versus 8 days, interquartile range 6 to 13 versus 6 to 12, median 0 days difference; low quality evidence).

Test-dependant dual therapy resulted in significantly more readmissions to hospital after 30 days than upfront dual therapy in adults hospitalised with community-acquired pneumonia (1 RCT, n=580, 7.9% versus 3.1%, RR 2.54, 95% CI 1.19 to 5.39, NNT 21 [12 to 91] [NICE analysis]; low quality evidence), however no significant difference in readmission rates was not found at day 90.

The total number of adverse events (including acute hepatitis, renal failure and minor allergic reactions) was not significantly different between test-dependant dual therapy and upfront dual therapy for adults hospitalised with community-acquired pneumonia (1 RCT, n=580, 1.4% versus 2.1%, RR 0.66, 95% CI 0.19 to 2.32; very low quality evidence).

See GRADE profile: **Table** 30

3.1.3 Choice of antibiotic in low-severity community-acquired pneumonia

The evidence review for a single antibiotic compared with another single antibiotic, and a single antibiotic compared with dual antibiotics in low-severity community-acquired pneumonia in adults is based on 3 systematic reviews (Pakhale et al. 2014 [11 randomised controlled trials [RCTs], n= 3,352], Maimon et al. 2008 [13 RCTs, n=4,314], and Raz-Pasteur et al. 2015 [16 RCTs, n=4,809]) and 3 RCTs (Llor et al. 2017 [n=43], Paris et al. 2008 [n=267] and Ige et al. 2015 [n=73]). Two RCTs (Llor et al. 2017 and Paris et al. 2008) were non-inferiority trials.

Community-acquired pneumonia was diagnosed by chest x-ray in most studies, with clinical signs and symptoms of pneumonia being used alone, or in conjunction with chest x-ray for diagnosis in other studies. The presence of comorbidity including major cardiac, pulmonary or renal dysfunction, bronchial asthma, diabetes mellitus or immunosuppression were clearly stated exclusion criteria by some studies (Maimon et al. 2008; Llor et al. 2017; Paris et al. 2008 and Ige et al. 2015). Both inpatients and outpatients were included. The evidence in adults with low-severity community-acquired pneumonia is presented here, with treatment setting (community or hospital) used as a proxy for severity where severity was not reported, consistent with the approach taken in the NICE guideline on pneumonia in adults: diagnosis and management 2014.

3.1.3.1 Single antibiotic compared with another single antibiotic

Amoxicillin versus phenoxymethylpenicillin

A non-inferiority trial (Llor et al. 2017) found that amoxicillin (oral, 1 g three times daily for 10 days) was not significantly different to phenoxymethylpenicillin (oral, 1,600,000 IU three times daily for 10 days) in adults with community-acquired pneumonia treated as outpatients for clinical cure (defined as absence of fever, resolution or improvement of cough, improvement of well-being and resolution or reduction of crackles) at day 14 in per protocol analysis (1 RCT, n=36, 100% versus 90.9%, relative risk [RR] 1.12, 95% confidence interval [CI] 0.90 to 1.40 [NICE analysis]; moderate quality evidence). However, amoxicillin was significantly more effective than phenoxymethylpenicillin in intention to treat analysis for clinical cure at day 14 (1 RCT, n=39, RR 1.40, 95% CI 1.00 to 1.96 [NICE analysis] number needed to treat [NNT] 4 [2 to 21]; moderate quality evidence).

Amoxicillin (same dosage and duration) was not significantly different to phenoxymethylpenicillin (same dosage and duration) in the same population for complete clinical resolution (defined as total resolution of acute symptoms and signs related to infection or adverse events) at day 14 in intention to treat analysis (1 RCT,

n=39, 48.0% versus 21.4%, RR 2.24, 95% CI 0.76 to 1.96 [NICE analysis]; low quality evidence), but amoxicillin was significantly more effective than phenoxymethylpenicillin at day 30 (1 RCT, n=39, 92.0% versus 57.1%, RR 1.61, 95% CI 1.01 to 2.57, NNT 3 [2 to 15] [NICE analysis]; moderate quality evidence). There was no significant difference between amoxicillin and phenoxymethylpenicillin in radiological cure in intention to treat analysis at day 30 (1 RCT, n=35, 83.3% versus 54.5%, RR 1.53, 95% CI 0.87 to 2.70; moderate quality evidence).

No safety or tolerability data was reported.

See GRADE profile: **Table** 31

Clarithromycin versus amoxicillin

A systematic review (Pakhale et al. 2014) found that clarithromycin (oral, unreported dose) was not different to amoxicillin (oral, unreported dose) in adults with community-acquired pneumonia treated as outpatients for cure rate (0% versus 0%, relative risk not estimable; low quality evidence).

No safety or tolerability data was reported.

See GRADE profile: **Table** 32

Clarithromycin versus erythromycin

A systematic review (Pakhale et al. 2014) found that clarithromycin (oral, 250 mg twice daily for 14 days) was not significantly different to erythromycin (oral, 500 mg four times daily for 14 days) in adults treated as outpatients evaluated at 4 to 6 weeks for clinical response (cure or improvement; 2 RCTs, n= 280, 97.4% versus 94.4%, RR 1.03, 95% CI 0.98 to 1.09 [NICE analysis]; moderate quality evidence), bacteriological cure (2 RCTs, n=57, 88.6% versus 100%, RR 0.90, 95% CI 0.78 to 1.05 [NICE analysis]; moderate quality evidence) or radiological cure (2 RCTs, n=276, 93.5% versus 94.3%, RR 0.99, 95% CI 0.94 to 1.06 [NICE analysis]; moderate quality evidence).

The number of adverse events with erythromycin was significantly higher than with clarithromycin (2 RCTs, n=476, 45.7% versus 21.4%, RR 0.46, 95% CI 0.35 to 0.61 [NICE analysis], NNT 5 [3 to 6]; moderate quality evidence).

See GRADE profile: **Table** 33

Azithromycin versus levofloxacin

A systematic review (Pakhale et al. 2014) found that azithromycin (oral, single 2 g dose; unreported duration) was not significantly different to levofloxacin (oral, 500 mg once daily for 7 days) in adults with low- to moderate-severity community-acquired pneumonia for clinical response at day 13 to 21 (1 RCT, n=363, 89.7% versus 93.7%, RR 0.96, 95% CI 0.90 to 1.02 [NICE analysis]; moderate quality evidence) or bacteriological cure (1 RCT, n= 237, 90.7% versus 92.3%, RR 0.98, 95% CI 0.91 to 1.06 [NICE analysis]; moderate quality evidence).

The number of adverse events with azithromycin was significantly higher than with levofloxacin (1 RCT, n=233, 19.9% versus 12.3%, RR 1.62, 95% CI 1.03 to 2.55 [NICE analysis], NNH 14 [6 to 148]; low quality evidence).

See GRADE profile: **Table** 34

Azithromycin versus clarithromycin

A systematic review (Pakhale et al. 2014) found that azithromycin (oral, single 2 g dose) was not significantly different to clarithromycin (oral, 500 mg once daily for 7 days) in adults with low- to moderate-severity community-acquired pneumonia for clinical response at day 14 to 21 (1 RCT, n=411, 92.6% versus 94.7%, RR 0.98, 95% CI 0.93 to 1.03 [NICE analysis]; high quality evidence) or bacteriological cure (1 RCT, n=303, 91.8% versus 90.5%, RR 1.01, 95% CI 0.95 to 1.09 [NICE analysis]; high quality evidence).

There was no significant difference in the number of adverse events with azithromycin and clarithromycin (1 RCT, n=499, 26.3% versus 24.6%, RR 1.07, 95% CI 0.79 to 1.44 [NICE analysis]; moderate quality evidence).

See GRADE profile: **Table** 35

Azithromycin versus co-amoxiclav

A non-inferiority trial (Paris et al. 2008) found that azithromycin (oral, 1 g once daily for 3 days) was not significantly different to co-amoxiclav (oral, 875/125 mg twice daily for 7 days) in adults with low-severity community-acquired pneumonia (pneumonia severity index [PSI] score I or II) for clinical success (defined as complete resolution or reduction of symptoms so that no additional antibiotic therapy was required) at day 8 to 12 (1 RCT, n=267, 92.6% versus 93.1%, RR 0.99, 95% CI 0.93 to 1.06 [NICE analysis]; high quality evidence) or at day 22 to 26. There was also no significant difference between azithromycin and co-amoxiclav for bacteriological response at day 8 to 12 or day 22 to 26 or radiological response at day 22 to 26 (high quality evidence).

There was no significant difference in the number of people reporting at least 1 adverse event, either total (1 RCT, n=268, 25.0% versus 16.7, RR 1.50, 95% CI 0.93 to 2.42 [NICE analysis]; moderate quality evidence), specifically drug related adverse events (1 RCT, n=268, 16.9% versus 9.1%, RR 1.86, 95% CI 0.97 to 3.58 [NICE analysis]; moderate quality evidence) or serious adverse events (1 RCT, n=268, 2.2% versus 2.3%, RR 0.97, 95% CI 0.20 to 4.72 [NICE analysis]; low quality evidence). There were no significant differences in the number of people reporting nausea, vomiting or diarrhoea, however, there were significantly more reports of abdominal pain in people given azithromycin compared with co-amoxiclav (1 RCT, n=268, 9.6% versus 1.5%, RR 6.31, 95% CI 1.45 to 27.42, NNH 13 [7 to 37] [NICE analysis]; low quality evidence).

See GRADE profile: **Table** 36

Cephalosporins versus co-amoxiclav

A systematic review (Maimon et al. 2008) found that cephalosporins (oral, cefuroxime [500 mg twice daily for 10 days] or cefditoren [200/400 mg twice daily for 14 days]),) were not significantly different to co-amoxiclav (oral, 125/500 mg three times daily for 10 days or 125/875 mg twice daily for 14 days) in adults with community-acquired pneumonia treated as outpatients for clinical success (2 RCTs, n=551, 90.7% versus 91.8%, RR 1.01, 95% CI 0.95 to 1.08; low quality evidence). There was also no significant difference in clinical success when analysis was restricted to antibiotics available in the UK.

No safety or tolerability data was reported.

See GRADE profile: **Table** 37

Cefixime versus ciprofloxacin

An RCT (Ige et al. 2015) found that cefixime (oral, 400 mg twice daily for 14 days) was not significantly different to ciprofloxacin (oral, 500 mg twice daily for 14 days) in adults with low-severity community-acquired pneumonia (CURB65 [confusion, urea, respiratory rate, blood pressure, age ≥65] score of 1 or 2) at reducing temperature by day 3 or day 14 (day 14: 1 RCT, n=73, mean difference 0.3°C, 95% CI −0.63 to 0.03; very low quality evidence) or pulse rate by day 3 or day 14 (day 14: 1 RCT, n=73, mean difference 2.6, 95% CI −5.99 to 0.79; low quality evidence). There was no significant difference in respiratory rate at day 3, but at day 14 cefixime significantly decreased respiratory rate (day 14: 1 RCT, n=73, mean 16.5 versus 17.7, mean difference 1.2, 95% CI 0.29 to 2.11; low quality evidence), presence of radiological consolidations (1 RCT, n=73, 10.3% versus 38.2%, RR 0.27, 95% CI 0.10 to 0.75, NNT 4 [2 to 12]; moderate quality evidence) and presence of bacterial isolates (1 RCT, n=73, 7.7% versus 38.2%, RR 0.20, 95% CI 0.06 to 0.65 NNT 4 [2 to 9]; moderate quality evidence) compared with ciprofloxacin.

No adverse events were reported in either treatment arm.

See GRADE profile: **Table** 38

3.1.3.2 Single antibiotic compared with dual antibiotics

Levofloxacin versus ceftriaxone plus azithromycin

A systematic review (Raz-Pasteur et al. 2015) included 1 RCT in adults with community-acquired pneumonia treated in the community. NICE subgroup analysis found that levofloxacin (intravenous or oral, 500 mg once daily for 7 to 14 days) was not significantly different to ceftriaxone (intravenous, 1 g daily for 7 to 14 days) plus azithromycin (intravenous, 500 mg once daily) for clinical failure rate (1 RCT, n=236, 13.0% versus 19.8%, RR 0.66, 95% CI 0.36 to 1.19 [NICE analysis]; moderate quality evidence).

No safety or tolerability data was reported.

See GRADE profile: **Table** 39

3.1.3.3 Dual antibiotics compared with other dual antibiotics

No systematic reviews or randomised controlled trials met the inclusion criteria.

3.1.4 Choice of antibiotic in moderate- to high-severity community-acquired pneumonia

The evidence for antibiotic choice for treatment of moderate- to high-severity community-acquired pneumonia comes from 7 systematic reviews (Eliakim-Raz et al. 2012, Nemeth et al. 2015 [33 RCTs, n=9,597], Skalsky et al. 2013 [16 RCTs, n=4,989], El Hajj et al. 2017 [6 RCTs, n=3,393], Yuan et al. 2012 [14 RCTs, n=6,923], Bai Nan et al. 2014 [8 RCTs, n=2,883] and Raz-Pasteur et al. 2015 [16 RCTs, n=4,809]) and 2 non-inferiority RCTs (Nicholson et al. 2012 [n=706] and Tamm et al. 2007 [n=278]).

Community-acquired pneumonia was diagnosed by chest x-ray in most studies, with clinical signs and symptoms of pneumonia being used alone, or in conjunction with chest x-ray for diagnosis in other studies. The presence of comorbidity including immunosuppression, impaired renal or hepatic function, bronchiectasis or cystic fibrosis were clearly stated exclusion criteria by some studies (Eliakim-Raz et al.

2012, Nemeth et al. 2015 and Tamm et al. 2007).The evidence in adults with moderate to high-severity community-acquired pneumonia is presented here, with treatment setting (community or hospital) used as a proxy for severity where severity was not reported, consistent with the approach taken in the NICE guideline on pneumonia in adults: diagnosis and management 2014.

3.1.4.1 Single antibiotic compared with another single antibiotic

Atypical versus non-atypical antibiotic coverage

A systematic review (Eliakim-Raz et al. 2012) compared antibiotics targeted at atypical pathogens (including fluoroquinolones, macrolides and pristinamycine) and antibiotics targeted at non-atypical pathogens (including co-amoxiclav, cephalosporins, carbapenems and penicillins). In all but 3 studies the atypical arm was given as a monotherapy. The antibiotics were administered orally in all but 8 studies, of which most switched to oral administration within a few days.

Atypical antibiotics were not significantly better than non-atypical antibiotics for adults hospitalised with community-acquired pneumonia for mortality rate (25 RCTs, n=5,444, 3.4% versus 2.8%, relative risk [RR] 1.14, 95% confidence interval [CI] 0.84 to 1.55; very low quality evidence). Atypical antibiotics were also not significantly better than non-atypical antibiotics in subgroup analysis of mortality in studies in adults under 65 years, over 65 years or conducted in Europe only.

There was also no significant difference between atypical and non-atypical antibiotics for clinical failure rate (27 RCTs, n=5,048, 21.4% versus 21.1%, RR 0.92, 95% CI 0.83 to 1.02; very low quality evidence), including in subgroup analysis of clinical failure in people under 65 years or over 65 years.

Subgroup analysis of studies conducted in Europe showed no significant difference between atypical antibiotics compared with non-atypical antibiotics in clinical failure (15 RCTs, n=3,084, 21.3% versus 21.0%, RR 1.01, 95% CI 0.88 to 1.16, number needed to treat [NNT] 425 [95% CI not estimable]; very low quality evidence); there was also no significant difference when only studies using antibiotics available in the UK were included (6 RCTs, n=719, 15.2% versus 20.2%, RR 0.75, 95% CI 0.54 to 1.03 [NICE analysis]; very low quality evidence). Clinical failure in people with any atypical pathogen infection or pneumococcal pneumonia infection was not significantly different between people given atypical and non-atypical antibiotics, however clinical failure in people with *Legionella pneumophila* infection was significantly lower in people given atypical antibiotics compared with non-atypical (5 RCTs, n=43, 0.0% versus 45%, RR 0.17, 95% CI 0.05 to 0.63, NNT 3 [1 to 4]; low quality evidence; all antibiotics unavailable in UK).

Atypical antibiotics also significantly reduced bacteriological failure compared with non-atypical antibiotics in adults hospitalised with community-acquired pneumonia (21 RCTs, n=2,310, 11.9% versus 14.7%, RR 0.80, 95% CI 0.65 to 0.98, NNT 36 [17 to 3178]; very low quality evidence), however, this effect was no longer significant in subgroup analysis of antibiotics available in the UK (8 RCTs, n=697, 13.5% versus 17.3%, RR 0.82, 95% CI 0.58 to 1.15 [NICE analysis]; low quality evidence).

Atypical antibiotics were not significantly different to non-atypical antibiotics in adults hospitalised with community-acquired pneumonia in the number of total adverse events (24 RCTs, n=4,918, 22.9% versus 21.9%, RR 1.02, 95% CI 0.93 to 1.13; very low quality evidence) or the number of adverse events requiring treatment discontinuation. There were significantly more gastrointestinal adverse events in people given non-atypical antibiotics compared with atypical antibiotics (16 RCTs,

n=4,129, 5.0% versus 3.6%, RR 0.70, 95% CI 0.53 to 0.92, NNH 76 [38 to 1300]; very low quality evidence), however this effect was no longer significant in subgroup analysis of antibiotics available in the UK (7 RCTs, n=1,928, 4.4% versus 3.6%, RR 0.81, 95% CI 0.53 to 1.24 [NICE analysis]; low quality evidence).

See GRADE profiles: Table 40 and Table 41

Macrolides versus non-atypical antibiotics

A systematic review (Eliakim-Raz et al. 2012) included a subgroup analysis of macrolides (azithromycin [oral, 500 mg twice daily loading dose followed by 500 mg once daily, unreported course length], clarithromycin [unreported dose and course length] and roxithromycin [oral, 150 mg twice daily, unreported course length]) compared with non-atypical antibiotics (including benzylpenicillin [intravenous, 1,000,000 IU four times daily, unreported course length], meropenem [intravenous, 500 mg three times daily, unreported course length], co-amoxiclav [intravenous, 1.2 g four times daily for 3 to 5 days, followed by oral, 625 mg three times daily], and cephradine [oral, 1 g twice daily]).

Macrolides were not significantly different to non-atypical antibiotics in adults hospitalised with community-acquired pneumonia for mortality (4 RCTs, n=540, 3.7% versus 3.0%, RR 1.25, 95% CI 0.52 to 3.01; very low quality evidence) or clinical failure (5 RCTs, n= 536, 16.9% versus 15.2%, RR 1.11, 95% CI 0.76 to 1.62; very low quality evidence). There was also no significant difference between macrolides and non-atypical antibiotics in mortality or clinical failure in subgroup analysis of antibiotics available in the UK (very low to low quality evidence, NICE analysis).

No safety or tolerability data was reported.

See GRADE profile: Table 42 and Table 43

Fluoroquinolones versus non-atypical antibiotics

A systematic review (Eliakim-Raz et al. 2012) included a subgroup analysis of fluoroquinolones compared with non-atypical antibiotics (including co-amoxiclav, cephalosporins and penicillins; see GRADE profile: Table 44 for details of antibiotics).

Fluoroquinolones were not significantly different to non-atypical antibiotics in adults hospitalised with community-acquired pneumonia for mortality (19 RCTs, n=3,698, 3.1% versus 3.1%, RR 0.98, 95% CI 0.69 to 1.39; very low quality evidence) or clinical failure (21 RCTs, n=3,704, 18.4% versus 20.4%, RR 0.89, 95% CI 0.79 to 1.02; very low quality evidence). There was also no significant difference between atypical and non-atypical antibiotics in mortality or clinical failure in subgroup analysis of antibiotics available in the UK (very low to moderate quality evidence; NICE analysis).

No safety or tolerability data was reported.

See GRADE profile: Table 44 and Table 45

Levofloxacin versus tigecycline

A systematic review (Nemeth et al. 2015) included 4 RCTs comparing levofloxacin with tigecycline in adults with community-acquired pneumonia. NICE subgroup analysis found that levofloxacin (unreported route of administration and dosage) was not significantly different to tigecycline (unreported route of administration and dosage) in adults with high-severity community-acquired pneumonia for clinical cure

(4 RCTs, n=1,940, 80.1% versus 81.6%, RR 0.98, 95% CI 0.94 to 1.03 [NICE analysis]; high quality evidence) or mortality (4 RCTs, n= 2,068, 2.4% versus 3.1%, RR 0.79, 95% CI 0.47 to 1.32 [NICE analysis]; moderate quality evidence).

No safety or tolerability data was reported.

See GRADE profile: Table 46

Levofloxacin versus doxycycline

A systematic review (Nemeth et al. 2015) included 1 RCT comparing levofloxacin with doxycycline in adults with community-acquired pneumonia. NICE subgroup analysis found that levofloxacin (unreported route of administration and dosage) was not significantly different to doxycycline (unreported route of administration and dosage) in adults with high-severity community-acquired pneumonia for clinical cure (1 RCT, n=65, 93.3% versus 97.1%, RR 0.96, 95% CI 0.86 to 1.07 [NICE analysis]; high quality evidence). There was no difference in mortality rates between levofloxacin and doxycycline (1 RCT, n=65, 0.0% versus 0.0%, RR not estimable [NICE analysis]; moderate quality evidence).

No safety or tolerability data was reported.

See GRADE profile: Table 47

Ofloxacin versus erythromycin

A systematic review (Skalsky et al. 2013) included 1 RCT comparing ofloxacin with erythromycin in adults with community-acquired pneumonia. NICE subgroup analysis found that ofloxacin (intravenous with oral switch, unreported dosage, for 5 to 14 days) was not significantly different to erythromycin (intravenous with oral switch, unreported dosage, for 5 to 14 days) in adults hospitalised with community-acquired pneumonia for mortality (1 RCT, n=102, 11.5% versus 12.0%, RR 0.96, 95% CI 0.33 to 2.78; moderate quality evidence), clinical failure (2 RCTs, n=199, 19.2% versus 19.0%, RR 1.00, 95% CI 0.57 to 1.76; low quality evidence) or microbiological failure (1 RCT, n=99, 0.0% versus 4.0%, RR 0.2, 95% CI 0.01 to 4.14; low quality evidence).

No safety or tolerability data was reported.

See GRADE profile: Table 48

Moxifloxacin versus levofloxacin

A systematic review (Yuan et al. 2012) included 3 RCTs comparing moxifloxacin with levofloxacin in adults with community-acquired pneumonia. NICE subgroup analysis found that moxifloxacin (intravenous or oral, 400 mg once daily for 7 to 14 days) was not significantly different to levofloxacin (intravenous or oral, 100 mg twice a day for 500 mg once a day for 7 to 14 days) in adults hospitalised with community-acquired pneumonia for mortality (3 RCTs, n=1,052, 5.6% versus 4.3%, RR 1.28, 95% CI 0.76 to 2.15 [NICE analysis]; moderate quality evidence), overall treatment success (defined as resolution of all or 2 or more baseline symptoms; 2 RCTs, n=808, 73.0% versus 73.7%, RR 0.99, 95% CI 0.97 to 1.08 [NICE analysis]; high quality evidence) or microbiological treatment success.

There was no significant difference in adverse events between moxifloxacin and levofloxacin in adults hospitalised with community-acquired pneumonia (3 RCTs, n=1,203, 29.3% versus 27.0%, RR 1.09, 95% CI 0.91 to 1.30 [NICE analysis]; moderate quality evidence).

See GRADE profile: **Table** 49

Ceftriaxone versus ceftaroline fosamil

A systematic review (El Hajj et al. 2017) included 3 RCTs comparing ceftriaxone (intravenous, 1 g once daily for 5 to 7 days) with ceftaroline fosamil (intravenous, 600 mg twice daily for 5 to 7 days). In 1 included study, participants in both groups also received clarithromycin (oral, 500 mg) on day 1 of treatment.

A subgroup analysis included in the systematic review showed that ceftaroline fosamil significantly increased clinical cure rate (defined as total resolution of all signs and symptoms so that no more antimicrobial therapy required) compared with ceftriaxone in adults with moderate-severity community-acquired pneumonia (majority of participants had pneumonia severity index (PSI) score III; 3 RCTs, n=2,011, 81.6% versus 72.8%, RR 1.12, 95% CI 1.07 to 1.18, number needed to treat [NNT] 12 [8 to 20]; moderate quality evidence), however there was no difference in mortality (3 RCTs, n=2,011, 1.8% versus 1.6%, RR 1.12, 95% CI 0.58 to 2.19; low quality evidence).

There was no significant difference between ceftriaxone and ceftaroline fosamil in the number of serious adverse events (3 RCTs, n=2,011, 9.8% versus 10.0%, RR 0.98, 95% CI 0.75 to 1.27; low quality evidence).

See GRADE profile: **Table** 50

Ertapenem versus ceftriaxone

A systematic review (Bai Nan et al. 2014) included 2 RCTs comparing ertapenem with ceftriaxone in adults with community-acquired pneumonia. NICE subgroup analysis found that ertapenem (intravenous or intramuscular, 1 g per day, followed by co-amoxiclav, unreported course length) was not significantly different to ceftriaxone (intravenous or intramuscular, 1 g per day followed by co-amoxiclav, unreported course length) in adults requiring injectable antibiotics for community-acquired pneumonia for treatment success (defined as disappearance of acute signs and symptoms with no further antibiotic required; 2 RCTs, n=658, 92.0% versus 91.8%, RR 1.00, 95% CI 0.96 to 1.05 [NICE analysis]; high quality evidence) or microbiological success.

No safety or tolerability data was reported.

See GRADE profile: **Table** 51

3.1.4.2 Single antibiotic compared with dual antibiotics

Fluoroquinolones versus macrolides plus beta-lactams

A systematic review (Raz-Pasteur et al. 2015) compared fluoroquinolones (levofloxacin [intravenous or oral, 500 to 750 mg once daily] or moxifloxacin [intravenous or oral, 400 mg once daily) with macrolides (azithromycin [intravenous or oral 500 mg once daily], erythromycin [intravenous 500 mg to 1 g once daily], clarithromycin [oral 500 mg twice daily], roxithromycin [oral 150 mg twice daily]) plus beta-lactams (ceftriaxone [intravenous 1 to 2 g once daily], co-amoxiclav [intravenous 500/1000 mg once daily; 1000/125 mg three times daily], amoxicillin [intravenous, unreported dosage], penicillin [unspecified; intravenous, unreported dosage], or cefoperazone [intravenous 2 g once daily]). Antibiotics were given for between 7 to 14 days. 1 RCT included people treated in the community.

Fluoroquinolones as monotherapy were not significantly different to macrolides plus beta-lactams as dual therapy in adults with community-acquired pneumonia (majority hospitalised; 1 RCT included adults treated in the community) for mortality (5 RCTs, n=2,683, RR 0.99, 95% CI 0.70 to 1.40 [raw data not available]; low quality evidence). However, fluoroquinolones as monotherapy significantly decreased clinical failure (defined as the need for antibiotic modifications related to perceived failure) compared with macrolides plus beta-lactams as dual therapy (9 RCTs, n= 2,441, RR 0.72, 95% CI 0.57 to 0.91 [raw data not available]; very low quality evidence), although this effect was no longer significant when only considering people with pneumococcal pneumonia (7 RCTs, n=145, RR 2.03, 95% CI 0.94 to 4.38 [raw data not available]; very low quality evidence). There was no significant difference between fluoroquinolone monotherapy and macrolides plus beta-lactams as dual therapy in microbiological failure.

Fluoroquinolones as monotherapy showed significantly lower treatment discontinuation (6 RCTs, n=2,179, RR 0.65, 95% CI 0.54 to 0.78 [raw data not available]; very low quality evidence), total adverse events (7 RCTs, n=2,727, RR 0.90, 95% CI 0.81 to 1.00 [raw data not available]; low quality evidence) and number of people reporting diarrhoea (3 RCTs, n=617, RR 0.13, 95% CI 0.05 to 0.34 [raw data not available]; low quality evidence) compared with macrolides plus beta-lactams as dual therapy.

See GRADE profile: **Table** 52

Fluoroquinolones versus fluoroquinolones plus beta-lactams

A systematic review (Raz-Pasteur et al. 2015) compared fluoroquinolones as monotherapy (levofloxacin [intravenous 500 mg twice daily], sparfloxacin [oral, 400 mg once daily] and moxifloxacin [intravenous, 400 mg once daily]) with fluoroquinolones (ofloxacin [intravenous, 200 mg twice daily] and levofloxacin [intravenous 500 mg once daily]) plus beta-lactams (ceftriaxone [intravenous 2 g once daily], cefotaxime [intravenous, 1 g three times daily] and amoxicillin [oral, 1 g three times daily]). Antibiotics were given for between 7 to 14 days.

Fluoroquinolones as monotherapy were not significantly different to fluoroquinolones plus beta-lactams as dual therapy in adults hospitalised with community-acquired pneumonia for mortality (2 RCTs, n=1,116, RR 1.00, 95% CI 0.69 to 1.45 [raw data not available]; moderate quality evidence), clinical failure (3 RCTs, n=1,252, RR 1.11, 95% CI 0.89 to 1.38 [raw data not available]; low quality evidence), including a subgroup analysis of people with pneumococcal pneumonia (3 RCTs, n=261, RR 0.92, 95% CI 0.53 to 1.59 [raw data not available]; very low quality evidence) or microbiological failure.

Fluoroquinolones as monotherapy were not significantly different to fluoroquinolones plus beta-lactams as dual therapy in adults hospitalised with community-acquired pneumonia for total adverse events (3 RCTs, n=1,339, RR 1.02, 95% CI 0.90 to 1.14 [raw data not available]; low quality evidence), however there was a significant increase in the number of people reporting diarrhoea with fluoroquinolones plus beta-lactam dual therapy compared with fluoroquinolone dual therapy (1 RCT, n=733, RR 2.05, 95% CI 1.13 to 3.73 [raw data not available]; moderate quality evidence).

See GRADE profile: **Table** 53

Macrolides versus macrolides plus beta-lactams

A systematic review (Raz-Pasteur et al. 2015) compared macrolides as monotherapy (azithromycin [intravenous 500 mg once daily] or clarithromycin [oral or intravenous,

500 mg once daily]) with macrolides (clarithromycin [oral, 500 mg once or twice daily] or erythromycin [intravenous oral, 500 to 1000 mg four times daily or intravenous 1 g three times daily]) plus beta-lactams (ceftriaxone [intravenous 2 g twice daily] and cefuroxime [oral 500 mg twice daily, or intravenous 750 mg to 1.5 g three times daily]) as dual therapy. The majority of participants were hospitalised, with 1 of 4 included studies also including outpatients (only included in analysis of clinical failure).

Macrolides as monotherapy were not significantly different to macrolides plus beta-lactams as dual therapy in adults with community-acquired pneumonia for mortality (3 RCTs, n=467, RR 1.00, 95% CI 0.40 to 2.46 [raw data not available]; low quality evidence), clinical failure (4 RCTs, n=557, RR 0.92, 95% CI 0.67 to 1.26 [raw data not available]; very low quality evidence), including a subgroup analysis of people with pneumococcal pneumonia (2 RCTs, n=59, RR 0.49, 95% CI 0.10 to 2.48 [raw data not available]; very low quality evidence) or microbiological failure.

Macrolides as monotherapy showed significantly fewer adverse events than macrolides plus beta-lactams as dual therapy in adults hospitalised with community-acquired pneumonia (3 RCTs, n=470, RR 0.62, 95% CI 0.50 to 0.78 [raw data not available]; very low quality evidence). However, there was no significant difference in treatment discontinuation (1 RCT, n=235, RR 0.85, 95% CI 0.53 to 1.38 [raw data not available]) or the incidence of diarrhoea (2 RCTs, n=325, RR 0.47, 95% CI 0.22 to 1.01 [raw data not available]; very low quality evidence).

See GRADE profile: **Table** 54

Ceftobiprole versus ceftriaxone plus linezolid

A non-inferiority trial (Nicholson et al. 2011) compared ceftobiprole (intravenous, 500 mg three times daily) plus placebo if methicillin-resistant *Staphylococcus aureus* (MRSA) infection was suspected (ceftobiprole monotherapy) with ceftriaxone (intravenous, 2 g once daily) plus linezolid (600 mg twice daily) if MRSA infection was suspected (ceftriaxone plus linezolid dual therapy). Minimum intravenous treatment length was 3 days, after which switch to oral cefuroxime (500 mg once daily) was permitted in people with clinical stability for a total course length of 7 to 14 days. The study included hospitalised adults, excluding people with suspected or confirmed atypical bacterial infection.

Ceftobiprole monotherapy was not significantly different to ceftriaxone plus linezolid dual therapy in adults hospitalised with community-acquired pneumonia for clinical cure (1 RCT, n= 638, 76.4% versus 79.3%, RR 0.96, 95% CI 0.89 to 1.05 [NICE analysis]; high quality evidence), including in subgroup analysis of people aged over 75, people with pneumonia severity index (PSI) score over 91, people with community-acquired pneumonia complicated by bacteraemia or people with *Klebsiella pneumoniae* infection. There was also no significant difference in mortality (1 RCT, n=638, 0.32% versus 0.93%, RR 0.34, 95% CI 0.04 to 3.29 [NICE analysis]; moderate quality evidence) or in microbiological eradication between the treatment arms.

Ceftobiprole monotherapy was not significantly different to ceftriaxone plus linezolid dual therapy in the number of discontinuations due to adverse events (1 RCT, n=632, 5.8% versus 3.7%, RR 1.56, 95% CI 0.76 to 3.18 [NICE analysis]; moderate quality evidence). The incidence of treatment related adverse events was higher with ceftobiprole monotherapy compared with ceftriaxone plus linezolid dual therapy (1 RCT, n unknown, 36% versus 26%, 10% difference, 95% CI 2.9% to 17.2%; moderate quality evidence).

See GRADE profile: **Table** 55

3.1.4.3 Dual antibiotics compared with other dual antibiotics

Ceftriaxone plus azithromycin versus ceftriaxone plus macrolides

A non-inferiority trial (Tamm et al. 2007) compared ceftriaxone (intravenous, 1 to 2 g once daily) plus azithromycin (intravenous, 500 mg once daily) for 2 to 5 days, with oral step down with azithromycin (500 mg once daily) for total course length of 7 to 10 days with ceftriaxone (intravenous 1 to 2 g daily) plus clarithromycin (intravenous 500 mg twice daily) or erythromycin (intravenous 1 g three times daily) for 2 to 5 days, with oral step down with the same antibiotic at the same dose for total course length 7 to 14 days.

Ceftriaxone plus azithromycin was not significantly different to ceftriaxone plus macrolides in adults hospitalised with moderate- to high-severity community-acquired pneumonia for bacterial eradication at day 28 to 35 (1 RCT, n= 87, 68.3% versus 60.9%, RR 1.12, 95% CI 0.82 to 1.53 [NICE analysis]; moderate quality evidence). At day 28 to 35 follow up, there was also no significant difference in clinical success between treatment arms for people with: *Streptococcus pneumoniae* infection (1 RCT, n=50, 75.0% versus 66.7%; RR 1.12, 95% CI 0.79 to 1.61 [NICE analysis]; low quality evidence), *Haemophilus influenza* infection (1 RCT, n=15, 92.3% versus 37.5%, RR 2.46, 95% CI 0.99 to 6.1 [NICE analysis]; very low quality evidence), *Staphylococcus aureus* infection (1 RCT, n=7, 83.3% versus 100%, RR 1.05, 95% CI 0.43 to 2.55 [NICE analysis]; very low quality evidence), *Mycoplasma pneumoniae* infection (1 RCT, n=18, 88.9% versus 77.8%, RR 1.14, 95% CI 0.75 to 1.74 [NICE analysis]; low quality evidence), *Chlamydia pneumoniae* infection (1 RCT, n=17, 100% versus 66.7%, RR 1.45, 95% CI 0.9 to 2.35 [NICE analysis]; low quality evidence) or *Legionella spp.* infection (1 RCT, n=9, 0.0% versus 75%, RR 0.35, 95% CI 0.03 to 3.95 [NICE analysis; very low quality evidence).

Ceftriaxone plus azithromycin (intravenous) was not significantly different to ceftriaxone plus clarithromycin or erythromycin (intravenous) for the incidence for adverse events (1 RCT, n=278, 32.6% versus 40.6%, RR 0.80, 95% CI 0.59 to 1.10 [NICE analysis]; low quality evidence), including all gastrointestinal adverse events (1 RCT, n=278, 12.6% versus 18.2%, RR 0.69, 95% CI 0.39 to 1.22 [NICE analysis]; low quality evidence), incidence of diarrhoea and incidence of nausea.

See GRADE profile: **Table** 56

3.1.5 Antibiotic dose in low-severity community-acquired pneumonia

The evidence for antibiotic dose in adults with low-severity community-acquired pneumonia comes from 2 non-inferiority randomised controlled trials (RCTs; Zhao et al. 2016, n=457; Siquier et al. 2006, n=566).

Community-acquired pneumonia was diagnosed by chest x-ray and the presence of two or more clinical symptoms of pneumonia, including fever, new or increased cough, changed sputum characteristics or elevated white blood cell count. Siquier et al. 2006 excluded people with a positive *Legionella* urine antigen test and some respiratory conditions such as cystic fibrosis and bronchiectasis. Zhao et al. 2016 excluded people with serious cardiac, hepatic or renal diseases or declined white blood cell count.

High-dose versus low-dose levofloxacin

A non-inferiority trial (Zhao et al. 2016) found that high-dose levofloxacin (intravenous, 750 mg/day for 5 days) was not significantly different to low-dose levofloxacin (intravenous, 500 mg/day with switch to oral 500 mg/day when stable, for 7 to 14 days) in adults with low-severity community-acquired pneumonia (CURB65 [confusion, urea, respiratory rate, blood pressure, age ≥65] score 0 to 2) for number of people with clinical improvement or cure (defined as resolution or improvement that requires no further antibiotic treatment; 1 RCT, n=448, 91.4% versus 94.3%, relative risk [RR] 0.97, 95% confidence interval [CI] 0.92 to 1.02 [NICE analysis]; high quality evidence), clinical relapse (1 RCT, n=418, 0.49% versus 1.4%, RR 0.35, 95% CI 0.04 to 3.30 [NICE analysis]; low quality evidence), fever resolution after 3 days or change in white blood cell count.

High-dose levofloxacin was not significantly different to low-dose levofloxacin in adults with low-severity community-acquired pneumonia in the number of people reporting adverse events (1 RCT, n=457, 15.4% versus 10.5%, RR 1.46, 95% CI 0.90 to 2.38 [NICE analysis]; moderate quality evidence), including nausea and vomiting (1 RCT, n=457, 2.6% versus 0.44%, RR 6.03, 95% CI 0.73 to 49.66 [NICE analysis]; low quality evidence), abdominal pain (1 RCT, n=457, 0.88% versus 0.44%, RR 2.01, 95% CI 0.18 to 22.0; low quality evidence), insomnia or headaches and dizziness.

See GRADE profile: Table 57

Higher-dose versus lower-dose co-amoxiclav

A non-inferiority trial (Siquier et al. 2006) found that a 4000/250 mg daily dose of co-amoxiclav (oral, 2000/125 mg twice daily for 7 to 10 days) was not significantly different to a 2625/375 mg daily dose of co-amoxiclav (oral, 875/125 mg three times daily for 7 to 10 days) in adults with low-severity community-acquired pneumonia (approximately 88% of population pneumonia severity index score [PSI] class I, II or III) for clinical response at test of cure (defined as no additional antibacterial therapy required; 1 RCT, n=566, 83.7% versus 82.3%, RR 1.02, 95% CI 0.94 to 1.10 [NICE analysis]; high quality evidence) or bacteriological response at test of cure (1 RCT, n=158, 85.3% versus 82.1%, RR 1.04, 95% CI 0.90 to 1.20 [NICE analysis]; high quality evidence). There was also no significant difference in clinical response between doses of co-amoxiclav in subgroup analysis of people with atypical pathogen infection, *S. pneumoniae* infection or *H. influenzae* infection.

The doses of co-amoxiclav were not significantly different in adults with low-severity community-acquired pneumonia for number of withdrawals due to adverse events (1 RCT, n=566, 3.2% versus 5.2%, RR 0.62, 95% CI 0.27 to 1.40 [NICE analysis]; low quality evidence), including withdrawals due to diarrhoea, vomiting or abdominal pain.

See GRADE profile: Table 58

3.1.6 Antibiotic dose in moderate- to high-severity community-acquired pneumonia

No systematic reviews or randomised controlled trials met the inclusion criteria.

3.1.7 Antibiotic dose frequency

No systematic reviews or randomised controlled trials met the inclusion criteria.

3.1.8 Antibiotic course length

The evidence for antibiotic course length is available in a population of adults with mixed severity community-acquired pneumonia. This evidence comes from 1 systematic review and meta-analysis of randomised controlled trials (RCTs; Li et al. 2007; 15 RCTs, n=2,796) and 1 RCT (El Moussaoui et al. 2006; n=119). Li et al. 2007 included adults with low- to moderate-severity community-acquired pneumonia which was confirmed by chest x-ray. Outcome assessment was performed between 10 to 42 days. El Moussaoui et al. 2006 included adults with clinical and radiological signs of pneumonia with low- to moderate-severity community-acquired pneumonia, defined as a pneumonia severity index (PSI) score of 110 or less (class I to IV), who had improved after 72 hours.

Short- versus long-course antibiotics

A systematic review (Li et al. 2007) found that short-course antibiotics (3 to 7 days; including macrolides [azithromycin or telithromycin], fluoroquinolones [levofloxacin or gemifloxacin] and cephalosporins [ceftriaxone or cefuroxime]; doses unreported) were not significantly different to long-course antibiotics (10 to 14 days; including co-amoxiclav, macrolides [clarithromycin, erythromycin, roxithromycin or josamycin], fluoroquinolones [levofloxacin] and cephalosporins [cefaclor, ceftriaxone or cefuroxime], in 1 study unspecified 'multiple antibiotics' given; doses unreported) in adults with low- to moderate-severity community-acquired pneumonia for mortality (8 RCTs, n unknown, relative risk [RR] 0.81, 95% confidence interval [CI] 0.46 to 1.43 [raw data not reported]; very low quality evidence) or clinical failure (15 RCTs, n=2,796, 21.4% versus 25.6%, RR 0.89, 95% CI 0.78 to 1.02; low quality evidence).

No safety or tolerability data was reported.

See GRADE profile: Table 59

Short- versus long-course macrolide

A subgroup analysis within the systematic review by Li et al. (2007) found that short-course macrolides (3 to 5 days; azithromycin or telithromycin [telithromycin used in 1 study]; doses unreported) were not significantly different to long-course macrolides (10 to 14 days; erythromycin, josamycin, clarithromycin or roxithromycin, in 1 study unspecified 'multiple antibiotics' given; doses unreported) in adults with low- to moderate-severity community-acquired pneumonia for clinical failure (10 RCTs, n=1,533, 17.2% versus 20.5%, RR 0.88, 95% CI 0.71 to 1.09; very low quality evidence).

No safety or tolerability data was reported.

See GRADE profile: Table 60

Short- versus long-course beta-lactam

A subgroup analysis within the systematic review by Li et al. (2007) found that short-course beta-lactams (5 to 7 days; ceftriaxone or cefuroxime; doses unreported) were not significantly different to long-course beta-lactams (10 days; ceftriaxone and cefuroxime; doses unreported) in adults with low- to moderate-severity community-acquired pneumonia for clinical failure (2 RCTs, n=296, 25.0, % versus 27.1%, RR 0.92, 95% CI 0.63 to 1.36; very low quality evidence).

No safety or tolerability data was reported.

See GRADE profile: Table 61

Short-course azithromycin versus long-course antibiotics

A subgroup analysis within the systematic review by Li et al. (2007) found that short-course azithromycin (3 days; doses and route of administration unreported) was not significantly different to long-course antibiotics (10 to 14 days; clarithromycin or roxithromycin, in 1 study unspecified 'multiple antibiotics' given; doses and route of administration unreported) in adults with low- to moderate-severity community-acquired pneumonia for clinical failure (6 RCTs, n=734, 13.1% versus 20.2%, RR 0.61, 95% CI 0.34 to 1.10; very low quality evidence). A fixed effect model reported by Li et al. indicated a significant improvement in clinical failure with long-course azithromycin, however due to significant heterogeneity (I^2 = 54%) the random effects model has been presented here.

No safety or tolerability data was reported.

See GRADE profile: Table 62

Short- versus long-course levofloxacin

A systematic review (Li et al. 2007) included 1 RCT comparing short- with long-course levofloxacin in adults with community acquired pneumonia. NICE subgroup analysis found that short course levofloxacin (5 days; unreported dose) was not significantly different to long course levofloxacin (10 days; unreported dose) in adults with low- to moderate-severity community-acquired pneumonia for clinical failure (1 RCTs, n=528, 28.5% versus 35.7%, RR 0.80, 95% CI 0.62 to 1.03 [NICE analysis]; low quality evidence).

No safety or tolerability data was reported.

See GRADE profile: Table 63

Short- versus long-course amoxicillin

An RCT (El Moussaoui et al. 2006) found that short-course amoxicillin (3 days; intravenous; unreported dose) was not significantly different to long-course amoxicillin (8 days total; intravenous [unreported dose] with switch after 3 days to oral, 750 mg three times daily) in adults with low- to moderate-severity community-acquired pneumonia for clinical cure at day 10 or at day 28 in intention to treat analysis (day 28: 1 RCT, n=119, 83.9% versus 77.8%, RR 1.08, 95% CI 0.91 to 1.18; low quality evidence), bacteriological success or radiological success. There was also no difference in the mean length of hospital stay between treatment arms (1 RCT, n=119, mean 7.9 days, standard deviation [SD] 6.5 to 9.3 versus 8.9 days SD 6.8 to 11.0, mean difference 1 day, 95% CI −1.3 to 3.2; low quality evidence).

Short-course amoxicillin was not significantly different to long-course amoxicillin in adults with low- to moderate-severity community-acquired pneumonia for the number of people reporting adverse events (1 RCT, n=119, 10.7% versus 20.6%, RR 0.52, 95% CI 0.21 to 1.27; very low quality evidence).

See GRADE profile: **Table** 64

3.1.9 Antibiotic route of administration in low-severity community-acquired pneumonia

No systematic reviews or randomised controlled trials met the inclusion criteria.

3.1.10 Antibiotic route of administration in moderate- to high-severity community-acquired pneumonia

The evidence for route of administration in adults with moderate- to high-severity community-acquired pneumonia comes from 1 systematic review and meta-analysis of randomised controlled trials (RCTs; Athanassa et al. 2008, 6 RCTs, n=1,219). Athanassa et al. 2008 included hospitalised adults with moderate- to high-severity community-acquired pneumonia, diagnosed through chest x-ray and the presence of clinical signs of pneumonia. High-severity pneumonia was defined through the presence of American Thoracic Society criteria for severe pneumonia, pneumonia severity index (PSI) class IV or V or CURB-65 (confusion, urea, respiratory rate, blood pressure, age >65) score III-V.

Intravenous antibiotics with switch to oral antibiotics versus continuous intravenous antibiotics

A systematic review (Athanassa et al. 2008) compared intravenous antibiotics (co-amoxiclav, ceftriaxone, levofloxacin or cefuroxime) plus a switch to oral antibiotics after 2 to 4 days of intravenous antibiotics and clinical improvement (co-amoxiclav, cefpodoxime plus clarithromycin, erythromycin, levofloxacin or cefuroxime) with continuous intravenous antibiotics (cefuroxime, ceftriaxone and co-amoxiclav). Total course length is not reported.

Intravenous antibiotics with switch to oral antibiotics was not significantly different to continuous intravenous antibiotics in adults with moderate- to high-severity community-acquired pneumonia for mortality (5 RCTs, n=1,132, 5.0% versus 6.1%, relative risk [RR] 0.82, 95% confidence interval [CI] 0.51 to 1.31 [NICE analysis]; very low quality evidence), treatment success (3 RCTs, n=987, 76.5% versus 78.3%, RR 0.95, 95% CI 0.84 to 1.06; low quality evidence) or the number of people with recurrent infection (very low quality evidence).

Intravenous antibiotics with switch to oral antibiotics resulted in significantly fewer days in hospital compared with continuous intravenous treatment in adults with moderate- to high-severity community-acquired pneumonia (5 RCTs, n=526, mean difference 3.34, 95 % CI 4.42 to 2.25; very low quality evidence).

Intravenous antibiotics with switch to oral antibiotics also resulted in significantly fewer people reporting adverse events (4 RCTs, n=877, 21.6% versus 30.1%, RR 0.73, 95% CI 0.59 to 0.92, number needed to harm [NNH] 12 [7 to 36] [NICE analysis]; very low quality evidence), people withdrawing due to adverse events (4 RCTs, n=867, 3.8% versus 7.8%, RR 0.51, 95% CI 0.29 to 0.91, NNH 26 [14 to 113] [NICE analysis]; very low quality evidence) and number of people reporting phlebitis (3 RCTs, n=987, 2.8% versus 8.7%, RR 0.35, 95% CI 0.20 to 0.62, NNH 17 [11 to 33]; low quality evidence). However, there was no significant difference in the number of people reporting gastrointestinal adverse events. The outcomes reported did not significantly change in NICE subgroup analysis of antibiotics available in the UK.

See GRADE profile: **Table** 65

3.2 Antibiotics in children

The evidence for antibiotics in children has been divided pragmatically into 2 groups, non-severe and severe community-acquired pneumonia. The reason for using this stratification, and not the one used in adults (low and moderate to high severity) is that the systematic review on antibiotics in children (Lodha et al. 2013) which makes

up a large proportion of the evidence presented in this section, stratifies evidence using the non- severe and severe criteria rather than the low and moderate to severe criteria. When the severity of community-acquired pneumonia was not reported by a study, treatment setting (community or hospital) has been used as a proxy for severity.

3.2.1 Antibiotic prescribing strategies in non-severe community-acquired pneumonia

No systematic reviews or randomised controlled trials met the inclusion criteria.

3.2.2 Antibiotic prescribing strategies in severe community-acquired pneumonia

The evidence for antibiotic prescribing strategies in children with severe community-acquired pneumonia comes from 1 non-inferiority randomised controlled trial (RCT; In-iw et al. 2015) including 57 children aged between 1 month to 5 years, hospitalised with community-acquired pneumonia (defined as at least 2 criteria from age-specific cut-offs for increased respiratory rate, chest retraction, respiratory distress and abnormal chest radiography). Children admitted to intensive care were excluded. Switch to oral antibiotics was based on core body temperature dropping below 37.8°C for at least 8 hours and clinical signs becoming stable. Standard medical procedure was based on switching to oral antibiotics after at least 48 hours dissipation of fever. The majority of children in both treatment arms started on intravenous 3rd generation cephalosporin and switched to oral co-amoxiclav or oral 3rd generation cephalosporin. There is a high risk of bias as treatment was given to both groups by the same physicians, who were shown to change their practice for standard medical practice according to the results found in the early switch arm.

Intravenous antibiotics with switch to oral antibiotics versus standard medical procedure

Intravenous antibiotics (most given 3rd generation cephalosporins [unspecified]; unreported dose or course length) with switch to oral antibiotics (co-amoxiclav or 3rd generation cephalosporin [unspecified]; unreported dose or course length) was significantly better at reducing the length of hospital stay compared with standard medical procedure (with the same antibiotics) in children aged 1 month to 5 years hospitalised with community-acquired pneumonia (1 RCT, n=57, mean [standard deviation] 3.81 days [1.6] versus 4.77 days [1.5], mean difference −0.96 days, 95% confidence interval [CI] −1.77 to −0.15; very low quality evidence). However, switch to oral antibiotics was not significantly different to standard medical procedure for readmission rate within 30 days of discharge (very low quality evidence).

See GRADE profile: **Table** 66

3.2.3 Choice of antibiotic in non-severe community-acquired pneumonia

The evidence review for a single antibiotic compared with another single antibiotic, and a single antibiotic compared with dual antibiotics in non-severe community-acquired pneumonia in children is based on 1 systematic review and meta-analysis of randomised controlled trials (RCTs; Lodha et al. 2013). The systematic review included 29 RCTs in 14,188 children and young people under 18 years of age with non-severe, severe or very severe community-acquired pneumonia. Community-acquired pneumonia was defined as the case definition of pneumonia, as given by the World Health Organization (WHO) or radiologically confirmed pneumonia

acquired in the community. The systematic review excluded studies of pneumonia acquired post-hospitalisation, in immunocompromised children, or children with underlying illnesses such as congenital heart disease or those with an immune deficient state.

The evidence in children with non-severe community-acquired pneumonia is presented here, with treatment setting (community or hospital) used as a proxy for severity where severity was not reported.

3.2.3.1 Single antibiotic compared with another single antibiotic

Azithromycin versus erythromycin

Azithromycin (oral; 10 mg/kg on day 1 followed by 5 mg/kg/day for 4 days or 10mg/kg/day for 3 days) was not significantly different to erythromycin (oral; 40 mg/kg/day for 10 days and unreported details in 1 RCT) in children aged between 1 month to 16 years with non-severe community-acquired pneumonia for cure rate between days 10 to 19 (3 RCTs, n=363, 77.8% versus 75.2%, relative risk [RR] 1.04, 95% confidence interval [CI] 0.92 to 1.18 [NICE analysis]; low quality evidence) or failure rate between days 10 to 19 (3 RCTs, n=392, 2.5% versus 3.8%, RR 0.69, 95% CI 0.21 to 2.29 [NICE analysis]; very low quality evidence).

Azithromycin was not significantly different to erythromycin for children with non-severe community-acquired pneumonia for the number of side effects (2 RCTs, n=153, 20.2% versus 20.3%, RR 0.93, 95% CI 0.25 to 3.46 [NICE analysis]; very low quality evidence).

See GRADE profile: **Table** 67

Clarithromycin versus erythromycin

Clarithromycin (oral; 15 mg/kg/day for 10 days) was not significantly different to erythromycin (oral; 40 mg/kg/day for 10 days) in children aged between 3 to 16 years with non-severe community-acquired pneumonia for cure rate (1 RCT, n=234, 83.9% versus 76.4%, RR 1.10, 95% CI 0.96 to 1.25 [NICE analysis]; high quality evidence), clinical success rate (1 RCT, n= 234, 97.6% versus 95.5%, RR 1.02, 95% CI 0.97 to 1.07 [NICE analysis]; high quality evidence) or failure rate (1 RCT, 234, 2.4% versus 4.5%, RR 0.53, 95% CI 0.13 to 2.18 [NICE analysis]; low quality evidence).

There was no significant difference in the number of adverse events between clarithromycin and erythromycin (1 RCT, n=260, 24.1% versus 22.8%, RR 1.05, 95% CI 0.68 to 1.64 [NICE analysis]; low quality evidence).

See GRADE profile: **Table** 68

Azithromycin versus co-amoxiclav

Azithromycin (oral; 10 mg/kg on day 1 followed by 5 mg/kg/day for 4 days) was not significantly different to co-amoxiclav (oral; 40 mg/kg/day for 10 days and unreported details in 1 RCT) in children aged between 6 months to 16 years with non-severe community-acquired pneumonia for cure rate (1 RCT, n=188, 67.2% versus 66.7%, RR 1.01, 95% CI 0.81 to 1.25 [NICE analysis]; high quality evidence), failure rate (2 RCT, n= 276, 7.3% versus 5.4%, RR 1.20, 95% CI 0.45 to 3.21 [NICE analysis]; low quality evidence), or improvement (1 RCT, n=188, 24.0% versus 27.0%, RR 0.89, 95% CI 0.53 to 1.48 [NICE analysis]; low quality evidence).

Azithromycin showed significantly fewer side effects than co-amoxiclav for children with non-severe community-acquired pneumonia (2 RCTs, n=278, 11.6% versus

46.4%, RR 0.27, 9% CI 0.17 to 0.45, number needed to harm [NNH] 3 [2 to 4], [NICE analysis]; moderate quality evidence).

See GRADE profile: **Table** 69

Co-amoxiclav versus amoxicillin

Co-amoxiclav (oral; 125 mg or 62.5 mg, plus amoxicillin 250 mg or 500 mg three times daily for 10 days) was significantly better than amoxicillin (oral; 250 mg or 500 mg three times daily for 10 days) in children aged between 2 to 12 years with non-severe community-acquired pneumonia for improving cure rate (1 RCT, n=100, 94.0% versus 60.0%, RR 1.57, 95% CI 1.24 to 1.99, number needed to treat [NNT] 3 [2 to 6] [NICE analysis]; low quality evidence), and improving poor or no response rate (1 RCT, n= 100, 2.0% versus 20%, RR 0.10, 95% CI 0.01 to 0.75, NNT 6 [3 to 16] [NICE analysis]; moderate quality evidence).

There was no significant difference in the number of complications or side effects between co-amoxiclav and amoxicillin (1 RCT, n=100, 4.0% versus 0.0%, RR 5.00, 95% CI 0.25 to 101.58 [NICE analysis]; very low quality evidence).

See GRADE profile: **Table** 70

Co-trimoxazole versus amoxicillin

Co-trimoxazole (oral; 7 to 11 mg/kg/day for 5 days or 20/4 mg/kg/day for 5 days) was not significantly different to amoxicillin (oral; 31 to 51 mg/kg/day for 3 days or 25 mg/kg/day for 5 days) in children aged 2 to 59 months with non-severe community-acquired pneumonia for cure rate (2 RCTs, n=1,732, 82.6% versus 84.2%, RR 1.00, 95% CI 0.92 to 1.09 [NICE analysis]; low quality evidence), failure rate (2 RCTs, n=1,750, 17.7% versus 15.7%, RR 1.16, 95% CI 0.94 to 1.43 [NICE analysis]; low quality evidence) or death rate (2 RCTs, n=2,050, 0.18% versus 0.0%, RR 2.10, 95% CI 0.23 to 19.50 [NICE analysis]; low quality evidence).

There was no significant difference in the number of children changing antibiotics between co-trimoxazole and amoxicillin (moderate quality evidence).

See GRADE profile: **Table** 71

Cefpodoxime versus co-amoxiclav

Cefpodoxime (oral; 5 to 12 mg/kg/day for 10 days) was not significantly different to co-amoxiclav (oral; 6 to 13 mg/kg/day for 10 days) in children aged between 3 months to 11.5 years with non-severe community-acquired pneumonia for response rate at end of treatment (1 RCT, n=278, 95.2% versus 96.7%, RR 0.98, 95% CI 0.94 to 1.04 [NICE analysis]; low quality evidence).

There was no significant difference in the number of adverse events between cefpodoxime and co-amoxiclav (very low quality evidence).

See GRADE profile: **Table** 72

Amoxicillin versus chloramphenicol

The systematic review (Lodha et al 2013) conducted an indirect comparison of amoxicillin (oral; 25 mg/kg/day or 45mg/kg/day for 5 days) compared with chloramphenicol (oral; unreported dose) in children aged between 2 to 59 months with non-severe community-acquired pneumonia. Amoxicillin was significantly better than chloramphenicol for improving cure rate (1 RCT, n=796, 83.9% versus 54.9%, RR 1.53, 95% CI 1.23 to 1.89, NNT 4 [3 to 6] [NICE analysis]; moderate quality

evidence) and reducing failure rate (1 RCT, n=1,065, 15.9% versus 22.5%, RR 0.70, 95% CI 0.49 to 0.99, NNT 16 [NICE analysis]; low quality evidence).

No safety or tolerability data was reported.

See GRADE profile: **Table** 73

Single antibiotic compared with dual antibiotics

No systematic reviews or randomised controlled trials met the inclusion criteria.

Dual antibiotics compared with other dual antibiotics

No systematic reviews or randomised controlled trials met the inclusion criteria.

3.2.4 Choice of antibiotic in severe community-acquired pneumonia

The evidence review for a single antibiotic compared with another single antibiotic, and a single antibiotic compared with dual antibiotics in severe community-acquired pneumonia in children is based on 1 systematic review and meta-analysis of randomised controlled trials (RCTs; Lodha et al. 2013; 29 RCTs, n=14,188) and 2 RCTs (Cannavino et al. 2016; n=161) and Blumer et al. 2016; n=40).

The evidence in children with severe community-acquired pneumonia is presented here, with treatment setting (community or hospital) used as a proxy for severity where severity was not reported.

Children and young people aged under 18 years of age were included if they were described as having severe or very severe community-acquired pneumonia, or as requiring hospitalisation.

Community acquired-pneumonia was defined as pneumonia acquired in the community: with the case definition of pneumonia, as given by the World Health Organization (WHO); radiologically confirmed pneumonia; or clinical symptoms of pneumonia with the presence of 1 physiological test result supportive of pneumonia diagnosis. Complicated community-acquired pneumonia was defined as pneumonia with at least one further complication, including: empyema, pulmonary abscess, previous influenza-type illness or treatment in an intensive care unit.

Exclusion criteria included co-morbidities including renal insufficiency, congenital heart disease and immune deficiency and in some cases children who were suspected to have a non-susceptible infection.

3.2.4.1 Single antibiotic compared with another single antibiotic

Amoxicillin versus penicillins

A systematic review (Lodha et al. 2013) found that amoxicillin (oral; 45 mg/kg/day, or for 6 months to 12 years of age 8 mg/kg/dose three times daily and above 12 years of age 500 mg three times daily; unreported course length) was not significantly different to penicillin (unspecified; intramuscular 200,000 IU/kg or intravenous 25 mg/kg/ dose four times daily; unreported course length) in children with severe community-acquired pneumonia aged between 3 to 59 months (as reported in 1 RCT; age not reported in 1 RCT) for failure rate at 48 hours, failure rate at 5 days or failure rate at 14 days (1 RCT, n=1,702, 27.0% versus 26.2%, RR 1.03, 95% CI 0.88 to 1.21 [NICE analysis]; high quality evidence). There was also no significant difference between amoxicillin and penicillin in death rate (2 RCTs, n=1,905, 0.0%

versus 0.7%, RR 0.07, 95% CI 0.0 to 1.18 [NICE analysis]; moderate quality evidence).

No safety or tolerability data was reported.

See GRADE profile: **Table** 74

Amoxicillin versus ampicillin

A systematic review (Lodha et al. 2013) found that amoxicillin (oral syrup; 80 to 90 mg/kg per day in 2 doses, unreported course length) was not significantly different to ampicillin (intravenous; 100 mg/kg per day in 4 doses for 48 hours) in children with severe community-acquired pneumonia, either hospitalised (ampicillin group) or treated at home (amoxicillin group), aged between 3 to 59 months for failure rate before day 14 (defined as clinical deterioration, inability to take oral medication due to persistent vomiting, development of a co-morbid condition requiring an antibiotic, persistence of fever or lower chest in-drawing, hospitalisation associated with pneumonia, serious adverse event, withdrawn from study or death; 1 RCT, n=2,037, 7.5% versus 8.6%, RR 0.87, 95% CI 0.65 to 1.17 [NICE analysis]; moderate quality evidence), relapse rates (1 RCT, n=1,873, 2.6% versus 3.4%, RR 0.79, 95% CI 0.47 to 1.32 [NICE analysis]; low quality evidence) or death (1 RCT, n=2,037, 0.1% versus 0.4%, RR 0.25, 95% CI 0.03 to 2.2 [NICE analysis]; low quality evidence).

See GRADE profile: **Table** 75

Amoxicillin versus cefuroxime

A systematic review (Lodha et al. 2013) found that amoxicillin (intravenous; 75 mg/kg/d in 3 doses) was not significantly different to cefuroxime (intravenous, 75 mg/kg/d in 3 doses) in children hospitalised with community-acquired pneumonia aged between 3 to 72 months for cure rate (defined as a return of respiratory rate to age specific normal range; unreported follow up period 1 RCT, n=84, 97.6% versus 95.2%, relative risk [RR] 1.02, 95% confidence interval [CI] 0.94 to 1.11 [NICE analysis]; moderate quality evidence).

No safety or tolerability data was reported.

See GRADE profile: **Table** 76

Amoxicillin versus clarithromycin

A systematic review (Lodha et al. 2013) found that amoxicillin (intravenous; 75 mg/kg/day in 3 doses) was not significantly different to clarithromycin (intravenous; 15 mg/kg/day in 2 doses) in children hospitalised with community-acquired pneumonia for cure rate (defined as return of respiratory rate to age specific normal range; unreported follow up period; 1 RCT, n=82, 97.6% versus 97.5%, RR 1.00, 95% CI 0.93 to 1.07 [NICE analysis]; moderate quality evidence).

No safety or tolerability data was reported.

See GRADE profile: **Table** 77

Levofloxacin versus beta-lactam antibiotics

A non-inferiority trial included in a systematic review (Lodha et al. 2013) found that levofloxacin (either oral 10mg/kg/dose twice daily or intravenous 10mg/kg/dose every 12 hours) was not significantly different to treatment with either co-amoxiclav (oral; twice daily, including amoxicillin at 22.5 mg/kg/dose, in 7:1 dose of amoxicillin: clavulanic acid) or ceftriaxone (intravenous 25 mg/kg/dose every 12 hours, up to

4 g/day) in children with severe community-acquired pneumonia aged between 6 months to 5 years for cure rate (defined as resolution of signs and symptoms associated with active infection along with an improvement or lack of progression of abnormal findings of chest roentgenogram at 10 to 17 days; 1 RCT, n= 539, 94.3% versus 94.0% RR 1.00, 95% CI 0.96 to 1.05 [NICE analysis]; moderate quality evidence).

No safety or tolerability data was reported.

See GRADE profile: **Table** 78

Cefuroxime versus clarithromycin

A systematic review (Lodha et al. 2013) found that cefuroxime (intravenous; 75 mg/kg/day in 3 doses, unreported course length) was not significantly different to clarithromycin (intravenous; 15 mg/kg/day in 2 doses, unreported course length) in children hospitalised with community-acquired pneumonia aged between 3 to 72 months for cure rate (defined as return of respiratory rate to age specific normal range; unreported follow up period; 1 RCT, n=82, 95.2% versus 97.5%, RR 0.98, 95% CI 0.90 to 1.06 [NICE analysis]; moderate quality evidence).

No safety or tolerability data was reported.

See GRADE profile: **Table** 79

Co-trimoxazole versus chloramphenicol

A systematic review (Lodha et al. 2013) found that co-trimoxazole (details unreported) was not significantly different to chloramphenicol (details not reported) in children with severe community-acquired pneumonia and malnutrition aged under 5 years for cure rate (1 RCT, n=111, 70.9% versus 69.6%, RR 1.02, 95% CI 0.80 to 1.30 [NICE analysis]; moderate quality evidence), failure rate (1 RCT, n=111, 29.1% versus 28.6%, RR 1.02, 95% CI 0.57 to 1.83 [NICE analysis]; low quality evidence), relapse rate (1 RCT, n=111, 7.3% versus 7.1%, RR 1.02, 95% CI 0.27 to 3.87 [NICE analysis]; low quality evidence) or death rate (1 RCT, n=111, 14.5% versus 7.1%, RR 2.04, 95% CI 0.65 to 6.37 [NICE analysis]; low quality evidence).

There was no significant difference in the number of children needing to change antibiotics between co-trimoxazole and chloramphenicol treatment (low quality evidence).

See GRADE profile: **Table** 80

Ceftaroline fosamil versus ceftriaxone

An RCT (Cannavino et al. 2016) found that ceftaroline fosamil (intravenous; <33kg, 12 mg/kg; >33kg, 400 mg, three times daily, after 3 days switched to co-amoxiclav if stable) was not significantly different to ceftriaxone (intravenous; 75 mg/kg/day to maximum 4 g/day, twice daily, after 3 days switched to co-amoxiclav if stable) in children hospitalised with community-acquired pneumonia aged between 2 months to 18 years for clinical response at day 4 (1 RCT, n=143, 69.2% versus 66.7%, RR 1.04, 95% CI 0.80 to 1.35 [NICE analysis]; moderate quality evidence), clinical cure at the end of treatment (1 RCT, n=143, 91.6% versus 88.9%, RR 1.03, 95% CI 0.91 to 1.17 [NICE analysis]; high quality evidence) or clinical failure at the end of treatment (1 RCT, n=143, 6.5% versus 11.1%, RR 0.59, 95% CI 0.18 to 1.90 [NICE analysis]; low quality evidence).

There was no significant difference in the number of children with 1 or more adverse events (1 RCT, n=160, 45.5% versus 46.2%, RR 0.98, 95% CI 0.67 to 1.46 [NICE analysis]; low quality evidence), with 1 or more serious adverse events (1 RCT, n=160, 5.0% versus 2.6%, RR 1.93, 95% CI 0.24 to 15.57 [NICE analysis]; low quality evidence), or discontinuing study drug due to an adverse event (low quality evidence) between ceftaroline fosamil and ceftriaxone.

See GRADE profile: **Table** 81

3.2.4.2 Single antibiotic compared with other dual antibiotics

Benzylpenicillin plus gentamicin versus co-amoxiclav

A systematic review (Lodha et al. 2013) found that benzylpenicillin (intravenous; 50,000 mg/kg) plus gentamicin (intravenous; 2.5 mg/kg, three times daily for at least 3 days, followed by oral amoxicillin substituted for benzylpenicillin) was not significantly different to co-amoxiclav (intravenous; 30 mg/kg twice daily for at least 3 days, followed by oral co-amoxiclav when able to feed) in children with severe or very severe community-acquired pneumonia with hypoxemia, aged between 2 to 59 months for failure rate (1 RCT, n=71, 2.6% versus 3.0%, RR 0.87, 95% CI 0.06 to 13.35 [NICE analysis]; low quality evidence).

No safety or tolerability data was reported.

See GRADE profile: **Table** 82

Penicillins plus chloramphenicol versus ampicillin

A systematic review (Lodha et al. 2013) found that ampicillin (intravenous or intramuscular; 100 mg/kg/day for 48 hours, followed by oral; unreported course length) was not significantly different to penicillins (unspecified; intravenous; 100,000 IU/kg/day) plus chloramphenicol (intravenous; 100 mg/kg/day) in children hospitalised with community-acquired pneumonia, aged between 5 months to 4 years for cure rate (unreported follow up; 1 RCT, n=101, 80.8% versus 89.8%, RR 0.90, 95% CI 0.76 to 1.06 [NICE analysis]; moderate quality evidence) or duration of hospital stay (1 RCT, n=101, mean [standard deviation] 6.19 days [2.78] versus 6.29 days [2.50], mean difference −0.1 days, 95% CI −1.13 to 0.93; moderate quality evidence).

No safety or tolerability data was reported.

See GRADE profile: **Table** 83

Benzylpenicillin plus chloramphenicol versus chloramphenicol

A systematic review (Lodha et al. 2013) found that benzylpenicillin (intramuscular; unreported dose or course length) plus chloramphenicol (intramuscular with oral switch; unreported dose or course length) was not significantly different to chloramphenicol (intramuscular with oral switch; unreported dose or course length) in children with severe community-acquired pneumonia (unclear age) for death rate (1 RCT, n=748, 12.7% versus 16.7%, RR 0.76, 95% CI 0.54 to 1.08 [NICE analysis]; moderate quality evidence).

There was no significant difference in the need to change antibiotics between penicillin plus chloramphenicol and chloramphenicol alone (low quality evidence).

See GRADE profile: **Table** 84

Chloramphenicol versus ampicillin plus gentamicin

A systematic review (Lodha et al. 2013) found that chloramphenicol (75 mg/kg/d given in 3 doses for minimum of 5 days, followed by oral chloramphenicol 75 mg/kg/d to complete 10 days antibiotic treatment; route of administration unclear) was significantly worse than ampicillin (200 mg/kg/d in 4 doses every 6 hours; route of administration unclear) plus gentamicin (7.5 mg/kg/d as a single daily dose; route of administration unclear) for a minimum of 5 days (followed by oral amoxicillin to complete 10 days antibiotic treatment) in children with very severe pneumonia, aged 2 to 59 months for failure at day 5 (1 RCT, n=958, 16.1% versus 11.3%, RR 1.43, 95% CI 1.03 to 1.97, number needed to treat [NNT] 21 [10 to 217] [NICE analysis]; moderate quality evidence), failure at day 10 (1 RCT, n=958, 19.2% versus 14.0%, RR 1.37, 95% CI 1.03 to 1.83, NNT 20 [10 to 193] [NICE analysis]; moderate quality evidence) and failure at day 21 (1 RCT, n=958, 21.5% versus 16.1%, RR 1.34, 95% CI 1.02 to 1.75, NNT 19 [9 to 203] [NICE analysis]; moderate quality evidence). However, there was no significant difference in death rate with chloramphenicol compared with ampicillin plus gentamicin (1 RCT, n=958, 8.4% versus 5.2%, RR 1.60, 95% CI 0.99 to 2.59 [NICE analysis]; moderate quality evidence).

Significantly more children given chloramphenicol compared with ampicillin plus gentamicin needed to change antibiotics before day 21 (1 RCT, n=958, 13.4% versus 8.6%, RR 1.56, 95% CI 1.08 to 2.26, NNH 21 [11 to 117] [NICE analysis]; moderate quality evidence).

See GRADE profile: **Table** 85

Penicillins plus gentamicin versus chloramphenicol

A systematic review (Lodha et al. 2013) found that penicillins (unspecified; 50 mg/kg every 6 hours; route of administration unclear) plus gentamicin (7.5 mg/kg/d single dose; route of administration unclear) for at least 5 days was not significantly different to chloramphenicol (intramuscular; 25 mg/kg every 6 hours for at least 5 days) in children with severe community-acquired pneumonia, aged 1 to 59 months for death rate (1 RCT, n=1,116, 5.2% versus 6.4%, RR 1.24, 95% CI 0.77 to 1.99 [NICE analysis]; moderate quality evidence). However, readmission to hospital before 30 days was significantly lower with penicillin plus gentamicin compared with chloramphenicol (1 RCT, n=1116, 5.7% versus 8.9%, RR 1.56, 95% CI 1.01 to 2.39, NNT 32 [16 to 690] [NICE analysis]; moderate quality evidence).

There was no significant difference in the number of adverse events or the need to change antibiotic between penicillin plus gentamicin and chloramphenicol (number of adverse events: 1 RCT, n=1,116, 22.1% versus 26.3%, RR 1.19, 95% CI 0.97 to 1.47 [NICE analysis]; moderate quality evidence).

See GRADE profile: **Table** 86

Chloramphenicol plus penicillins versus ceftriaxone

A systematic review (Lodha et al. 2013) found that chloramphenicol (intravenous; 15 mg/kg every 6 hours) plus penicillin (unspecified; 25,000 IU/kg every 4 hours) was not significantly different to ceftriaxone (intravenous; 50 mg/kg every 12 hours) in children with severe community-acquired pneumonia, aged 6 months to 16 years for cure rate (unreported follow up; 1 RCT, n=97, 84.8% versus 80.4%, RR 1.05, 95% CI 0.88 to 1.27 [NICE analysis]; low quality evidence).

No safety or tolerability data was reported.

See GRADE profile: **Table** 87

Ceftriaxone plus vancomycin versus ceftaroline fosamil

An RCT (Blumer et al. 2016) found that ceftaroline fosamil (intravenous; 15mg/kg [or 600 mg if weight <40 kg] for >6 months or 10mg/kg for <6 months of age, every 8 hours for a minimum of 3 days) was not significantly different to ceftriaxone (intravenous; 75mg/kg/day [up to 4g/day] for a minimum of 3 days) plus vancomycin (intravenous; 15 mg/kg every 6 hours for a minimum of 3 days) in children hospitalised for community-acquired pneumonia, aged between 2 months and 18 years for clinical cure at the end of treatment (1 RCT, n=38, 82.8% versus 77.8%, RR 1.06, 95% CI 0.72 to 1.57 [NICE analysis]; low quality evidence), clinical response at day 4 (1 RCT, n=38, 51.7% versus 66.7%, RR 0.78, 95% CI 0.43 to 1.39 [NICE analysis]; low quality evidence), or clinical failure (1 RCT, n=38, 10.3% versus 0.0%, RR 2.33, 95% CI 0.13 to 41.48 [NICE analysis]; low quality evidence).

Significantly fewer children had 1 or more adverse events with ceftaroline fosamil compared with ceftriaxone plus vancomycin (1 RCT, n=40, 40.0% versus 80.0%, RR 0.50, 95% CI 0.29 to 0.86, NNH 3 [1 to 10] [NICE analysis]; moderate quality evidence). However, there was no significant difference between ceftaroline fosamil and ceftriaxone plus vancomycin for the number of children with 1 or more serious adverse events (1 RCT, n=40, 0.0% versus 10.0%, RR 0.12, 95% CI 0.01 to 2.69 [NICE analysis]; low quality evidence), or discontinuation of IV study drug due to adverse event (low quality evidence).

See GRADE profile: **Table** 88

3.2.4.3 Dual antibiotics compared with other dual antibiotics

No systematic reviews or randomised controlled trials met the inclusion criteria.

3.2.5 Antibiotic dose in non-severe community-acquired pneumonia

The evidence for antibiotic dose in children with non-severe community-acquired pneumonia comes from 1 non-inferiority randomised controlled trial (RCT; Hazir et al. 2007; n=876). High- versus low-dose amoxicillin was compared including children with non-severe community-acquired pneumonia (defined by age specific respiratory rate, without lower chest indwelling).

Low-dose versus high-dose amoxicillin

Low-dose amoxicillin (45 mg/kg/day divided into 3 doses for 3 days) was not significantly different to high-dose amoxicillin (90 mg/kg/day divided into 3 doses for 3 days) in children aged between 2 to 59 months with non-severe community-acquired pneumonia for improvement by day 5 (defined as respiratory rate more than 5 breaths/minute slower than baseline; 1 RCT, n=876, 95.4% versus 94.3%, risk ratio [RR] 1.01, 95% confidence interval [CI] 0.98 to 1.04; moderate quality evidence) or clinical cure by day 14 (defined as respiratory rate less than age specific range; 1 RCT, n=876, 94.1% versus 92.0%, RR 1.02, 95% CI 0.99 to 1.06 [NICE analysis]; moderate quality evidence).

No safety or tolerability data was reported.

See GRADE profile: **Table** 89

3.2.6 Antibiotic dose in severe community-acquired pneumonia

The evidence for antibiotic dose in children (aged 3 months to 15 years) with severe community-acquired pneumonia comes from 1 randomised controlled trial (RCT;

Amarilyo et al. 2014; n=35). High- versus low-dose intravenous benzylpenicillin was compared in stable, hospitalised children with community-acquired pneumonia (defined as fever over 38.0°C and chest radiograph evidence of lobar segmental pneumonia). When appropriate, children in both arms were switched to oral amoxicillin to complete 14 days of treatment.

Low-dose versus high-dose benzylpenicillin

Low-dose benzylpenicillin (intravenous; 200,000 IU/kg/day divided into 4 doses) was not significantly different to high-dose benzylpenicillin (intravenous, 400,000 IU/kg/day divided into 4 doses) for children aged 3 months to 15 years hospitalised with community-acquired pneumonia for duration of hospital stay (1 RCT, n=35, mean [standard deviation] 2.63 days [0.5] versus 3.06 days [1.47], mean difference 0.43 days, 95% confidence interval [CI] −1.15 to 0.29; low quality evidence), duration of intravenous treatment or decreasing levels of c-reactive protein (low quality evidence).

No safety or tolerability data was reported.

See GRADE profile: **Table** 90

3.2.7 Antibiotic dose frequency in non-severe community-acquired pneumonia

The evidence for dose frequency in children with non-severe community-acquired pneumonia comes from 1 non-inferiority randomised controlled trial (RCT; Vilas-Boas et al. 2014, n=820). Amoxicillin twice daily was compared with amoxicillin three times daily in children aged between 2 to 59 months with non-severe community-acquired pneumonia (defined as respiratory complaints and the detection of lower respiratory findings plus presence of pulmonary infiltrate or consolidation on the chest radiograph). Children with signs of severe community-acquired pneumonia, including lower chest indwelling or danger signs such as seizures, inability to drink and somnolence were excluded.

Amoxicillin twice daily versus three times daily

Amoxicillin (oral, 50mg/kg/day for 10 days [plus placebo]) given twice daily was not significantly different to amoxicillin (oral, 50mg/kg/day for 10 days) three times daily in children aged 2 to 59 months with non-severe community-acquired pneumonia for failure rates at day 5 (1 RCT, n=773, 23.0% versus 21.8%, relative risk [RR] 1.05, 95% confidence interval [CI] 0.81 to 1.37 [NICE analysis]; low quality evidence) or failure rates at day 14 (1 RCT, n=745, 32.8% versus 36.7%, RR 0.89, 95% CI 0.73 to 1.09 [NICE analysis]; low quality evidence).

No safety or tolerability data was reported.

See GRADE profile: **Table** 91

3.2.8 Antibiotic dose frequency in severe community-acquired pneumonia

No systematic reviews or randomised controlled trials met the inclusion criteria.

3.2.9 Antibiotic course length in non-severe community-acquired pneumonia

Evidence on antibiotic course length in non-severe community-acquired pneumonia is based on 1 systematic review and meta-analysis (Haider et al. 2008; 4 randomised

controlled trials [RCTs], n=6,177) and 1 non-inferiortiy RCT (Greenberg et al. 2014, n=66).

Three day courses of amoxicillin or co-trimoxazole were compared with 5 day courses of the same antibiotic, in children aged between 2 to 59 months with non-severe community-acquired pneumonia (defined as community-acquired pneumonia with cough or difficult, fast breathing with respiratory rate of 50 breaths per minute or more for children aged 2 months to 11 months, or respiratory rate of 40 breaths per minute or more for children aged 12 months to 59 months). Children with severe or very severe community-acquired pneumonia or chronic illness were excluded, and the studies were set in India, Pakistan, Philippines, Indonesia and Bangladesh (Haider et al. 2008).

Ten day courses of amoxicillin were compared with 3 and 5 day courses in children treated in the community aged between 6 to 59 months with radiologically confirmed alveolar community-acquired pneumonia (defined as a dense opacity that may be fluffy consolidation within the lung). The study was conducted in Israel (Greenberg et al. 2014).

3 days versus 5 days treatment with the same antibiotic

A systematic review (Haider et al. 2008) found that a 3 day course of amoxicillin (oral, 125mg or 15 mg/kg every 8 hours) or co-trimoxazole (oral, 30 to 45 mg/kg/day or 80 mg twice daily [aged >12 months] or 40 mg twice daily [aged <12 months]) was not significantly different to a 5 day course of the same antibiotic in children aged 2 to 59 months with non-severe community-acquired pneumonia for clinical cure (3 RCTs, n=5,763, 89.3% versus 90.0%, relative risk [RR] 0.99, 95% confidence interval [CI] 0.97 to 1.01, moderate quality evidence) or relapse rate (4 RCTs, n=5,469, 4.0% versus 3.7%, RR 1.09, 95% CI 0.84 to 1.42, low quality evidence).

No safety or tolerability data was reported.

See GRADE profile: **Table** 92

3 days versus 5 days amoxicillin

A subgroup analysis within a systematic review (Haider et al. 2008) found that a 3 day course of amoxicillin (oral, 125mg or 15 mg/kg every 8 hours) was not significantly different to a 5 day course of amoxicillin (same dose) in children with non-severe community-acquired pneumonia for clinical cure (2 RCTs, n=4,012, 88.6% versus 89.7%, RR 0.99, 95% CI 0.97 to 1.01, moderate quality evidence) or relapse rate (2 RCTs, n=3,577, 2.5% versus 2.3%, RR 1.05, 95% CI 0.69 to 1.60, very low quality evidence).

No safety or tolerability data was reported.

See GRADE profile: **Table** 93

3 days versus 5 days co-trimoxazole

A subgroup analysis within a systematic review (Haider et al. 2008) found that a 3 day course of co-trimoxazole (oral, 30 to 45 mg/kg/day, 80 mg twice daily [aged >12 months] or 40 mg twice daily [aged <12 months]) was not significantly different to a 5 day course of co-trimoxazole (same dose) in children with non-severe community-acquired pneumonia for clinical cure (1 RCT, n=1,751, 90.9% versus 90.6%, RR 1.00, 95% CI 0.97 to 1.03, moderate quality evidence) or relapse rate (2 RCTs, n= 1,892, 6.9% versus 6.2%, RR 1.12, 95% CI 0.80 to 1.58, low quality evidence).

No safety or tolerability data was reported.

See GRADE profile: **Table** 94

3 days versus 10 days amoxicillin

A non-inferoirty trial (Greenberg et al. 2014) found that a 3 day course of amoxicillin (80 mg/kg/day divided into 3 doses) was significantly worse than a 10 day course of amoxicillin (same dose) in children aged 6 to 59 months with community-acquired pneumonia treated in the community when measuring treatment failure (1 RCT, n=66, 40.0% versus 0.0%, RR 46.64, 95% CI 2.7 to 805.9, NNT 3 [2 to 11] [NICE analysis]; low quality evidence; very serious imprecision due to small sample size, including 10 participants in the 3 day arm).

No safety or tolerability data was reported.

See GRADE profile: **Table** 95

5 days versus 10 days amoxicillin

A non-inferiority trial (Greenberg et al. 2014) found that a 5 day course of amoxicillin (80 mg/kg/day divided into 3 doses) was not significantly different to a 10 day course of amoxicillin (same dose) in children aged 6 to 59 months with community-acquired pneumonia treated in the community when measuring treatment failure (1 RCT, n=98, 0% versus 0%, moderate quality evidence). However, c-reactive protein concentration at day 5 to 7 was significantly higher (worse indicated by higher value) with 5 days amoxicillin compared with 10 days amoxicillin treatment (1 RCT, n=115, mean [standard deviation]: 28.0 mg/L [28.0] versus 16.3 mg/L [12.0], mean difference 11.7 mg/L, 95% CI 3.75 to 19.65, moderate quality evidence).

No safety or tolerability data was reported.

See GRADE profile: **Table** 96

3.2.10 Antibiotic course length in severe community-acquired pneumonia

No systematic reviews or randomised controlled trials met the inclusion criteria.

3.2.11 Antibiotic route of administration in children with non-severe community-acquired pneumonia

Evidence for route of antibiotic administration in children with non-severe community-acquired pneumonia comes from 1 systematic review and meta-analysis (Lodha et al. 2013), including a total of 29 RCTs and 14,188 children. Four RCTs including 2,426 children were included which covered route of administration in children who were treated on an ambulatory basis. Community-acquired pneumonia was defined as the case definition of pneumonia, as given by the World Health Organization (WHO) or radiologically confirmed pneumonia acquired in the community. The systematic review excluded studies of pneumonia acquired post-hospitalisation, in immunocompromised children, or children with underlying illnesses such as congenital heart disease or those with an immune deficient state.

Oral antibiotics versus injectable penicillins

Oral antibiotics (co-trimoxazole [5 days, at an unreported dose or 40 mg/kg/day for 10 days] or amoxicillin [syrup 80 to 90 mg/kg per day in 2 doses or 50 mg/kg/day]) were not significantly different to injectable penicillins (procaine penicillin [unspecified; intramuscular, unreported dose or 50,000 IU/kg/day for 10 days] or

intravenous ampicillin [100 mg/kg per day in 4 doses for 48 hours]) in children treated as outpatients with community-acquired pneumonia aged between 1 month and 18 years for failure rate (4 RCTs, n= 2,426, 8.2% versus 10.6%, relative risk [RR] 0.62, 95% confidence interval [CI] 0.30 to 1.28 [NICE analysis]; very low quality evidence).

No safety or tolerability data was reported.

See GRADE profile: **Table** 97

3.2.12 Antibiotic route of administration in children with severe community-acquired pneumonia

The evidence for route of antibiotic administration in children with severe or very severe community-acquired pneumonia comes from 1 systematic review and meta-analysis (Lodha et al. 2013), including a total of 29 RCTs and 14,188 children. Six RCTs were included which covered route of administration in severe community-acquired pneumonia. Community-acquired pneumonia was defined as the case definition of pneumonia, as given by the World Health Organization (WHO) or radiologically confirmed pneumonia acquired in the community. The systematic review excluded studies of pneumonia acquired post-hospitalisation, in immunocompromised children, or children with underlying illnesses such as congenital heart disease or those with an immune deficient state.

Oral antibiotics versus injectable penicillins

Oral antibiotics (amoxicillin [for 6 months to 12 years of age 8 mg/kg/dose three times daily, above 12 years of age 500 mg three times daily, 45mg/kg/day, 50 mg/kg/day or syrup 80 to 90 mg/kg per day in 2 doses] or co-trimoxazole [40 mg/kg/day for 10 days]) were not significantly different to injectable penicillins (intravenous benzylpenicillin [25 mg/kg/ dose four times a day], intramuscular procaine penicillin [50,000 IU/kg/day for 10 days], penicillin [unspecified; 200,000 IU/kg] or intravenous ampicillin [100 mg/kg per day in 4 doses for 48 hours]) in children aged between 3 months and 18 years with severe community-acquired pneumonia for cure rate (2 RCTs, n=334, 97.1% versus 87.0%, relative risk [RR] 1.21, 95% confidence interval [CI] 0.80 to 1.81 [NICE analysis]; low quality evidence), failure rate at day 6 (6 RCTs, n=4,331, 13.4% versus 14.8%, RR 0.86, 95% CI 0.62 to 1.20 [NICE analysis]; low quality evidence), hospitalisation rate (3 RCTs, n=458, 3.6% versus 2.6%, RR 1.12, 95% CI 1.40 to 3.15 [NICE analysis]; very low quality evidence) or relapse rate (2 RCTs, n=2,076, 3.0% versus 3.2%, RR 1.26, 95% CI 0.35 to 4.54 [NICE analysis]; very low quality evidence).

There was also no significant difference between oral antibiotics and injectable penicillins in subgroup analysis of failure rate in children under 5 (3 RCTs, n=3,870, 14.3% versus 15.5%, RR 0.93, 95% CI 0.80 to 1.07 [NICE analysis]; high quality evidence). However, oral antibiotics were significantly better than injectable penicillins for death rates (3 RCTs, n=3,942, 0.05% versus 0.56%, RR 0.13, 95% CI 0.02 to 0.72, NNT 198 [117 to 611] [NICE analysis]; absolute difference: 5 fewer per 1000, from 5 fewer to 1 fewer, high quality evidence).

In a subgroup analysis of oral amoxicillin (6 months to 12 years of age 8 mg/kg/dose three times daily, above 12 years of age 500 mg three times daily; 45 mg/kg/day; 50 mg/kg/day or syrup, 80 to 90 mg/kg per day in 2 doses) compared with injectable penicillins (benzylpenicillin [25 mg/kg/ dose four times a day], ampicillin [100 mg/kg per day in 4 doses for 48 hours] or procaine penicillin [intramuscular; 50,000 IU/kg/day]), oral amoxicillin was not significantly different to injectable penicillins in children aged between 3 months to 18 years with severe community-acquired

pneumonia for failure rate (4 RCTs, n=4,112, 13.8% versus 14.6%, RR 0.94, 95% CI 0.81 to 1.09 [NICE analysis]; high quality evidence).

No safety or tolerability data was reported.

See GRADE profiles: **Table** 98 and **Table** 99

4 Terms used in the guideline

Severity assessment in adults

The NICE guideline on pneumonia in adults recommends that healthcare professionals use clinical judgement along with CRB65 or CURB65 score to assess the severity of community-acquired pneumonia..

Severe community-acquired pneumonia in children and young people

Features of severe community-acquired pneumonia in children and young people include difficulty breathing, oxygen saturation < 90%, raised heart rate, grunting, very severe chest indrawing, inability to breastfeed or drink, lethargy and a reduced level of consciousness.

CRB65

CRB65 is used to assess 30-day mortality risk in primary care in adults with pneumonia. The score is calculated by giving 1 point for each of the following prognostic features: **c**onfusion, **r**espiratory rate ≥ 30/min, low systolic [< 90 mm Hg] or diastolic [≤ 60 mm Hg] **b**lood pressure, age ≥**65**). 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).

CURB65

CURB65 is used to assess 30-day mortality risk in hospital in adults with pneumonia. The score is calculated by giving 1 point for each of the following prognostic features: (**c**onfusion, **u**rea > 7 mmol/l, **r**espiratory rate ≥ 30/min, low systolic [< 90 mm Hg] or diastolic [≤ 60 mm Hg] **b**lood pressure, age ≥**65**). 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).

Adults with score of 1 and particularly 2 are at increased risk of death (should be considered for hospital referral) and people with a score of 3 or more are at high risk of death (require urgent hospital admission).

Appendices

Appendix A: Evidence sources

Key area	Key question(s)	Evidence sources
Background	• What is the natural history of the infection? • What is the expected duration and severity of symptoms with or without antimicrobial treatment? • What are the most likely causative organisms? • What are the usual symptoms and signs of the infection? • What are the known complication rates of the infection, with and without antimicrobial treatment? • Are there any diagnostic or prognostic factors to identify people who may or may not benefit from an antimicrobial?	• British Thoracic Society (BTS) guideline on management of community-acquired pneumonia in adults, 2009 • NICE clinical knowledge summaries: chest infections • NICE guideline pneumonia in adults: diagnosis and management (CG191) • Jain et al. 2015 • Lim et al. 2003
Safety information	• What safety netting advice is needed for managing the infection? • What symptoms and signs suggest a more serious illness or condition (red flags)?	• NICE guideline NG63: NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population (2017) • NICE clinical knowledge summaries: chest infections • NICE clinical knowledge summary (CKS): diarrhoea – antibiotic associated • British National Formulary (BNF), August 2019 • NHS - pneumonia • Committee experience
Antimicrobial resistance	• What resistance patterns, trends and levels of resistance exist both locally and nationally for the causative organisms of the infection • What is the need for broad or narrow spectrum antimicrobials?	• NICE guideline NG15: Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) • Chief medical officer (CMO) report (2011) • ESPAUR report (2018)

Key area	Key question(s)	Evidence sources
	• What is the impact of specific antimicrobials on the development of future resistance to that and other antimicrobials?	
Resource impact	• What is the resource impact of interventions (such as escalation or de-escalation of treatment)?	• NHSBSA Drug Tariff
Medicines adherence	• What are the problems with medicines adherence (such as when longer courses of treatment are used)?	• NICE guideline NG76: Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence (2009)
Regulatory status	• What is the regulatory status of interventions for managing the infection or symptoms?	• Summary of product characteristics
Antimicrobial prescribing strategies	• What is the clinical effectiveness and safety of antimicrobial prescribing strategies (including back-up prescribing) for managing the infection or symptoms?	• Evidence review – see appendix F for included studies
Antimicrobials	• Which people are most likely to benefit from an antimicrobial?	• Evidence review – see appendix F for included studies
	• Which antimicrobial should be prescribed if one is indicated (first, second and third line treatment, including people with drug allergy)?	• Evidence review – see appendix F for included studies
	• What is the optimal dose, duration and route of administration of antimicrobials?	• Evidence review – see appendix F for included studies • British National Formulary (BNF) August 2019 • BNF for children (BNF-C) August 2019 • Summary of product characteristics

Appendix B: Review protocol

I	Review question	What antimicrobial interventions are effective in managing community-acquired pneumonia?	• antimicrobials include antibiotics • search will include terms for lower respiratory tract infection, pneumonia and chest infection
II	Types of review question	Intervention questions will primarily be addressed through the search.	These will, for example, also identify natural history in placebo groups and causative organisms in studies that use laboratory diagnosis, and relative risks of differing management options.
III	Objective of the review	To determine the effectiveness of prescribing and other interventions in managing community-acquired pneumonia in line with the major goals of antimicrobial stewardship. This includes interventions that lead prescribers to: • optimise outcomes for individuals • reduce overuse, misuse or abuse of antimicrobials All of the above will be considered in the context of national antimicrobial resistance patterns where available, if not available committee expertise will be used to guide decision-making.	The secondary objectives of the review of studies will include: • indications for prescribing an antimicrobial (individual patient factors [including adverse events] and illness severity) • indications for no or delayed antimicrobials • antimicrobial choice, optimal dose, duration and route for specified antimicrobial(s) • the natural history of the infection
IV	Eligibility criteria – population/ disease/ condition/ issue/domain	Population: Adults and children (aged 72 hours and older) with community-acquired pneumonia, including nursing home-acquired pneumonia. Studies that use for example symptoms or signs (prognosis), clinical diagnosis, chest x-ray, imaging, microbiological methods, or laboratory testing of blood for diagnosing the condition.	Subgroups of interest, those: • with protected characteristics under the Equality Act 2010. • with chronic conditions (such as high blood pressure, diabetes or heart disease).

			• at high risk of serious complications because of pre-existing comorbidity[1] • with symptoms and signs suggestive of serious illness and/or complications[2] • <18 years (children) including those with fever and additional intermediate or high risk factors[3] • people older than 65 years and older than 80 years[4] • with low, moderate or high-severity community-acquired pneumonia • with asthma.
V	Eligibility criteria – intervention(s)/ exposure(s)/ prognostic factor(s)	The review will include studies which include: • Antimicrobial pharmacological interventions[5]. For the treatment of community-acquired pneumonia as outlined above, in primary, secondary or other care settings (for example walk-in-centres, urgent care, and minor ailment schemes) either by prescription or by any other legal means of supply of medicine (for example patient group direction).	Limited to those interventions commonly in use (as agreed by the committee).
VI	Eligibility criteria – comparator(s)/ control or reference	Any other plausible strategy or comparator, including: • Placebo • Non-pharmacological interventions • Non-antimicrobial pharmacological interventions	

[1] significant heart, lung, renal, liver or neuromuscular disease, immunosuppression, and young children who were born prematurely
[2] Including heart, lung, kidney, liver or neuromuscular disease, or immunosuppression
[3] Outlined in more detail in CG160 Fever in under 5s: assessment and initial management
[4] hospitalisation in previous year; type 1 or type 2 diabetes, history of congestive heart failure, current use of oral glucocorticoids.
[5] Antimicrobial pharmacological interventions include: delayed (back-up) prescribing, standby or rescue therapy, narrow or broad spectrum, single, dual or triple therapy, escalation or de-escalation of treatment. Antibiotics included in the search include those named in current guidance (plus the class to which they belong) plus other antibiotics agreed by the committee

	(gold) standard	• Other antimicrobial interventions	
VII	Outcomes and prioritisation	a) Clinical outcomes such as: • mortality • infection cure rates (number or proportion of people with resolution of symptoms at a given time point, incidence of escalation of treatment) • time to clinical cure (mean or median time to resolution of illness) • reduction in symptoms (duration or severity) • rate of complications with or without treatment • safety, tolerability, and adverse effects. b) Changes in antimicrobial resistance patterns, trends and levels as a result of treatment. c) Patient-reported outcomes, such as medicines adherence, patient experience and patient satisfaction. d) Ability to carry out activities of daily living. e) Service user experience. f) Health and social care related quality of life, including long-term harm or disability. g) Health and social care utilisation (including length of stay, planned and unplanned contacts). The Committee considered which outcomes should be prioritised when multiple outcomes are reported (critical and important outcomes). Additionally, the Committee were asked	The committee have agreed that the following outcomes are critical: • reduction in symptoms (duration or severity) for example difference in time to substantial improvement • time to clinical cure (mean or median time to resolution of illness) • rate of complications[6] (including mortality) with or without treatment, including escalation of treatment • health and social care utilisation (including length of stay, ITU stays, planned and unplanned contacts). The committee have agreed that the following outcomes are important: • patient-reported outcomes, such as medicines adherence, patient experience, sickness absence • changes in antimicrobial resistance patterns, trends and levels as a result of treatment

[6] These would include but are not limited to more common complications e.g. pleural effusion and empyema, lung abscess, and septicaemia

		to consider what clinically important features of study design may be important for this condition (for example length of study follow-up, treatment failure/recurrence, important outcomes of interest such as sequela or progression to more severe illness).	
VIII	Eligibility criteria – study design	The search will look for: • Systematic review of randomised controlled trials (RCTs) • RCTs If insufficient evidence is available progress to: • Controlled trials • Systematic reviews of non-randomised controlled trials • Non-randomised controlled trials • Observational and cohort studies • Pre and post intervention studies (before and after) • Time series studies	Committee to advise the NICE project team on the inclusion of information from other condition specific guidance and on whether to progress due to insufficient evidence.
IX	Other inclusion exclusion criteria	The scope sets out what the guidelines will and will not include (exclusions). Further exclusions specific to this guideline include: • non-English language papers, studies that are only available as abstracts • hospital-acquired pneumonia, including ventilator-associated pneumonia • aspiration pneumonia • a lower respiratory tract infection without a confirmed diagnosis of pneumonia i.e. acute or chronic bronchitis • pneumonia associated with	

		○ exacerbations of chronic obstructive pulmonary disease ○ cystic fibrosis ○ bronchiectasis • non-antimicrobial interventions • non-pharmacological interventions	
X	Proposed sensitivity/ sub-group analysis, or meta-regression	The search may identify studies in population subgroups (for example adults, older adults, children (those aged under 18 years of age), and people with co-morbidities or characteristics that are protected under the Equality Act 2010 or in the NICE equality impact assessment). These will be analysed within these categories to enable the production of management recommendations.	
XI	Selection process – duplicate screening/ selection/ analysis	All references from the database searches will be downloaded, de-duplicated and screened on title and abstract against the criteria above. A randomly selected initial sample of 10% of records will be screened by two reviewers independently. The rate of agreement for this sample will be recorded, and if it is over 90% then remaining references will be screened by one reviewer only. Disagreement will be resolved through discussion. Where abstracts meet all the criteria, or if it is unclear from the study abstract whether it does, the full text will be retrieved. If large numbers of papers are identified and included at full text, the Committee may consider prioritising the evidence for example, evidence of higher quality in terms of study type or evidence with critical or highly important outcomes.	

XII	Data management (software)	Data management will be undertaken using EPPI-reviewer software. GRADEpro will be used to assess the quality of evidence for each outcome.	
XIII	Information sources – databases and dates	The following sources will be searched: • Cochrane Central Register of Controlled Trials (CENTRAL) via Wiley • Cochrane Database of Systematic Reviews (CDSR) via Wiley • Database of Abstracts of Effectiveness (DARE) via Wiley – legacy, last updated April 2015 • Embase via Ovid • Health Technology Assessment (HTA) via Wiley • MEDLINE via Ovid • MEDLINE-in-Process via Ovid The search strategy will be developed in MEDLINE and then adapted or translated as appropriate for the other sources, taking into account their size, search functionality and subject coverage. Database functionality will be used, where available, to exclude: • non-English language papers • animal studies • editorials, letters, news items, case reports and commentaries • conference abstracts and posters • theses and dissertations	

		• duplicates. Date limits will be applied to restrict the search results to: • studies published from 2006 to the present day The results will be downloaded in the following mutually exclusive sets: • Systematic reviews and meta-analysis • Randomised controlled trials • Observational and comparative studies • Other results See appendix B for further details on the search strategy. Duplicates will be removed using automated and manual processes. The de-duplicated file will be uploaded into EPPI-Reviewer for data screening.	
XV	Author contacts	Web: https://www.nice.org.uk/guidance/indevelopment/gid-ng10050/consultation/html-content Email: infections@nice.org.uk	
XVI	Highlight if amendment to previous protocol	For details please see the interim process guide (2017).	
XVII	Search strategy – for	For details see appendix C.	

	one database		
XVIII	Data collection process – forms/duplicate	GRADE profiles will be used, for details see appendix H.	
XIX	Data items – define all variables to be collected	GRADE profiles will be used, for details see appendix H.	
XX	Methods for assessing bias at outcome/ study level	Standard study checklists were used to critically appraise individual studies. For details please see the interim process guide (2017). The risk of bias across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/	
XXI	Criteria for quantitative synthesis (where suitable)	For details please see the interim process guide (2017).	
XXII	Methods for analysis – combining studies and exploring (in)consistency	For details please see the interim process guide (2017).	

XXIII	Meta-bias assessment – publication bias, selective reporting bias	For details please see the interim process guide (2017).	
XXIV	Assessment of confidence in cumulative evidence	For details please see the interim process guide (2017).	
XXV	Rationale/ context – Current management	For details please see the interim process guide (2017).	
XXVI	Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by NICE and chaired by Dr Tessa Lewis in line with the interim process guide (2017). Staff from NICE undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods chapter of the full guideline.	
XXVII	Sources of funding/support	Developed and funded by NICE.	
XXVIII	Name of sponsor	Developed and funded by NICE.	
XXIX	Roles of sponsor	NICE funds and develops guidelines for those working in the NHS, public health, and social care in England.	

Appendix C: Literature search strategy

	No. of hits in MEDLINE	Position in the strategy
Search with limits and Systematic Reviews	5376	Line 247
Search with limits and RCTs (not SRs)	3431	Line 266
Search with limits and Observational Studies (not SRs or RCTs)	5648	Line 289
Search with limits (without SRs, RCTs, Observational)	10093	Line 290
Total for screening	24548	

Key to search operators

/	Medical Subject Heading (MeSH) term
Exp	Explodes the MeSH terms to retrieve narrower terms in the hierarchy
.ti	Searches the title field
.ab	Searches the abstract field
*	Truncation symbol (searches all word endings after the stem)
adj*n*	Adjacency operator to retrieve records containing the terms within a specified number (*n*) of words of each other

Database(s): **Ovid MEDLINE(R)** 1946 to October Week 1 2017**, Ovid MEDLINE(R) Epub Ahead of Print** October 16, 2017**, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations** October 16, 2017**, Ovid MEDLINE(R) Daily Update** October 16, 2017

Search Strategy:

#	Searches	Results
1	Cough/	15165
2	cough*.ti,ab.	45432

3	((postnasal* or post nasal*) adj3 drip*).ti,ab.	589
4	Bronchitis/	21093
5	(bronchit* or tracheobronchit*).ti,ab.	22136
6	(bronchial adj2 infect*).ti,ab.	782
7	Respiratory Tract Infections/	37036
8	Respiratory Syncytial Virus Infections/	6243
9	((pulmonary or lung* or airway* or airflow* or bronch* or respirat*) adj3 syncytial virus*).ti,ab.	12118
10	Pneumovirus*.ti,ab.	343
11	(("respiratory tract*" or "acute respiratory" or "lower respiratory" or chest) adj3 (infect* or cough*)).ti,ab.	30623
12	LRTI.ti,ab.	980
13	exp Pneumonia/	88843
14	(pneumon* or bronchopneumon* or pleuropneumon* or tracheobronchit*).ti,ab.	176553
15	or/1-14	323542
16	limit 15 to yr="2006 -Current"	133940
17	limit 16 to english language	120589
18	Animals/ not (Animals/ and Humans/)	4643829
19	17 not 18	108249
20	limit 19 to (letter or historical article or comment or editorial or news or case reports)	18545
21	19 not 20	89704
22	anti-infective agents/ or exp anti-bacterial agents/ or exp anti-infective agents, local/	908739
23	(antibacter* or anti-bacter* or "anti bacter*" or antimicrobial or anti-microbial or "anti microbial" or antibiot* or anti-biot* or "anti biot*").ti,ab.	433955
24	or/22-23	1095907

25	Amoxicillin/	9361
26	(Amoxicillin* or Amoxycillin* or Amoxil*).ti,ab.	16425
27	Ampicillin/	13807
28	Ampicillin*.ti,ab.	22039
29	Azithromycin/	4771
30	(Azithromycin* or Azithromicin* or Zithromax*).ti,ab.	7221
31	Aztreonam/	1437
32	(Aztreonam* or Azactam*).ti,ab.	2951
33	Penicillin G/	9348
34	(Benzylpenicillin* or "Penicillin G").ti,ab.	8206
35	Cefaclor/	881
36	(Cefaclor* or Distaclor* or Keftid*).ti,ab.	1741
37	Cefixime/	772
38	(Cefixime* or Suprax*).ti,ab.	1569
39	Cefotaxime/	5575
40	Cefotaxime*.ti,ab.	8120
41	(Ceftaroline* or Zinforo*).ti,ab.	583
42	Ceftazidime/	3797
43	(Ceftazidime* or Fortum* or Tazidime*).ti,ab.	8387
44	(Ceftobiprole* or Zevtera*).ti,ab.	262
45	(Ceftolozane* or Tazobactam* or Zerbaxa*).ti,ab.	3869
46	Ceftriaxone/	5707
47	(Ceftriaxone* or Rocephin* or Rocefin*).ti,ab.	9632

48	Cefuroxime/	2190
49	(Cefuroxime* or Cephuroxime* or Zinacef* or Zinnat* or Aprokam*).ti,ab.	4248
50	Chloramphenicol/	20280
51	(Chloramphenicol* or Cloranfenicol* or Kemicetine* or Kloramfenikol*).ti,ab.	26700
52	Ciprofloxacin/	12735
53	(Ciprofloxacin* or Ciproxin*).ti,ab.	23629
54	Clarithromycin/	6001
55	(Clarithromycin* or Clarie* or Klaricid* or Xetinin*).ti,ab.	8465
56	Clindamycin/	5646
57	(Clindamycin* or Dalacin* or Zindaclin*).ti,ab.	9899
58	Amoxicillin-Potassium Clavulanate Combination/	2501
59	(Co-amoxiclav* or Coamoxiclav* or Amox-clav* or Amoxicillin-Clavulanic Acid* or Amoxicillin-Potassium Clavulanate Combination* or Amoxi-Clavulanate* or Clavulanate Potentiated Amoxycillin Potassium* or Clavulanate-Amoxicillin Combination* or Augmentin*).ti,ab.	14738
60	Trimethoprim, Sulfamethoxazole Drug Combination/	6860
61	(Septrin* or Co-trimoxazole* or Cotrimoxazole* or Sulfamethoxazole Trimethoprim Comb* or Trimethoprim Sulfamethoxazole Comb*).ti,ab.	6035
62	Colistin/	3468
63	(Colistin* or Colistimethate* or Colimycin* or Coly-Mycin* or Colymycin* or Colomycin* or Promixin*).ti,ab.	4884
64	Doxycycline/	9238
65	(Doxycycline* or Efracea* or Periostat* or Vibramycin*).ti,ab.	12343
66	(Ertapenem* or Invanz*).ti,ab.	1256
67	Erythromycin/	14229

68	Erythromycin Estolate/	154
69	Erythromycin Ethylsuccinate/	522
70	(Erythromycin* or Erymax* or Tiloryth* or Erythrocin* or Erythrolar* or Erythroped*).ti,ab.	20574
71	Fosfomycin/	1839
72	(Fosfomycin* or Phosphomycin* or Fosfocina* or Monuril* or Monurol* or Fomicyt*).ti,ab.	2623
73	Floxacillin/	739
74	(Floxacillin* or Flucloxacillin*).ti,ab.	842
75	Gentamicins/	18583
76	(Gentamicin* or Gentamycin* or Cidomycin*).ti,ab.	25954
77	Imipenem/	4016
78	(Imipenem* or Primaxin*).ti,ab.	9709
79	Levofloxacin/	2965
80	(Levofloxacin* or Evoxil* or Tavanic*).ti,ab.	6626
81	Linezolid/	2599
82	(Linezolid* or Zyvox*).ti,ab.	4911
83	Meropenem*.ti,ab.	5187
84	(Moxifloxacin* or Avelox*).ti,ab.	4045
85	Ofloxacin/	6224
86	(Ofloxacin* or Tarivid*).ti,ab.	6844
87	Piperacillin/	2713
88	(Piperacillin* or Tazobactam* or Tazocin*).ti,ab.	6818
89	Rifampin/	17357
90	(Rifampicin* or Rifampin* or Rifadin* or Rimactane*).ti,ab.	22688

91	Teicoplanin/	2234
92	(Teicoplanin* or Targocid*).ti,ab.	3467
93	(Telavancin* or Vibativ*).ti,ab.	369
94	(Temocillin* or Negaban*).ti,ab.	302
95	(Tigecycline* or Tygacil*).ti,ab.	2562
96	Vancomycin/	12899
97	(Vancomycin* or Vancomicin* or Vancocin*).ti,ab.	24386
98	or/25-97	276644
99	exp Aminoglycosides/	154042
100	Aminoglycoside*.ti,ab.	18162
101	exp Penicillins/	81338
102	Penicillin*.ti,ab.	54151
103	exp beta-Lactamase inhibitors/	7519
104	(("beta Lactamase*" or betaLactamase*) adj3 (antagonist* or agonist* or agent* or inhibitor* or blocker*)).ti,ab.	2897
105	beta-Lactams/	6140
106	("beta-Lactam" or betaLactam or "beta Lactam " or "beta-Lactams" or betaLactams or "beta Lactams").ti,ab.	19809
107	exp Carbapenems/	9627
108	Carbapenem*.ti,ab.	10899
109	exp Cephalosporins/	42255
110	Cephalosporin*.ti,ab.	21163
111	exp Fluoroquinolones/	31349
112	Fluoroquinolone*.ti,ab.	14729

113	exp Macrolides/	105782
114	Macrolide*.ti,ab.	14603
115	exp Polymyxins/	8638
116	Polymyxin*.ti,ab.	6747
117	exp Quinolones/	45007
118	Quinolone*.ti,ab.	13119
119	exp Tetracyclines/	47435
120	Tetracycline*.ti,ab.	34131
121	or/99-120	497907
122	Bronchodilator Agents/	19033
123	(Bronchodilator* or broncholytic* or bronchial dilat* or bronchodilating* or bronchodilatant*).ti,ab.	14064
124	analgesics/	46460
125	exp analgesics, non-narcotic/	322666
126	analgesics, short-acting/	8
127	antipyretics/	2591
128	(analgesic* or antipyretic*).ti,ab.	77553
129	Acetaminophen/	17280
130	(paracetamol* or acetaminophen* or Panadol* or perfalgan* or calpol*).ti,ab.	22807
131	Cholinergic antagonists/	4933
132	(Anticholinergic* or "Anti-cholinergic*" or "Anti cholinergic*" or Antimuscarinic* or Anti muscarinic* or Anti-muscarinic*).ti,ab.	14963
133	(("adrenergic beta" or "beta adrenergic" or beta2 or "beta 2") adj3 (antagonist* or agonist* or agent* or inhibitor* or blocker*)).ti,ab.	23087
134	Adrenergic beta-2 Receptor Agonists/	2581

135	(("adrenergic beta" or "beta adrenergic" or beta2 or "beta 2") adj3 (antagonist* or agonist* or agent* or inhibitor* or blocker*)).ti,ab.	23087
136	Albuterol/	9858
137	(Salbutamol* or Albuterol* or Salbulin* or Ventolin* or Salamol*).ti,ab.	9742
138	exp Codeine/	6616
139	(Codeine* or Pholcodine* or Covonia* or Galenphol* or Pavacol* or Galcodine*).ti,ab.	4854
140	Adrenal Cortex Hormones/	63302
141	(Corticosteroid* or corticoid* or Adrenal Cortex Hormone*).ti,ab.	102411
142	Nonprescription Drugs/	5876
143	(non prescription* or nonprescription* or otc or "over the counter*" or "over-the-counter*").ti,ab.	12255
144	Antitussive Agents/	2841
145	Antitussive*.ti,ab.	1887
146	(cough* adj3 (suppressant* or mixture* or syrup* or medicine* or medicinal* or remedy* or remedies* or product or products)).ti,ab.	915
147	exp Histamine Antagonists/	63352
148	Antazoline/	212
149	Brompheniramine/	351
150	Chlorpheniramine/	1989
151	Cinnarizine/	805
152	Cyproheptadine/	2322
153	Diphenhydramine/	4027
154	Doxylamine/	384
155	Ergotamine/	2436
156	Hydroxyzine/	1451

157	Ketotifen/	1175
158	Pizotyline/	283
159	Promethazine/	3130
160	Trimeprazine/	327
161	Triprolidine/	309
162	(histamin* adj3 (antagonist* or agonist* or agent* or inhibitor* or blocker*)).ti,ab.	9260
163	(antihistamin* or anti-histamin* or Alimemazine* or Trimeprazine* or Antazoline* or Brompheniramine* or Chlorpheniramine* or Chlorphenamine* or Cinnarizine* or Stugeron* or Cyproheptadine* or Periactin* or Diphenhydramine* or Doxylamine* or Ergotamine* or Migril* or Hydroxyzine* or Atarax* or Ketotifen* or Zaditen* or Promethazine* or Phenergan* or Sominex* or Pizotifen* or Pizotyline* or Triprolidine* or Acrivastine*).ti,ab.	28590
164	Demulcents/	4
165	(demulcent* or mucoprotective* or muco protective* or Linctus*).ti,ab.	227
166	Glycerol/	25266
167	(Glycerol* or Glycerine*).ti,ab.	48554
168	Menthol/	1800
169	menthol*.ti,ab.	2448
170	exp Prednisolone/	51015
171	(Prednisolone* or Fluprednisolone* or Methylprednisolone* or Deltacortril* or Dilacort* or Pevanti* or Deltastab* or Predsol*).ti,ab.	38273
172	exp Anti-Inflammatory Agents, Non-Steroidal/	193330
173	nsaid*.ti,ab.	23343
174	((nonsteroid* or non steroid*) adj3 (anti inflammator* or antiinflammator*)).ti,ab.	37248
175	Ibuprofen/	8334

176	(ibuprofen* or arthrofen* or ebufac* or rimafen* or brufen* or calprofen* or feverfen* or nurofen* or orbifen*).ti,ab.	12307
177	Dextromethorphan/	1806
178	Dextromethorphan*.ti,ab.	2510
179	Leukotriene Antagonists/	3063
180	(leukotriene* adj3 (antagonist* or agonist* or agent* or inhibitor* or blocker*)).ti,ab.	3798
181	Montelukast*.ti,ab.	1980
182	(Zafirlukast* or Accolate*).ti,ab.	419
183	exp Expectorants/	16597
184	exp Guaifenesin/	776
185	Ipecac/	639
186	(expectorant* or mucolytic* or guaifenesin* or ipecac* or ipecacuanha*).ti,ab.	3101
187	Mannitol/	12719
188	(Mannitol* or Osmohale* or Bronchitol*).ti,ab.	17698
189	(Dornase alfa* or Dornase alpha* or Pulmozyme*).ti,ab.	240
190	or/122-189	850363
191	Honey/	3396
192	Apitherapy/	114
193	(honey* or lemon*).ti,ab.	22587
194	or/191-193	22919
195	Drugs, Chinese Herbal/	37457
196	Plants, Medicinal/	58533
197	exp Geraniaceae/	607

198	Echinacea/	740
199	Fallopia Japonica/	181
200	Thymus Plant/	1219
201	Eucalyptus/	2144
202	Forsythia/	161
203	exp Glycyrrhiza/	2539
204	Andrographis/	392
205	(herb* or Geraniaceae* or Pelargonium* or Geranium* or Kaloba* or Echinacea* or Coneflower* or Japonica* or Knotweed* or Thyme* or Thymus* or Eucalyptus* or Forsythia* or Forsythiae* or Goldenbell* or Lian Qiao* or Glycyrrhiza* or Licorice* or Liquorice* or Andrographis*).ti,ab.	164139
206	((medicine* or medical* or medicinal* or product or products or remedies* or remedy*) adj3 (plant* or plants or root or roots or flower or flowers or bark or barks or seed or seeds or shrub or shrubs or botanic*)).ti,ab.	22856
207	or/195-206	250647
208	Fluid therapy/	19132
209	Drinking/	14141
210	Drinking Behavior/	6828
211	exp Beverages/	124467
212	((water* or fluid* or liquid* or beverage* or drinks) adj3 (consumption* or consume* or consuming* or intake* or drink* or hydrat* or rehydrat* or therap*)).ti,ab.	93975
213	or/208-212	232893
214	watchful waiting/	2801
215	"no intervention*".ti,ab.	6967
216	(watchful* adj2 wait*).ti,ab.	2321
217	(wait adj2 see).ti,ab.	1352

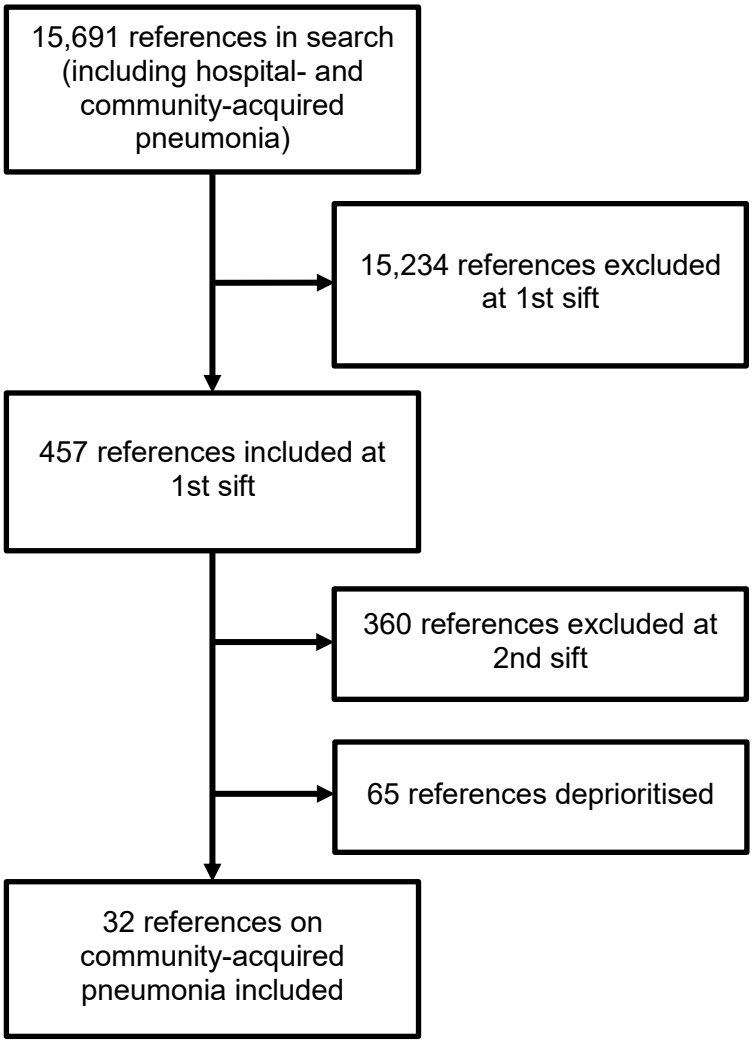
218	(active* adj2 surveillance*).ti,ab.	6517
219	(expectant* adj2 manage*).ti,ab.	3048
220	or/214-219	21495
221	Self Care/	31538
222	Self medication/	4616
223	((self or selves or themsel*) adj4 (care or manag*)).ti,ab.	37143
224	or/221-223	59581
225	Inappropriate prescribing/	2110
226	((delay* or defer*) adj3 (treat* or therap* or interven*)).ti,ab.	29049
227	((prescription* or prescrib*) adj3 ("red flag" or strateg* or appropriat* or inappropriat* or unnecessary or defer* or delay* or no or non or behaviour* or behavior* or optimal or optimi* or reduc* or decreas* or declin* or rate* or improv* or back-up* or backup* or immediate* or rapid* or short* or long* or standby or "stand by" or rescue or escalat* or "de-escalat*" or misuse* or "mis-use*" or overuse* or "over-use*" or "over-prescri*" or abuse*)).ti,ab.	24600
228	((bacter* or antibacter* or anti-bacter* or "anti bacter*" or antimicrobial or anti-microbial or "anti microbial" or antibiot* or anti-biot* or "anti biot*") adj3 ("red flag" or strateg* or appropriat* or inappropriat* or unnecessary or defer* or delay* or no or non or behaviour* or behavior* or optimal or optimi* or reduc* or decreas* or declin* or rate* or improv* or back-up* or backup* or immediate* or rapid* or short* or long* or standby or "stand by" or rescue or escalat* or "de-escalat*" or misuse* or "mis-use*" or overuse* or "over-use*" or "over-prescri*" or abuse*)).ti,ab.	103402
229	or/225-228	154677
230	24 or 98 or 121 or 190 or 194 or 207 or 213 or 220 or 224 or 229	2645544
231	21 and 230	30468
232	Meta-Analysis.pt.	91779
233	Network Meta-Analysis/	220
234	Meta-Analysis as Topic/	17154

235 Review.pt.	2443246
236 exp Review Literature as Topic/	10197
237 (metaanaly* or metanaly* or (meta adj3 analy*)).ti,ab.	130880
238 (review* or overview*).ti.	435300
239 (systematic* adj5 (review* or overview*)).ti,ab.	130897
240 ((quantitative* or qualitative*) adj5 (review* or overview*)).ti,ab.	8451
241 ((studies or trial*) adj2 (review* or overview*)).ti,ab.	40696
242 (integrat* adj3 (research or review* or literature)).ti,ab.	9912
243 (pool* adj2 (analy* or data)).ti,ab.	25735
244 (handsearch* or (hand adj3 search*)).ti,ab.	8417
245 (manual* adj3 search*).ti,ab.	5300
246 or/232-245	2725485
247 231 and 246	5376
248 98 or 121 or 190 or 194 or 207 or 213 or 220 or 224 or 229	2086858
249 21 and 248	23218
250 Randomized Controlled Trial.pt.	497031
251 Controlled Clinical Trial.pt.	99256
252 Clinical Trial.pt.	548028
253 exp Clinical Trials as Topic/	332203
254 Placebos/	36433
255 Random Allocation/	99660
256 Double-Blind Method/	157533
257 Single-Blind Method/	26574

258 Cross-Over Studies/	45016
259 ((random* or control* or clinical*) adj3 (trial* or stud*)).ti,ab.	1115406
260 (random* adj3 allocat*).ti,ab.	31822
261 placebo*.ti,ab.	209215
262 ((singl* or doubl* or trebl* or tripl*) adj (blind* or mask*)).ti,ab.	167858
263 (crossover* or (cross adj over*)).ti,ab.	82346
264 or/250-263	1895644
265 249 and 264	4969
266 265 not 247	3431
267 Observational Studies as Topic/	2818
268 Observational Study/	46520
269 Epidemiologic Studies/	7973
270 exp Case-Control Studies/	948245
271 exp Cohort Studies/	1823837
272 Cross-Sectional Studies/	269121
273 Controlled Before-After Studies/	297
274 Historically Controlled Study/	149
275 Interrupted Time Series Analysis/	369
276 Comparative Study.pt.	1908513
277 case control*.ti,ab.	114928
278 case series.ti,ab.	59535
279 (cohort adj (study or studies)).ti,ab.	156605
280 cohort analy*.ti,ab.	6292

281 (follow up adj (study or studies)).ti,ab.	47161
282 (observational adj (study or studies)).ti,ab.	81605
283 longitudinal.ti,ab.	210546
284 prospective.ti,ab.	509033
285 retrospective.ti,ab.	431491
286 cross sectional.ti,ab.	278740
287 or/267-286	4334061
288 249 and 287	7941
289 288 not (247 or 266)	5648
290 249 not (247 or 266 or 289)	10093

Appendix D: Study flow diagram



Appendix E: Evidence prioritisation

Key questions	Included studies[1]		Studies not prioritised[2]	
	Systematic reviews	RCTs	Systematic reviews	RCTs
Which prescribing strategy is most effective in adults with community acquired pneumonia?				
Prescribing strategy	-	Aliberti 2017 Falguera 2009 Garin 2014 Uranga 2016	-	-
Which antibiotic is most effective in adults with low-severity community acquired pneumonia?				
Macrolide vs fluoroquinolone	Pakhale 2014	-	Skalsky 2013 Vardakas 2008	Udupa 2011
Macrolide vs penicillin	Pakhale 2014	-	-	Udupa 2011
Macrolide vs co-amoxiclav	-	Paris 2008	-	-
Macrolide vs macrolide	Pakhale 2014	-	-	-
Cephalosporin vs beta-lactam/lactamase inhibitors	Maimon 2008	-	-	-
Fluoroquinolone vs penicillin	Yuan 2012	-	Vardakas 2008	-
Fluoroquinolone vs cephalosporin + macrolide	Raz-Pasteur 2015	-	-	-
Penicillin vs penicillin	-	Llor 2017	-	-
Fluoroquinolone vs cephalosporin	-	Ige 2015	-	-
Antibiotics not available in UK (see Appendix I: studies not-prioritised for details of antibiotics)	-	-	-	Barrera 2016 English 2012 Liu 2017 Oldach 2013 Paladino 2007 Van Rensburg 2010
Which antibiotic is most effective in adults with moderate- to high-severity community acquired pneumonia?				

Key questions	Included studies[1]		Studies not prioritised[2]	
	Systematic reviews	RCTs	Systematic reviews	RCTs
Atypical vs non-atypical coverage	Eliakim-Raz 2012	-	An 2010 Eljaaly 2017 Vardakas 2008	Garau 2010
Fluoroquinolone vs tetracycline	Nemeth 2013		-	Bergallo 2009 Dartois 2013 Mokabberi 2010 Tanaseanu 2009
Macrolide vs fluoroquinolone	Skalsky 2013	-	Asadi 2012 Vardakas 2008	-
5th generation cephalosporin vs 3rd generation cephalosporin	El Hajj 2017	-	-	File 2010 File 2011 Loidise 2015 Low 2011 Shorr 2013 Zhong 2015
Fluoroquinolone vs fluoroquinolone	Yuan 2012	-	-	Anzueto 2006
Carbapenem vs cephalosporin	Bai Nan 2014	-	-	-
Fluoroquinolone monotherapy vs beta-lactam dual therapy	Raz-Pasteur 2015	-	Horita 2016	Lee 2012 Lin 2007 Postma 2015 Torres 2008 Xu 2006
Macrolide monotherapy vs beta-lactam dual therapy	Raz-Pasteur 2015	-	-	-
5th generation cephalosporin vs 3rd generation cephalosporin +/- linezolid	-	Nicholson 2012	-	-
Cephalosporin/macrolide dual therapy vs different cephalosporin/macrolide dual therapy	-	Tamm 2007	-	-

Key questions	Included studies[1]		Studies not prioritised[2]	
	Systematic reviews	RCTs	Systematic reviews	RCTs
Antibiotics not available in UK (see Appendix I: studies not-prioritised for details of antibiotics)	-	-	Fogarty 2006 Granzio 2006 Granzio 2009	Barrera 2016 Chaundhary 2018 Dean 2006 File 2016 Kohno 2013 Seki 2009 Yanagihara 2006
What is the optimal dose, duration and route of administration in adults with community acquired pneumonia?				
Dose and/or frequency	-	Siquier 2006 Zhao 2016	-	Shorr 2006 Zhao 2014
Course length	Li 2007	El Moussaoui 2006	Dimpopoulous 2008 Montassier 2013	File 2007
Route of administration	Athanassa 2008	-	Chalmers 2011	Oosterheert 2006
Which prescribing strategy is most effective in children with community acquired pneumonia?				
Prescribing strategy	-	In-Iw 2015	-	-
Is an antibiotic effective in children with community-acquired pneumonia?				
Antibiotics versus placebo	-	-	-	Awasthi 2008a Hazir 2011
Which antibiotic is most effective in children with community-acquired pneumonia?				
Various antibiotic comparisons	Lodha 2013	Blumer 2016 Cannavino 2016	Das Rashmi 2013 Laopaiboon 2015 Lassi 2016 Lodha 2016	Agweyu 2015 Amarilyo 2014 Asghar 2008 Atkinson 2007 Awasthi 2008b Bansal 2006 Bradely 2007 Hazir 2008

Key questions	Included studies[1]		Studies not prioritised[2]	
	Systematic reviews	RCTs	Systematic reviews	RCTs
				Lee 2008 Rajesh 2013 Ribeiro 2011
What is the optimal dose, duration and route of administration of antibiotic in children with community acquired pneumonia?				
Dose and/or frequency studies	-	Amarilyo 2014 Hazir 2007 Vilas-Boas 2014	-	-
Course length studies	Haider 2008	Greenberg 2014	Sutijone 2011 Dimpopoulous 2008	-
Route of administration studies	Lodha 2013	-	Rojas-Reyes 2006	-

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

Appendix F: Included studies

Aliberti Stefano, Ramirez Julio, Giuliani Fabio, Wiemken Timothy, Sotgiu Giovanni, Tedeschi Sara, Carugati Manuela, Valenti Vincenzo, Marchioni Marco, Camera Marco, Piro Roberto, Del Forno , Manuela , Milani Giuseppe, Faverio Paola, Richeldi Luca, Deotto Martina, Villani Massimiliano, Voza Antonio, Tobaldini Eleonora, Bernardi Mauro, Bellone Andrea, Bassetti Matteo, and Blasi Francesco (2017) Individualizing duration of antibiotic therapy in community-acquired pneumonia. Pulmonary pharmacology & therapeutics 45, 191-201

Amarilyo Gil, Glatstein Miguel, Alper Arik, Scolnik Dennis, Lavie Moran, Schneebaum Nira, Grisaru-Soen Galia, Assia Ayala, Ben-Sira Liat, and Reif Shimon (2014) IV Penicillin G is as effective as IV cefuroxime in treating community-acquired pneumonia in children. American journal of therapeutics 21(2), 81-4

Athanassa Zoe, Makris Gregory, Dimopoulos George, and Falagas Matthew E (2008) Early switch to oral treatment in patients with moderate to severe community-acquired pneumonia: a meta-analysis. Drugs 68(17), 2469-81

Bai Nan, Sun Chunguang, Wang Jin, Cai Yun, Liang Beibei, Zhang Lei, Liu Youning, and Wang Rui (2014) Ertapenem versus ceftriaxone for the treatment of complicated infections: a meta-analysis of randomized controlled trials. Chinese medical journal 127(6), 1118-25

Blumer Jeffrey L, Ghonghadze Tina, Cannavino Christopher, O'Neal Tanya, Jandourek Alena, Friedland Hillel David, and Bradley John S (2016) A Multicenter, Randomized, Observer-blinded, Active-controlled Study Evaluating the Safety and Effectiveness of Ceftaroline Compared With Ceftriaxone Plus Vancomycin in Pediatric Patients With Complicated Community-acquired Bacterial Pneumonia. The Pediatric infectious disease journal 35(7), 760-6

Cannavino Christopher R, Nemeth Agnes, Korczowski Bartosz, Bradley John S, O'Neal Tanya, Jandourek Alena, Friedland H David, and Kaplan Sheldon L (2016) A Randomized, Prospective Study of Pediatric Patients With Community-acquired Pneumonia Treated With Ceftaroline Versus Ceftriaxone. The Pediatric infectious disease journal 35(7), 752-9

El Hajj , Maguy Saffouh, Turgeon Ricky D, and Wilby Kyle John (2017) Ceftaroline fosamil for community-acquired pneumonia and skin and skin structure infections: a systematic review. International journal of clinical pharmacy 39(1), 26-32

el Moussaoui , Rachida , de Borgie , Corianne A J. M, van den Broek , Peterhans , Hustinx Willem N, Bresser Paul, van den Berk , Guido E L, Poley Jan-Werner, van den Berg , Bob , Krouwels Frans H, Bonten Marc J. M, Weenink Carla, Bossuyt Patrick M. M, Speelman Peter, Opmeer Brent C, and Prins Jan M (2006) Effectiveness of discontinuing antibiotic treatment after three days versus eight days in mild to moderate-severe community acquired pneumonia: randomised, double blind study. BMJ (Clinical research ed.) 332(7554), 1355

Eliakim-Raz Noa, Robenshtok Eyal, Shefet Daphna, Gafter-Gvili Anat, Vidal Liat, Paul Mical, and Leibovici Leonard (2012) Empiric antibiotic coverage of atypical pathogens for community-acquired pneumonia in hospitalized adults. The Cochrane database of systematic reviews (9), CD004418

Falguera M, Ruiz-Gonzalez A, Schoenenberger J A, Touzon C, Gazquez I, Galindo C, and Porcel J M (2010) Prospective, randomised study to compare empirical treatment versus targeted treatment on the basis of the urine antigen results in hospitalised patients with community-acquired pneumonia. Thorax 65(2), 101-106

Garin Nicolas, Genne Daniel, Carballo Sebastian, Chuard Christian, Eich Gerhardt, Hugli Olivier, Lamy Olivier, Nendaz Mathieu, Petignat Pierre-Auguste, Perneger Thomas, Rutschmann Olivier, Seravalli Laurent, Harbarth Stephan, and Perrier Arnaud (2014) beta-Lactam monotherapy vs beta-lactam-macrolide combination treatment in moderately severe community-acquired pneumonia: a randomized noninferiority trial. JAMA internal medicine 174(12), 1894-901

Greenberg David, Givon-Lavi Noga, Sadaka Yair, Ben-Shimol Shalom, Bar-Ziv Jacob, and Dagan Ron (2014) Short-course antibiotic treatment for community-acquired alveolar pneumonia in ambulatory children: a double-blind, randomized, placebo-controlled trial. The Pediatric infectious disease journal 33(2), 136-42

Haider Batool A, Saeed Muhammad Ammad, and Bhutta Zulfiqar A (2008) Short-course versus long-course antibiotic therapy for non-severe community-acquired pneumonia in children aged 2 months to 59 months. The Cochrane database of systematic reviews (2), CD005976

Hazir Tabish, Qazi Shamim A, Bin Nisar, Yasir , Maqbool Sajid, Asghar Rai, Iqbal Imran, Khalid Sobia, Randhawa Sajid, Aslam Shazia, Riaz Sobia, and Abbasi Saleem (2007) Comparison of standard versus double dose of amoxicillin in the treatment of non-severe pneumonia in children aged 2-59 months: a multi-centre, double blind, randomised controlled trial in Pakistan. Archives of disease in childhood 92(4), 291-7

Ige O M, and Okesola A O (2015) Comparative efficacy and safety of cefixime and ciprofloxacin in the management of adults with community-acquired pneumonia in Ibadan, Nigeria. Annals of Ibadan postgraduate medicine 13(2), 72-8

In-Iw S, Winijkul G, Sonjaipanich S, and Manaboriboon B (2015) Comparison between the efficacy of switch therapy and conventional therapy in pediatric community-acquired pneumonia. Journal of the Medical Association of Thailand 98(9), 858-863

Li Jonathan Z, Winston Lisa G, Moore Dan H, and Bent Stephen (2007) Efficacy of short-course antibiotic regimens for community-acquired pneumonia: a meta-analysis. The American journal of medicine 120(9), 783-90

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Appendix G: Quality assessment of included studies

G.1 Antibiotic prescribing strategy in adults

Table 11: Overall risk of bias/quality assessment – randomised controlled trials (RCT checklist)

Study reference	Uranga et al. 2016	Falguera et al. 2009	Garin et al. 2014	Aliberti et al. 2017
Did the trial address a clearly focused issue?	Yes	Yes	Yes	Yes
Was the assignment of patients to treatments randomised?	Yes	Yes	Yes	Yes
Were patients, health workers and study personnel blinded?	No[a]	No[a]	Yes	No[a]
Were the groups similar at the start of the trial?	Yes	Yes	Yes	Yes
Aside from the experimental intervention, were the groups treated equally?	Yes	Yes	Yes	Yes
Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes	Yes	Yes	Yes
How large was the treatment effect?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles
How precise was the estimate of the treatment effect?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles
Can the results be applied in your context? (or to the local population)	No[b]	No[b]	Yes	No[b]
Were all clinically important outcomes considered?	Yes	Yes	Yes	Yes
Are the benefits worth the harms and costs?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles

[a] Blinding inappropriate for the study design
[b] Some participants have chronic obstructive pulmonary disease, however it is unclear if pneumonia associated with an exacerbation

G.2 Antibiotic choice in adults

Table 12: Overall risk of bias/quality assessment – systematic reviews (SR checklist)

Study reference	Pakhale et al. 2014	Maimon et al. 2008	Raz-Pasteur et al. 2015	Eliakim-Raz et al. 2012

Did the review address a clearly focused question?	Yes	Yes	Yes	Yes
Did the authors look for the right type of papers?	Yes	Yes	Yes	Yes
Do you think all the important, relevant studies were included?	Yes	Yes	Yes	Yes
Did the review's authors do enough to assess the quality of the included studies?	Yes	Yes	Yes	Yes
If the results of the review have been combined, was it reasonable to do so?	Yes	Yes	Yes	Yes
What are the overall results of the review?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles
How precise are the results?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles
Can the results be applied to the local population?	Yes	No[a]	Yes	Yes
Were all important outcomes considered?	Yes	Yes	Yes	Yes
Are the benefits worth the harms and costs?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles
Study reference	**Nemeth et al. 2015**	**Skalsky et al. 2013**	**El Hajj et al. 2017**	**Yuan et al. 2012**
Did the review address a clearly focused question?	No[b]	Yes	No[d]	Yes
Did the authors look for the right type of papers?	Yes	Yes	Yes	Yes
Do you think all the important, relevant studies were included?	Yes	Yes	Yes	Yes
Did the review's authors do enough to assess the quality of the included studies?	Yes	Yes	Yes	Yes
If the results of the review have been combined, was it reasonable to do so?	No[c]	Yes	Yes	Yes
What are the overall results of the review?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles
How precise are the results?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles
Can the results be applied to the local population?	Yes	Yes	Yes	Yes
Were all important outcomes considered?	Yes	Yes	Yes	Yes
Are the benefits worth the harms and costs?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles

Study reference	Bai Nan et al. 2014
Did the review address a clearly focused question?	No[d]
Did the authors look for the right type of papers?	Yes
Do you think all the important, relevant studies were included?	Yes
Did the review's authors do enough to assess the quality of the included studies?	Yes
If the results of the review have been combined, was it reasonable to do so?	Yes
What are the overall results of the review?	See GRADE profiles
How precise are the results?	See GRADE profiles
Can the results be applied to the local population?	Yes
Were all important outcomes considered?	No[e]
Are the benefits worth the harms and costs?	See GRADE profiles

[a] Includes antibiotics not available in the UK which cannot be analysed separately
[b] A range of serious bacterial infections are included in the analysis
[c] Studies on a range of serious bacterial infections have been combined in meta-analysis (however data available to perform analysis of community-acquired pneumonia population)
[d] Multiple types of infection are included in the study, although analysis is separated
[e] Mortality was not reported

Table 13: Overall risk of bias/quality assessment – randomised controlled trials (RCT checklist)

Study reference	Llor et al. 2017	Paris et al. 2008	Ige et al. 2015	Nicholson et al. 2012
Did the trial address a clearly focused issue?	Yes	Yes	Yes	Yes
Was the assignment of patients to treatments randomised?	Yes	Yes	Yes	Yes
Were patients, health workers and study personnel blinded?	Yes	No[b]	No[b]	Yes
Were the groups similar at the start of the trial?	Yes	Yes	Yes	Yes
Aside from the experimental intervention, were the groups treated equally?	Yes	Yes	Yes	Yes
Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes	Yes	Yes	Yes[e]

How large was the treatment effect?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles
How precise was the estimate of the treatment effect?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles
Can the results be applied in your context? (or to the local population)	Yes	Yes	No[c]	Yes
Were all clinically important outcomes considered?	No[a]	Yes	No[d]	Yes
Are the benefits worth the harms and costs?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles

Study reference	**Tamm et al. 2007**
Did the trial address a clearly focused issue?	Yes
Was the assignment of patients to treatments randomised?	Yes
Were patients, health workers and study personnel blinded?	No[b]
Were the groups similar at the start of the trial?	No[e]
Aside from the experimental intervention, were the groups treated equally?	Yes
Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes
How large was the treatment effect?	See GRADE profiles
How precise was the estimate of the treatment effect?	See GRADE profiles
Can the results be applied in your context? (or to the local population)	Yes
Were all clinically important outcomes considered?	Yes
Are the benefits worth the harms and costs?	See GRADE profiles

[a] Mortality was not reported
[b] Study was open label
[c] Unclear applicability as study was conducted in Nigeria
[d] Overall clinical response and mortality were not reported
[e] Signficant difference between groups in the number of people who smoked

G.3 Antibiotic dose in adults

Table 14: Overall risk of bias/quality assessment – randomised controlled trials (RCT checklist)

Study reference	Zhao et al. 2016	Siquier et al. 2006
Did the trial address a clearly focused issue?	Yes	Yes
Was the assignment of patients to treatments randomised?	Yes	Yes
Were patients, health workers and study personnel blinded?	No[a]	Yes
Were the groups similar at the start of the trial?	Yes	Yes
Aside from the experimental intervention, were the groups treated equally?	Yes	Yes
Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes	Yes
How large was the treatment effect?	See GRADE profiles	See GRADE profiles
How precise was the estimate of the treatment effect?	See GRADE profiles	See GRADE profiles
Can the results be applied in your context? (or to the local population)	Yes	Yes
Were all clinically important outcomes considered?	Yes	Yes
Are the benefits worth the harms and costs?	See GRADE profiles	See GRADE profiles
[a] Unblinded		

G.4 Antibiotic course length in adults

Table 15: Overall risk of bias/quality assessment – systematic reviews (SR checklist)

Study reference	Li et al. 2007
Did the review address a clearly focused question?	Yes
Did the authors look for the right type of papers?	Yes
Do you think all the important, relevant studies were included?	Yes
Did the review's authors do enough to assess the quality of the included studies?	No[a]
If the results of the review have been combined, was it reasonable to do so?	Yes

What are the overall results of the review?	See GRADE profiles
How precise are the results?	See GRADE profiles
Can the results be applied to the local population?	Yes
Were all important outcomes considered?	Yes
Are the benefits worth the harms and costs?	See GRADE profiles
[a]Jadad score used to assess quality of studies, however, the quality of each individual study or the individual scoring domains not reported	

Table 16: Overall risk of bias/quality assessment – randomised controlled trials (RCT checklist)

Study reference	El Moussaoui et al. 2006
Did the trial address a clearly focused issue?	Yes
Was the assignment of patients to treatments randomised?	Yes
Were patients, health workers and study personnel blinded?	Yes
Were the groups similar at the start of the trial?	No[a]
Aside from the experimental intervention, were the groups treated equally?	Yes
Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes
How large was the treatment effect?	See GRADE profiles
How precise was the estimate of the treatment effect?	See GRADE profiles
Can the results be applied in your context? (or to the local population)	Yes
Were all clinically important outcomes considered?	Yes
Are the benefits worth the harms and costs?	See GRADE profiles
[a]Larger number of smokers and more severe symptoms present in people randomised to day 3 treatment	

G.5 Antibiotic route of administration in adults

Table 17: Overall risk of bias/quality assessment – systematic reviews (SR checklist)

Study reference	Athanassa et al. 2008
Did the review address a clearly focused question?	Yes
Did the authors look for the right type of papers?	Yes
Do you think all the important, relevant studies were included?	Yes

Did the review's authors do enough to assess the quality of the included studies?	Yes
If the results of the review have been combined, was it reasonable to do so?	Yes
What are the overall results of the review?	See GRADE profiles
How precise are the results?	See GRADE profiles
Can the results be applied to the local population?	Yes
Were all important outcomes considered?	Yes
Are the benefits worth the harms and costs?	See GRADE profiles

G.6 Antibiotic prescribing strategy in children

Table 18: Overall risk of bias/quality assessment – randomised controlled trials (RCT checklist)

Study reference	In-iw et al. 2015
Did the trial address a clearly focused issue?	Yes
Was the assignment of patients to treatments randomised?	Yes
Were patients, health workers and study personnel blinded?	No[a]
Were the groups similar at the start of the trial?	Yes
Aside from the experimental intervention, were the groups treated equally?	No[b]
Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes
How large was the treatment effect?	See GRADE profiles
How precise was the estimate of the treatment effect?	See GRADE profiles
Can the results be applied in your context? (or to the local population)	No[c]
Were all clinically important outcomes considered?	No[d]
Are the benefits worth the harms and costs?	See GRADE profiles

[a] Unblinded
[b] Physicians treated children in both treatment arms; the control group consisted of physician-guided switching, and physicians were shown to change their practice according to results in the intervention arm
[c] Control arm treatment strategy was based on standard medical procedures - as the study was performed in Thailand, this may not be relevant to UK practice
[d] Clinical response and mortality were not reported

G.7 Antibiotic choice in children

Table 19: Overall risk of bias/quality assessment – systematic reviews (SR checklist)

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

Table 20: Overall risk of bias/quality assessment – randomised controlled trials (RCT checklist)

Study reference	Cannavino et al. 2016	Blumer et al. 2016
Did the trial address a clearly focused issue?	Yes	Yes
Was the assignment of patients to treatments randomised?	Yes	Yes
Were patients, health workers and study personnel blinded?	No[a]	No[a]
Were the groups similar at the start of the trial?	Yes	Yes
Aside from the experimental intervention, were the groups treated equally?	Yes	Yes
Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes	Yes
How large was the treatment effect?	See GRADE profiles	See GRADE profiles
How precise was the estimate of the treatment effect?	See GRADE profiles	See GRADE profiles
Can the results be applied in your context? (or to the local population)	Yes	Yes
Were all clinically important outcomes considered?	Yes	Yes
Are the benefits worth the harms and costs?	See GRADE profiles	See GRADE profiles
[a] Blinding inappropriate for the study design, although observer outcome reporting was blinded		

G.8 Antibiotic dose in children

Table 21: Overall risk of bias/quality assessment – randomised controlled trials (RCT checklist)

Study reference	Hazir et al. 2007	Amarilyo et al. 2014
Did the trial address a clearly focused issue?	Yes	No[b]
Was the assignment of patients to treatments randomised?	Yes	Yes
Were patients, health workers and study personnel blinded?	Yes	Unclear[c]
Were the groups similar at the start of the trial?	Yes	Yes
Aside from the experimental intervention, were the groups treated equally?	Yes	Yes
Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes	Unclear[d]
How large was the treatment effect?	See GRADE profiles	See GRADE profiles
How precise was the estimate of the treatment effect?	See GRADE profiles	See GRADE profiles
Can the results be applied in your context? (or to the local population)	No[a]	Yes
Were all clinically important outcomes considered?	Yes	No[e]
Are the benefits worth the harms and costs?	See GRADE profiles	No[f]

[a] Study conducted in Pakistan which may not be applicable to UK practice
[b] Study addressed both dosage of penicillin and efficacy of penicillin compared with cefuroxime
[c] Unclear if blinded
[d] Raw data or percentages not reported, so cannot determine if results include entire population who entered the trial
[f] Clinical response not reported

G.9 Antibiotic dose frequency in children

Table 22: Overall risk of bias/quality assessment – randomised controlled trials (RCT checklist)

Study reference	Vilas-Boas et al. 2014	Greenberg et al. 2014
Did the trial address a clearly focused issue?	Yes	Yes
Was the assignment of patients to treatments randomised?	Yes	Yes
Were patients, health workers and study personnel blinded?	Yes	Yes

Were the groups similar at the start of the trial?	Yes	Yes
Aside from the experimental intervention, were the groups treated equally?	Yes	Yes
Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes	Yes
How large was the treatment effect?	See GRADE profiles	See GRADE profiles
How precise was the estimate of the treatment effect?	See GRADE profiles	See GRADE profiles
Can the results be applied in your context? (or to the local population)	No[a]	Yes
Were all clinically important outcomes considered?	Yes	No[b]
Are the benefits worth the harms and costs?	See GRADE profiles	See GRADE profiles
[a] Study conducted in Brazil which may not be applicable to UK practice [b] Mortality is not reported		

Table 23: Overall risk of bias/quality assessment – systematic reviews (SR checklist)

Study reference	Haider et al. 2008
Did the review address a clearly focused question?	Yes
Did the authors look for the right type of papers?	Yes
Do you think all the important, relevant studies were included?	Yes
Did the review's authors do enough to assess the quality of the included studies?	Yes
If the results of the review have been combined, was it reasonable to do so?	Yes
What are the overall results of the review?	See GRADE profiles
How precise are the results?	See GRADE profiles
Can the results be applied to the local population?	No[a]
Were all important outcomes considered?	Yes
Are the benefits worth the harms and costs?	See GRADE profiles
[a] Included studies conducted in Asia which may not be applicable to UK practice	

Appendix H: GRADE profiles

H.1 Antibiotic prescribing strategies in adults with moderate- to high-severity community-acquired pneumonia

Table 24: GRADE profile – broad-spectrum antibiotics versus targeted antibiotics

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Broad-spectrum[1, 2]	Targeted treatment[1, 3]	Relative (95% CI)	Absolute		
Mortality												
1[4]	randomised trials	no serious risk of bias	NA	serious[5]	serious[6]	none	0/89 (0%)	1/88 (1.1%)	NICE analysis: RR 0.33 (0.01 to 7.98)	8 fewer per 1000 (from 11 fewer to 79 more)	⊕⊕OO LOW	CRITICAL
Clinical relapse												
1[4]	randomised trials	no serious risk of bias	NA	serious[5]	very serious[7]	none	2/89 (2.2%)	4/88 (4.5%)	NICE analysis: RR 0.49 (0.09 to 2.63)	23 fewer per 1000 (from 41 fewer to 74 more)	⊕OOO VERY LOW	CRITICAL
Admission to intensive care												
1[4]	randomised trials	no serious risk of bias	NA	serious[5]	very serious[7]	none	1/89 (1.1%)	0/88 (0%)	NICE analysis: RR 2.97 (0.12 to 71.85)	-	⊕OOO VERY LOW	CRITICAL
Length of hospital stay (days)												
1[4]	randomised trials	no serious risk of bias	NA	serious[5]	no serious imprecision	none	Mean 7.1 (SD 3.8) N= 89	Mean 7.1 (SD 4.0) N= 88	-	MD 0 higher (1.15 lower to 1.15 higher)	⊕⊕⊕O MODERATE	CRITICAL
Readmission												
1[4]	randomised trials	no serious risk of bias	NA	serious[5]	very serious[7]	none	2/89 (2.2%)	4/88 (4.5%)	NICE analysis: RR 0.49 (0.09 to 2.63)	23 fewer per 1000 (from 41 fewer to 74 more)	⊕OOO VERY LOW	IMPORTANT
Adverse events												
1[4]	randomised trials	no serious risk of bias	NA	serious[5]	very serious[8]	none	16/89 (18%)	8/88 (9.1%)	NICE analysis: RR 1.98 (0.89 to 4.38)	89 more per 1000 (from 10 fewer to 307 more)	⊕OOO VERY LOW	CRITICAL
Length of antimicrobial treatment (days)												
1[4]	randomised trials	no serious risk of bias	NA	serious[5]	serious[9]	none	Mean 10.5 (SD 1.3) N= 89	Mean 10.8 (SD 1.6) N= 88	-	MD 0.3 lower (0.73 lower to 0.13 higher)	⊕⊕OO LOW	CRITICAL
Length of intravenous treatment (days)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Broad-spectrum[1, 2]	Targeted treatment[1, 3]	Relative (95% CI)	Absolute		
1[4]	randomised trials	no serious risk of bias	NA	serious[5]	no serious imprecision	none	Mean 5.0 (SD 2.6) N= 89	Mean 5.2 (SD 1.6) N= 88	-	MD 0.2 lower (1.04 lower to 0.64 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Abbreviations: CI – confidence interval; NA – not applicable; RR – risk ratio; SD – standard deviation; MD – mean difference												

[1] At admission, all participants received beta-lactam (co-amoxiclav or ceftriaxone) plus a macrolide (azithromycin) or a fluoroquinolone (levofloxacin) and were randomised if stable after 2 to 6 days treatment
[2] Participants who initially received beta-lactam and macrolide were switched to co-amoxiclav (875/125mg three times a day) or cefditoren (400mg twice a day) to complete 5 days treatment; participants who initially received levofloxacin were continued on levofloxacin (750mg daily) to complete 10 days treatment
[3] If a pneumococcal urine antigen test was positive, participants were switched to oral amoxicillin (1g three times daily) to complete a 10 day course; if a L. pneumophilae urine antigen test was positive, participants were switched to oral azithromycin (500mg daily) to complete a 5 day course; participants with a negative urine antigen test were given the same treatment as the broad-spectrum group
[4] Falguera et al. 2009
[5] Downgraded 1 level - 22% of the total population (18% in broad-spectrum treatment arm and 23% in targeted treatment arm) have chronic obstructive pulmonary disease (COPD), although unclear if pneumonia associated with an exacerbation of COPD
[6] Downgraded 1 level - at a minimal important difference of 0% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with appreciable benefit or appreciable harm
[7] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm
[8] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable with broad-spectrum treatment; wide confidence intervals
[9] Downgraded 1 level - at a minimal important difference of 0.5x standard deviation of empirical treatment arm, data are consistent with no meaningful difference or appreciable harm with targeted treatment

Table 25: GRADE profile – broad-spectrum antibiotics versus targeted antibiotics (analysis stratified by treatment received)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Broad-spectrum[1, 2]	Antigen result targeted treatment[1, 3]	Relative (95% CI)	Absolute		
Mortality												
1[4]	randomised trials	no serious risk of bias	NA	serious[5]	serious[6]	none	1/152 (0.66%)	0/25 (0%)	NICE analysis: RR 0.51 (0.02 to 12.18)	-	⊕⊕OO LOW	CRITICAL
Clinical relapse												
1[4]	randomised trials	no serious risk of bias	NA	serious[5]	serious[7]	none	3/152 (2%)	3/25 (12%)	NICE analysis: RR 0.16 (0.04 to 0.77)	101 fewer per 1000 (from 28 fewer to 115 fewer)	⊕⊕OO LOW	CRITICAL
Admission to intensive care												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Broad-spectrum[1, 2]	Antigen result targeted treatment[1, 3]	Relative (95% CI)	Absolute		
1[4]	randomised trials	no serious risk of bias	NA	serious[5]	very serious[8]	none	1/152 (0.66%)	0/25 (0%)	NICE analysis: RR 0.51 (0.02 to 12.18)	-	⊕OOO VERY LOW	CRITICAL
Length of hospital stay (days)												
1[4]	randomised trials	no serious risk of bias	NA	serious[5]	serious[9]	none	Mean 7.0 (SD 3.7) N= 152	Mean 7.2 (SD 4.2) N= 25	-	MD 0.2 lower (1.95 lower to 1.55 higher)	⊕⊕OO LOW	CRITICAL
Readmission												
1[4]	randomised trials	no serious risk of bias	NA	serious[5]	serious[7]	none	4/152 (2.6%)	3/25 (12%)	NICE analysis: RR 0.22 (0.05 to 0.92)	94 fewer per 1000 (from 10 fewer to 114 fewer)	⊕⊕OO LOW	IMPORTANT
Adverse events												
1[4]	randomised trials	no serious risk of bias	NA	serious[5]	very serious[8]	none	22/152 (14.5%)	2/25 (8%)	NICE analysis: RR 1.81 (0.45 to 7.22)	65 more per 1000 (from 44 fewer to 498 more)	⊕OOO VERY LOW	CRITICAL
Length of antimicrobial treatment (days)												
1[4]	randomised trials	no serious risk of bias	NA	serious[5]	serious[9]	none	Mean 10.4 (SD 1.4) N= 152	Mean 10.8 (SD 1.9) N= 25	-	MD 0.4 lower (1.18 lower to 0.38 higher)	⊕⊕OO LOW	CRITICAL

Abbreviations: CI – confidence interval; NA – not applicable; RR – risk ratio; SD – standard deviation; MD – mean difference

[1] At admission, all participants received beta-lactam (co-amoxiclav or ceftriaxone) plus a macrolide (azithromycin) or a fluoroquinolone (levofloxacin) and were randomised if stable after 2 to 6 days treatment

[2] Participants who initially received beta-lactam and macrolide were switched to co-amoxiclav (875/125mg three times a day) or cefditoren (400mg twice a day) to complete 5 days treatment; participants who initially received levofloxacin were continued on levofloxacin (750mg daily) to complete 10 days treatment

[3] If a pneumococcal urine antigen test was positive, participants were switched to oral amoxicillin (1g three times daily) to complete a 10 day course; if a L. pneumophilae urine antigen test was positive, participants were switched to oral azithromycin (500mg daily) to complete a 5 day course; only includes people with a positive antigen test

[4] Falguera et al. 2009

[5] Downgraded 1 level - 22% of the total population have chronic obstructive pulmonary disease (COPD), although unclear if pneumonia associated with an exacerbation

[6] Downgraded 1 level - at a minimal important difference of 0% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with appreciable benefit or appreciable harm

[7] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with antigen result targeted treatment

[8] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm

[9] Downgraded 1 level - at a minimal important difference of 0.5x standard deviation of empirical treatment arm, data are consistent with no meaningful difference of appreciable harm with antigen result targeted treatment

H.2 Antibiotic prescribing strategies in a mixed severity population of adults with community-acquired pneumonia

Table 26: GRADE profile – stopping antibiotics: guideline-based compared with physician-guided

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic stopped based on guidelines[1]	Physician-guided stopping[2]	Relative (95% CI)	Absolute		
Mortality (at day 30)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	serious[6]	none	3/146 (2.1%)	3/137 (2.2%)	RR 1.07 (0.22 to 5.19)	1 more per 1000 (from 16 fewer to 86 more)	⊕⊕OO LOW	CRITICAL
Recurrence (by day 30)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	very serious[7]	none	4/146 (2.7%)	6/137 (4.4%)	RR 0.63 (0.18 to 2.17)	16 fewer per 1000 (from 36 fewer to 51 more)	⊕OOO VERY LOW	IMPORTANT
Length of hospital stay (days)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	no serious imprecision	none	Mean 5.7, SD 2.8 N= 146	Mean 5.5, SD 2.3 N= 137	-	MD 0.2 higher (0.40 lower to 0.80 higher)	⊕⊕⊕O MODERATE	CRITICAL
Community-acquired pneumonia symptom questionnaire score at day 5 (intention to treat analysis; better indicated by lower score, range 0-90)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	no serious imprecision	none	Mean 27.2, SD 12.5 N= 162	Mean 24.7, SD 11.4 N= 150	-	MD 2.5 higher (0.15 lower to 5.15 higher)	⊕⊕⊕O MODERATE	CRITICAL
Community-acquired pneumonia symptom questionnaire score at day 10 (intention to treat analysis; better indicated by lower score, range 0-90)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	no serious imprecision	none	Mean 17.9, SD 7.6 N= 162	Mean 18.6, SD 9.0 N= 150	-	MD 0.7 lower (2.56 lower to 1.16 higher)	⊕⊕⊕O MODERATE	CRITICAL
Community-acquired pneumonia symptom questionnaire score at day 5 (per protocol analysis; better indicated by lower score, range 0-90)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	no serious imprecision	none	Mean 26.6, SD 12.1 N= 146	Mean 24.3, SD 11.4 N= 137	-	MD 2.3 higher (0.44 lower to 5.04 higher)	⊕⊕⊕O MODERATE	CRITICAL
Community-acquired pneumonia symptom questionnaire score at day 10 (per protocol analysis; better indicated by lower score, range 0-90)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	no serious imprecision	none	Mean 17.6, SD 7.4 N= 146	Mean 18.1, SD 8.5 N= 137	-	MD 0.5 lower (2.36 lower to 1.36 higher)	⊕⊕⊕O MODERATE	CRITICAL
Time taking antibiotics (days)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	serious[5]	none	Median 5, IQR 5 to 6.5 N=146	Median 10, IQR 10 to 11 N=137	-	-	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic stopped based on guidelines[1]	Physician-guided stopping[2]	Relative (95% CI)	Absolute		
Time taking intravenous antibiotics (days)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	serious[5]	none	Median 3, IQR 2 to 4 N=146	Median 2, IQR 1 to 4 N=137	-	-	⊕⊕OO LOW	IMPORTANT
Time until returning to normal activity (days)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	serious[5]	none	Median 15, IQR 10 to 21 N=146	Median 18, IQR 9 to 25 N=137	-	-	⊕⊕OO LOW	CRITICAL
Adverse events												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	very serious[7]	none	17/146 (11.6%)	18/137 (13.1%)	RR 0.89 (0.48 to 1.65)	14 fewer per 1000 (from 68 fewer to 85 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI – confidence interval; NA – not applicable; SD – standard deviation; MD – mean difference; IQR – interquartile range; RR – risk ratio												

[1] Antibiotics given for minimum of 5 days, with stopping at day 5 if body temperature was less than 37.8°C for 48 hours and there was no more than 1 community-acquired pneumonia-associated sign of clinical instability; 80% of total population received a fluoroquinolone
[2] Duration of antibiotics determined by physicians; 80% of total population received a fluoroquinolone
[3] Uranga et al. 2016
[4] Downgraded 1 level - 15% of the total population also have chronic obstructive pulmonary disease (COPD), although it is unknown if pneumonia is associated with an exacerbation of COPD
[5] Downgraded 1 level - not assessable
[6] Downgraded 1 level - at a minimal important difference of 0% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with appreciable benefit or appreciable harm
[7] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 27: GRADE profile – stopping antibiotics: guideline-based versus physician-guided (subgroup analysis of people with pneumonia severity index score I to III)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic stopping based on guidelines[1]	Physician-guided stopping[2]	Relative (95% CI)	Absolute		
Clinical success at day 10 (intention to treat analysis)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	serious[5]	none	58/101 (57.4%)	41/86 (47.7%)	NICE analysis: RR 1.20 (0.91 to 1.59)	95 more per 1000 (from 43 fewer to 281 more)	⊕⊕OO LOW	CRITICAL
Clinical success at day 10 (per protocol analysis)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic stopping based on guidelines[1]	Physician-guided stopping[2]	Relative (95% CI)	Absolute		
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	serious[5]	none	58/94 (61.7%)	39/80 (48.8%)	NICE analysis: RR 1.27 (0.96 to 1.67)	132 more per 1000 (from 20 fewer to 327 more)	⊕⊕OO LOW	CRITICAL
Clinical success at day 30 (intention to treat analysis)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	no serious imprecision	none	93/102 (91.2%)	83/88 (94.3%)	NICE analysis: RR 0.97 (0.89 to 1.05)	28 fewer per 1000 (from 104 fewer to 47 more)	⊕⊕⊕O MODERATE	CRITICAL
Clinical success at day 30 (per protocol analysis)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	no serious imprecision	none	89/95 (93.7%)	80/82 (97.6%)	NICE analysis: RR 0.96 (0.90 to 1.02)	39 fewer per 1000 (from 98 fewer to 20 more)	⊕⊕⊕O MODERATE	CRITICAL

Abbreviations: CI – confidence interval; NA – not applicable; RR – risk ratio

[1] Antibiotics given for minimum of 5 days, with stopping at day 5 if body temperature was less than 37.8°C for 48 hours and there was no more than 1 community-acquired pneumonia-associated sign of clinical instability; 80% of total population received a fluoroquinolone
[2] Duration of antibiotics determined by physicians; 80% of total population received a fluoroquinolone
[3] Uranga et al. 2016
[4] Downgraded 1 level - 15% of the total population also have chronic obstructive pulmonary disease (COPD), although it is unknown if pneumonia is associated with an exacerbation of COPD
[5] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with antibiotic stopping based on guideline

Table 28: GRADE profile – stopping antibiotics: guideline-based versus physician-guided (subgroup analysis of people with pneumonia severity index IV or V)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic stopping based on guidelines[1]	Physician-guided stopping[2]	Relative (95% CI)	Absolute		
Clinical success at day 10 (intention to treat analysis)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	serious[5]	none	32/59 (54.2%)	30/60 (50.0%)	RR 1.08 (0.77 to 1.53)	40 more per 1000 (from 115 fewer to 265 more)	⊕⊕OO LOW	CRITICAL
Clinical success at day 10 (per protocol analysis)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	very serious[6]	none	28/50 (56%)	28/53 (52.8%)	RR 1.06 (0.74 to 1.51)	32 more per 1000 (from 137 fewer to 269 more)	⊕OOO VERY LOW	CRITICAL
Clinical success at day 30 (intention to treat analysis)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic stopping based on guidelines[1]	Physician-guided stopping[2]	Relative (95% CI)	Absolute		
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	serious[5]	none	54/58 (93.1%)	49/61 (80.3%)	RR 1.16 (1.01 to 1.34)	129 more per 1000 (from 8 more to 273 more)	⊕⊕OO LOW	CRITICAL
Clinical success at day 30 (per protocol analysis)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	serious[5]	none	47/49 (95.9%)	46/54 (85.2%)	RR 1.13 (0.99 to 1.28)	111 more per 1000 (from 9 fewer to 239 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI – confidence interval; NA – not applicable; RR – risk ratio												

[1] Antibiotics given for minimum of 5 days, with stopping at day 5 if body temperature was less than 37.8°C for 48 hours and there was no more than 1 community-acquired pneumonia-associated sign of clinical instability; 80% of total population received a fluoroquinolone
[2] Duration of antibiotics determined by physicians; 80% of total population received a fluoroquinolone
[3] Uranga et al. 2016
[4] Downgraded 1 level - 15% of the total population also have chronic obstructive pulmonary disease (COPD), although it is unknown if pneumonia is associated with an exacerbation of COPD
[5] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with antibiotic stopping based on guidelines
[6] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 29: GRADE profile – stopping antibiotics: guideline-based versus physician-guided

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Physician-guided stopping[1]	Stopping based on guidelines[2]	Relative (95% CI)	Absolute		
Pneumonia related failure within 30 days (intention to treat analysis)												
1[3]	randomised trials	serious[4]	NA	serious[5]	very serious[6]	none	3/135 (2.2%)	4/125 (3.2%)	NICE analysis: RR 0.69 (0.16 to 3.04)	10 fewer per 1000 (from 27 fewer to 65 more)	⊕OOO VERY LOW	CRITICAL
Pneumonia related failure within 30 days (per protocol analysis)												
1[3]	randomised trials	serious[4]	NA	serious[5]	very serious[6]	none	3/135 (2.2%)	3/81 (3.7%)	NICE analysis: RR 0.6 (0.12 to 2.9)	15 fewer per 1000 (from 33 fewer to 70 more)	⊕OOO VERY LOW	CRITICAL
Death due to pneumonia (intention to treat analysis)												
1[3]	randomised trials	serious[4]	NA	serious[5]	serious[7]	none	0/135 (0%)	0/125 (0%)	-	-	⊕OOO VERY LOW	CRITICAL
Death due to pneumonia (per protocol analysis)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Physician-guided stopping[1]	Stopping based on guidelines[2]	Relative (95% CI)	Absolute		
1[3]	randomised trials	serious[4]	NA	serious[5]	serious[7]	none	0/135 (0%)	0/81 (0%)	-	-	⊕OOO VERY LOW	CRITICAL
Total mortality (intention to treat analysis)												
1[3]	randomised trials	serious[4]	NA	serious[5]	serious[8]	none	1/135 (0.74%)	4/125 (3.2%)	NICE analysis: RR 0.23 (0.03 to 2.04)	25 fewer per 1000 (from 31 fewer to 33 more)	⊕OOO VERY LOW	CRITICAL
Total mortality (per protocol analysis)												
1[3]	randomised trials	serious[4]	NA	serious[5]	serious[8]	none	1/135 (0.74%)	2/81 (2.5%)	NICE analysis: RR 0.3 (0.03 to 3.26)	17 fewer per 1000 (from 24 fewer to 56 more)	⊕OOO VERY LOW	CRITICAL
Diarrhoea (30 days; intention to treat analysis)												
1[3]	randomised trials	serious[4]	NA	serious[5]	very serious[6]	none	4/135 (3%)	4/125 (3.2%)	NICE analysis: RR 0.93 (0.24 to 3.62)	2 fewer per 1000 (from 24 fewer to 84 more)	⊕OOO VERY LOW	CRITICAL
Diarrhoea (30 days; per protocol analysis)												
1[3]	randomised trials	serious[4]	NA	serious[5]	very serious[6]	none	4/135 (3%)	1/81 (1.2%)	NICE analysis: RR 2.4 (0.27 to 21.1)	17 more per 1000 (from 9 fewer to 248 more)	⊕OOO VERY LOW	CRITICAL
Vomiting (30 days; intention to treat analysis)												
1[3]	randomised trials	serious[4]	NA	serious[5]	very serious[6]	none	1/135 (0.74%)	0/125 (0%)	NICE analysis: RR 2.78 (0.11 to 67.6)	-	⊕OOO VERY LOW	CRITICAL
Vomiting (30 days; per protocol analysis)												
1[3]	randomised trials	serious[4]	NA	serious[5]	very serious[6]	none	1/135 (0.74%)	0/81 (0%)	NICE analysis: RR 1.81 (0.07 to 43.88)	-	⊕OOO VERY LOW	CRITICAL
Abdominal pain (30 days; intention to treat analysis)												
1[3]	randomised trials	serious[4]	NA	serious[5]	very serious[6]	none	1/135 (0.74%)	0/125 (0%)	NICE analysis: RR 2.78 (0.11 to 67.6)	-	⊕OOO VERY LOW	CRITICAL
Abdominal pain (30 days; per protocol analysis)												
1[3]	randomised trials	serious[4]	NA	serious[5]	very serious[6]	none	1/135 (0.74%)	0/81 (0%)	NICE analysis: RR 1.81 (0.07 to 43.88)	-	⊕OOO VERY LOW	CRITICAL
Nausea (30 days; intention to treat analysis)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Physician-guided stopping[1]	Stopping based on guidelines[2]	Relative (95% CI)	Absolute		
1[3]	randomised trials	serious[4]	NA	serious[5]	very serious[6]	none	1/135 (0.74%)	0/125 (0%)	NICE analysis: RR 2.78 (0.11 to 67.6)	-	⊕OOO VERY LOW	CRITICAL
Nausea (30 days; per protocol analysis)												
1[3]	randomised trials	serious[4]	NA	serious[5]	very serious[6]	none	1/135 (0.74%)	0/81 (0%)	NICE analysis: RR 1.81 (0.07 to 43.88)	-	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI – confidence interval; NA – not applicable; RR – risk ratio												

[1] Treated for duration dictated by the physician; majority of people were given either macrolides, cephalosporins or fluoroquinolones
[2] Treated according to clinical response: antibiotic was discontinued 48 hours after clinical stability with at least 5 days of antibiotic treatment; majority of people were given either macrolides, cephalosporins or fluoroquinolones
[3] Aliberti et al. 2017
[4] Downgraded 1 level - 17% of participants violated protocol; the trial was discontinued early due to increased total mortality in the individualised treatment arm
[5] Downgraded 1 level - 19% of participants have chronic obstructive pulmonary disease (COPD), although it is unclear if pneumonia is associated with exacerbations of COPD
[6] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm
[7] Downgraded 1 level – not assessable
[8] Downgraded 1 level - at a minimal important difference of 0% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with appreciable benefit or appreciable harm

Table 30: GRADE profile – upfront dual therapy versus test-dependant dual therapy

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Test-dependant dual therapy[1, 2]	Upfront dual therapy[2, 3]	Relative (95% CI)	Absolute		
People not reaching clinical stability at day 7 (per protocol)												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	serious[6]	none	120/291 (41.2%)	97/289 (33.6%)	HR 0.93 (0.76 to 1.13) NICE analysis: RR 1.23 (0.99 to 1.52)	77 more per 1000 (from 3 fewer to 175 more)	⊕⊕OO LOW	IMPORTANT
Clinical stability (adjusted for age and PSI category)												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	no serious imprecision	none	n= 291	n= 289	HR 0.92 (0.76 to 1.12)	-	⊕⊕⊕O MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Test-dependant dual therapy[1, 2]	Upfront dual therapy[2, 3]	Relative (95% CI)	Absolute		
Clinical stability in people with atypical infection												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	no serious imprecision	none	n= 31		HR 0.33 (0.13 to 0.85)	-	⊕⊕⊕O MODERATE	IMPORTANT
Clinical stability in people with non-atypical infection												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	no serious imprecision	none	n= 549		HR 0.99 (0.80 to 1.22)	-	⊕⊕⊕O MODERATE	IMPORTANT
Admission to intensive care (per protocol)												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	very serious[7]	none	12/291 (4.1%)	14/289 (4.8%)	NICE analysis: RR 0.85 (0.40 to 1.81)	7 fewer per 1000 (from 29 fewer to 39 more)	⊕OOO VERY LOW	CRITICAL
Complicated pleural effusion (requiring chest tube insertion or thoracic surgery)												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	very serious[7]	none	8/291 (2.7%)	14/289 (4.8%)	NICE analysis: RR 0.57 (0.24 to 1.33)	21 fewer per 1000 (from 37 fewer to 16 more)	⊕OOO VERY LOW	IMPORTANT
Length of hospital stay (days)												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	serious[8]	none	291	289	-	median 0 days difference (8 days [IQR 6 to 13] versus 8 days [IQR 6 to 12])	⊕⊕OO LOW	IMPORTANT
Any change in initial antibiotic treatment												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	serious[9]	none	39/291 (13.4%)	46/289 (15.9%)	NICE analysis: RR 0.84 (0.57 to 1.25)	25 fewer per 1000 (from 68 fewer to 40 more)	⊕⊕OO LOW	IMPORTANT
Death at day 90												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	serious[10]	none	24/291 (8.2%)	20/289 (6.9%)	NICE analysis: RR 1.19 (0.67 to 2.11)	13 more per 1000 (from 23 fewer to 77 more)	⊕⊕OO LOW	CRITICAL
Death at day 30												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Test-dependant dual therapy[1, 2]	Upfront dual therapy[2, 3]	Relative (95% CI)	Absolute		
1[4]	randomised trials	serious[5]	NA	no serious indirectness	serious[10]	none	14/291 (4.8%)	10/289 (3.5%)	NICE analysis: RR 1.39 (0.63 to 3.08)	13 more per 1000 (from 13 fewer to 72 more)	⊕⊕OO LOW	CRITICAL
In hospital death												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	serious[10]	none	8/291 (2.7%)	7/289 (2.4%)	NICE analysis: RR 1.14 (0.42 to 3.09)	3 more per 1000 (from 14 fewer to 51 more)	⊕⊕OO LOW	CRITICAL
30 day readmission												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	serious[6]	none	23/291 (7.9%)	9/289 (3.1%)	NICE analysis: RR 2.54 (1.19 to 5.39)	48 more per 1000 (from 6 more to 137 more)	⊕⊕OO LOW	IMPORTANT
90 day readmission												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	serious[6]	none	47/291 (16.2%)	37/289 (12.8%)	NICE analysis: RR 1.26 (0.85 to 1.88)	33 more per 1000 (from 19 fewer to 113 more)	⊕⊕OO LOW	IMPORTANT
New pneumonia within 30 days												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	very serious[7]	none	10/291 (3.4%)	6/289 (2.1%)	NICE analysis: RR 1.66 (0.61 to 4.49)	14 more per 1000 (from 8 fewer to 72 more)	⊕OOO VERY LOW	IMPORTANT
Adverse events (including acute hepatitis, renal failure and minor allergic reactions)												
1[4]	randomised trials	serious[5]	NA	no serious indirectness	very serious[7]	none	4/291 (1.4%)	6/289 (2.1%)	RR 0.66 (0.19 to 2.32)	7 fewer per 1000 (from 17 fewer to 27 more)	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI – confidence interval; NA – not applicable; HR – hazard ratio; RR – relative risk; PSI – pneumonia severity index; IQR – interquartile range

[1] Beta-lactam (cefuroxime [intravenous 1.5g, three times a day] or co-amoxiclav [intravenous 1.2g, four times a day]) plus clarithromycin (intravenous or oral, 500mg twice daily) added to beta-lactam treatment if *Legionella pneumophilla* positive in urine test result
[2] Median antibiotic treatment length was 10 days
[3] Beta-lactam (cefuroxime [intravenous 1.5g, three times a day] or co-amoxiclav [intravenous 1.2g, four times a day]) plus clarithromycin (intravenous or oral, 500mg twice daily)
[4] Garin et al. 2014
[5] Downgraded 1 level - only per-protocol analysis reported, as a non-inferiority study intention to treat analysis would also be expected; imbalance between treatment arms in the number of people with *Legionella* which could have favoured the combination treatment arm

[6] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with monotherapy
[7] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm
[8] Downgraded 1 level – not assessable
[9] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with dual therapy
[10] Downgraded 1 level - at a minimal important difference of 0% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with appreciable benefit or appreciable harm

H.3 Antibiotics in adults with low-severity community-acquired pneumonia

H.3.1 Single antibiotic compared with another single antibiotic

Table 31: GRADE profile – amoxicillin versus phenoxymethylpenicillin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Amoxicillin[1]	Phenoxy-methylpenicillin[2]	Relative (95% CI)	Absolute		
Clinical cure (per protocol analysis; day 14)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[4]	none	25/25 (100%)	10/11 (90.9%)	NICE analysis: RR 1.12 (0.90 to 1.40)	109 more per 1000 (from 91 fewer to 364 more)	⊕⊕⊕O MODERATE	CRITICAL
Clinical cure (intention to treat analysis; day 14)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[4]	none	25/25 (100%)	10/14 (71.4%)	NICE analysis: RR 1.40 (1.00 to 1.96)	286 more per 1000 (from 0 more to 686 more)	⊕⊕⊕O MODERATE	CRITICAL
Complete clinical resolution (intention to treat analysis; day 14)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[5]	none	12/25 (48.0%)	3/14 (21.4%)	NICE analysis: RR 2.24 (0.76 to 6.61)	266 more per 1000 (from 51 fewer to 1000 more)	⊕⊕OO LOW	CRITICAL
Clinical cure (intention to treat analysis; day 30)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[4]	none	25/25 (100%)	10/14 (71.4%)	NICE analysis: RR 1.40	286 more per 1000 (from 0 more to 686 more)	⊕⊕⊕O MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Amoxicillin[1]	Phenoxy-methylpenicillin[2]	Relative (95% CI)	Absolute		
									(1.00 to 1.96)			
Complete clinical resolution (intention to treat analysis; day 30)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[4]	none	23/25 (92.0%)	8/14 (57.1%)	NICE analysis: RR 1.61 (1.01 to 2.57)	349 more per 1000 (from 6 more to 897 more)	⊕⊕⊕O MODERATE	CRITICAL
Radiological resolution (intention to treat analysis; day 30)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[4]	none	20/24 (83.3%)	6/11 (54.5%)	NICE analysis: RR 1.53 (0.87 to 2.70)	289 more per 1000 (from 71 fewer to 927 more)	⊕⊕⊕O MODERATE	CRITICAL

Abbreviations: CI – confidence interval; NA – not applicable; RR – relative risk

[1] Oral, 1g, three times a day for 10 days
[2] Oral, 1,600,000 IU three times a day for 10 days
[3] Llor et al. 2017
[4] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with amoxicillin
[5] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with amoxicillin; wide confidence intervals

Table 32: GRADE profile – clarithromycin versus amoxicillin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clarithromycin[1]	Amoxicillin[1]	Relative (95% CI)	Absolute		
Cure rate												
1[2]	randomised trials	serious[3]	NA	no serious indirectness	serious[4]	none	0/18 (0%)	0/24 (0%)	-	-	⊕⊕OO LOW	CRITICAL

Abbreviations: CI – confidence interval; NA – not applicable

[1] Oral (no details reported)
[2] Pakhale et al. 2014
[3] Downgraded 1 level - systematic review authors judged study to be at unclear risk of bias in 3 domains: allocation concealment, blinding and incomplete outcome data
[4] Downgraded 1 level – not assessable

Table 33: GRADE profile – clarithromycin versus erythromycin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clarithromycin[1]	Erythromycin[2]	Relative (95% CI)	Absolute		
Clinical response (cure and improvement; at 4 to 6 weeks)												
2[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	152/156 (97.4%)	117/124 (94.4%)	OR 2.27 (0.66 to 7.80) NICE analysis: RR 1.03 (0.98 to 1.09)	28 more per 1000 (from 19 fewer to 85 more)	⊕⊕⊕O MODERATE	CRITICAL
Bacteriological cure (at 4 to 6 weeks)												
2[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	31/35 (88.6%)	22/22 (100%)	OR 0.28 (0.03 to 2.57) NICE analysis: RR 0.90 (0.78 to 1.05)	100 fewer per 1000 (from 220 fewer to 50 more)	⊕⊕⊕O MODERATE	IMPORTANT
Radiological cure (at 4 to 6 weeks)												
2[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	143/153 (93.5%)	116/123 (94.3%)	OR 0.91 (0.33 to 2.49) NICE analysis: RR 0.99 (0.94 to 1.06)	9 fewer per 1000 (from 57 fewer to 57 more)	⊕⊕⊕O MODERATE	IMPORTANT
Adverse events (at 4 to 6 weeks)												
2[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	49/229 (21.4%)	113/247 (45.7%)	OR 0.30 (0.20 to 0.46) NICE analysis: RR 0.46 (0.35 to 0.61)	247 fewer per 1000 (from 178 fewer to 297 fewer)	⊕⊕⊕O MODERATE	CRITICAL

Abbreviations: CI – confidence interval; OR – odds ratio; RR – relative risk

[1] 250mg twice daily for 14 days, given at least 1 hour before or 2 hours after meals, mean treatment duration 13 days
[2] 500mg four times daily for 14 days, given at least 1 hour before or 2 hours after meals, mean treatment duration 10 days
[3] Pakhale et al. 2014
[4] Downgraded 1 level - systematic review authors judged studies to be at unclear risk of bias in either 2 or 3 domains: random sequence generation, allocation concealment and source of funding (pharmaceutical sponsor probable)

Table 34: GRADE profile – azithromycin versus levofloxacin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azithromycin microspheres[1]	Levofloxacin[2]	Relative (95% CI)	Absolute		
Clinical response (at test of cure, day 13 to 21; per protocol analysis)												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	no serious imprecision	none	156/174 (89.7%)	177/189 (93.7%)	OR 0.59 (0.27 to 1.26) NICE analysis: RR 0.96 (0.90 to 1.02)	37 fewer per 1000 (from 94 fewer to 19 more)	⊕⊕⊕O MODERATE	CRITICAL
Bacteriological cure												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	no serious imprecision	none	97/107 (90.7%)	120/130 (92.3%)	OR 0.81 (0.32 to 2.02) NICE analysis: RR 0.98 (0.91 to 1.06)	18 fewer per 1000 (from 83 fewer to 55 more)	⊕⊕⊕O MODERATE	IMPORTANT
Adverse events												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	serious[5]	none	42/211 (19.9%)	26/212 (12.3%)	OR 1.78 (1.04 to 3.03) NICE analysis: RR 1.62 (1.03 to 2.55)	76 more per 1000 (from 4 more to 190 more)	⊕⊕OO LOW	CRITICAL

Abbreviations: CI – confidence interval; NA – not applicable; OR – odds ratio; RR – relative risk

[1] Single, 2g dose of azithromycin
[2] 500mg once daily for 7 days
[3] Pakhale et al. 2014
[4] Downgraded 1 level - systematic review authors judged study to be at unclear risk of bias in 3 domains: random sequence generation, allocation concealment and source of funding (sponsored by pharmaceutical company, with 3 of 5 authors employed by same company)
[5] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with azithromycin microspheres

Table 35: GRADE profile – azithromycin versus clarithromycin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azithromycin microspheres[1]	Clarithromycin[2]	Relative (95% CI)	Absolute		
Clinical response (day 14 to 21; per protocol analysis)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	187/202 (92.6%)	198/209 (94.7%)	OR 0.69 (0.31 to 1.55)	19 fewer per 1000 (from	⊕⊕⊕⊕	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azithromycin microspheres[1]	Clarithromycin[2]	Relative (95% CI)	Absolute		
									NICE analysis: RR 0.98 (0.93 to 1.03)	66 fewer to 28 more)	HIGH	
Bacteriological cure												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	123/134 (91.8%)	153/169 (90.5%)	OR 1.17 (0.52 to 2.61) NICE analysis: RR 1.01 (0.95 to 1.09)	9 more per 1000 (from 45 fewer to 81 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Adverse events												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[4]	none	65/247 (26.3%)	62/252 (24.6%)	OR 1.09 (0.73 to 1.64) NICE analysis: RR 1.07 (0.79 to 1.44)	17 more per 1000 (from 52 fewer to 108 more)	⊕⊕⊕O MODERATE	CRITICAL

Abbreviations: CI – confidence interval; NA – not applicable; OR – odds ratio; RR – relative risk

[1] Single 2g dose of azithromycin, administered as an oral suspension
[2] Extended-release clarithromycin administered orally as 2 500mg capsules once daily for 7 days
[3] Pakhale et al. 2014
[4] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm

Table 36: GRADE profile – azithromycin versus co-amoxiclav

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azithromycin[1]	Co-amoxiclav[2]	Relative (95% CI)	Absolute		
Clinical success (end of treatment, day 8-12)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	126/136 (92.6%)	122/131 (93.1%)	NICE analysis: RR 0.99 (0.93 to 1.06)	9 fewer per 1000 (from 65 fewer to 56 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Bacteriological response (end of treatment, day 8-12)												
1[3]	randomised trials	no serious	NA	no serious indirectness	no serious imprecision	none	32/35 (91.4%)	30/33 (90.9%)	NICE analysis: RR 1.01 (0.87 to 1.17)[4]	9 more per 1000 (from 118 fewer to 155 more)	⊕⊕⊕⊕ HIGH	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azithromycin[1]	Co-amoxiclav[2]	Relative (95% CI)	Absolute		
		risk of bias										
Clinical success (follow up visit, day 22-26)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	125/135 (92.6%)	120/129 (93%)	NICE analysis: RR 1 (0.93 to 1.06)[4]	0 fewer per 1000 (from 65 fewer to 56 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Bacteriological response (day 22-26)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	21/22 (95.5%)	15/16 (93.8%)	NICE analysis: RR 1.02 (0.87 to 1.19)[4]	19 more per 1000 (from 122 fewer to 178 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Radiological response (day 22-26)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	125/126 (99.2%)	121/121 (100%)	NICE analysis: RR 0.99 (0.97 to 1.01)[4]	10 fewer per 1000 (from 30 fewer to 10 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Number of people reporting at least 1 adverse event												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[5]	none	34/136 (25.0%)	22/132 (16.7%)	NICE analysis: RR 1.50 (0.93 to 2.42)	83 more per 1000 (from 12 fewer to 237 more)	⊕⊕⊕O MODERATE	CRITICAL
Number of people reporting drug related adverse events												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[5]	none	23/136 (16.9%)	12/132 (9.1%)	NICE analysis: RR 1.86 (0.97 to 3.58)	78 more per 1000 (from 3 fewer to 235 more)	⊕⊕⊕O MODERATE	CRITICAL
Number of people reporting serious adverse events												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[6]	none	3/136 (2.2%)	3/132 (2.3%)	NICE analysis: RR 0.97 (0.20 to 4.72)	1 fewer per 1000 (from 18 fewer to 85 more)	⊕⊕OO LOW	CRITICAL
Number of people reporting abdominal pain												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[7]	none	13/136 (9.6%)	2/132 (1.5%)	NICE analysis: RR 6.31 (1.45 to 27.42)	80 more per 1000 (from 7 more to 400 more)	⊕⊕OO LOW	CRITICAL
Number of people reporting nausea												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azithromycin[1]	Co-amoxiclav[2]	Relative (95% CI)	Absolute		
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[6]	none	9/136 (6.6%)	7/132 (5.3%)	NICE analysis: RR 1.25 (0.48 to 3.25)	13 more per 1000 (from 28 fewer to 119 more)	⊕⊕OO LOW	CRITICAL
Number of people reporting vomiting												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[6]	none	2/136 (1.5%)	3/132 (2.3%)	NICE analysis: RR 0.65 (0.11 to 3.81)	8 fewer per 1000 (from 20 fewer to 64 more)	⊕⊕OO LOW	CRITICAL
Number of people reporting diarrhoea												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[6]	none	3/136 (2.2%)	0/132 (0%)	NICE analysis: RR 6.8 (0.35 to 130.3)	-	⊕⊕OO LOW	CRITICAL
Abbreviations: CI – confidence interval; NA – not applicable; RR – relative risk												

[1] Oral, 1g once daily for 3 days
[2] Oral, 875/125mg twice daily for 7 days
[3] Paris et al. 2008
[4] Authors judged discrepancy in intention to treat (ITT) and per protocol population to be negligible, therefore only reported ITT analysis
[5] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with azithromycin
[6] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm
[7] Downgraded 2 levels - very wide confidence intervals

Table 37: GRADE profile – cephalosporins versus co-amoxiclav

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cephalosporins[1]	Co-amoxiclav[2]	Relative (95% CI)	Absolute		
Clinical success (including antibiotics unavailable in UK)												
2[3]	randomised trials	serious[4]	no serious inconsistency	serious[5]	no serious imprecision	none	323/356 (90.7%)	179/195 (91.8%)	RR 1.01 (0.95 to 1.08)	9 more per 1000 (from 46 fewer to 73 more)	⊕⊕OO LOW	CRITICAL
Clinical success (not including antibiotics unavailable in UK)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cephalosporins[1]	Co-amoxiclav[2]	Relative (95% CI)	Absolute		
1[3]	randomised trials	serious[4]	NA	no serious indirectness	no serious imprecision	none	55/55 (100%)	49/51 (96.1%)	RR 1.04 (0.97 to 1.11)	38 more per 1000 (from 29 fewer to 106 more)	⊕⊕⊕O MODERATE	CRITICAL

Abbreviations: CI – confidence interval; RR – relative risk; NA – not applicable

[1] Cefuroxime, 500mg twice daily for 10 days or cefditoren, 200/400mg twice daily for 14 days
[2]125/500mg three times daily for 10 days or 125/875mg twice daily for 14 days
[3] Maimon et al. 2008
[4] Downgraded 1 level - systematic review authors judge studies to be at high or unclear risk of bias in multiple domains, as unclear if the populations in each arm are comparable, and either unclear or important differences in the care received by each arm; also unclear if randomisation adequate in 1 trial
[5] Downgraded 1 level - cefditoren is not currently licenced for any indication in the UK

Table 38: GRADE profile – cefixime versus ciprofloxacin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cefixime[1]	Ciprofloxacin[2]	Relative (95% CI)	Absolute		
Temperature (day 3)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	very serious[5]	none	Mean 37.2, SD 0.9 N= 39	Mean 37.5, SD 0.5 N= 34	-	MD 0.3 lower (0.63 lower to 0.03 higher)	⊕OOO VERY LOW	IMPORTANT
Temperature (day 14)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	serious[6]	none	Mean 36.8, SD 0.4 N= 39	Mean 37.0, SD 0.5 N= 34	-	MD 0.2 lower (0.41 lower to 0.01 higher)	⊕⊕OO LOW	IMPORTANT
Respiratory rate (day 3)												
1	randomised trials	no serious risk of bias	NA	serious[4]	very serious[5]	none	Mean 21.5, SD 11.2 N= 39	Mean 20.7, SD 2.6 N= 34	-	MD 0.8 higher (2.82 lower to 4.42 higher)	⊕OOO VERY LOW	IMPORTANT
Respiratory rate (day 14)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	serious[7]	none	Mean 16.5, SD 1.1 N= 39	Mean 17.7, SD 2.5 N= 34	-	MD 1.2 higher (0.29 to 2.11 higher)	⊕⊕OO LOW	IMPORTANT
Pulse rate (day 3)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	very serious[5]	none	Mean 103.9, SD 147.6	Mean 81.1, SD 18.6 N= 34	-	MD 22.8 higher (23.94 lower to 69.54 higher)	⊕OOO VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cefixime[1]	Ciprofloxacin[2]	Relative (95% CI)	Absolute		
							N= 39					
Pulse rate (day 14)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	serious[6]	none	Mean 75.1, SD 6.6 N= 39	Mean 77.7, SD 8.0 N= 34	-	MD 2.6 higher (0.79 lower to 5.99 higher)	⊕⊕OO LOW	IMPORTANT
Number of people with radiological consolidations (day 14)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	no serious imprecision	none	4/39 (10.3%)	13/34 (38.2%)	RR 0.27 (0.10 to 0.75)	279 fewer per 1000 (from 96 fewer to 344 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
Number of people with bacterial isolates (day 3)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	serious[8]	none	30/39 (76.9%)	29/34 (85.3%)	RR 0.9 (0.72 to 1.13)	85 fewer per 1000 (from 239 fewer to 111 more)	⊕⊕OO LOW	IMPORTANT
Number of people with bacterial isolates (day 14)												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	no serious imprecision	none	3/39 (7.7%)	13/34 (38.2%)	RR 0.20 (0.06 to 0.65)	306 fewer per 1000 (from 134 fewer to 359 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
Abbreviations: CI – confidence interval; NA – not applicable; SD – standard deviation; MD – mean difference; RR – relative risk												

[1] 400mg twice daily for 14 days
[2] 500mg twice daily for 14 days
[3] Ige et al. 2015
[4] Downgraded 1 level – may not be applicable to UK practice as study conducted in Nigeria; however, antibiotics used are available in UK
[5] Downgraded 2 levels - at a minimal important difference of 0.5x standard deviation of ciprofloxacin, the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm
[6] Downgraded 1 level - at a minimal important difference of 0.5x standard deviation of cefixime, the effect estimate is consistent with no meaningful difference or appreciable harm with ciprofloxacin
[7] Downgraded 1 level - at a minimal important difference of 0.5x standard deviation of cefixime, the effect estimate is consistent with no meaningful difference or appreciable harm with cefixime
[8] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with ciprofloxacin

H.3.2 Single antibiotic compared with dual antibiotics

Table 39: GRADE profile – levofloxacin versus ceftriaxone plus azithromycin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Levofloxacin[1]	Ceftriaxone plus azithromycin[2]	Relative (95% CI)	Absolute		
Clinical failure[3]												
1[4]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[5]	none	15/115 (13.0%)	24/121 (19.8%)	RR 0.66 (0.36 to 1.19)	67 fewer per 1000 (from 127 fewer to 38 more)	⊕⊕⊕O MODERATE	CRITICAL
Abbreviations: CI – confidence interval; NA – not applicable; RR – relative risk												

[1] Intravenous or oral levofloxacin, 500mg once daily
[2] Intravenous ceftriaxone, 1g daily plus intravenous azithromycin 500mg daily
[3] Only including studies reported within the systematic review as a population with low-severity community-acquired pneumonia or treated in the commmunity
[4] Raz-Pasteur et al. 2015
[5] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with cephalosporin plus macrolide therapy

H.3.3 Dual antibiotics compared with other dual antibiotics

No systematic reviews or randomised controlled trials met the inclusion criteria.

H.4 Antibiotics in adults with moderate- to high-severity community-acquired pneumonia

H.4.1 Single antibiotic compared with another single antibiotic

Table 40: GRADE profile – atypical versus non-atypical antibiotic coverage (all antibiotic comparisons)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Atypical[1]	Non-atypical[2]	Relative (95% CI)	Absolute		
Mortality												
25[3]	randomised trials	serious[4]	no serious inconsistency	very serious[5]	serious[6]	none	99/2930 (3.4%)	71/2514 (2.8%)	RR 1.14 (0.84 to 1.55)	4 more per 1000 (from 5 fewer to 16 more)	⊕OOO VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Atypical[1]	Non-atypical[2]	Relative (95% CI)	Absolute		
Mortality in studies with mean age under 65 years old												
15[3]	randomised trials	serious[4]	no serious inconsistency	very serious[5]	serious[6]	none	52/2117 (2.5%)	28/1703 (1.6%)	RR 1.21 (0.75 to 1.94)	3 more per 1000 (from 4 fewer to 15 more)	⊕OOO VERY LOW	CRITICAL
Mortality in studies with mean age over 65 years old												
8[3]	randomised trials	serious[4]	no serious inconsistency	very serious[5]	serious[6]	none	42/720 (5.8%)	38/719 (5.3%)	RR 1.10 (0.72 to 1.69)	3 more per 1000 (from 17 fewer to 33 more)	⊕OOO VERY LOW	CRITICAL
Mortality - Europe only												
14[3]	randomised trials	serious[4]	no serious inconsistency	very serious[5]	serious[6]	none	58/1805 (3.2%)	34/1404 (2.4%)	RR 1.22 (0.79 to 1.89)	5 more per 1000 (from 5 fewer to 22 more)	⊕OOO VERY LOW	CRITICAL
Mortality - ITT analysis												
12[3]	randomised trials	serious[4]	no serious inconsistency	very serious[5]	serious[6]	none	40/1256 (3.2%)	19/887 (2.1%)	RR 1.23 (0.70 to 2.15)	5 more per 1000 (from 6 fewer to 25 more)	⊕OOO VERY LOW	CRITICAL
Clinical failure												
27[3]	randomised trials	serious[4]	no serious inconsistency	very serious[5]	no serious imprecision	none	583/2730 (21.4%)	488/2318 (21.1%)	RR 0.92 (0.83 to 1.02)	17 fewer per 1000 (from 36 fewer to 4 more)	⊕OOO VERY LOW	CRITICAL
Clinical failure in studies with mean age under 65 years old												
15[3]	randomised trials	serious[4]	no serious inconsistency	very serious[5]	no serious imprecision	none	419/1979 (21.2%)	307/1575 (19.5%)	RR 0.93 (0.81 to 1.06)	14 fewer per 1000 (from 37 fewer to 12 more)	⊕OOO VERY LOW	CRITICAL
Clinical failure in studies with mean age over 65 years old												
8[3]	randomised trials	serious[4]	serious	very serious[5]	no serious imprecision	none	152/720 (21.1%)	167/719 (23.2%)	RR 0.91 (0.75 to 1.10)	21 fewer per 1000 (from 58 fewer to 23 more)	⊕OOO VERY LOW	CRITICAL
Clinical failure per geographical area - Europe												
15[3]	randomised trials	serious[4]	no serious inconsistency	very serious[5]	no serious imprecision	none	370/1739 (21.3%)	283/1345 (21.0%)	RR 1.01 (0.88 to 1.16)	32 fewer per 1000 (from 4 fewer to 55 fewer)	⊕OOO VERY LOW	CRITICAL
Clinical failure - ITT analysis												
15[3]	randomised trials	serious[4]	no serious inconsistency	very serious[5]	no serious imprecision	none	470/1952 (24.1%)	489/1897 (25.8%)	RR 0.94 (0.84 to 1.05)	15 fewer per 1000 (from 41 fewer to 13 more)	⊕OOO VERY LOW	CRITICAL
Clinical failure - pneumococcal pneumonia												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Atypical[1]	Non-atypical[2]	Relative (95% CI)	Absolute		
18[3]	randomised trials	serious[4]	no serious inconsistency	very serious[5]	serious	none	67/549 (12.2%)	48/472 (10.2%)	RR 1.22 (0.88 to 1.70)	22 more per 1000 (from 12 fewer to 71 more)	⊕OOO VERY LOW	CRITICAL
Clinical failure - atypical pathogens												
4[3]	randomised trials	serious[4]	no serious inconsistency	serious[7]	serious[8]	none	8/80 (10%)	17/78 (21.8%)	RR 0.52 (0.24 to 1.10)	105 fewer per 1000 (from 166 fewer to 22 more)	⊕OOO VERY LOW	CRITICAL
Clinical failure - Legionella pneumophila												
5[3]	randomised trials	serious[4]	no serious inconsistency	serious[7]	no serious imprecision	none	0/23 (0%)	9/20 (45%)	RR 0.17 (0.05 to 0.63)	373 fewer per 1000 (from 167 fewer to 427 fewer)	⊕⊕OO LOW	CRITICAL
Bacteriological failure												
21[3]	randomised trials	serious[4]	no serious inconsistency	very serious[5]	serious[8]	none	149/1251 (11.9%)	156/1059 (14.7%)	RR 0.80 (0.65 to 0.98)	29 fewer per 1000 (from 3 fewer to 52 fewer)	⊕OOO VERY LOW	IMPORTANT
Adverse events - total												
24[3]	randomised trials	serious[4]	no serious inconsistency	very serious[5]	no serious imprecision	none	564/2467 (22.9%)	536/2451 (21.9%)	RR 1.02 (0.93 to 1.13)	4 more per 1000 (from 15 fewer to 28 more)	⊕OOO VERY LOW	CRITICAL
Adverse events - gastrointestinal events												
16[3]	randomised trials	serious[4]	no serious inconsistency	very serious[5]	serious[8]	none	83/2279 (3.6%)	92/1850 (5%)	RR 0.70 (0.53 to 0.92)	15 fewer per 1000 (from 4 fewer to 23 fewer)	⊕OOO VERY LOW	CRITICAL
Adverse events - requiring discontinuation of treatment												
12[3]	randomised trials	serious[4]	no serious inconsistency	very serious[5]	very serious[9]	none	77/2121 (3.6%)	63/1685 (3.7%)	RR 1.01 (0.72 to 1.41)	0 more per 1000 (from 10 fewer to 15 more)	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI – confidence interval; RR – relative risk; ITT – intention to treat

[1] Including fluoroquinolones (21 studies), macrolides (5 studies) and pristinamycine (1 study); given as monotherapy in all but 3 studies; dual therapy studies included a fluoroquinolone plus teicoplanin and a macrolide plus either cephalosporin, ceftriaxone or aminoglycoside; drugs administered orally in all but 8 studies, of which most switched to oral administration within a few days

[2] Including beta-lactams (9 studies), beta-lactam plus beta-lactamase inhibitors (3 studies), cephalosporins (11 studies), carbapenems (2 studies) or penicillin (1 study); all beta-lactams, 1 cephalosporin and 2 beta-lactam plus beta-lactamase inhibitors (12 studies) were administered orally, 1 cephalosporin was given intra-muscularly and the remaining drugs (15 studies) were administered intravenously

[3] Eliakim-Raz et al. 2012

[4] Downgraded 1 level - all studies judged to be at high and/or unclear risk of bias by systematic review authors in several domains

[5] Downgraded 2 levels - includes antibiotics not licensed in the UK; includes a small proportion of people excluded from the evidence review protocol (hospital acquired pneumonia, COPD, bronchitis, other non-pneumonia respiratory tract infections)

[6] Downgraded 1 level - at a minimal important difference of 0% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with appreciable benefit or appreciable harm

[7] Downgraded 1 level - all antibiotics not licensed in the UK

[8] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with non-atypical antibiotics

[9] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 41: GRADE profile – atypical versus non-atypical antibiotics (subgroup analysis excluding antibiotics not available in UK)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Atypical[1]	Non-atypical[2]	Relative (95% CI)	Absolute		
Mortality												
11[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	48/1069 (4.5%)	46/1069 (4.3%)	NICE analysis: RR 1.03 (0.69 to 1.52)	1 more per 1000 (from 13 fewer to 22 more)	⊕⊕OO LOW	CRITICAL
Mortality in studies with mean age under 65 years old												
5[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	9/438 (2.1%)	9/442 (2%)	NICE analysis: RR 0.92 (0.37 to 2.29)	2 fewer per 1000 (from 13 fewer to 26 more)	⊕⊕OO LOW	CRITICAL
Mortality in studies with mean age over 65 years old												
6[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	39/631 (6.2%)	37/627 (5.9%)	NICE analysis: RR 1.05 (0.68 to 1.62)	3 more per 1000 (from 19 fewer to 37 more)	⊕⊕OO LOW	CRITICAL
Mortality - Europe only												
5[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	16/329 (4.9%)	13/326 (4%)	NICE analysis: RR 1.27 (0.62 to 2.58)	11 more per 1000 (from 15 fewer to 63 more)	⊕⊕OO LOW	CRITICAL
Mortality - ITT analysis												
3[3]	randomised trials	serious[4]	NA[6]	no serious indirectness	serious[5]	none	2/88 (2.3%)	2/112 (1.8%)	NICE analysis: RR 1.08 (0.17 to 7.1)	1 more per 1000 (from 15 fewer to 109 more)	⊕⊕OO LOW	CRITICAL
Clinical failure												
14[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	418/1748 (23.9%)	302/1329 (22.7%)	NICE analysis: RR 0.94 (0.82 to 1.07)	14 fewer per 1000 (from 41 fewer to 16 more)	⊕⊕⊕O MODERATE	CRITICAL
Clinical failure in studies with mean age under 65 years old												
5[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[7]	none	71/433 (16.4%)	74/438 (16.9%)	NICE analysis: RR 0.95 (0.71 to 1.27)	8 fewer per 1000 (from 49 fewer to 46 more)	⊕OOO VERY LOW	CRITICAL
Clinical failure in studies with mean age over 65 years old												
6[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	140/631 (22.2%)	152/627 (24.2%)	NICE analysis: RR 0.91 (0.75 to 1.12)	22 fewer per 1000 (from 61 fewer to 29 more)	⊕⊕⊕O MODERATE	CRITICAL
Clinical failure - Europe only												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Atypical[1]	Non-atypical[2]	Relative (95% CI)	Absolute		
6[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[8]	none	55/362 (15.2%)	72/357 (20.2%)	NICE analysis: RR 0.75 (0.54 to 1.03)	50 fewer per 1000 (from 93 fewer to 6 more)	⊕OOO VERY LOW	CRITICAL
Clinical failure - ITT analysis												
7[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	211/933 (22.6%)	222/887 (25%)	NICE analysis: RR 0.91 (0.77 to 1.07)	23 fewer per 1000 (from 58 fewer to 18 more)	⊕⊕⊕O MODERATE	CRITICAL
Clinical failure - pneumococcal pneumonia												
7[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[7]	none	20/168 (11.9%)	16/173 (9.2%)	NICE analysis: RR 1.27 (0.7 to 2.3)	25 more per 1000 (from 28 fewer to 120 more)	⊕OOO VERY LOW	CRITICAL
Bacteriological failure												
8[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[8]	none	48/355 (13.5%)	59/342 (17.3%)	NICE analysis: RR 0.82 (0.58 to 1.15)	31 fewer per 1000 (from 72 fewer to 26 more)	⊕⊕OO LOW	CRITICAL
Adverse events - total												
11[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	355/1215 (29.2%)	318/1207 (26.3%)	NICE analysis: RR 1.08 (0.96 to 1.21)	21 more per 1000 (from 11 fewer to 55 more)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events - gastrointestinal events												
7[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[8]	none	35/974 (3.6%)	42/954 (4.4%)	NICE analysis: RR 0.81 (0.53 to 1.24)	8 fewer per 1000 (from 21 fewer to 11 more)	⊕⊕OO LOW	CRITICAL
Adverse events - requiring discontinuation of treatment												
6[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[7]	none	29/783 (3.7%)	36/766 (4.7%)	NICE analysis: RR 0.79 (0.49 to 1.27)	10 fewer per 1000 (from 24 fewer to 13 more)	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI – confidence interval; ITT – intention to treat; NA – not applicable; RR – relative risk

[1] Including: ciprofloxacin, levofloxacin, moxifloxacin, teicoplanin, azithromycin, clarithromycin plus ceftriaxone, clarithromycin
[2] Including: amoxicillin, co-amoxiclav, amoxicillin, ceftriaxone, benzylpenicillin, meropenem plus imipenem/cilastatin
[3] Eliakim-Raz et al. 2012
[4] Downgraded 1 level - all studies judged to be at high and/or unclear risk of bias by systematic review authors in several domains
[5] Downgraded 1 level - at a minimal important difference of 0% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with appreciable benefit or appreciable harm
[6] Heterogeneity not applicable as 2 of 3 studies have no events in either arm
[7] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm
[8] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with non-atypical treatment

Table 42: GRADE profile – macrolides versus non-atypical antibiotics (all antibiotic comparisons)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Macrolide[1]	Non-atypical[2]	Relative (95% CI)	Absolute		
Mortality												
4[3]	randomised trials	serious[4]	no serious inconsistency	serious[5]	very serious[6]	none	10/273 (3.7%)	8/267 (3.0%)	RR 1.25 (0.52 to 3.01)	7 more per 1000 (from 14 fewer to 60 more)	⊕OOO VERY LOW	CRITICAL
Clinical failure												
5[3]	randomised trials	serious[4]	no serious inconsistency	serious[5]	serious[7]	none	46/272 (16.9%)	40/264 (15.2%)	RR 1.11 (0.76 to 1.62)	17 more per 1000 (from 36 fewer to 94 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI – confidence interval; RR – relative risk												

[1] Including: azithromycin [oral, 500 mg twice daily loading dose followed by 500 mg once daily, unreported course length], clarithromycin [unreported dose and course length] and roxithromycin [oral, 150 mg twice daily, unreported course length]
[2] Including: benzylpenicillin [intravenous, 1,000,000 IU four times daily, unreported course length], meropenem [intravenous, 500 mg three times daily, unreported course length], co-amoxiclav [intravenous, 1.2 g four times daily for 3 to 5 days, followed by oral, 625 mg three times daily], and cephradine [oral, 1 g twice daily]
[3] Eliakim-Raz et al. 2012
[4] Downgraded 1 level - all studies judged to be at high and/or unclear risk of bias by systematic review authors in several domains
[5] Downgraded 1 level - includes antibiotics not licenced in UK
[6] Downgraded 1 level - at a minimal important difference of 0% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with appreciable benefit or appreciable harm
[7] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with macrolides

Table 43: GRADE profile – macrolides versus non-atypical antibiotics (subgroup analysis excluding antibiotics not available in UK)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Macrolide[1]	Non-atypical[2]	Relative (95% CI)	Absolute		
Mortality												
3[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	9/193 (4.7%)	8/189 (4.2%)	NICE analysis: RR 1.14 (0.45 to 2.88)	6 more per 1000 (from 23 fewer to 80 more)	⊕⊕OO LOW	CRITICAL
Clinical failure												
4[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[6]	none	43/226 (19%)	40/220 (18.2%)	NICE analysis: RR 1.04 (0.70 to 1.52)	7 more per 1000 (from 55 fewer to 95 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI – confidence interval; RR – relative risk												

[1] Including: azithromycin, clarithromycin plus ceftriaxone, clarithromycin
[2] Including: co-amoxiclav, benzylpenicillin, meropenem plus imipenem/cilastatin
[3] Eliakim-Raz et al. 2012
[4] Downgraded 1 level - all studies judged to be at high and/or unclear risk of bias by systematic review authors in several domains
[5] Downgraded 1 level - at a minimal important difference of 0% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with appreciable benefit or appreciable harm

[6] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 44: GRADE profile – fluoroquinolones versus non-atypical antibiotics (all antibiotic comparisons)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fluoroquinolone[1]	Non-atypical[2]	Relative (95% CI)	Absolute		
Mortality												
19[3]	randomised trials	serious[4]	no serious inconsistency	very serious[5]	serious[6]	none	57/1848 (3.1%)	57/1850 (3.1%)	RR 0.98 (0.69 to 1.39)	1 fewer per 1000 (from 10 fewer to 12 more)	⊕OOO VERY LOW	CRITICAL
Clinical failure												
21[3]	randomised trials	serious[4]	no serious inconsistency	very serious[5]	no serious imprecision	none	340/1849 (18.4%)	379/1855 (20.4%)	RR 0.89 (0.79 to 1.02)	22 fewer per 1000 (from 43 fewer to 4 more)	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI – confidence interval; RR – relative risk

[1] Including: (oral unless otherwise stated; course length not reported unless otherwise stated): pefloxacin (400 mg twice daily or 1200 mg once daily), ciprofloxacin (200 to 750 mg twice daily), enoxacin (600 mg once daily), levofloxacin (500 mg twice daily [intravenous or oral], 500 mg once daily for 7 to 14 days, or 200 mg three times daily), ofloxacin (200 mg twice daily or 400 mg twice daily), temafloxacin (600 mg twice daily), sparfloxacin (400 mg once daily or 200 mg once daily), moxifloxacin (400 mg once daily), pefloxacine (1,200 mg once daily), gemifloxacin (320 mg once daily for 7 days), trovafloxacin (200 mg once daily), teicoplanin (intravenous 400 mg loading dose followed by 400 or 200 mg once daily) and sitfloxacin (intravenous 400 mg once daily)

[2] Including: cephalosporins (course length not reported unless otherwise stated) - ceftazidime (intravenous, 1 to 2 g twice daily to three times daily), cefamondole (intramuscular, 1 g four times daily), ceftriaxone (intravenous 2 g twice daily followed by intramuscular 1 g once daily; intravenous 1 g twice daily for 7 to 14 days; 4 g once daily or 2 g once daily) and ceftazidime (intravenous, 2 g twice daily); penicillins - (oral unless otherwise stated; unreported course length unless otherwise stated): amoxicillin (250 mg to 750 mg three times daily; 375 mg four times daily; 1 g once daily; 1 g three times daily for 10 days) and co-amoxiclav (intravenous 1 g three times daily; 1 g/125 mg three times daily for 10 days)

[3] Eliakim-Raz et al. 2012

[4] Downgraded 1 level - all studies judged to be at high and/or unclear risk of bias by systematic review authors in several domains

[5] Downgraded 2 levels - includes antibiotics not licensed in the UK; includes people excluded from the evidence review protocol (hospital acquired pneumonia, COPD, bronchitis, other non-pneumonia respiratory tract infections)

[6] Downgraded 1 level - at a minimal important difference of 0% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with appreciable benefit or appreciable harm

Table 45: GRADE profile – fluoroquinolones versus non-atypical antibiotics (subgroup analysis excluding antibiotics not available in UK)

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fluoroquinolone[1]	Non-atypical[2]	Relative (95% CI)	Absolute		
Mortality												
8[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	39/876 (4.5%)	38/880 (4.3%)	NICE analysis: RR 1.00 (0.65 to 1.54)	0 fewer per 1000 (from 15 fewer to 23 more)	⊕⊕OO LOW	CRITICAL
Clinical failure												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fluoroquinolone[1]	Non-atypical[2]	Relative (95% CI)	Absolute		
9[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	178/913 (19.5%)	193/910 (21.2%)	NICE analysis: RR 0.92 (0.77 to 1.09)	17 fewer per 1000 (from 49 fewer to 19 more)	⊕⊕⊕O MODERATE	CRITICAL
Abbreviations: CI – confidence interval; RR – relative risk												

[1] Including: ciprofloxacin, levofloxacin, moxifloxacin and teicoplanin
[2] Including: amoxicillin, co-amoxiclav, amoxicillin and ceftriaxone
[3] Eliakim-Raz et al. 2012
[4] Downgraded 1 level - all studies judged to be at high and/or unclear risk of bias by systematic review authors in several domains
[5] Downgraded 1 level - at a minimal important difference of 0% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with appreciable benefit or appreciable harm

Table 46: GRADE profile – levofloxacin versus tigecycline

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Levofloxacin[1]	Tigecycline[2]	Relative (95% CI)	Absolute		
Clinical cure												
4[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	784/979 (80.1%)	784/961 (81.6%)	NICE analysis: RR 0.98 (0.94 to 1.03)	16 fewer per 1000 (from 49 fewer to 24 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Mortality												
4[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	25/1030 (2.4%)	32/1038 (3.1%)	NICE analysis: RR 0.79 (0.47 to 1.32)	6 fewer per 1000 (from 16 fewer to 10 more)	⊕⊕⊕O MODERATE	CRITICAL
Abbreviations: CI – confidence interval; RR – relative risk												

[1] Levofloxacin (unreported dosage)
[2] Tigecycline (unreported dosage)
[3] Nemeth et al. 2015
[4] Downgraded 1 level - at a minimal important difference of 0% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with appreciable benefit or appreciable harm

Table 47: GRADE profile – levofloxacin versus doxycycline

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Levofloxacin[1]	Doxycycline[2]	Relative (95% CI)	Absolute		
Clinical cure												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Levofloxacin[1]	Doxycycline[2]	Relative (95% CI)	Absolute		
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	28/30 (93.3%)	34/35 (97.1%)	RR 0.96 (0.86 to 1.07)	39 fewer per 1000 (from 136 fewer to 68 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Mortality												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[4]	none	0/30 (0%)	0/35 (0%)	-	-	⊕⊕⊕O MODERATE	CRITICAL

Abbreviations: CI – confidence interval; NA- not applicable; RR – relative risk

[1] Levofloxacin (unreported dosage)
[2] Doxycycline (unreported dosage)
[3] Nemeth et al. 2015
[4] Downgraded 1 level – not assessable

Table 48: GRADE profile – ofloxacin versus erythromycin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ofloxacin[1]	Erythromycin[2]	Relative (95% CI)	Absolute		
Mortality												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[4]	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)	⊕⊕⊕O MODERATE	CRITICAL
Clinical failure												
2[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[5]	none	19/99 (19.2%)	19/100 (19%)	RR 1.00 (0.57 to 1.76)	0 fewer per 1000 (from 82 fewer to 144 more)	⊕⊕OO LOW	CRITICAL
Microbiological failure												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[5]	none	0/49 (0.0%)	2/50 (4.0%)	RR 0.2 (0.01 to 4.14)	32 fewer per 1000 (from 40 fewer to 126 more)	⊕⊕OO LOW	CRITICAL

Abbreviations: CI – confidence interval; NA- not applicable; RR – relative risk

[1] Ofloxacin for 5 to 14 days (unreported dosage)
[2] Erythromycin for 5 to 14 days (unreported dosage)
[3] Skalsky et al. 2013
[4] Downgraded 1 level - at a minimal important difference of 0% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with appreciable benefit or appreciable harm
[5] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 49: GRADE profile – moxifloxacin versus levofloxacin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Moxifloxacin[1]	Levofloxacin[2]	Relative (95% CI)	Absolute		
Mortality												
3[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	29/521 (5.6%)	23/531 (4.3%)	OR 1.30 (0.74 to 2.27) NICE analysis: RR 1.28 (0.76 to 2.15)	12 more per 1000 (from 10 fewer to 50 more)	⊕⊕⊕O MODERATE	CRITICAL
Treatment success (evaluable population)												
3[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	290/397 (73.0%)	303/411 (73.7%)	OR 1.09 (0.69 to 1.72) NICE analysis: RR 1.01 (0.97 to 1.05)	7 fewer per 1000 (from 66 fewer to 59 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Microbiological treatment success (evaluable population)												
3[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	119/137 (86.9%)	133/156 (85.3%)	OR 1.12 (0.57 to 2.19) NICE analysis: RR 1.02 (0.93 to 1.11)	17 more per 1000 (from 60 fewer to 94 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Total adverse events												
3[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[4]	none	174/593 (29.3%)	165/610 (27.0%)	OR 1.13 (0.87 to 1.46) NICE analysis: RR 1.09 (0.91 to 1.30)	24 more per 1000 (from 24 fewer to 81 more)	⊕⊕⊕O MODERATE	CRITICAL

Abbreviations: CI – confidence interval; RR – relative risk; OR – odds ratio

[1] Intravenous or oral moxifloxacin 400mg a day for 7 to 14 days
[2] Intravenous or oral levofloxacin 100mg twice a day or 500mg/day for 7 to 14 days
[3] Yuan et al. 2012
[4] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with moxifloxacin
[5] Downgraded 1 level - at a minimal important difference of 0% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with appreciable benefit or appreciable harm

Table 50: GRADE profile – ceftriaxone versus ceftaroline fosamil

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftaroline fosamil[1,2]	Ceftriaxone[1,3]	Relative (95% CI)	Absolute		
Clinical cure												
3[4]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	784/961 (81.6%)	695/955 (72.8%)	RR 1.12 (1.07 to 1.18)	87 more per 1000 (from 51 more to 131 more)	⊕⊕⊕O MODERATE	CRITICAL
Mortality												
3[4]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[6]	none	18/1006 (1.8%)	16/1005 (1.6%)	RR 1.12 (0.58 to 2.19)	2 more per 1000 (from 7 fewer to 19 more)	⊕⊕OO LOW	CRITICAL
Serious adverse events												
3[4]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[7]	none	99/1006 (9.8%)	101/1005 (10.0%)	RR 0.98 (0.75 to 1.27)	2 fewer per 1000 (from 25 fewer to 27 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI – confidence interval; RR – relative risk												

[1] In 1 study, patients in both groups received macrolide therapy; oral clarithromycin 500mg given to all participants every 12 hours for 2 doses on day 1
[2] Ceftaroline fosamil 600mg intravenous every 12 hours for 5 to 7 days
[3] Ceftriaxone 1g intravenous every 24 hours for 5 to 7 days
[4] El Hajj et al. 2017
[5] Downgraded 1 level - all studies judged by systematic review authors as high or unclear risk of bias in at least 1 domain
[6] Downgraded 1 level - at a minimal important difference of 0% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with appreciable benefit or appreciable harm
[7] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or harm with ceftriaxone

Table 51: GRADE profile – ertapenem versus ceftriaxone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ertapenem[1]	Ceftriaxone[2]	Relative (95% CI)	Absolute		
Treatment success (disappearance of acute signs and symptoms and no requirement for further antibiotic therapy; clinically evaluable)												
2[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	335/364 (92.0%)	270/294 (91.8%)	NICE analysis: RR 1.00 (0.96 to 1.05)	0 fewer per 1000 (from 37 fewer to 46 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Microbiological success (eradication of baseline pathogens, or presumed eradication based on clinical outcomes when post-treatment cultures were not performed; clinically evaluable)												
2[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	92/101 (91.1%)	87/96 (90.6%)	NICE analysis: RR 1.01 (0.91 to 1.11)	9 more per 1000 (from 82 fewer to 100 more)	⊕⊕⊕⊕ HIGH	IMPORTANT

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ertapenem[1]	Ceftriaxone[2]	Relative (95% CI)	Absolute		
Abbreviations: CI – confidence interval; RR – relative risk												

[1] Intravenous or intramuscular ertapenem 1g/day followed by co-amoxiclav
[2] Intravenous or intramuscular ceftriaxone 1g/day followed by co-amoxiclav
[3] Bai Nan et al. 2014

H.4.2 Single antibiotic compared with dual antibiotics

Table 52: GRADE profile – fluoroquinolones versus macrolides plus beta-lactams

Quality assessment							No of patients	Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fluoroquinolone[1] versus beta-lactam[2] plus macrolide[3]	Relative (95% CI)		
Mortality (30 days)										
5[4]	randomised trials	no serious risk of bias	no serious inconsistency	serious[5]	serious[6]	none	n= 2683[7]	RR 0.99 (0.70 to 1.40)[8]	⊕⊕OO LOW	CRITICAL
Clinical failure (antibiotic modifications related to perceived failure)										
9[4]	randomised trials	serious[9]	no serious inconsistency	serious[5]	serious[10]	none	n= 2441[7]	RR 0.72 (0.57 to 0.91)[8]	⊕OOO VERY LOW	CRITICAL
Clinical failure in pneumococcal pneumonia										
7[4]	randomised trials	serious[9]	no serious inconsistency	serious[5]	serious[11]	none	n= 145[7]	RR 2.03 (0.94 to 4.38)[8]	⊕OOO VERY LOW	CRITICAL
Treatment discontinuation										
6[4]	randomised trials	serious[12]	no serious inconsistency	serious[5]	serious[10]	none	n= 2179[7]	RR 0.65 (0.54 to 0.78)[8]	⊕OOO VERY LOW	CRITICAL
Microbiological failure										
7[4]	randomised trials	serious[12]	no serious inconsistency	serious[5]	very serious[13]	none	n= 35[7]	RR 0.93 (0.63 to 1.38)[8]	⊕OOO VERY LOW	IMPORTANT
Any adverse events										
7[4]	randomised trials	serious[12]	no serious inconsistency	serious[5]	no serious imprecision	none	n= 2727[7]	RR 0.90 (0.81 to 1.00)[8]	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients	Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fluoroquinolone[1] versus beta-lactam[2] plus macrolide[3]	Relative (95% CI)		
Diarrhoea										
3[4]	randomised trials	no serious risk of bias	serious[14]	serious[5]	no serious imprecision	none	n= 617[7]	RR 0.13 (0.05 to 0.34)[8]	⊕⊕OO LOW	CRITICAL
Abbreviations: CI – confidence interval; RR – relative risk										

[1] Levofloxacin (intravenous or oral, 500 to 750 mg once daily) or moxifloxacin (oral or intravenous 400 mg once daily)
[2] Beta-lactams included ceftriaxone (intravenous 1 to 2 g once daily), co-amoxiclav (intravenous 500/1000 mg once daily; 1000/125 mg three times daily), amoxicillin (intravenous, unreported dosage), penicillin (intravenous, unreported dosage), or cefoperazone (intravenous 2 g once daily)
[3]Macrolides included azithromycin (intravenous or oral 500 mg once daily), erythromycin (intravenous 500 mg to 1 g once daily), clarithromycin (oral 500 mg twice daily), roxithromycin (oral 150 mg twice daily)
[4] Raz-Pasteur et al. 2015
[5] Downgraded 1 level - includes (or very likely to include) antibiotics not licensed in the UK; includes 1 RCT of people with community-acquired pneumonia treated in the community
[6] Downgraded 1 level - at a minimal important difference of 0% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with appreciable benefit or appreciable harm
[7] Events data for each arm not reported
[8]RR < 1 favours fluoroquinolone monotherapy
[9] Downgraded 1 level - systematic review authors report unclear risk of bias in allocation concealment in majority of studies, and unclear allocation generation in some studies
[10] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with dual therapy
[11] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with monotherapy
[12] Downgraded 1 level - systematic review authors describe low risk of bias in allocation generation and concealment and blinding in only a minority of studies; unclear which studies are high or low risk of bias
[13] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm
[14] Downgraded 1 level - heterogeneity >50%

Table 53: GRADE profile – fluoroquinolone versus fluoroquinolones plus beta-lactams

Quality assessment							No of patients	Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fluoroquinolone[1] versus beta-lactam[2] plus fluoroquinolone[3]	Relative (95% CI)		
Mortality										
2[4]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[5]	none	n= 1116[6]	RR 1.00 (0.69 to 1.45)[7]	⊕⊕⊕O MODERATE	CRITICAL
Clinical failure										
3[4]	randomised trials	no serious risk of bias	no serious inconsistency	serious[8]	serious[9]	none	n= 1252[6]	RR 1.11 (0.89 to 1.38)[7]	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients	Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Fluoroquinolone[1] versus beta-lactam[2] plus fluoroquinolone[3]	Relative (95% CI)		
Clinical failure in pneumococcal pneumonia										
3[4]	randomised trials	no serious risk of bias	no serious inconsistency	serious[8]	very serious[10]	none	n= 261[6]	RR 0.92 (0.53 to 1.59)[7]	⊕OOO VERY LOW	CRITICAL
Microbiological failure										
3[4]	randomised trials	no serious risk of bias	no serious inconsistency	serious[8]	very serious[10]	none	n= 255[6]	RR 1.15 (0.71 to 1.86)[7]	⊕OOO VERY LOW	CRITICAL
Any adverse events										
3[4]	randomised trials	no serious risk of bias	serious[11]	serious[8]	no serious imprecision	none	n= 1339[6]	RR 1.02 (0.90 to 1.14)[7]	⊕⊕OO LOW	CRITICAL
Diarrhoea										
1[4]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[9]	none	n= 733[6]	RR 2.05 (1.13 to 3.73)[7]	⊕⊕⊕O MODERATE	CRITICAL
Abbreviations: CI – confidence interval; RR – relative risk; NA- not applicable										

[1] Fluoroquinolones (as monotherapy) included levofloxacin (intravenous 500 mg twice daily), sparfloxacin (oral, 400 mg once daily) and moxifloxacin (intravenous, 400 mg once daily)
[2] Beta lactams included ceftriaxone (intravenous 2 g once daily), cefotaxime (intravenous, 1 g three times daily) and amoxicillin (oral, 1 g three times daily)
[3] Fluoroquinolones (in dual therapy) included ofloxacin (intravenous, 200 mg twice daily) and levofloxacin (intravenous 500 mg once daily)
[4] Raz-Pasteur et al. 2015
[5] Downgraded 1 level - at a minimal important difference of 0% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with appreciable benefit or appreciable harm
[6] Events data for each arm not reported
[7] RR < 1 favours fluoroquinolone monotherapy
[8] Downgraded 1 level - includes antibiotics not licensed in the UK
[9] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with dual therapy
[10] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm
[11] Downgraded 1 level - heterogeneity >50%

Table 54: GRADE profile – macrolides versus macrolides plus beta-lactams

Quality assessment							No of patients	Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Macrolide[1] versus beta-lactam[2] plus macrolide[3]	Relative (95% CI) Absolute		
Mortality										
3[4]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[6]	none	n= 467[7]	RR 1.00 (0.40 to 2.46)[8]	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients	Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Macrolide[1] versus beta-lactam[2] plus macrolide[3]	Relative (95% CI) Absolute		
Clinical failure										
4[4]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	very serious[9]	none	n= 557[7]	RR 0.92 (0.67 to 1.26)[8]	⊕OOO VERY LOW	CRITICAL
Clinical failure in pneumococcal pneumonia										
2[4]	randomised trials	serious[5]	serious[10]	no serious indirectness	very serious[9]	none	n= 59[7]	RR 0.49 (0.10 to 2.48)[8]	⊕OOO VERY LOW	CRITICAL
Treatment discontinuation										
1[4]	randomised trials	serious[9]	NA	no serious indirectness	very serious[9]	none	n= 235[7]	RR 0.85 (0.53 to 1.38)[8]	⊕OOO VERY LOW	CRITICAL
Microbiological failure										
2[4]	randomised trials	serious[5]	serious[10]	no serious indirectness	very serious[9]	none	n= 117[7]	RR 0.88 (0.43 to 1.81)[8]	⊕OOO VERY LOW	CRITICAL
Any adverse event										
3[4]	randomised trials	serious[5]	serious[10]	no serious indirectness	serious[11]	none	n= 470[7]	RR 0.62 (0.50 to 0.78)[8]	⊕OOO VERY LOW	CRITICAL
Diarrhoea										
2[4]	randomised trials	serious[5]	serious[10]	no serious indirectness	serious[11]	none	n= 325[7]	RR 0.47 (0.22 to 1.01)[8]	⊕OOO VERY LOW	CRITICAL

[1] Macrolides (as monotherapy) include azithromycin (intravenous 500 mg once daily) and clarithromycin (oral or intravenous, 500 mg once daily)
[2] Beta-lactams include ceftriaxone (intravenous 2 g twice daily) and cefuroxime (oral 500 mg twice daily, or intravenous 750 mg to 1.5 g three times daily)
[3] Macrolides (in dual therapy) include clarithromycin (oral, 500 mg once or twice daily) and erythromycin (intravenous oral, 500 to 1000 mg four times daily or intravenous 1 g three times daily)
[4] Raz-Pasteur et al. 2015
[5] Downgraded 1 level - systematic review authors report unclear risk of bias in allocation concealment in all studies, and unclear allocation generation in the majority of studies
[6] Downgraded 1 level - at a minimal important difference of 0% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with appreciable benefit or appreciable harm

[7] Events data for each arm not reported
[8] RR < 1 favours fluoroquinolone monotherapy
[9] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm
[10] Downgraded 1 level - heterogeneity >50%
[11] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with monotherapy

Table 55: GRADE profile – ceftobiprole versus ceftriaxone plus linezolid

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftobiprole[1]	Ceftriaxone +/- linezolid[2]	Relative (95% CI)	Absolute		
Clinical cure (ITT)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	240/314 (76.4%)	257/324 (79.3%)	NICE analysis: RR 0.96 (0.89 to 1.05)[4]	32 fewer per 1000 (from 87 fewer to 40 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Clinical cure (clinically evaluable)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	200/231 (86.6%)	208/238 (87.4%)	NICE analysis: RR 0.99 (0.92 to 1.06)[4]	9 fewer per 1000 (from 70 fewer to 52 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Clinical cure in people receiving only IV therapy (clinically evaluable)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	77/103 (74.8%)	73/101 (72.3%)	NICE analysis: RR 1.03 (0.88 to 1.22)[4]	22 more per 1000 (from 87 fewer to 159 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Clinical cure in people switching to oral therapy (clinically evaluable)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	123/128 (96.1%)	135/137 (98.5%)	NICE analysis: RR 0.98 (0.94 to 1.02)[4]	20 fewer per 1000 (from 59 fewer to 20 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Clinical cure in people aged over 75 (clinically evaluable)												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	no serious imprecision	none	36/39 (92.3%)	43/50 (86%)	NICE analysis: RR 1.07 (0.93 to 1.24)[4]	60 more per 1000 (from 60 fewer to 206 more)	⊕⊕⊕O MODERATE	CRITICAL
Clinical cure in people with PSI score ≥ 91												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	no serious imprecision	none	46/51 (90.2%)	49/58 (84.5%)	NICE analysis: RR 1.07 (0.93 to 1.23)[4]	59 more per 1000 (from 59 fewer to 194 more)	⊕⊕⊕O MODERATE	CRITICAL
Clinical cure in people with community acquired pneumonia complicated by bacteraemia												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	very serious[5]	none	6/7 (85.7%)	12/14 (85.7%)	NICE analysis: RR 1 (0.69 to 1.45)	0 fewer per 1000 (from 266 fewer to 386 more)	⊕OOO VERY LOW	CRITICAL
Clinical cure in people with Streptococcus pneumoniae												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	no serious imprecision	none	26/28 (92.9%)	32/36 (88.9%)	NICE analysis: RR 1.04 (0.9 to 1.22)	36 more per 1000 (from 89 fewer to 196 more)	⊕⊕⊕O MODERATE	CRITICAL
Clinical cure in people with Klebsiella pneumoniae												
1	randomised trials	serious[4]	NA	no serious indirectness	very serious[5]	none	4/5 (80%)	7/7 (100%)	NICE analysis: RR 0.80 (0.49 to 1.31)	200 fewer per 1000 (from 510 fewer to 310 more)	⊕OOO VERY LOW	CRITICAL
Microbiological eradication (ITT)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftobiprole[1]	Ceftriaxone +/- linezolid[2]	Relative (95% CI)	Absolute		
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	70/87 (80.5%)	79/97 (81.4%)	NICE analysis: RR 0.99 (0.86 to 1.14)	8 fewer per 1000 (from 114 fewer to 114 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Microbiological eradication (microbiologically evaluable)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[6]	none	60/68 (88.2%)	70/87 (80.5%)	NICE analysis: RR 1.10 (0.96 to 1.26)	80 more per 1000 (from 32 fewer to 209 more)	⊕⊕⊕O MODERATE	IMPORTANT
Discontinuation due to adverse event												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[7]	none	18/310 (5.8%)	12/322 (3.7%)	NICE analysis: RR 1.56 (0.76 to 3.18)	21 more per 1000 (from 9 fewer to 81 more)	⊕⊕⊕O MODERATE	CRITICAL
Mortality (at 30 days)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[8]	none	1/314 (0.32%)	3/324 (0.93%)	NICE analysis: RR 0.34 (0.04 to 3.29)	6 fewer per 1000 (from 9 fewer to 21 more)	⊕⊕⊕O MODERATE	CRITICAL
Incidence of treatment related adverse events												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[9]	none	n unknown (36%)	n unknown (26%)	-	10% lower (2.9% to 17.2%)	⊕⊕⊕O MODERATE	CRITICAL
Incidence of treatment related nausea												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[9]	none	n unknown (7%)	n unknown (2%)	-	5% lower (1.7% to 8.2%)	⊕⊕⊕O MODERATE	CRITICAL
Incidence of treatment related vomiting												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[9]	none	n unknown (5%)	n unknown (2%)	-	3% lower (1.1% to 6.8%)	⊕⊕⊕O MODERATE	CRITICAL
Incidence of injection site adverse event												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[9]	none	n unknown (7%)	n unknown (5%)	-	2% higher (-1.6% to 5.8%)	⊕⊕⊕O MODERATE	CRITICAL
Incidence of hyponatraemia												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[9]	none	n unknown (1%)	n unknown (3%)	-	2% lower (-3.7% to 0.7%)	⊕⊕⊕O MODERATE	CRITICAL
Incidence of hepatic adverse events												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[9]	none	n unknown (7%)	n unknown (7%)	-	-	⊕⊕⊕O MODERATE	CRITICAL

Abbreviations: CI – confidence interval; ITT – intention to treat; NA – not applicable; RR – relative risk; IV – intravenous; PSI – pneumonia severity score

[1] 500mg by infusion over 120 mins every 8 hours; if investigator suspected methicillin-resistant Staphylococcus aureus, placebo was added to treatment; target duration was 7 days, with minimum 3 days intravenous study drug which could be extended to 14 days

[2] 2g infused over 30 mins once per day; if investigator suspected methicillin-resistant Staphylococcus aureus, linezolid 600mg every 12 hours was added to treatment; target duration was 7 days, with minimum 3 days intravenous study drug which could be extended to 14 days

[3] Nicholson et al. 2011
[4] Downgraded 1 level - only clinically evaluable analysis reported, as a non-inferiority trial, intention to treat analysis would also be expected
[5] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm
[6] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with ceftobiprole
[7] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with ceftobiprole
[8] Downgraded 1 level - at a minimal important difference of 0% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with appreciable benefit or appreciable harm
[9] Downgraded 1 level - not assessable

H.4.3 Dual antibiotics compared with other dual antibiotics

Table 56: GRADE profile – ceftriaxone plus azithromycin versus ceftriaxone plus macrolides

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftriaxone plus azithromycin[1]	Ceftriaxone plus macrolide[2]	Relative (95% CI)	Absolute		
Bacteriological eradication EOT (day 12-16)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[4]	none	30/41 (73.2%)	31/46 (67.4%)	NICE analysis: RR 1.09 (0.83 to 1.43)	61 more per 1000 (from 115 fewer to 290 more)	⊕⊕⊕O MODERATE	IMPORTANT
Bacteriological eradication EOS (day 28-35)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[4]	none	28/41 (68.3%)	28/46 (60.9%)	NICE analysis: RR 1.12 (0.82 to 1.53)	73 more per 1000 (from 110 fewer to 323 more)	⊕⊕⊕O MODERATE	IMPORTANT
Bacteriological eradication EOT, evaluable participants (day 12-16)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[5]	none	24/31 (77.4%)	25/31 (80.6%)	NICE analysis: RR 0.96 (0.74 to 1.24)	32 fewer per 1000 (from 210 fewer to 194 more)	⊕⊕⊕O MODERATE	IMPORTANT
Bacteriological eradication EOS, evaluable participants (day 28-35)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[6]	none	16/22 (72.7%)	23/31 (74.2%)	NICE analysis: RR 0.98 (0.71 to 1.36)	15 fewer per 1000 (from 215 fewer to 267 more)	⊕⊕OO LOW	IMPORTANT
Clinical success in Streptococcus pneumoniae EOT (day 12-16)												
1[3]	randomised trials	serious[7]	NA	no serious indirectness	serious[4]	none	17/21 (81%)	21/30 (70%)	NICE analysis: RR 1.16 (0.85 to 1.58)	112 more per 1000 (from 105 fewer to 406 more)	⊕⊕OO LOW	CRITICAL
Clinical success in Streptococcus pneumoniae EOS (day 28-35)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftriaxone plus azithromycin[1]	Ceftriaxone plus macrolide[2]	Relative (95% CI)	Absolute		
1[3]	randomised trials	serious[7]	NA	no serious indirectness	serious[4]	none	15/20 (75.0%)	20/30 (66.7%)	NICE analysis: RR 1.12 (0.79 to 1.61)	80 more per 1000 (from 140 fewer to 407 more)	⊕⊕OO LOW	IMPORTANT
Clinical success in Haemophilus influenzae EOT (day 12-16)												
1[3]	randomised trials	serious[7]	NA	no serious indirectness	serious[4]	none	12/13 (92.3%)	4/8 (50%)	NICE analysis: RR 1.85 (0.91 to 3.76)	425 more per 1000 (from 45 fewer to 1000 more)	⊕⊕OO LOW	CRITICAL
Clinical success in Haemophilus influenzae EOS (day 28-35)												
1[3]	randomised trials	serious[7]	NA	no serious indirectness	very serious[8]	none	12/13 (92.3%)	3/8 (37.5%)	NICE analysis: RR 2.46 (0.99 to 6.10)	548 more per 1000 (from 4 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Clinical success in Staphylococcus aureus EOT (day 12-16)												
1[3]	randomised trials	serious[7]	NA	no serious indirectness	very serious[6]	none	5/6 (83.3%)	1/1 (100%)	NICE analysis: RR 1.05 (0.43 to 2.55)	50 more per 1000 (from 570 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Clinical success in Staphylococcus aureus EOS (day 28-35)												
1[3]	randomised trials	serious[7]	NA	no serious indirectness	very serious[6]	none	5/6 (83.3%)	1/1 (100%)	NICE analysis: RR 1.05 (0.43 to 2.55)	50 more per 1000 (from 570 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Clinical success in Mycoplasma pneumoniae EOT (day 12-16)												
1[3]	randomised trials	serious[7]	NA	no serious indirectness	serious[4]	none	8/9 (88.9%)	7/9 (77.8%)	NICE analysis: RR 1.14 (0.75 to 1.74)	109 more per 1000 (from 194 fewer to 576 more)	⊕⊕OO LOW	CRITICAL
Clinical success in Mycoplasma pneumoniae EOS (day 28-35)												
1[3]	randomised trials	serious[7]	NA	no serious indirectness	serious[4]	none	8/9 (88.9%)	7/9 (77.8%)	NICE analysis: RR 1.14 (0.75 to 1.74)	109 more per 1000 (from 194 fewer to 576 more)	⊕⊕OO LOW	CRITICAL
Clinical success in Chlamydia pneumoniae EOT (day 12-16)												
1[3]	randomised trials	serious[7]	NA	no serious indirectness	serious[4]	none	6/6 (100%)	7/9 (77.8%)	NICE analysis: RR 1.24 (0.82 to 1.87)	187 more per 1000 (from 140 fewer to 677 more)	⊕⊕OO LOW	CRITICAL
Clinical success in Chlamydia pneumoniae EOS (day 28-35)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftriaxone plus azithromycin[1]	Ceftriaxone plus macrolide[2]	Relative (95% CI)	Absolute		
1[3]	randomised trials	serious[7]	NA	no serious indirectness	serious[4]	none	8/8 (100%)	6/9 (66.7%)	NICE analysis: RR 1.45 (0.9 to 2.35)	300 more per 1000 (from 67 fewer to 900 more)	⊕⊕OO LOW	CRITICAL
Clinical success in Legionella spp. EOT (day 12-16)												
1[3]	randomised trials	serious[7]	NA	no serious indirectness	very serious[6]	none	1/2 (50%)	5/7 (71.4%)	NICE analysis: RR 0.7 (0.16 to 3.02)	214 fewer per 1000 (from 600 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Clinical success in Legionella spp. EOS (day 28-35)												
1[3]	randomised trials	serious[7]	NA	no serious indirectness	very serious[6]	none	0/1 (0%)	6/8 (75%)	NICE analysis: RR 0.35 (0.03 to 3.95)	488 fewer per 1000 (from 728 fewer to 1000 more)	⊕OOO VERY LOW	CRITICAL
Clinical success in people with positive blood cultures EOT (day 12-16)												
1[3]	randomised trials	serious[7]	NA	no serious indirectness	very serious[6]	none	8/12 (66.7%)	10/17 (58.8%)	NICE analysis: RR 1.13 (0.64 to 1.99)	76 more per 1000 (from 212 fewer to 582 more)	⊕OOO VERY LOW	CRITICAL
Clinical success in people with positive blood cultures EOS (day 28-35)												
1[3]	randomised trials	serious[7]	NA	no serious indirectness	very serious[6]	none	8/12 (66.7%)	9/17 (52.9%)	NICE analysis: RR 1.26 (0.69 to 2.3)	138 more per 1000 (from 164 fewer to 688 more)	⊕OOO VERY LOW	CRITICAL
Adverse events												
1[3]	randomised trials	serious[7]	NA	no serious indirectness	serious[9]	none	44/135 (32.6%)[10]	58/143 (40.6%)[11]	NICE analysis: RR 0.80 (0.59 to 1.10)	81 fewer per 1000 (from 166 fewer to 41 more)	⊕⊕OO LOW	CRITICAL
Gastrointestinal adverse events												
1[3]	randomised trials	serious[7]	NA	no serious indirectness	serious[9]	none	17/135 (12.6%)	26/143 (18.2%)	NICE analysis: RR 0.69 (0.39 to 1.22)	56 fewer per 1000 (from 111 fewer to 40 more)	⊕⊕OO LOW	CRITICAL
Incidence of diarrhoea												
1[3]	randomised trials	serious[7]	NA	no serious indirectness	very serious[6]	none	10/135 (7.4%)	12/143 (8.4%)	NICE analysis: RR 0.88 (0.39 to 1.98)	10 fewer per 1000 (from 51 fewer to 82 more)	⊕OOO VERY LOW	CRITICAL
Incidence of nausea												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftriaxone plus azithromycin[1]	Ceftriaxone plus macrolide[2]	Relative (95% CI)	Absolute		
1[3]	randomised trials	serious[7]	NA	no serious indirectness	very serious[6]	none	2/135 (1.5%)	7/143 (4.9%)	NICE analysis: RR 0.30 (0.06 to 1.43)	34 fewer per 1000 (from 46 fewer to 21 more)	⊕OOO VERY LOW	IMPORTANT
Abbreviations: CI – confidence interval; EOT – end of treatment; NA – not applicable; RR – relative risk; EOS – end of study												

[1] Intravenous ceftriaxone 1-2g once-daily plus intravenous azithromycin 500mg once-daily for 2-5 days, followed by step down to oral azithromycin 500mg once-daily for a total therapy duration of 7-10 days
[2] Intravenous ceftriaxone 1-2g once-daily plus either intravenous clarithromycin 500mg twice-daily or erythromycin 1g three times for 2-5 days, followed by step down to either oral clarithromycin 500mg twice-daily or erythromycin 1g three times a day for a total of 7-14 days.
[3] Tamm et al. 2007
[4] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with ceftriaxone plus azithromycin
[5] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with ceftriaxone plus erythromycin macrolide
[6] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm
[7] Downgraded 1 level - only modified intention to treat analysis reported, as a non-inferiority study per protocol analysis would also be expected
[8] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with ceftriaxone with azithromycin; very wide confidence intervals
[9] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with ceftriaxone plus clarithromycin or erythromycin
[10] All adverse events classified as mild or moderate-severity
[11] Three adverse events classified as severe, comprising injection site inflammation (leading to discontinuation), injection site pain (antibiotics switched) and hepatic enzyme increase

H.5 Antibiotic dose in adults with low-severity community-acquired pneumonia

Table 57: GRADE profile – high-dose versus low-dose levofloxacin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV 750mg levofloxacin[1]	IV/oral 500mg levofloxacin[2]	Relative (95% CI)	Absolute		
Number of people with clinical improvement or cure (intention to treat analysis)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	202/221 (91.4%)	214/227 (94.3%)	OR 0.65 (0.31 to 1.34)		⊕⊕⊕⊕	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV 750mg levofloxacin[1]	IV/oral 500mg levofloxacin[2]	Relative (95% CI)	Absolute		
									NICE analysis: RR 0.97 (0.92 to 1.02)	28 fewer per 1000 (from 75 fewer to 19 more)	HIGH	
Number of people with clinical improvement or cure (per protocol analysis)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	195/208 (93.8%)	210/219 (95.9%)	OR 0.64 (0.27 to 1.54) NICE analysis: RR 0.98 (0.94 to 1.02)	19 fewer per 1000 (from 58 fewer to 19 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Fever resolution after 3 days												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	124/164 (75.6%)	124/162 (76.5%)	NICE analysis: RR 0.99 (0.87 to 1.12)	8 fewer per 1000 (from 100 fewer to 92 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Clinical relapse												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[4]	none	1/205 (0.49%)	3/213 (1.4%)	NICE analysis: RR 0.35 (0.04 to 3.30)	9 fewer per 1000 (from 14 fewer to 32 more)	⊕⊕OO LOW	CRITICAL
Change in white blood cell count from baseline to the end of treatment												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	Mean -1.64, SD 2.85 N= 215	Mean -1.95, SD 3.73 N= 221	-	MD 0.31 higher (0.31 lower to 0.93 higher)	⊕⊕⊕⊕ HIGH	IMPORTANT
Number of people reporting adverse events												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[5]	none	35/228 (15.4%)	24/229 (10.5%)	NICE analysis: RR 1.46 (0.90 to 2.38)	48 more per 1000 (from 10 fewer to 145 more)	⊕⊕⊕O MODERATE	CRITICAL
Number of people reporting nausea and vomiting												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[4]	none	6/228 (2.6%)	1/229 (0.44%)	NICE analysis: RR 6.03 (0.73 to 49.66)	22 more per 1000 (from 1 fewer to 212 more)	⊕⊕OO LOW	CRITICAL
Number of people reporting abdominal pain												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[4]	none	2/228 (0.88%)	1/229 (0.44%)	NICE analysis: RR 2.01 (0.18 to 22.0)	4 more per 1000 (from 4 fewer to 92 more)	⊕⊕OO LOW	CRITICAL
Number of people reporting headaches or dizziness												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[4]	none	3/228 (1.3%)	2/229 (0.87%)	NICE analysis: RR 1.51 (0.25 to 8.93)	4 more per 1000 (from 7 fewer to 69 more)	⊕⊕OO LOW	CRITICAL
Number of people reporting insomnia												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IV 750mg levofloxacin[1]	IV/oral 500mg levofloxacin[2]	Relative (95% CI)	Absolute		
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[4]	none	4/228 (1.8%)	1/229 (0.44%)	NICE analysis: RR 4.02 (0.45 to 35.67)	13 more per 1000 (from 2 fewer to 151 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: IV – intravenous; CI – confidence interval; NA – not applicable; OR – odds ratio; RR – risk ratio; SD – standard deviation; MD – mean difference												

[1] Intravenous levofloxacin, 750mg/day for 5 days
[2] Intravenous levofloxacin, 500mg/day with switch to oral levofloxacin, 500mg/day when symptoms were significantly improved with decreased body temperature and white blood cell count and ability to take oral medication; total of 7 to 14 days treatment
[3] Zhao et al. 2016
[4] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm
[5] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with 750mg levofloxacin

Table 58: GRADE profile – higher-dose versus lower-dose co-amoxiclav

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	2000/125mg 2 times/day[1]	875/125mg 3 times/day[2]	Relative (95% CI)	Absolute		
Clinical response at test of cure (day 21-28 post therapy; per protocol analysis)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	266/288 (92.4%)	135/148 (91.2%)	NICE analysis: RR 1.01 (0.95 to 1.08)	9 more per 1000 (from 46 fewer to 73 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Clinical response at test of cure (day 21-28 post therapy; intention to treat analysis)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	313/374 (83.7%)	158/192 (82.3%)	NICE analysis: RR 1.02 (0.94 to 1.10)	16 more per 1000 (from 49 fewer to 82 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Clinical response at end of treatment (day 2-4 post therapy; per protocol analysis)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	302/317 (95.3%)	153/160 (95.6%)	NICE analysis: RR 1 (0.96 to 1.04)	0 fewer per 1000 (from 38 fewer to 38 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Clinical response at end of treatment (day 2-4 post therapy; intention to treat analysis)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	331/374 (88.5%)	168/192 (87.5%)	NICE analysis: RR 1.01 (0.95 to 1.08)	9 more per 1000 (from 44 fewer to 70 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Bacteriological response at test of cure (21-28 days post therapy; per protocol analysis)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	2000/125mg 2 times/day[1]	875/125mg 3 times/day[2]	Relative (95% CI)	Absolute		
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	79/87 (90.8%)	43/50 (86.0%)	NICE analysis: RR 1.06 (0.93 to 1.2)	52 more per 1000 (from 60 fewer to 172 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Bacteriological response at test of cure (day 21-28 post therapy; intention to treat analysis)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	87/102 (85.3%)	46/56 (82.1%)	NICE analysis: RR 1.04 (0.90 to 1.20)	33 more per 1000 (from 82 fewer to 164 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Bacteriological response at end of treatment (day 2-4 post therapy; per protocol analysis)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	89/94 (94.7%)	47/52 (90.4%)	NICE analysis: RR 1.05 (0.95 to 1.16)	45 more per 1000 (from 45 fewer to 145 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Bacteriological response at end of treatment (day 2-4 post therapy; intention to treat analysis)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	93/102 (91.2%)	48/56 (85.7%)	NICE analysis: RR 1.06 (0.94 to 1.2)	51 more per 1000 (from 51 fewer to 171 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Radiological response at test of cure (day 21-28 post therapy; per protocol analysis)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	271/288 (94.1%)	141/148 (95.3%)	NICE analysis: RR 0.99 (0.94 to 1.03)	10 fewer per 1000 (from 57 fewer to 29 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Radiological response at test of cure (day 21-28 post therapy; intention to treat analysis)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	322/374 (86.1%)	167/192 (87%)	NICE analysis: RR 0.99 (0.92 to 1.06)	9 fewer per 1000 (from 70 fewer to 52 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Clinical response at test of cure in people with atypical pathogen infection only (21-28 days post therapy; per protocol analysis)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	70/77 (90.9%)	32/36 (88.9%)	NICE analysis: RR 1.02 (0.89 to 1.17)	18 more per 1000 (from 98 fewer to 151 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Clinical response at test of cure in people with atypical pathogen infection only (21-28 days post therapy; intention to treat analysis)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	80/100 (80%)	40/48 (83.3%)	NICE analysis: RR 0.96 (0.82 to 1.13)	33 fewer per 1000 (from 150 fewer to 108 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Clinical response at test of cure in people with atypical or typical pathogen infection (21-28 days post therapy; per protocol analysis)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	18/20 (90%)	16/17 (94.1%)	NICE analysis: RR 0.96 (0.79 to 1.15)	38 fewer per 1000 (from 198 fewer to 141 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Clinical response at test of cure in people with atypical or typical pathogen infection (21-28 days post therapy; intention to treat analysis)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	20/22 (90.9%)	17/18 (94.4%)	NICE analysis: RR 0.96 (0.81 to 1.14)	38 fewer per 1000 (from 179 fewer to 132 more)	⊕⊕⊕⊕ HIGH	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	2000/125mg 2 times/day[1]	875/125mg 3 times/day[2]	Relative (95% CI)	Absolute		
Clinical response at end of treatment in people with S. pneumoniae infection (2-4 days post therapy; per protocol analysis)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	66/68 (97.1%)	28/30 (93.3%)	NICE analysis: RR 1.04 (0.94 to 1.15)	37 more per 1000 (from 56 fewer to 140 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Clinical response at test of cure in people with S. pneumoniae infection (21-28 days post therapy; per protocol analysis)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	62/64 (96.9%)	27/30 (90%)	NICE analysis: RR 1.08 (0.95 to 1.22)	72 more per 1000 (from 45 fewer to 198 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Clinical response at end of treatment in people with H. influenzae infection (2-4 days post therapy; per protocol analysis)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	21/22 (95.5%)	19/21 (90.5%)	NICE analysis: RR 1.06 (0.89 to 1.25)	54 more per 1000 (from 100 fewer to 226 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Clinical response at test of cure in people with H. influenzae infection (21-28 days post therapy; per protocol analysis)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[4]	none	17/19 (89.5%)	15/19 (78.9%)	NICE analysis: RR 1.13 (0.86 to 1.50)	103 more per 1000 (from 111 fewer to 395 more)	⊕⊕⊕O MODERATE	CRITICAL
Number of withdrawals due to adverse events												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[5]	none	12/374 (3.2%)	10/192 (5.2%)	NICE analysis: RR 0.62 (0.27 to 1.40)	20 fewer per 1000 (from 38 fewer to 21 more)	⊕⊕OO LOW	CRITICAL
Number of people reporting diarrhoea leading to withdrawal												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[5]	none	4/374 (1.1%)	5/192 (2.6%)	NICE analysis: RR 0.41 (0.11 to 1.51)	15 fewer per 1000 (from 23 fewer to 13 more)	⊕⊕OO LOW	CRITICAL
Number of people reporting vomiting leading to withdrawal												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[5]	none	3/374 (0.8%)	0/192 (0%)	NICE analysis: RR 3.6 (0.19 to 69.39)	-	⊕⊕OO LOW	CRITICAL
Number of people reporting abdominal pain/discomfort leading to withdrawal												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[5]	none	2/374 (0.53%)	2/192 (1%)	NICE analysis: RR 0.51 (0.07 to 3.62)	5 fewer per 1000 (from 10 fewer to 27 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI – confidence interval; NA – not applicable; RR – risk ratio												

[1] Oral co-amoxiclav 1000/62.5mg (2 tablets, twice daily) plus matching co-amoxiclav 875/125mg placebo (one tablet three times a day); tablets taken before meals for either 7 or 10 days depending on severity and co-morbid factors

[2] Co-amoxiclav 875/125mg (one tablet three times daily) plus matching co-amoxiclav 1000/62.5mg placebo (2 tablets twice daily); tablets taken before meals for either 7 or 10 days depending on severity and co-morbid factors

[3] Siquier et al. 2006

[4] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable

benefit with 2000/125mg co-amoxiclav
[5] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm

H.6 Antibiotic dose in adults with moderate- to high-severity community-acquired pneumonia

No systematic reviews or randomised controlled trials met the inclusion criteria.

H.7 Antibiotic dose frequency

No systematic reviews or randomised controlled trials met the inclusion criteria.

H.8 Antibiotic course length

Table 59: GRADE profile – short- versus long-course antibiotics

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short course[1]	Long course[2]	Relative (95% CI)	Absolute		
Clinical failure (all antibiotic comparisons)												
15[3]	randomised trials	serious[4]	no serious inconsistency	serious[5]	no serious imprecision	none	326/1521 (21.4%)	326/1275 (25.6%)	RR 0.89 (0.78 to 1.02)	28 fewer per 1000 (from 56 fewer to 5 more)	⊕⊕OO LOW	CRITICAL
Clinical failure (excluding antibiotics not available in UK)												
11[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	206/836 (24.6%)	241/834 (28.9%)	NICE analysis: RR 0.87 (0.75 to 1.02)	38 fewer per 1000 (from 72 fewer to 6 more)	⊕⊕⊕O MODERATE	CRITICAL
Mortality (all antibiotic comparisons)												
8[3]	randomised trials	serious[4]	no serious inconsistency	serious[5]	serious[6]	none	-	-	RR 0.81 (0.46 to 1.43)	-	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI – confidence interval; RR – risk ratio												

[1] Included: azithromycin, levofloxacin, gemifloxacin, ceftriaxone, cefuroxime or telithromycin, for 3 to 7 days
[2] Included: erythromycin, josamycin, levofloxacin, cefaclor, clarithromycin, co-amoxiclav, ceftriaxone, roxithromycin or cefuroxime (in 1 study unnamed 'multiple antibiotics' given) for 10 to 14 days (majority of studies 10 days, 1 study 14 days)
[3] Li et al. 2007
[4] Downgraded 1 level - systematic review authors report that 7 of 15 studies have a Jadad score of 1 or 2
[5] Downgraded 1 level - includes antibiotics not licenced in the UK
[6] Downgraded 1 level - at a minimal important difference of 0% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with appreciable benefit or appreciable harm

Table 60: GRADE profile – short- versus long-course macrolide

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short course[1]	Long course macrolide[2]	Relative (95% CI)	Absolute		
Clinical failure (all antibiotic comparisons)												
10[3]	randomised trials	serious[4]	no serious inconsistency	serious[5]	no serious imprecision	none	154/893 (17.2%)	131/640 (20.5%)	RR 0.88 (0.71 to 1.09)	27 fewer per 1000 (from 59 fewer to 14 more)	⊕OOO VERY LOW	CRITICAL
Clinical failure (excluding antibiotics not available in UK)												
7[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[6]	none	72/375 (19.2%)	78/352 (22.2%)	NICE analysis: RR 0.88 (0.67 to 1.17)	27 fewer per 1000 (from 73 fewer to 38 more)	⊕⊕OO LOW	CRITICAL

Abbreviations: CI – confidence interval; RR – risk ratio

[1] Includes: azithromycin and telithromycin (telithromycin used in 1 study) for 3 to 5 days
[2] Includes: erythromycin, josamycin, clarithromycin and roxithromycin (1 study unreported 'multiple antibiotics' given), for 10 to 14 days
[3] Li et al. 2007
[4] Downgraded 1 level - systematic review authors report that 7 of 15 studies have a Jadad score of 1 or 2
[5] Downgraded 1 level - includes antibiotics not licenced in the UK
[6] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with long courses

Table 61: GRADE profile – short versus long course beta-lactam

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short course[1]	Long course[2]	Relative (95% CI)	Absolute		
Clinical failure												
2[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[5]	none	38/152 (25%)	39/144 (27.1%)	RR 0.92 (0.63 to 1.36)	22 fewer per 1000 (from 100 fewer to 97 more)	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI – confidence interval; RR – risk ratio

[1] Includes: ceftriaxone (5 days) and cefuroxime (7 days)
[2] Includes: ceftriaxone (10 days) and cefuroxime (10 days)
[3] Li et al. 2007
[4] Downgraded 1 level - systematic review authors report that 7 of 15 studies have a Jadad score of 1 or 2; unclear which studies are high risk of bias
[5] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 62: GRADE profile – short-course azithromycin versus long-course antibiotics

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 day course azithromycin	10 to 14 day antibiotic course[1]	Relative (95% CI)	Absolute		
Clinical failure (fixed effect; excluding antibiotics not available in UK)												
5[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[6]	none	49/298 (16.4%)	60/286 (21%)	NICE analysis: RR 0.82 (0.59 to 1.14)	38 fewer per 1000 (from 86 fewer to 29 more)	⊕⊕OO LOW	CRITICAL
Clinical failure (random effect; all antibiotic comparisons)												
6[2]	randomised trials	serious[3]	serious[4]	serious[5]	serious[6]	none	51/388 (13.1%)	70/346 (20.2%)	RR 0.61 (0.34 to 1.10)	79 fewer per 1000 (from 134 fewer to 20 more)	⊕OOO VERY LOW	CRITICAL
Clinical failure (random effect; excluding antibiotics not available in UK)												
5[2]	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[6]	none	49/298 (16.4%)	60/286 (21%)	NICE analysis: RR 0.84 (0.57 to 1.25)	34 fewer per 1000 (from 90 fewer to 52 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI – confidence interval; RR – risk ratio												

[1] Includes: clarithromycin and roxithromycin (1 study unspecified 'multiple antibiotics' given), for 10 to 14 days
[2] Li et al. 2007
[3] Downgraded 1 level - systematic review authors report that 7 of 15 studies have a Jadad score of 1 or 2; unclear which studies are high risk of bias
[4] Downgraded 1 level - heterogeneity >50%
[5] Downgraded 1 level - includes antibiotics not licenced in the UK
[6] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with long courses

Table 63: GRADE profile – short- versus long-course levofloxacin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short course[1]	Long course[2]	Relative (95% CI)	Absolute		
Clinical failure												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	serious[5]	none	73/256 (28.5%)	97/272 (35.7%)	NICE analysis: RR 0.80 (0.62 to 1.03)	71 fewer per 1000 (from 136 fewer to 11 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI – confidence interval; RR – risk ratio												

[1] Levofloxacin for 5 days
[2] Levofloxacin for 10 days
[3] Li et al. 2007
[4] Downgraded 1 level - systematic review authors report that 7 of 15 studies have a Jadad score of 1 or 2; unclear which studies are high risk of bias
[5] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with long courses

Table 64: GRADE profile – short versus long course amoxicillin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 day[1]	8 day amoxicillin[2]	Relative (95% CI)	Absolute		
Clinical cure (day 10; per protocol analysis)												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	no serious imprecision	none	50/54 (92.6%)	56/60 (93.3%)	NICE analysis: RR 0.99 (0.9 to 1.1)	1 fewer per 100 (from 9 fewer to 9 more)	⊕⊕⊕O MODERATE	CRITICAL
Clinical cure (day 10; intention to treat analysis)												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	no serious imprecision	none	50/56 (89.3%)	56/63 (88.9%)	NICE analysis: RR 1 (0.89 to 1.14)	0 fewer per 1000 (from 98 fewer to 124 more)	⊕⊕⊕O MODERATE	CRITICAL
Bacteriological success (day 10)												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	no serious imprecision	none	22/25 (88%)	19/20 (95%)	NICE analysis: RR 0.93 (0.78 to 1.10)	66 fewer per 1000 (from 209 fewer to 95 more)	⊕⊕⊕O MODERATE	IMPORTANT
Radiological success (day 10)												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	no serious imprecision	none	48/56 (85.7%)	52/63 (82.5%)	NICE analysis: RR 1.04 (0.89 to 1.21)	33 more per 1000 (from 91 fewer to 173 more)	⊕⊕⊕O MODERATE	IMPORTANT
Clinical cure (day 28; per protocol analysis)												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	no serious imprecision	none	47/52 (90.4%)	49/56 (87.5%)	NICE analysis: RR 1.03 (0.9 to 1.18)	26 more per 1000 (from 88 fewer to 157 more)	⊕⊕⊕O MODERATE	CRITICAL
Clinical cure (day 28; intention to treat analysis)												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	serious[5]	none	47/56 (83.9%)	49/63 (77.8%)	NICE analysis: RR 1.08 (0.91 to 1.29)	62 more per 1000 (from 70 fewer to 226 more)	⊕⊕OO LOW	CRITICAL
Bacteriological success (day 28)												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	serious[5]	none	20/25 (80%)	15/20 (75%)	NICE analysis: RR 1.07 (0.77 to 1.47)	53 more per 1000 (from 173 fewer to 353 more)	⊕⊕OO LOW	IMPORTANT
Radiological success (day 28)												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	serious[5]	none	48/56 (85.7%)	50/63 (79.4%)	NICE analysis: RR 1.08 (0.92 to 1.27)	63 more per 1000 (from 63 fewer to 214 more)	⊕⊕OO LOW	IMPORTANT
Length of hospital stay												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	serious[6]	none	Mean 7.9 days (6.5 to 9.3)	Mean 8.9 days (6.8 to 11)	-	MD 1.00 days (-1.3 to 3.2)	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 day[1]	8 day amoxicillin[2]	Relative (95% CI)	Absolute		
							N= 56	N= 63				
Number of people reporting adverse events												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	very serious[7]	none	6/56 (10.7%)	13/63 (20.6%)	RR 0.52 (0.21 to 1.27)	99 fewer per 1000 (from 163 fewer to 56 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI – confidence interval; NA – not applicable; RR – risk ratio; MD – mean difference												

[1] 3 days of intravenous amoxicillin given, after which placebo oral tablets given three times daily for 5 days
[2] 3 days intravenous amoxicillin given, after which oral 750mg amoxicillin given three times daily for 5 days
[3] El Moussaoui et al. 2006
[4] Downgraded 1 level - differences between the treatment arms present at baseline, including a larger number of smokers and more severe symptoms present in people randomised to 3 day treatment
[5] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with 3 day treatment
[6] Downgraded 1 level - not assessable
[7] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm

H.9 Antibiotic route of administration in adults with low-severity community-acquired pneumonia

No systematic reviews or randomised controlled trials met the inclusion criteria.

H.10 Antibiotic route of administration in adults with moderate- to high-severity community-acquired pneumonia

Table 65: GRADE profile – intravenous antibiotics with switch to oral antibiotics versus continuous intravenous antibiotics

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to oral treatment[1]	Continuous intravenous treatment[2]	Relative (95% CI)	Absolute		
Duration of hospitalisation (days)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to oral treatment[1]	Continuous intravenous treatment[2]	Relative (95% CI)	Absolute		
5[3]	randomised trials	serious[4]	serious[5]	serious[6]	serious[7]	none	N= 259	N= 267	-	MD 3.34 lower (4.42 to 2.25 lower)	⊕OOO VERY LOW	CRITICAL
Mortality												
5[3]	randomised trials	serious[4]	no serious inconsistency	serious[6]	serious[8]	none	29/577 (5%)	34/555 (6.1%)	OR 0.81 (0.49 to 1.33) NICE analysis: RR 0.82 (0.51 to 1.31)	11 fewer per 1000 (from 30 fewer to 19 more)	⊕OOO VERY LOW	CRITICAL
Treatment success (intention to treat)												
3[3]	randomised trials	serious[4]	serious[5]	no serious indirectness	no serious imprecision	none	378/494 (76.5%)	386/493 (78.3%)	OR 0.76 (0.36 to 1.59) NICE analysis: RR 0.95 (0.84 to 1.06)	16 fewer per 1000 (from 63 fewer to 39 more)	⊕⊕OO LOW	CRITICAL
Treatment success (clinically evaluable)												
6[3]	randomised trials	serious[4]	no serious inconsistency	serious[6]	no serious imprecision	none	333/386 (86.3%)	341/394 (86.5%)	OR 0.92 (0.61 to 1.39) NICE analysis: RR 0.99 (0.94 to 1.05)	9 fewer per 1000 (from 52 fewer to 43 more)	⊕⊕OO LOW	CRITICAL
Number of people with recurrent infection												
5[3]	randomised trials	serious[4]	no serious inconsistency	serious[6]	very serious[9]	none	10/189 (5.3%)	5/196 (2.6%)	OR 1.81 (0.70 to 4.72) NICE analysis: RR 1.77 (0.71 to 4.45)	20 more per 1000 (from 7 fewer to 88 more)	⊕OOO VERY LOW	IMPORTANT
Number of people reporting adverse events												
4[3]	randomised trials	serious[4]	no serious inconsistency	serious[6]	serious[10]	none	96/445 (21.6%)	127/422 (30.1%)	OR 0.65 (0.48 to 0.89) NICE analysis: RR 0.73 (0.59 to 0.92)	81 fewer per 1000 (from 24 fewer to 123 fewer)	⊕OOO VERY LOW	CRITICAL
Number of withdrawals as a result of adverse events												
4[3]	randomised trials	serious[4]	no serious inconsistency	serious[6]	serious[10]	none	17/445 (3.8%)	33/422 (7.8%)	OR 0.49 (0.27 to 0.89)			CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to oral treatment[1]	Continuous intravenous treatment[2]	Relative (95% CI)	Absolute		
									NICE analysis: RR 0.51 (0.29 to 0.91)	38 fewer per 1000 (from 7 fewer to 56 fewer)	⊕OOO VERY LOW	
Number of people reporting phlebitis												
3[3]	randomised trials	serious[4]	serious[5]	no serious indirectness	no serious imprecision	none	14/494 (2.8%)	43/493 (8.7%)	RR 0.35 (0.2 to 0.62)	57 fewer per 1000 (from 33 fewer to 70 fewer)	⊕⊕OO LOW	CRITICAL
Number of people reporting gastrointestinal adverse events												
4[3]	randomised trials	serious[4]	no serious inconsistency	serious[6]	very serious[9]	none	25/445 (5.6%)	30/422 (7.1%)	RR 0.81 (0.49 to 1.33)	14 fewer per 1000 (from 36 fewer to 23 more)	⊕OOO VERY LOW	CRITICAL
Duration of hospitalisation (days; excluding antibiotics not available in UK)												
4[3]	randomised trials	serious[4]	serious[5]	no serious indirectness	serious[7]	none	N= 201	N= 230	-	NICE analysis: MD 3.66 lower (4.77 to 2.56 lower)	⊕OOO VERY LOW	CRITICAL
Mortality (excluding antibiotics not available in UK)												
5[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[8]	none	29/577 (5%)	34/555 (6.1%)	NICE analysis: RR 0.82 (0.51 to 1.31)	11 fewer per 1000 (from 30 fewer to 19 more)	⊕⊕OO LOW	CRITICAL
Treatment success (excluding antibiotics not available in UK; clinically evaluable)												
5[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	278/328 (84.8%)	305/357 (85.4%)	NICE analysis: RR 0.99 (0.93 to 1.06)	9 fewer per 1000 (from 60 fewer to 51 more)	⊕⊕⊕O MODERATE	CRITICAL
Number of people with recurrent infection (excluding antibiotics not available in UK)												
4[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[9]	none	8/147 (5.4%)	5/165 (3%)	NICE analysis: RR 1.59 (0.6 to 4.21)	18 more per 1000 (from 12 fewer to 97 more)	⊕OOO VERY LOW	CRITICAL
Number of people reporting adverse events (excluding antibiotics not available in UK)												
4[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[10]	none	96/445 (21.6%)	127/422 (30.1%)	NICE analysis: RR 0.73 (0.59 to 0.92)	81 fewer per 1000 (from 24 fewer to 123 fewer)	⊕⊕OO LOW	CRITICAL
Number of withdrawals as a result of adverse events (excluding antibiotics not available in UK)												
3[3]	randomised trials	serious[4]	serious[5]	no serious indirectness	serious[10]	none	16/387 (4.1%)	32/385 (8.3%)	NICE analysis: RR 0.5 (0.28 to 0.91)	42 fewer per 1000 (from 7 fewer to 60 fewer)	⊕OOO VERY LOW	CRITICAL
Number of people reporting gastrointestinal adverse events (excluding antibiotics not available in UK)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to oral treatment[1]	Continuous intravenous treatment[2]	Relative (95% CI)	Absolute		
3[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[9]	none	23/387 (5.9%)	26/385 (6.8%)	NICE analysis: RR 0.9 (0.52 to 1.53)	7 fewer per 1000 (from 32 fewer to 36 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI – confidence interval; MD – mean difference; OR – odds ratio; RR – risk ratio												

[1] Transition from intravenous to oral antibiotics in clinically improving patients was performed after 2 to 4 days for a total of 7 to 12 days treatment; antibiotics included cefuroxime, cefaclor, cefamondole, cefpodoxime, co-amoxiclav and levofloxacin
[2] Intravenous antibiotic treatment for 5 to 10 days; antibiotics used include cefuroxime, ceftriaxone and co-amoxiclav
[3] Athanassa et al. 2008
[4] Downgraded 1 level - systematic review authors judged all studies to have a Jadad score ≤3
[5] Downgraded 1 level - heterogeneity >50%
[6] Downgraded 1 level - includes 1 study using an antibiotic not available in the UK
[7] Downgraded 1 level - not assessable
[8] Downgraded 1 level - at a minimal important difference of 0% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with appreciable benefit or appreciable harm
[9] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm
[10] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with continuous intravenous treatment

H.11 Antibiotic prescribing strategies in children with non-severe community acquired pneumonia

No systematic reviews or randomised controlled trials met the inclusion criteria.

H.12 Antibiotic prescribing strategies in children with severe community-acquired pneumonia

Table 66: GRADE profile – intravenous antibiotics with switch to oral antibiotics versus standard medical procedure

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to oral[1]	Standard medical procedure[2]	Relative (95% CI)	Absolute		
Length of hospital stay (days)												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Switch to oral[1]	Standard medical procedure[2]	Relative (95% CI)	Absolute		
1[3]	randomised trials	very serious[4]	NA	serious[5]	serious[6]	none	Mean, SD: 3.81 ± 1.6 n=26	Mean, SD: 4.77 ± 1.5 n=31	-	MD 0.96 lower (1.77 lower to 0.15 lower); p=0.019	⊕OOO VERY LOW	IMPORTANT
Readmission within 30 days discharge												
1[3]	randomised trials	very serious[4]	NA	serious[5]	very serious[7]	none	1/26 (3.8%)[8]	2/31 (6.5%)[9]	RR 0.6 (0.06 to 6.21)	26 fewer per 1000 (from 61 fewer to 336 more)	⊕OOO VERY LOW	IMPORTANT
Abbreviations: CI – confidence interval; NA – not applicable; SD – standard deviation; MD – mean difference												

[1] Switched to oral treatment from intravenous when core body temperature dropped below 37.8°C for at least 8 hours and clinical signs stable; majority started on intravenous 3rd generation cephalosporin and switched to oral co-amoxiclav or oral 3rd generation cephalosporin
[2] Standard medical procedures for pneumonia, including switching from intravenous to oral administration of antibiotics at least 48 hours after fever has dissipated; majority started on intravenous 3rd generation cephalosporin and switched to oral co-amoxiclav or oral 3rd generation cephalosporin
[3] In-Iw et al. 2015
[4] Downgraded 2 levels - physicians treated children in both treatment arms; the control group consisted of physician-guided switching, and physicians were shown to change their practice according to results in the intervention arm
[5] Downgraded 1 level - control arm treatment strategy was based on standard medical procedures - as the study was performed in Thailand, this may not be relevant to UK practice
[6] Downgraded 1 level - at a default minimal important difference of 25% of 0.5xSD of standard medical procedure arm, the effect estimate is consistent with no meaningful difference or appreciable harm with standard medical procedure
[7] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk, the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm
[8] Diagnosed with acute diarrhoea on readmission
[9] Diagnosed with pneumonia on readmission

H.13 Antibiotics in children with non-severe community-acquired pneumonia

H.13.1 Single antibiotic compared with another single antibiotic

Table 67: GRADE profile – azithromycin versus erythromycin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azithromycin[1]	Erythromycin[2]	Relative (95% CI)	Absolute		
Cure rate												
3[3]		serious[4]			serious[5]	none			OR 1.22 (0.50 to 2.94)			CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azithromycin[1]	Erythromycin[2]	Relative (95% CI)	Absolute		
	randomised trials		no serious inconsistency	no serious indirectness			179/230 (77.8%)	100/133 (75.2%)	NICE analysis: RR 1.04 (0.92 to 1.18)	53 more per 1000 (from 68 fewer to 195 more)	⊕⊕OO LOW	
Failure rate												
3[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	very serious[6]	none	6/236 (2.5%)	6/156 (3.8%)	OR 0.73 (0.18 to 2.89) NICE analysis: RR 0.69 (0.21 to 2.29)	10 fewer per 1000 (from 31 fewer to 68 more)	⊕OOO VERY LOW	CRITICAL
Side effects												
2[3]	randomised trials	serious[7]	serious[8]	no serious indirectness	very serious[6]	none	17/84 (20.2%)	14/69 (20.3%)	OR 0.92 (0.18 to 4.73) NICE analysis: RR 0.93 (0.25 to 3.46)	14 fewer per 1000 (from 152 fewer to 499 more)	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI – confidence interval; OR – odds ratio; RR – relative risk

[1] Azithromycin included: oral, 10 mg/kg on day 1 followed by 5 mg/kg/day for 4 days or oral, 10mg/kg/day for 3 days
[2] Erythromycin included: 40 mg/kg/day for 10 days and unreported details in 1 RCT (reporting cure and failure rates)
[3] Lodha et al. 2013
[4] Downgraded 1 level - 2 of 3 studies judged to be at high or unclear risk of bias by systematic review authors in several domains: lack of or unclear allocation concealment, unclear random sequence generation, open-label and unclear source of funding or pharmaceutical industry sponsored
[5] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with azithromycin
[6] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm
[7] Downgraded 1 level - 2 of 2 studies judged to be at high or unclear risk of bias by systematic review authors in several domains: high risk or unclear allocation concealment, unclear random sequence generation, open-label and unknown funding source/pharmaceutical industry sponsored
[8] Downgraded 1 level - heterogeneity >50%

Table 68: GRADE profile – clarithromycin versus erythromycin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clarithromycin[1]	Erythromycin[2]	Relative (95% CI)	Absolute		
Cure rates												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	104/124 (83.9%)	84/110 (76.4%)	OR 1.61 (0.84 to 3.08) NICE analysis: RR	76 more per 1000 (from 31 fewer to 191 more)	⊕⊕⊕⊕ HIGH	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Clarithromycin[1]	Erythromycin[2]	Relative (95% CI)	Absolute		
									1.1 (0.96 to 1.25)			
Clinical success rate												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	121/124 (97.6%)	105/110 (95.5%)	OR 1.92 (0.45 to 8.23) NICE analysis: RR 1.02 (0.97 to 1.07)	19 more per 1000 (from 29 fewer to 67 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Failure rate												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[4]	none	3/124 (2.4%)	5/110 (4.5%)	OR 0.52 (0.12 to 2.23) NICE analysis: RR 0.53 (0.13 to 2.18)	21 fewer per 1000 (from 40 fewer to 54 more)	⊕⊕OO LOW	CRITICAL
Adverse events												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[4]	none	32/133 (24.1%)	29/127 (22.8%)	OR 1.07 (0.60 to 1.90) NICE analysis: RR 1.05 (0.68 to 1.64)	11 more per 1000 (from 73 fewer to 146 more)	⊕⊕OO LOW	CRITICAL

Abbreviations: CI – confidence interval; NA – not applicable; OR – odds ratio; RR – relative risk

[1] Oral clarithromycin 15 mg/kg/day for 10 days
[2] Oral erythromycin 40 mg/kg/day for 10 days
[3] Lodha et al. 2013
[4] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 69: GRADE profile – azithromycin versus co-amoxiclav

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Azithromycin[1]	Co-amoxiclav[2]	Relative (95% CI)	Absolute		
Cure rate												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	84/125 (67.2%)	42/63 (66.7%)	OR 1.02 (0.54 to 1.95) NICE analysis: RR 1.01 (0.81 to 1.25)	7 more per 1000 (from 127 fewer to 167 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Failure rate												
2[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	12/164 (7.3%)	6/112 (5.4%)	OR 1.21 (0.42 to 3.53) NICE analysis: RR 1.20 (0.45 to 3.21)	11 more per 1000 (from 30 fewer to 122 more)	⊕⊕OO LOW	CRITICAL
Improved												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[4]	none	30/125 (24%)	17/63 (27%)	OR 0.85 (0.43 to 1.71) NICE analysis: RR 0.89 (0.53 to 1.48)	30 fewer per 1000 (from 127 fewer to 130 more)	⊕⊕OO LOW	CRITICAL
Side effects												
2[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	19/164 (11.6%)	52/112 (46.4%)	OR 0.15 (0.04 to 0.61) NICE analysis: RR 0.27 (0.17 to 0.45)	334 fewer per 1000 (from 209 fewer to 395 fewer)	⊕⊕⊕O MODERATE	CRITICAL

Abbreviations: CI – confidence interval; NA – not applicable; RR – relative risk

[1] Oral 10 mg/kg on day 1 followed by 5 mg/kg/day for 4 days
[2] Co-amoxiclav included: 40 mg/kg/day for 10 days and unreported details in 1 RCT
[3] Lodha et al. 2013
[4] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 70: GRADE profile – co-amoxiclav versus amoxicillin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Co-amoxiclav[1]	Amoxicillin[2]	Relative (95% CI)	Absolute		
Cure rate												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Co-amoxiclav[1]	Amoxicillin[2]	Relative (95% CI)	Absolute		
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[4]	none	47/50 (94%)	30/50 (60%)	OR 10.44 (2.85 to 38.21 NICE analysis: RR 1.57 (1.24 to 1.99)	342 more per 1000 (from 144 more to 594 more)	⊕⊕OO LOW	CRITICAL
Poor or no response												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	1/50 (2%)	10/50 (20%)	OR 0.08 (0.01 to 0.67) NICE analysis: RR 0.1 (0.01 to 0.75)	180 fewer per 1000 (from 50 fewer to 198 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Complications												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[5]	none	2/50 (4%)	0/50 (0%)	OR 5.21 (0.24 to 111.24) NICE analysis: RR 5 (0.25 to 101.58)	-	⊕OOO VERY LOW	CRITICAL
Side effects												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[5]	none	2/50 (4%)	0/50 (0%)	OR 5.21 (0.24 to 111.24) NICE analysis: RR 5 (0.25 to 101.58)	-	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI – confidence interval; NA- not applicable; OR – odds ratio; RR – relative risk

[1] Co-amoxiclav 125 mg or 62.5 mg, plus amoxicillin 500 mg or 250 mg three times daily for 10 days
[2] 250 mg or 500 mg three times daily for 10 days
[3] Lodha et al. 2013
[4] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with co-amoxiclav
[5] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 71: GRADE profile – co-trimoxazole versus amoxicillin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Co-trimoxazole[1]	Amoxicillin[2]	Relative (95% CI)	Absolute		
Cure rate												
2[3]	randomised trials	serious[4]	serious[5]	no serious indirectness	no serious imprecision	none	720/872 (82.6%)	724/860 (84.2%)	OR 1.03 (0.56 to 1.89) NICE analysis: RR 1.00 (0.92 to 1.09)	0 fewer per 1000 (from 67 fewer to 76 more)	⊕⊕OO LOW	CRITICAL
Failure rate												
2[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[6]	none	164/929 (17.7%)	129/821 (15.7%)	OR 1.18 (0.91 to 1.51) NICE analysis: RR 1.16 (0.94 to 1.43)	25 more per 1000 (from 9 fewer to 68 more)	⊕⊕OO LOW	CRITICAL
Death rate												
2[3]	randomised trials	serious[4]	no serious inconsistency	no serious indirectness	serious[7]	none	2/1132 (0.18%)	0/918 (0%)	OR 2.08 (0.22 to 20.06) NICE analysis: RR 2.10 (0.23 to 19.50)	-	⊕OOO LOW	CRITICAL
Change of antibiotics												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[6]	none	121/734 (16.5%)	98/725 (13.5%)	OR 1.26 (0.95 to 1.69) NICE analysis: RR 1.22 (0.95 to 1.56)	30 more per 1000 (from 7 fewer to 76 more)	⊕⊕⊕O MODERATE	CRITICAL

Abbreviations: CI – confidence interval; RR – relative risk; OR – odds ratio; NA – not applicable

[1] Co-trimoxazole includes: oral, 20 mg trimethoprim per tablet given twice a day (7 to 11 mg/kg/day) for 5 days, or 20/4 mg/kg/day for 5 days
[2] Amoxicillin includes: oral, 125 mg given three times a day (31 to 51 mg/kg/day) for 3 days, or oral, 25 mg/kg/day for 5 days
[3] Lodha et al. 2013
[4] Downgraded 1 level - 1 of 2 studies judged to be at high or unclear risk of bias by systematic review authors in several domains: unclear random sequence generation, unclear allocation concealment, open label, unclear source of funding
[5] Downgraded 1 level - heterogeneity <50%
[6] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with co-trimoxazole
[7] Downgraded 2 levels - at a minimal important difference of 0% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with appreciable benefit or appreciable harm

Table 72: GRADE profile – cefpodoxime versus co-amoxiclav

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cefpodoxime[1]	Co-amoxiclav[2]	Relative (95% CI)	Absolute		
Response rate at end of treatment												
1[3]	randomised trials	serious[4]	NA	serious[5]	no serious imprecision	none	179/188 (95.2%)	87/90 (96.7%)	OR 0.69 (0.18 to 2.60) NICE analysis: RR 0.98 (0.94 to 1.04)	19 fewer per 1000 (from 58 fewer to 39 more)	⊕⊕OO LOW	CRITICAL
Adverse events												
1[3]	randomised trials	serious[4]	NA	serious[5]	very serious[6]	none	7/188 (3.7%)	7/90 (7.8%)	OR 0.46 (0.16 to 1.35) NICE analysis: RR 0.48 (0.17 to 1.32)	40 fewer per 1000 (from 65 fewer to 25 more)	⊕OOO VERY LOW	CRITICAL

Abbreviations: CI – confidence interval; NA – not applicable; OR – odds ratio; RR – relative risk

[1] Oral, 5 to 12 mg/kg/day for 10 days
[2] Oral, 6 to 13mg/kg/day for 10 days
[3] Lodha et al. 2013
[4] Downgraded 1 level - study judged to be at unclear risk of bias by systematic review authors in all domains: allocation concealment, blinding, selective reporting, incomplete data, source of funding
[5] Downgraded 1 level - population of children with lower respiratory tract infection; systematic review authors state that there are no details of the children excluded from the study, therefore unclear if this is a pneumonia population
[6] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 73: GRADE profile – amoxicillin versus chloramphenicol

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Amoxicillin[1]	Chloramphenicol[2]	Relative (95% CI)	Absolute		
Cure rate												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[4]	none	608/725 (83.9%)	39/71 (54.9%)	OR 4.26 (2.57 to 7.08) NICE analysis: RR 1.53 (1.23 to 1.89)	291 more per 1000 (from 126 more to 489 more)	⊕⊕⊕O MODERATE	CRITICAL
Failure rates												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Amoxicillin[1]	Chloramphenicol[2]	Relative (95% CI)	Absolute		
2[3]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[6]	none	147/923 (15.9%)	32/142 (22.5%)	OR 0.64 (0.41 to 1.00) NICE analysis: RR 0.70 (0.49 to 0.99)	68 fewer per 1000 (from 2 fewer to 115 fewer)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI – confidence interval; NA- not applicable; OR – odds ratio; RR – relative risk												

[1] Oral, 25 mg/kg/day or 45mg/kg/day for 5 days
[2] Oral, unreported dose
[3] Lodha et al. 2013
[4] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with amoxicillin
[5] Downgraded 1 level - 1 of 2 studies judged to be at high or unclear risk of bias by systematic review authors in several domains: unclear random sequence generation, unclear allocation concealment, open label, unclear source of funding
[6] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with chloramphenicol

H.13.2 Single antibiotic compared with dual antibiotics

No systematic reviews or randomised controlled trials met the inclusion criteria.

H.13.3 Dual antibiotics compared with other dual antibiotics

No systematic reviews or randomised controlled trials met the inclusion criteria.

H.14 Antibiotics in children with severe community-acquired pneumonia

H.14.1 Single antibiotic compared with another single antibiotic

Table 74: GRADE profile – amoxicillin versus penicillin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Amoxicillin[1]	Penicillin[2]	Relative (95% CI)	Absolute		
Failure rate at 48 hours												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	167/857 (19.5%)	161/845 (19.1%)	OR 1.03 (0.81 to 1.31) NICE analysis: RR 1.02 (0.84 to 1.24)	4 more per 1000 (from 30 fewer to 46 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Failure rate on day 5												
2[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	192/960 (20%)	190/945 (20.1%)	OR 1.15 (0.58 to 2.30) NICE analysis: RR 1.00 (0.83 to 1.19)	28 more per 1000 (from 80 fewer to 235 more)	⊕⊕OO LOW	CRITICAL
Failure rate on day 14												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	231/857 (27%)	221/845 (26.2%)	OR 1.04 (0.84 to 1.29) NICE analysis: RR 1.03 (0.88 to 1.21)	8 more per 1000 (from 31 fewer to 55 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Death rates												
2[3]	randomised trials	no serious risk of bias	NA[5]	no serious indirectness	serious[6]	none	0/945 (0%)	7/960 (0.73%)	OR 0.07 (0.00 to 1.18) NICE analysis: RR 0.07 (0 to 1.18)	7 fewer per 1000 (from 7 fewer to 1 more)	⊕⊕⊕O MODERATE	CRITICAL

Abbreviations: CI – confidence interval; NA – not applicable; OR – odds ratio; RR – relative risk

[1] 45 mg/kg/day, or for 6 months to 12 years of age 8 mg/kg/dose three times a day above 12 years of age 500 mg three times a day
[2] Unspecified; intramuscular 200,000 IU/kg or intravenous 25 mg/kg/ dose four times a day
[3] Lodha et al. 2013
[4] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm
[5] Heterogeneity not assessable as 1 of 2 studies had no events in either treatment group
[6] Downgraded 1 level - at a minimal important difference of 0% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with appreciable benefit or appreciable harm

Table 75: GRADE profile – amoxicillin versus ampicillin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Amoxicillin[1]	Ampicillin[2]	Relative (95% CI)	Absolute		
Failure rates (up to or before day 14)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[4]	none	77/1025 (7.5%)	87/1012 (8.6%)	OR 0.86 (0.63 to 1.19) NICE analysis: RR 0.87 (0.65 to 1.17)	11 fewer per 1000 (from 30 fewer to 15 more)	⊕⊕⊕O MODERATE	CRITICAL
Relapse rates												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[5]	none	25/948 (2.6%)	31/925 (3.4%)	OR 0.78 (0.46 to 1.33) NICE analysis: RR 0.79 (0.47 to 1.32)	7 fewer per 1000 (from 18 fewer to 11 more)	⊕⊕OO LOW	CRITICAL
Death rates												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[6]	none	1/1025 (0.1%)	4/1012 (0.4%)	OR 0.25 (0.03 to 2.21) NICE analysis: RR 0.25 (0.03 to 2.2)	3 fewer per 1000 (from 4 fewer to 5 more)	⊕⊕OO LOW	CRITICAL

Abbreviations: CI – confidence interval; NA – not applicable; OR – odds ratio; RR – relative risk

[1] Oral syrup 80 to 90 mg/kg per day in 2 doses
[2] Intravenous ampicillin 100 mg/kg per day in 4 doses for 48 hours
[3] Lodha et al. 2013
[4] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or harm with ampicillin
[5] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm
[6] Downgraded 1 level - at a minimal important difference of 0% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with appreciable benefit or appreciable harm

Table 76: GRADE profile – amoxicillin versus cefuroxime

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Amoxicillin[1]	Cefuroxime[2]	Relative (95% CI)	Absolute		
Cure rates												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Amoxicillin[1]	Cefuroxime[2]	Relative (95% CI)	Absolute		
1[3]	randomised trials	serious[4]	NA	no serious indirectness	no serious imprecision	none	41/42 (97.6%)	40/42 (95.2%)	OR 2.05 (0.18 to 23.51) NICE analysis: RR 1.02 (0.94 to 1.11)	19 more per 1000 (from 57 fewer to 105 more)	⊕⊕⊕O MODERATE	CRITICAL
Abbreviations: CI – confidence interval; NA- not applicable RR – relative risk												

[1] Intravenous, 75 mg/kg/d in 3 doses
[2] Intravenous, 75 mg/kg/d in 3 doses
[3] Lodha et al. 2013
[4] Downgraded 1 level - study judged to be at high or unclear risk of bias by systematic review authors in several domains: unclear random sequence generation, unclear allocation concealment, open label, selective reporting, and unclear source of funding

Table 77: GRADE profile – amoxicillin versus clarithromycin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Amoxicillin[1]	Clarithromycin[2]	Relative (95% CI)	Absolute		
Cure rates												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	no serious imprecision	none	41/42 (97.6%)	39/40 (97.5%)	OR 1.05 (0.06 to 17.40) NICE analysis: RR 1.00 (0.93 to 1.07)	0 fewer per 1000 (from 68 fewer to 68 more)	⊕⊕⊕O MODERATE	CRITICAL
Abbreviations: CI – confidence interval; NA – not applicable; OR odds ratio; RR – relative risk												

[1] Intravenous 75 mg/kg/d in 3 doses
[2] Intravenous, mg/kg/day in 2 doses
[3] Lodha et al. 2013
[4] Downgraded 1 level - study judged to be at high or unclear risk of bias by systematic review authors in several domains: unclear random sequence generation, unclear allocation concealment, open label, selective reporting, unclear source of funding

Table 78: GRADE profile – levofloxacin versus beta-lactam antibiotics

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Levofloxacin[1]	Beta-lactams	Relative (95% CI)	Absolute		
Cure rates												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	no serious imprecision	none	382/405 (94.3%)	126/134 (94.0%)	OR 1.05 (0.46 to 2.42) NICE analysis: RR 1.00 (0.96 to 1.05)	0 fewer per 1000 (from 38 fewer to 47 more)	⊕⊕⊕O MODERATE	CRITICAL
Abbreviations: CI – confidence interval; NA- not applicable; OR – odds ratio; RR – relative risk												

[1] Children aged 6 months to 5 years: either oral 10mg/kg/dose twice daily or intravenous 10mg/kg/dose every 12 hours;
[2] Children aged 6 months to 5 years: oral co-amoxiclav twice daily, including amoxicillin at 22.5 mg/kg/dose or intravenous ceftriaxone at 25 mg/kg/dose every 12 hours
[3] Lodha et al. 2013
[4] Downgraded 1 level - study judged to be at high or unclear risk of bias by systematic review authors in several domains: unclear random sequence generation, unclear allocation concealment, open label, selective reporting, incomplete outcome data, funded by pharmaceutical industry

Table 79: GRADE profile – cefuroxime versus clarithromycin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Cefuroxime[1]	Clarithromycin[2]	Relative (95% CI)	Absolute		
Cure rates												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	no serious imprecision	none	40/42 (95.2%)	39/40 (97.5%)	OR 0.51 (0.04 to 5.89) NICE analysis: RR 0.98 (0.90 to 1.06)	19 fewer per 1000 (from 98 fewer to 58 more)	⊕⊕⊕O MODERATE	CRITICAL
Abbreviations: CI – confidence interval; NA – not applicable; OR – odds ratio; RR – relative risk												

[1] Intravenous 75 mg/kg/day in 3 doses
[2] Intravenous 15 mg/kg/day in 2 doses
[3] Lodha et al. 2013
[4] Downgraded 1 level - study judged to be at high or unclear risk of bias by systematic review authors in several domains: unclear random sequence generation, unclear allocation concealment, open label, selective reporting, unclear source of funding

Table 80: GRADE profile – co-trimoxazole versus chloramphenicol

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Co-trimoxazole[1]	Chloramphenicol[2]	Relative (95% CI)	Absolute		
Cure rate												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[4]	none	39/55 (70.9%)	39/56 (69.6%)	OR 1.06 (0.47 to 2.40) NICE analysis: RR 1.02 (0.80 to 1.30)	14 more per 1000 (from 139 fewer to 209 more)	⊕⊕⊕O MODERATE	CRITICAL
Failure rate												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[5]	none	16/55 (29.1%)	16/56 (28.6%)	OR 1.03 (0.45 to 2.33) NICE analysis: RR 1.02 (0.57 to 1.83)	6 more per 1000 (from 123 fewer to 237 more)	⊕⊕OO LOW	CRITICAL
Relapse rate												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[5]	none	4/55 (7.3%)	4/56 (7.1%)	OR 1.02 (0.24 to 4.30) NICE analysis: RR 1.02 (0.27 to 3.87)	1 more per 1000 (from 52 fewer to 205 more)	⊕⊕OO LOW	CRITICAL
Death rate												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[6]	none	8/55 (14.5%)	4/56 (7.1%)	OR 2.21 (0.63 to 7.83) NICE analysis: RR 2.04 (0.65 to 6.37)	74 more per 1000 (from 25 fewer to 384 more)	⊕⊕OO LOW	CRITICAL
Need for change in antibiotics												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[5]	none	8/55 (14.5%)	6/56 (10.7%)	OR 1.42 (0.46 to 4.40) NICE analysis: RR 1.36 (0.5 to 3.66)	39 more per 1000 (from 54 fewer to 285 more)	⊕⊕OO LOW	CRITICAL

Abbreviations: CI – confidence interval; NA – not applicable; OR – odds ratio; RR – relative risk

[1] Details unreported
[2] Details unreported
[3] Lodha et al. 2013
[4] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with co-trimoxazole
[5] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm

[6] Downgraded 2 levels - at a minimal important difference of 0% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with appreciable benefit or appreciable harm; wide absolute value confidence intervals

Table 81: GRADE profile – ceftaroline fosamil versus ceftriaxone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftaroline fosamil[1]	Ceftriaxone[1]	Relative (95% CI)	Absolute		
Clinical response at day 4												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[4]	none	74/107 (69.2%)	24/36 (66.7%)	NICE analysis: RR 1.04 (0.80 to 1.35)	27 more per 1000 (from 133 fewer to 233 more)	⊕⊕⊕O MODERATE	CRITICAL
Clinical cure (end of treatment)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	no serious imprecision	none	98/107 (91.6%)	32/36 (88.9%)	NICE analysis: RR 1.03 (0.91 to 1.17)	27 more per 1000 (from 80 fewer to 151 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Clinical failure (end of treatment)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[5]	none	7/107 (6.5%)	4/36 (11.1%)	NICE analysis: RR 0.59 (0.18 to 1.9)	46 fewer per 1000 (from 91 fewer to 100 more)	⊕⊕OO LOW	CRITICAL
Children with 1 or more adverse event												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[5]	none	55/121 (45.5%)	18/39 (46.2%)	NICE analysis: RR 0.98 (0.67 to 1.46)	9 fewer per 1000 (from 152 fewer to 212 more)	⊕⊕OO LOW	CRITICAL
Children with 1 or more serious adverse events												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[5]	none	6/121 (5.0%)	1/39 (2.6%)	NICE analysis: RR 1.93 (0.24 to 15.57)	24 more per 1000 (from 19 fewer to 374 more)	⊕⊕OO LOW	CRITICAL
Discontinuation of study drug due to adverse event												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[5]	none	3/121 (2.5%)	0/39 (0%)	NICE analysis: RR 2.3 (0.12 to 43.48)	-	⊕⊕OO LOW	CRITICAL
Abbreviations: CI – confidence interval; NA – not applicable; RR – relative risk												

[1] <33kg, 12 mg/kg; >33kg, 400 mg, infused over 60 minutes, every 8 hours; after 3 days, switched to co-amoxiclav if stable
[2] 75 mg/kg/day to maximum 4 g/day, infused over 30 minutes every 12 hours; after 3 days, switched to co-amoxiclav if stable
[3] Cannavino et al. 2016
[4] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with ceftaroline fosamil

[5] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm

H.14.2 Single antibiotic compared with dual antibiotics

Table 82: GRADE profile – benzylpenicillin plus gentamicin versus co-amoxiclav

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Benzylpenicillin plus gentamicin[1]	Co-amoxiclav[2]	Relative (95% CI)	Absolute		
Failure rates												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[4]	none	1/38 (2.6%)	1/33 (3.0%)	OR 0.86 (0.05 to 14.39) NICE analysis: RR 0.87 (0.06 to 13.35)	4 fewer per 1000 (from 28 fewer to 374 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI – confidence interval; NA – not applicable; OR – odds ratio; RR – risk ratio												

[1] Benzylpenicillin 50,000 mg/kg IV every 6 hours plus gentamicin 2.5 mg/kg, IV every 8 hours for at least 3 days, followed by oral amoxicillin substituted for benzylpenicillin
[2] Co-amoxiclav 30 mg/kg IV every 12 hours for at least 3 days, changed to oral co-amoxiclav when able to feed
[3] Lodha et al. 2013
[4] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 83: GRADE profile – penicillins plus chloramphenicol versus ampicillin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ampicillin[1]	Penicillin plus chloramphenicol[2]	Relative (95% CI)	Absolute		
Cure rates												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	no serious imprecision	none	42/52 (80.8%)	44/49 (89.8%)	OR 0.48 (0.15 to 1.51) NICE analysis: RR 0.90 (0.76 to 1.06)	90 fewer per 1000 (from 216 fewer to 54 more)	⊕⊕⊕O MODERATE	CRITICAL
Duration of hospital stay												
1[3]	randomised trials	serious[4]	NA	no serious indirectness	no serious imprecision	none	Mean, SD: 6.19 ± 2.78 n=52	Mean, SD: 6.29 ± 2.50 n=49	-	MD 0.1 lower (1.13 lower to 0.93 higher)	⊕⊕⊕O MODERATE	CRITICAL
Abbreviations: CI – confidence interval; NA – not applicable; OR – odds ratio; RR – risk ratio; SD – standard deviation; MD – mean difference												

[1] Intravenous or intramuscular ampicillin 100 mg/kg/day for 48 hours, followed by oral

[2] Intravenous penicillin (unspecified; 100,000 IU/kg/day) plus chloramphenicol (100 mg/kg/day)
[3] Lodha et al. 2013
[4] Downgraded 1 level - study judged to be at high or unclear risk of bias by systematic review authors in several domains: unclear allocation concealment, open label, selective reporting, incomplete outcome data, source of funding unclear

Table 84: GRADE profile – benzylpenicillin plus chloramphenicol versus chloramphenicol

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chloramphenicol[1]	Benzylpenicillin plus chloramphenicol [2]	Relative (95% CI)	Absolute		
Death rates												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[4]	none	48/377 (12.7%)	62/371 (16.7%)	OR 0.73 (0.48 to 1.09) NICE analysis: RR 0.76 (0.54 to 1.08)	40 fewer per 1000 (from 77 fewer to 13 more)	⊕⊕⊕O MODERATE	CRITICAL
Need for change of antibiotics												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[5]	none	3/377 (0.8%)	6/371 (1.6%)	OR 0.49 (0.12 to 1.97) NICE analysis: RR 0.49 (0.12 to 1.95)	8 fewer per 1000 (from 14 fewer to 15 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI – confidence interval; NA – not applicable; OR – odds ratio; RR – risk ratio												

[1] Intramuscular chloramphenicol daily until switched to oral
[2] Intramuscular chloramphenicol with benzylpenicillin until switched to oral
[3] Lodha et al. 2013
[4] Downgraded 1 level - at a minimal important difference of 0%, the effect estimate is consistent with appreciable benefit or appreciable harm
[5] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 85: GRADE profile – chloramphenicol versus ampicillin plus gentamicin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chloramphenicol[1]	Ampicillin plus gentamicin[2]	Relative (95% CI)	Absolute		
Failure rates on day 5												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[4]	none	77/479 (16.1%)	54/479 (11.3%)	OR 1.51 (1.04 to 2.19)	48 more per 1000 (from 3		CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chloramphenicol[1]	Ampicillin plus gentamicin[2]	Relative (95% CI)	Absolute		
									NICE analysis: RR 1.43 (1.03 to 1.97)	more to 109 more)	⊕⊕⊕O MODERATE	
Failure rates on day 10												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[4]	none	92/479 (19.2%)	67/479 (14.0%)	OR 1.46 (1.04 to 2.06) NICE analysis: RR 1.37 (1.03 to 1.83)	52 more per 1000 (from 4 more to 116 more)	⊕⊕⊕O MODERATE	CRITICAL
Failure rates on day 21												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[4]	none	103/479 (21.5%)	77/479 (16.1%)	OR 1.43 (1.03 to 1.98) NICE analysis: RR 1.34 (1.02 to 1.75)	55 more per 1000 (from 3 more to 121 more)	⊕⊕⊕O MODERATE	CRITICAL
Death rates												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[5]	none	40/479 (8.4%)	25/479 (5.2%)	OR 1.65 (0.99 to 2.77) NICE analysis: RR 1.60 (0.99 to 2.59)	31 more per 1000 (from 1 fewer to 83 more)	⊕⊕⊕O MODERATE	CRITICAL
Need for change in antibiotics (day 21)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[4]	none	64/479 (13.4%)	41/479 (8.6%)	OR 1.65 (1.09 to 2.49) NICE analysis: RR 1.56 (1.08 to 2.26)	48 more per 1000 (from 7 more to 108 more)	⊕⊕⊕O MODERATE	CRITICAL

Abbreviations: CI – confidence interval; NA – not applicable; OR – odds ratio; RR – risk ratio

[1] Chloramphenicol 75 mg/kg/d given in 3 doses, every 8 hours for minimum of 5 days, up to 10 days
[2] Ampicillin 200 mg/kg/d in 4 doses every 6 hours, and gentamicin 7.5 mg/kg/d as a single daily dose, for a minimum of 5 days, followed by oral amoxicillin to complete 10 days antibiotic treatment
[3] Lodha et al. 2013
[4] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with chloramphenicol
[5] Downgraded 1 level - at a minimal important difference of 0%, the effect estimate is consistent with appreciable benefit or appreciable harm

Table 86: GRADE profile – penicillins plus gentamicin versus chloramphenicol

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chloramphenicol[1]	Penicillins plus gentamicin[2]	Relative (95% CI)	Absolute		
Death												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[4]	none	36/559 (6.4%)	29/557 (5.2%)	OR 1.25 (0.76 to 2.07) NICE analysis: RR 1.24 (0.77 to 1.99)	12 more per 1000 (from 12 fewer to 52 more)	⊕⊕⊕O MODERATE	CRITICAL
Readmission before 30 days												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[5]	none	50/559 (8.9%)	32/557 (5.7%)	OR 1.61 (1.02 to 2.55) NICE analysis: RR 1.56 (1.01 to 2.39)	32 more per 1000 (from 1 more to 80 more)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[5]	none	147/559 (26.3%)	123/557 (22.1%)	OR 1.26 (0.96 to 1.66) NICE analysis: RR 1.19 (0.97 to 1.47)	42 more per 1000 (from 7 fewer to 104 more)	⊕⊕⊕O MODERATE	CRITICAL
Change of antibiotics												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[6]	none	49/559 (8.8%)	60/557 (10.8%)	OR 0.80 (0.54 to 1.18) NICE analysis: RR 0.81 (0.57 to 1.16)	20 fewer per 1000 (from 46 fewer to 17 more)	⊕⊕⊕O MODERATE	CRITICAL

Abbreviations: CI – confidence interval; NA – not applicable; OR – odds ratio; RR – risk ratio

[1] Intramuscular chloramphenicol 25 mg/kg 6-hourly for at least 5 days
[2] Penicillin (unspecified; 50 mg/kg 6-hourly) and gentamicin (7.5 mg/kg/d single dose) for at least 5 days
[3] Lodha et al. 2013
[4] Downgraded 1 level - at a minimal important difference of 0%, the effect estimate is consistent with appreciable benefit or appreciable harm
[5] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with chloramphenicol
[6] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with penicillin plus gentamicin

Table 87: GRADE profile – chloramphenicol plus penicillin versus ceftriaxone

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Chloramphenicol plus penicillin[1]	Ceftriaxone[2]	Relative (95% CI)	Absolute		
Cure rates												
1[1]	randomised trials	serious[2]	NA	no serious indirectness	serious[3]	none	39/46 (84.8%)	41/51 (80.4%)	OR 1.36 (0.47 to 3.93) NICE analysis: RR 1.05 (0.88 to 1.27)	40 more per 1000 (from 96 fewer to 217 more)	⊕⊕OO LOW	CRITICAL

Abbreviations: CI – confidence interval; NA – not applicable; OR – odds ratio; RR – risk ratio

[1] Intravenous chloramphenicol 15 mg/kg every 6 hours plus penicillin 25,000 IU/kg every 4 hours, for 10 days
[2] 50 mg/kg every 12 hours
[3] Lodha et al. 2013
[4] Downgraded 1 level - study judged to be at high or unclear risk of bias by systematic review authors in several domains: unclear random sequence generation, lack of allocation concealment, open label, unclear funding source
[5] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with chloramphenicol plus penicillin

Table 88: GRADE profile – ceftriaxone plus vancomycin versus ceftaroline fosamil

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftaroline fosamil[1]	Ceftriaxone plus vancomycin[2]	Relative (95% CI)	Absolute		
Clinical cure (end of treatment)												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[4]	none	24/29 (82.8%)	7/9 (77.8%)	NICE analysis: RR 1.06 (0.72 to 1.57)	47 more per 1000 (from 218 fewer to 443 more)	⊕⊕OO LOW	CRITICAL
Clinical response at day 4												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[4]	none	15/29 (51.7%)	6/9 (66.7%)	NICE analysis: RR 0.78 (0.43 to 1.39)	147 fewer per 1000 (from 380 fewer to 260 more)	⊕⊕OO LOW	CRITICAL
Clinical failure												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[4]	none	3/29 (10.3%)	0/9 (0.0%)	NICE analysis: RR 2.33 (0.13 to 41.38)	-	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Ceftaroline fosamil[1]	Ceftriaxone plus vancomycin[2]	Relative (95% CI)	Absolute		
Children with 1 or more adverse events												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[5]	none	12/30 (40.0%)	8/10 (80.0%)	NICE analysis: RR 0.5 (0.29 to 0.86)	400 fewer per 1000 (from 112 fewer to 568 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Children with 1 or more serious adverse events												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[4]	none	0/30 (0.0%)	1/10 (10.0%)	NICE analysis: RR 0.12 (0.01 to 2.69)	88 fewer per 1000 (from 99 fewer to 169 more)	⊕⊕OO LOW	CRITICAL
Discontinuation of IV study drug due to adverse events												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[4]	none	2/30 (6.7%)	0/10 (0.0%)	NICE analysis: RR 1.77 (0.09 to 34.15)	-	⊕⊕OO LOW	CRITICAL

Abbreviations: CI – confidence interval; NA – not applicable; RR – risk ratio

[1] Intravenous ceftaroline fosamil over 120 mins, 15mg/kg (or 600 mg if weight <40 kg) for >6 months or 10mg/kg for <6 months of age, every 8 hours
[2] Intravenous ceftriaxone over 30 mins every 12 hours, 75mg/kg/day (up to 4g/day) plus initial empiric intravenous vancomycin (15 mg/kg every 6 hours)
[3] Blumer et al. 2016
[4] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm
[5] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with ceftriaxone plus vancomycin

H.14.3 Dual antibiotics compared with other dual antibiotics

No systematic reviews or randomised controlled trials met the inclusion criteria.

H.15 Antibiotic dose in children with non-severe community-acquired pneumonia

Table 89: GRADE profile – low-dose versus high-dose amoxicillin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Low dose[1]	High dose[2]	Relative (95% CI)	Absolute		
Improved at day 5												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	no serious imprecision	none	417/437 (95.4%)	414/439 (94.3%)	NICE analysis: RR 1.01 (0.98 to 1.04)	9 more per 1000 (from 19 fewer to 38 more)	⊕⊕⊕O MODERATE	IMPORTANT
Clinical cure by day 14												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	no serious imprecision	none	411/437 (94.1%)	404/439 (92.0%)	NICE analysis: RR 1.02 (0.99 to 1.06)	18 more per 1000 (from 9 fewer to 55 more)	⊕⊕⊕O MODERATE	CRITICAL

Abbreviations: CI – confidence interval; NA – not applicable; RR – relative risk

[1] 45 mg/kg/day divided into 3 doses for 3 days; oral salbutamol and paracetamol given when needed
[2] 90 mg/kg/day divided into 3 doses for 3 days; oral salbutamol and paracetamol given when needed
[3] Hazir et al. 2007
[4] Downgraded 1 level – study conducted in Pakistan which may not be applicable to UK practice

H.16 Antibiotic dose in children with severe community-acquired pneumonia

Table 90: GRADE profile – low-dose versus high-dose benzylpenicillin

Quality assessment							No of patients		Absolute effect (95% CI)	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Low dose[1]	High dose[2]			
Duration in hospital (days)											
1[3]	randomised trials	serious[4]	NA	no serious indirectness	very serious[5]	none	Mean, SD: 2.63 ± 0.5 n=17	Mean, SD: 3.06 ± 1.47 n=18	MD 0.43 higher (1.15 lower to 0.29 higher)	⊕⊕OO LOW	CRITICAL
Duration of intravenous treatment (days)											
1[3]	randomised trials	serious[4]	NA	no serious indirectness	very serious[5]	none	Mean, SD: 2.56 ± 0.51 n=17	Mean, SD: 2.94 ± 1.48 n=18	MD 0.38 higher (1.11 lower to 0.35 higher)	⊕⊕OO LOW	IMPORTANT
Decrease in c-reactive protein (µg/mL)											

Quality assessment							No of patients		Absolute effect (95% CI)	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Low dose[1]	High dose[2]			
1[3]	randomised trials	serious[4]	NA	no serious indirectness	serious[6]	none	Mean, SD: 0.09 ± 0.56 n=17	Mean, SD: 0.27 ± 0.56 n=18	MD 0.18 higher (0.55 lower to 0.19 higher)	⊕⊕OO LOW	IMPORTANT
Abbreviations: CI – confidence interval; NA – not applicable; SD – standard deviation; MD: mean difference											

[1] Intravenous benzylpenicillin sodium 200,000 U/kg/day divided into 4 doses followed by switch to oral amoxicillin for 14 days total treatment
[2] Intravenous high dose benzylpenicillin sodium 400,000 U/kg/day divided into 4 doses followed by switch to oral amoxicillin for 14 days total treatment
[3] Amarilyo et al. 2014
[4] Downgraded 1 level - unclear if allocation concealment or blinding attempted, or how random sequence generation conducted; unclear how many enrolled completed treatment
[5] Downgraded 2 levels - at a default minimal important difference of 0.5xSD of low dose, the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm
[6] Downgraded 1 level - at a default minimal important difference of 0.5xSD of low dose, the effect estimate is consistent with no meaningful difference or appreciable benefit with high dose

H.17 Antibiotic dose frequency in children with non-severe community-acquired pneumonia

Table 91: GRADE profile – amoxicillin twice daily versus three times daily

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	2 times daily[1]	3 times daily[1]	Relative (95% CI)	Absolute		
Failure by day 5 (intention to treat analysis)												
1[2]	randomised trials	no serious risk of bias	NA	serious[3]	serious[4]	none	113/408 (28.0%)	107/412 (26.0%)	NICE analysis: RR 1.01 (0.81 to 1.26)[5]	11 more per 1000 (from 41 fewer to 81 more)	⊕⊕OO LOW	CRITICAL
Failure by day 5 (per protocol analysis)												
1[2]	randomised trials	no serious risk of bias	NA	serious[3]	serious[4]	none	88/383 (23.0%)	85/390 (21.8%)	NICE analysis: RR 1.05 (0.81 to 1.37)[6]	11 more per 1000 (from 41 fewer to 81 more)	⊕⊕OO LOW	CRITICAL
Failure by day 14 (intention to treat analysis)												
1[2]	randomised trials	no serious risk of bias	NA	serious[3]	no serious imprecision	none	160/408 (39.0%)	174/412 (42.0%)	NICE analysis: RR 0.93 (0.79 to 1.10)[7]	40 fewer per 1000 (from 99 fewer to 33 more)	⊕⊕⊕O MODERATE	CRITICAL
Failure by day 14 (per protocol analysis)												
1[2]	randomised trials	no serious risk of bias	NA	serious[3]	serious[5]	none	121/369 (32.8%)	138/376 (36.7%)	NICE analysis: RR 0.89 (0.73 to 1.09)[9]	40 fewer per 1000 (from 99 fewer to 33 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI – confidence interval; NA – not applicable; RR – relative risk												

[1] Oral amoxicillin, 50 mg/kg/day for 10 days
[2] Vilas-Boas et al. 2014

[3] Downgraded 1 level - study conducted in Brazil which may not be applicable to UK practice
[4] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with 2 times daily amoxicillin
[5] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with 3 time daily amoxicillin

H.18 Antibiotic dose frequency in children with severe community-acquired pneumonia

No systematic reviews or randomised controlled trials met the inclusion criteria.

H.19 Antibiotic course length in children with non-severe community-acquired pneumonia

Table 92: GRADE profile – 3 days versus 5 days treatment with the same antibiotic

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 days[1]	5 days[2]	Relative (95% CI)	Absolute		
Clinical cure												
3[3]	randomised trials	no serious risk of bias	no serious inconsistency	serious[4]	no serious imprecision	none	2582/2892 (89.3%)	2584/2871 (90.0%)	RR 0.99 (0.97 to 1.01)	9 fewer per 1000 (from 27 fewer to 9 more)	⊕⊕⊕O MODERATE	CRITICAL
Treatment failure												
3[3]	randomised trials	no serious risk of bias	no serious inconsistency	serious[4]	no serious imprecision	none	310/2892 (10.7%)	287/2871 (10%)	RR 1.07 (0.92 to 1.25)	7 more per 1000 (from 8 fewer to 25 more)	⊕⊕⊕O MODERATE	CRITICAL
Relapse rate												
4[3]	randomised trials	no serious risk of bias	no serious inconsistency	serious[4]	serious[5]	none	110/2735 (4%)	100/2734 (3.7%)	RR 1.09 (0.84 to 1.42)	3 more per 1000 (from 6 fewer to 15 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI – confidence interval; RR – relative risk												

[1] Either: oral amoxicillin 125mg, oral amoxicillin 15 mg/kg every 8 hours, oral co-trimoxazole 30-45 mg/kg/day, oral co-trimoxazole 80 mg twice daily (aged >12 months) or oral co-trimoxazole 40 mg twice daily (aged <12 months)
[2] Same treatment as 3 day arm, continued to complete 5 days treatment
[3] Haider et al. 2008
[4] Downgraded 1 level - included studies conducted in Asia which may not be applicable to UK practice
[5] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with 3 day treatment

Table 93: GRADE profile – 3 days versus 5 days amoxicillin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 days amoxicillin[1]	5 days amoxicillin[2]	Relative (95% CI)	Absolute		
Clinical cure												
2[3]	randomised trials	no serious risk of bias	no serious inconsistency	serious[4]	no serious imprecision	none	1783/2013 (88.6%)	1794/1999 (89.7%)	RR 0.99 (0.97 to 1.01)	9 fewer per 1000 (from 27 fewer to 9 more)	⊕⊕⊕O MODERATE	CRITICAL
Treatment failure												
2[3]	randomised trials	no serious risk of bias	no serious inconsistency	serious[4]	serious[5]	none	230/2013 (11.4%)	205/1999 (10.3%)	RR 1.11 (0.94 to 1.33)	11 more per 1000 (from 6 fewer to 34 more)	⊕⊕OO LOW	CRITICAL
Relapse rate												
2[3]	randomised trials	no serious risk of bias	no serious inconsistency	serious[4]	very serious[6]	none	44/1783 (2.5%)	42/1794 (2.3%)	RR 1.05 (0.69 to 1.60)	1 more per 1000 (from 7 fewer to 14 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI – confidence interval; RR – relative risk												

[1] Oral amoxicillin 125mg or oral amoxicillin 15 mg/kg every 8 hours
[2] Same treatment as 3 day arm, continued to complete 5 days treatment
[3] Haider et al. 2008
[4] Downgraded 1 level - included studies conducted in Asia which may not be applicable to UK practice
[5] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with 3 day treatment
[6] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 94: GRADE profile – 3 days versus 5 days co-trimoxazole

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 days co-trimoxazole[1]	5 days co-trimoxazole[2]	Relative (95% CI)	Absolute		
Clinical cure												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	no serious imprecision	none	799/879 (90.9%)	790/872 (90.6%)	RR 1.00 (0.97 to 1.03)	0 fewer per 1000 (from 27 fewer to 27 more)	⊕⊕⊕O MODERATE	CRITICAL
Treatment failure												
1[3]	randomised trials	no serious risk of bias	NA	serious[4]	very serious[5]	none	80/879 (9.1%)	82/872 (9.4%)	RR 0.97 (0.72 to 1.3)	3 fewer per 1000 (from 26 fewer to 28 more)	⊕OOO VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 days co-trimoxazole[1]	5 days co-trimoxazole[2]	Relative (95% CI)	Absolute		
Relapse rate												
2[3]	randomised trials	no serious risk of bias	no serious inconsistency	serious[4]	serious[6]	none	66/952 (6.9%)	58/940 (6.2%)	RR 1.12 (0.80 to 1.58)	7 more per 1000 (from 12 fewer to 36 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI – confidence interval; NA – not applicable; RR – relative risk												

[1] Oral co-trimoxazole 30-45 mg/kg/day, oral co-trimoxazole 80 mg twice daily (aged >12 months) or oral co-trimoxazole 40 mg twice daily (aged <12 months)
[2] Same treatment as 3 day arm, continued to complete 5 days treatment
[3] Haider et al. 2008
[4] Downgraded 1 level - included studies conducted in Asia which may not be applicable to UK practice
[5] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm
[6] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with 3 day treatment

Table 95: GRADE profile – 3 days versus 10 days amoxicillin

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	3 days amoxicillin[1]	10 days amoxicillin[1]	Relative (95% CI)	Absolute		
Treatment failure												
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	very serious[4]	none	4/10 (40%)	0/56 (0%)	NICE analysis: RR 46.64 (2.7 to 805.88)	-	⊕⊕OO LOW	CRITICAL
Abbreviations: CI – confidence interval; NA – not applicable; RR – relative risk												

[1] Amoxicillin 80 mg/kg/day divided into 3 doses for 3 days, followed by placebo for 7 days
[2] Amoxicillin 80 mg/kg/day divided into 3 doses for 10 days
[3] Greenberg et al. 2014
[4] Downgraded 2 levels - small sample size in 1 study arm (10); very wide confidence intervals

Table 96: GRADE profile – 5 days versus 10 days amoxicillin

Quality assessment							No of patients		Absolute Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	5 days amoxicillin[1]	10 days amoxicillin[1]			
Treatment failure											

Quality assessment							No of patients		Absolute Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	5 days amoxicillin[1]	10 days amoxicillin[1]			
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[4]	none	0/42 (0%)	0/56 (0%)	-	⊕⊕⊕O MODERATE	CRITICAL
Body temperature at day 5-7											
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[4]	none	Mean, SD: 36.7 ± 0.6 n=56	Mean, SD: 36.6 ± 0.4 n=59	MD 0.1 higher (0.09 lower to 0.29 higher)	⊕⊕⊕O MODERATE	IMPORTANT
C-reactive protein concentration (mg/L) at day 5-7											
1[3]	randomised trials	no serious risk of bias	NA	no serious indirectness	serious[4]	none	Mean, SD: 28.0 ± 28.0 n=56	Mean, SD: 16.3 ± 12.0 n=59	MD 11.7 higher (3.75 higher to 19.65 higher)	⊕⊕⊕O MODERATE	IMPORTANT
Abbreviations: NA – not applicable; SD – standard deviation; MD – mean difference											

[1] Amoxicillin 80 mg/kg/day divided into 3 doses for 5 days, followed by placebo for 5 days
[2] Amoxicillin 80 mg/kg/day divided into 3 doses for 10 days
[3] Greenberg et al. 2014
[4] Downgraded 1 level - at a default minimal important difference of 0.5xSD of 10 days treatment, the effect estimate is consistent with no meaningful difference or appreciable harm with 5 days treatment

H.20 Antibiotic course length in children with severe community-acquired pneumonia

No systematic reviews or randomised controlled trials met the inclusion criteria.

H.21 Antibiotic route of administration in children with non-severe community-acquired pneumonia

Table 97: GRADE profile – oral antibiotics versus injectable pencillins

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral antibiotics[1]	Injectable antibiotics[2]	Relative (95% CI)	Absolute		
Failure rate												
4[3]	randomised trials	serious[4]	serious[5]	no serious indirectness	very serious[6]	none	99/1214 (8.2%)	129/1212 (10.6%)	OR 0.56 (0.24 to 1.32) NICE analysis: RR 0.62 (0.30 to 1.28)	40 fewer per 1000 (from 75 fewer to 30 more)	⊕OOO VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral antibiotics[1]	Injectable antibiotics[2]	Relative (95% CI)	Absolute		
Abbreviations: CI – confidence interval; OR – odds ratio; RR – relative risk												

[1] Oral antibiotics included co-trimoxazole (5 days, unreported dose; 40 mg/kg/day for 10 days) and amoxicillin (syrup 80 to 90 mg/kg per day in 2 doses; 50 mg/kg/day)
[2] Injectable antibiotics included procaine penicillin (intramuscular; unreported dose); intramuscular procaine penicillin (50,000 IU/kg/day for 10 days) and intravenous ampicillin (100 mg/kg per day in 4 doses for 48 hours)
[3] Lodha et al. 2013
[4] Downgraded 1 level - 2 of 4 studies judged to be at high or unclear risk of bias by systematic review authors in several domains: unclear random sequence generation, lack of allocation concealment, selective reporting, incomplete outcome data, unclear funding source
[5] Downgraded 1 level - >50% heterogeneity
[6] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with oral antibiotics

H.22 Antibiotic route of administration in children with severe community-acquired pneumonia

Table 98: GRADE profile – oral antibiotics versus injectable penicillins

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral antibiotics[1]	Injectable antibiotics[2]	Relative (95% CI)	Absolute		
Cure rate												
2[3]	randomised trials	serious[4]	serious[5]	no serious indirectness	serious[6]	none	167/172 (97.1%)	141/162 (87.0%)	OR 5.05 (1.19 to 21.33) NICE analysis: RR 1.21 (0.80 to 1.81)	183 more per 1000 (from 174 fewer to 705 more)	⊕⊕OO LOW	CRITICAL
Failure rates on day 3												
3[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	247/1982 (12.5%)	255/1960 (13%)	OR 0.95 (0.78 to 1.15) NICE analysis: RR 0.96 (0.81 to 1.12)	5 fewer per 1000 (from 25 fewer to 18 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Failure rates on day 6												
6[3]	randomised trials	no serious risk of bias	serious[5]	no serious indirectness	serious[7]	none	291/2174 (13.4%)	319/2157 (14.8%)	OR 0.84 (0.56 to 1.24) NICE analysis: RR 0.86 (0.62 to 1.20)	21 fewer per 1000 (from 56 fewer to 30 more)	⊕⊕OO LOW	CRITICAL
Hospitalisation												
3[3]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	very serious[9]	none	7/192 (3.6%)	7/266 (2.6%)	OR 1.13 (0.38 to 3.34) NICE analysis: RR 1.12 (0.40 to 3.15)	3 more per 1000 (from 16 fewer to 57 more)	⊕OOO VERY LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral antibiotics[1]	Injectable antibiotics[2]	Relative (95% CI)	Absolute		
Relapse rates												
2[3]	randomised trials	no serious risk of bias	serious[8]	no serious indirectness	very serious[9]	none	31/1048 (3.0%)	33/1028 (3.2%)	OR 1.28 (0.34 to 4.82) NICE analysis: RR 1.26 (0.35 to 4.54)	8 more per 1000 (from 21 fewer to 114 more)	⊕OOO VERY LOW	CRITICAL
Failure rate in children below 5 years of age												
3[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	279/1948 (14.3%)	297/1922 (15.5%)	OR 0.91 (0.76 to 1.09) NICE analysis: RR 0.93 (0.80 to 1.07)	11 fewer per 1000 (from 31 fewer to 12 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Death rates												
3[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1/1970 (0.05%)	11/1972 (0.56%)	OR 0.15 (0.03 to 0.87) NICE analysis: RR 0.13 (0.02 to 0.72)	5 fewer per 1000 (from 5 fewer to 1 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL

Abbreviations: CI – confidence interval; RR – relative risk

[1] Oral antibiotics includes amoxicillin (doses for 6 months to 12 years of age 8 mg/kg/dose three times a day, above 12 years of age 500 mg three times a day; 45mg/kg/day; 50 mg/kg/day; syrup 80 to 90 mg/kg per day in 2 doses) and co-trimoxazole (40 mg/kg/day for 10 days)

[2] Injectable antibiotics includes intravenous benzylpenicillin (doses 25 mg/kg/ dose four times a day); intramuscular procaine penicillin (50,000 IU/kg/day for 10 days); penicillin (200,000 IU/kg) and intravenous ampicillin (100 mg/kg per day in 4 doses for 48 hours)

[3] Lodha et al. 2013

[4] Downgraded 1 level - 1 of 2 studies judged to be at high or unclear risk of bias by systematic review authors in several domains: unclear random sequence generation, lack of allocation concealment, unclear source of funding

[5] Downgraded 1 level - >50% heterogeneity

[6] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable benefit with oral treatment

[7] Downgraded 1 level - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference or appreciable harm with parenteral treatment

[8] Downgraded 1 level - 2 of 3 studies judged to be at high or unclear risk of bias by systematic review authors in several domains: unclear random sequence generation, lack of allocation concealment, selective reporting, incomplete outcome data and unclear source of funding

[9] Downgraded 2 levels - at a default minimal important difference of 25% of relative risk increase (RRI)/reduction (RRR), the effect estimate is consistent with no meaningful difference, appreciable benefit or appreciable harm

Table 99: GRADE profile – oral amoxicillin versus injectable penicillins

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral amoxicillin[1]	Injectable antibiotics[2]	Relative (95% CI)	Absolute		
Failure rates												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Oral amoxicillin[1]	Injectable antibiotics[2]	Relative (95% CI)	Absolute		
4[3]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	284/2062 (13.8%)	300/2050 (14.6%)	OR 0.92 (0.77 to 1.10) NICE analysis: RR 0.94 (0.81 to 1.09)	9 fewer per 1000 (from 28 fewer to 13 more)	⊕⊕⊕⊕ HIGH	CRITICAL

Abbreviations: CI – confidence interval; OR – odds ratio; RR – relative risk

[1] Oral amoxicillin doses included: for 6 months to 12 years of age 8 mg/kg/dose three times a day, above 12 years of age 500 mg three times a day; 45 mg/kg/day; syrup, 80 to 90 mg/kg per day in 2 doses and 50 mg/kg/day

[2] Injectable antibiotics included benzylpenicillin (doses 25 mg/kg/ dose four times a day); penicillin (200,000 IU/kg); ampicillin (100 mg/kg per day in 4 doses for 48 hours) and procaine penicillin intramuscular (50,000 IU/kg/day)

[3] Lodha et al. 2013

Appendix I: Studies not-prioritised

Study reference	Reason
Agweyu Ambrose, Gathara David, Oliwa Jacquie, Muinga Naomi, Edwards Tansy, Allen Elizabeth, Maleche-Obimbo Elizabeth, English Mike, Severe Pneumonia Study, and Group (2015) Oral amoxicillin versus benzyl penicillin for severe pneumonia among kenyan children: a pragmatic randomized controlled noninferiority trial. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 60(8), 1216-24	A systematic review has been prioritised on this area over this RCT (Lodha et al. 2013)
An Mao Mao, Zou Zui, Shen Hui, Gao Ping Hui, Cao Yong Bing, and Jiang Yuan Ying (2010) Moxifloxacin monotherapy versus beta-lactam-based standard therapy for community-acquired pneumonia: a meta-analysis of randomised controlled trials. International journal of antimicrobial agents 36(1), 58-65	A higher quality systematic review has been prioritised in this area (Eliakim-Raz et al. 2012; An et al. 2010 includes RCTs excluded in Eliakim-Raz et al. 2012 due to potential for participants in each arm to receive intervention treatment)
Anzueto Antonio, Niederman Michael S, Pearle James, Restrepo Marcos I, Heyder Albrecht, Choudhri Shurjeel H, Community-Acquired Pneumonia Recovery in the Elderly Study, and Group (2006) Community-Acquired Pneumonia Recovery in the Elderly (CAPRIE): efficacy and safety of moxifloxacin therapy versus that of levofloxacin therapy. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 42(1), 73-81	RCT included in prioritised systematic review (Yuan et al. 2012)
Asadi Leyla, Sligl Wendy I, Eurich Dean T, Colmers Isabelle N, Tjosvold Lisa, Marrie Thomas J, and Majumdar Sumit R (2012) Macrolide-based regimens and mortality in hospitalized patients with community-acquired pneumonia: a systematic review and meta-analysis. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 55(3), 371-80	A higher quality systematic review has been prioritised in this area (Raz-Pasteur et al. 2015; Asadi et al. 2012 is also an older systematic review, and 3 of 5 RCTs are included in Raz-Pasteur et al. 2012)
Asghar Rai, Banajeh Salem, Egas Josefina, Hibberd Patricia, Iqbal Imran, Katep-Bwalya Mary, Kundi Zafarullah, Law Paul, MacLeod William, Maulen-Radovan Irene, Mino Greta, Saha Samir, Sempertegui Fernando, Simon Jonathon, Santosham Mathuram, Singhi Sunit, Thea Donald M, Qazi Shamim, Severe Pneumonia Evaluation Antimicrobial Research Study, and Group (2008) Chloramphenicol versus ampicillin plus gentamicin for community acquired very severe pneumonia among children aged 2-59 months in low resource settings: multicentre randomised controlled trial (SPEAR study). BMJ (Clinical research ed.) 336(7635), 80-4	RCT included in prioritised systematic review (Lodha et al. 2013)

Study reference	Reason
Atkinson Maria, Lakhanpaul Monica, Smyth Alan, Vyas Harish, Weston Vivienne, Sithole Jabulani, Owen Victoria, Halliday Katharine, Sammons Helen, Crane Jo, Guntupalli Narayan, Walton Lynda, Ninan Titus, Morjaria Anu, and Stephenson Terence (2007) Comparison of oral amoxicillin and intravenous benzyl penicillin for community acquired pneumonia in children (PIVOT trial): a multicentre pragmatic randomised controlled equivalence trial. Thorax 62(12), 1102-6	RCT included in prioritised systematic review (Lodha et al. 2013)
Awasthi Shally, Agarwal Girdhar, Kabra Sushil K, Singhi Sunit, Kulkarni Madhuri, More Vaishali, Niswade Abhimanyu, Pillai Raj Mohan, Luke Ravi, Srivastava Neeraj M, Suresh Saradha, Verghese Valsan P, Raghupathy P, Lodha R, and Walter Stephen D (2008) Does 3-day course of oral amoxycillin benefit children of non-severe pneumonia with wheeze: a multicentric randomised controlled trial. PloS one 3(4), e1991	Low relevance to UK practice (antibiotic versus placebo)
Awasthi Shally, Agarwal Girdhar, Singh J V, Kabra S K, Pillai R M, Singhi Sunit, Nongkynrih Baridalyne, Dwivedi Rashmi, More Vaishali B, Kulkarni Madhuri, Niswade A K, Bharti Bhavneet, Ambast Ankur, Dhasmana Puneet, and Group I CMR-IndiaClen Pneumonia Project (2008) Effectiveness of 3-day amoxycillin vs. 5-day co-trimoxazole in the treatment of non-severe pneumonia in children aged 2-59 months of age: a multi-centric open labeled trial. Journal of tropical pediatrics 54(6), 382-9	RCT included in prioritised systematic review (Lodha et al. 2013)
Bansal Arun, Singhi Sunit C, and Jayashree M (2006) Penicillin and gentamicin therapy vs amoxicillin/clavulanate in severe hypoxemic pneumonia. Indian journal of pediatrics 73(4), 305-9	RCT included in prioritised systematic review (Lodha et al. 2013)
Barrera Carlos M, Mykietiuk Analia, Metev Hristo, Nitu Mimi Floarea, Karimjee Najumuddin, Doreski Pablo Alexis, Mitha Ismail, Tanaseanu Cristina Mihaela, Molina Joseph McDermott, Antonovsky Yuri, Van Rensburg , Dirkie Johanna, Rowe Brian H, Flores-Figueroa Jose, Rewerska Barbara, Clark Kay, Keedy Kara, Sheets Amanda, Scott Drusilla, Horwith Gary, Das Anita F, Jamieson Brian, Fernandes Prabhavathi, Oldach David, and Team Solitaire-Oral Pneumonia (2016) Efficacy and safety of oral solithromycin versus oral moxifloxacin for treatment of community-acquired bacterial pneumonia: a global, double-blind, multicentre, randomised, active-controlled, non-inferiority trial (SOLITAIRE-ORAL). The Lancet. Infectious diseases 16(4), 421-30	Low relevance to UK practice (solithromycin is not available in UK)
Bergallo Carlos, Jasovich Abel, Teglia Osvaldo, Oliva Maria Eugenia, Lentnek Arnold, de Wouters , Luisa , Zlocowski Juan Carlos, Dukart Gary, Cooper Angel, Mallick Rajiv, and Study Group (2009) Safety and efficacy of intravenous tigecycline in treatment of community-acquired pneumonia: results from a double-blind randomized phase 3 comparison study with levofloxacin. Diagnostic microbiology and infectious disease 63(1), 52-61	RCT included in prioritised systematic review (Nemeth et al. 2015)
Bradley John S, Arguedas Adriano, Blumer Jeffrey L, Saez-Llorens Xavier, Melkote Rama, and Noel Gary J (2007) Comparative study of levofloxacin in the treatment of children with community-acquired pneumonia. The Pediatric infectious disease journal 26(10), 868-78	RCT included in prioritised systematic review (Lodha et al. 2013)

Study reference	Reason
Cai Yun, Wang Rui, Liang Beibei, Bai Nan, and Liu Youning (2011) Systematic review and meta-analysis of the effectiveness and safety of tigecycline for treatment of infectious disease. Antimicrobial agents and chemotherapy 55(3), 1162-72	A higher quality systematic review has been prioritised in this area (Nemeth et al. 2015; Cai et al. 2011 also only included 2 relevant RCTs which are included in Nemeth et al. 2015)
Chalmers J D, Akram A R, and Hill A T (2011) Increasing outpatient treatment of mild community-acquired pneumonia: Systematic review and meta-analysis. European Respiratory Journal 37(4), 858-864	A higher quality systematic review has been prioritised in this area (Athanassa et al. 2008; Chalmers et al. 2011 is lower quality than Athanassa et al. 2008 as only includes 1 RCT within a mixed RCT and observational study analysis)
Chaudhary Manu, Ayub Shiekh G, Mir Mohd A, and protocol group (2018) Comparative efficacy and safety analysis of CSE-1034: An open labeled phase III study in community acquired pneumonia. Journal of infection and public health ,	Low relevance to UK practice (CSE-1034 is not available in the UK)
Dartois Nathalie, Cooper C Angel, Castaing Nathalie, Gandjini Hassan, and Sarkozy Denise (2013) Tigecycline versus levofloxacin in hospitalized patients with community-acquired pneumonia: an analysis of risk factors. The open respiratory medicine journal 7, 13-20	A systematic review (Nemeth et al. 2015) has been prioritised in this area over this post hoc analysis; Dartois et al. 2013 includes analysis of 2 RCTs which are included in Nemeth
Das Rashmi Ranjan, and Singh Meenu (2013) Treatment of severe community-acquired pneumonia with oral amoxicillin in under-five children in developing country: a systematic review. PloS one 8(6), e66232	A higher quality systematic review has been prioritised in this area (Lodha et al. 2013; Das Rashmi et al. 2013 includes 5 relevant RCTs, of which 2 are included in Lodha et al. 2013, 2 are excluded from Lodha et al. 2013 due to lack of data and 1 is outside the scope of Lodha et al. 2013 as it compares the same antibiotic in different treatment settings)
Dean Nathan C, Sperry Paul, Wikler Matthew, Suchyta Mary S, and Hadlock Carol (2006) Comparing gatifloxacin and clarithromycin in pneumonia symptom resolution and process of care. Antimicrobial agents and chemotherapy 50(4), 1164-9	Low relevance to UK practice (gatifloxacin is not available in the UK)

Study reference	Reason
Dimopoulos George, Matthaiou Dimitrios K, Karageorgopoulos Drosos E, Grammatikos Alexandros P, Athanassa Zoe, and Falagas Matthew E (2008) Short- versus long-course antibacterial therapy for community-acquired pneumonia : a meta-analysis. Drugs 68(13), 1841-54	A higher quality systematic review has been prioritised in this area (Li et al. 2007; 2 of 4 RCTs in Dimopoulos et al. 2008 are included in Li et al. 2007; of 2 RCTs not included in Li et al. 2007, 1 is prioritised and 1 includes an antibiotic not available in the UK; Li et al. 2007 includes 15 RCTs)
Eljaaly Khalid, Alshehri Samah, Aljabri Ahmed, Abraham Ivo, Al Mohajer, Mayar , Kalil Andre C, and Nix David E (2017) Clinical failure with and without empiric atypical bacteria coverage in hospitalized adults with community-acquired pneumonia: a systematic review and meta-analysis. BMC infectious diseases 17(1), 385	A higher quality systematic review has been prioritised in this area (Eliakim-Raz et al. 2012; also fewer RCTs included in Eljaaly et al. 2017 as exclusion criteria includes RCTs with poor activity against *s. pnueomoniae* and macrolide monotherapy; 4 of the 5 RCTs in Eljaaly et al. 2017 are included in Eliakim-Raz et al. 2012)
English Marci L, Fredericks Christine E, Milanesio Nancy A, Rohowsky Nestor, Xu Ze-Qi, Jenta Tuah R. J, Flavin Michael T, and Eiznhamer David A (2012) Cethromycin versus clarithromycin for community-acquired pneumonia: comparative efficacy and safety outcomes from two double-blinded, randomized, parallel-group, multicenter, multinational noninferiority studies. Antimicrobial agents and chemotherapy 56(4), 2037-47	Low relevance to UK practice (cethromycin is not available in the UK)
File Thomas M, Jr , Low Donald E, Eckburg Paul B, Talbot George H, Friedland H David, Lee Jon, Llorens Lily, Critchley Ian A, Thye Dirk A, and investigators Focus (2011) FOCUS 1: a randomized, double-blinded, multicentre, Phase III trial of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in community-acquired pneumonia. The Journal of antimicrobial chemotherapy 66 Suppl 3, iii19-32	RCT included in prioritised systematic review (El Hajj et al. 2017)
File Thomas M, Jr , Low Donald E, Eckburg Paul B, Talbot George H, Friedland H David, Lee Jon, Llorens Lily, Critchley Ian, and Thye Dirk (2010) Integrated analysis of FOCUS 1 and FOCUS 2: randomized, doubled-blinded, multicenter phase 3 trials of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in patients with community-acquired pneumonia. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 51(12), 1395-405	Secondary analysis of 2 RCTs included in prioritised systematic review (El Hajj et al. 2017)
File Thomas M, Jr , Mandell Lionel A, Tillotson Glenn, Kostov Kosta, and Georgiev Ognian (2007) Gemifloxacin once daily for 5 days versus 7 days for the treatment of community-acquired pneumonia: a randomized, multicentre, double-blind study. The Journal of antimicrobial chemotherapy 60(1), 112-20	Low relevance to UK practice (gemifloxacin is not available in the UK)

Study reference	Reason
File Thomas M, Jr , Rewerska Barbara, Vucinic-Mihailovic Violeta, Gonong Joven Roque V, Das Anita F, Keedy Kara, Taylor David, Sheets Amanda, Fernandes Prabhavathi, Oldach David, and Jamieson Brian D (2016) SOLITAIRE-IV: A Randomized, Double-Blind, Multicenter Study Comparing the Efficacy and Safety of Intravenous-to-Oral Solithromycin to Intravenous-to-Oral Moxifloxacin for Treatment of Community-Acquired Bacterial Pneumonia. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 63(8), 1007-1016	Low relevance to UK practice (solithromycin is not available in the UK)
Fogarty Charles M, Buchanan Patricia, Aubier Michel, Baz Malik, van Rensburg , Dirkie , Rangaraju Manickam, and Nusrat Roomi (2006) Telithromycin in the treatment of pneumococcal community-acquired respiratory tract infections: a review. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases 10(2), 136-47	Low relevance to UK practice (telithromycin is not available in the UK)
Garau J, Fritsch A, Arvis P, and Read R C (2010) Clinical efficacy of moxifloxacin versus comparator therapies for community-acquired pneumonia caused by Legionella spp. Journal of chemotherapy (Florence, and Italy) 22(4), 264-6	Secondary analysis of 4 RCTs included in included systematic reviews
Granizo J J, Aguilar L, Gimenez M J, Coronel P, Gimeno M, and Prieto J (2009) Safety profile of cefditoren. A pooled analysis of data from clinical trials in community-acquired respiratory tract infections. Revista espanola de quimioterapia : publicacion oficial de la Sociedad Espanola de Quimioterapia 22(2), 57-61	Low relevance to UK practice (cefditoren is not available in the UK)
Granizo Juan Jose, Gimenez Maria Jose, Barberan Jose, Coronel Pilar, Gimeno Mercedes, and Aguilar Lorenzo (2006) The efficacy of cefditoren pivoxil in the treatment of lower respiratory tract infections, with a focus on the per-pathogen bacteriologic response in infections caused by Streptococcus pneumoniae and Haemophilus influenzae: a pooled analysis of seven clinical trials. Clinical therapeutics 28(12), 2061-9	Low relevance to UK practice (cefditoren pivoxil is not available in the UK)
Hazir Tabish, Fox LeAnne M, Nisar Yasir Bin, Fox Matthew P, Ashraf Yusra Pervaiz, MacLeod William B, Ramzan Afroze, Maqbool Sajid, Masood Tahir, Hussain Waqar, Murtaza Asifa, Khawar Nadeem, Tariq Parveen, Asghar Rai, Simon Jonathon L, Thea Donald M, Qazi Shamim A, New Outpatient Short-Course Home Oral Therapy for Severe Pneumoni, and Group (2008) Ambulatory short-course high-dose oral amoxicillin for treatment of severe pneumonia in children: a randomised equivalency trial. Lancet (London, and England) 371(9606), 49-56	RCT included in prioritised systematic review (Lodha et al. 2013)
Hazir Tabish, Nisar Yasir Bin, Abbasi Saleem, Ashraf Yusra Pervaiz, Khurshid Joza, Tariq Perveen, Asghar Rai, Murtaza Asifa, Masood Tahir, and Maqbool Sajid (2011) Comparison of oral amoxicillin with placebo for the treatment of world health organization-defined nonsevere pneumonia in children aged 2-59 months: a multicenter, double-blind, randomized, placebo-controlled trial in pakistan. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 52(3), 293-300	Low relevance to UK practice (antibiotic versus placebo)

Study reference	Reason
Horita Nobuyuki, Otsuka Tatsuya, Haranaga Shusaku, Namkoong Ho, Miki Makoto, Miyashita Naoyuki, Higa Futoshi, Takahashi Hiroshi, Yoshida Masahiro, Kohno Shigeru, and Kaneko Takeshi (2016) Beta-lactam plus macrolides or beta-lactam alone for community-acquired pneumonia: A systematic review and meta-analysis. Respirology (Carlton, and Vic.) 21(7), 1193-200	A higher quality systematic review has been prioritised in this area (Raz-Pasteur et al. 2015; Horita et al. 2016 is low quality, also including observational studies; Horita et al. 2016 includes 2 RCTs, 1 RCT is included in Raz-Pasteur et al. 2015 and 1 RCT is prioritised [Garin et al 2014])
Kohno Shigeru, Yanagihara Katsunori, Yamamoto Yoshihiro, Tokimatsu Issei, Hiramatsu Kazufumi, Higa Futoshi, Tateyama Masao, Fujita Jiro, and Kadota Jun-Ichi (2013) Early switch therapy from intravenous sulbactam/ampicillin to oral garenoxacin in patients with community-acquired pneumonia: a multicenter, randomized study in Japan. Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy 19(6), 1035-41	Low relevance to UK practice (garenoxacin is not available in the UK)
Laopaiboon Malinee, Panpanich Ratana, Swa Mya, and Kyaw (2015) Azithromycin for acute lower respiratory tract infections. The Cochrane database of systematic reviews (3), CD001954	A higher quality systematic review has been prioritised in this area (Lodha et al. 2013; all studies in children are included in Lodha et al. 2013; Laopaiboon et al. 2015 is a lower quality systematic review, which includes conditions other than pneumonia and 4 RCTs on community-acquired pneumonia)
Lassi Zohra S, Das Jai K, Haider Syed Waqas, Salam Rehana A, Qazi Shamim A, and Bhutta Zulfiqar A (2014) Systematic review on antibiotic therapy for pneumonia in children between 2 and 59 months of age. Archives of disease in childhood 99(7), 687-93	A higher quality systematic review has been prioritised in this area (Lodha et al. 2013; Lassi et al. 2014 is unclear in methodology used to complete searches)
Lee Jin Hwa, Kim Seo Woo, Kim Ji Hye, Ryu Yon Ju, and Chang Jung Hyun (2012) High-dose levofloxacin in community-acquired pneumonia: a randomized, open-label study. Clinical drug investigation 32(9), 569-76	RCT included in prioritised systematic review (Raz-pasteur et al. 2015)
Lee Ping-Ing, Wu Mei-Hwan, Huang Li-Min, Chen Jong-Min, and Lee Chin-Yun (2008) An open, randomized, comparative study of clarithromycin and erythromycin in the treatment of children with community-acquired pneumonia. Journal of microbiology, immunology, and and infection = Wei mian yu gan ran za zhi 41(1), 54-61	A systematic review has been prioritised on this area over this RCT (Lodha et al. 2013)
Lin Ting-Yu, Lin Shu-Min, Chen Hao-Cheng, Wang Chih-Jan, Wang Yu-Min, Chang Min-Li, Wang Chun-Hua, Liu Chien-Ying, Lin Horng-Chyuan, Yu Chih-Ten, Hsieh Ling-Ling, Kuo Han-Pin, and Huang Chien-Da (2007) An open-label, randomized comparison of levofloxacin and amoxicillin/clavulanate plus clarithromycin for the treatment of hospitalized patients with community-acquired pneumonia. Chang Gung medical journal 30(4), 321-32	RCT included in prioritised systematic review (Raz-Pasteur et al. 2015)

Study reference	Reason
Liu Yang, Zhang Yingyuan, Wu Jufang, Zhu Demei, Sun Shenghua, Zhao Li, Wang Xuefeng, Liu Hua, Ren Zhenyi, Wang Changzheng, Xiu Qingyu, Xiao Zuke, Cao Zhaolong, Cui Shehuai, Yang Heping, Liang Yongjie, Chen Ping, Lv Yuan, Hu Chengping, Lv Xiaoju, Liu Shuang, Kuang Jiulong, Li Jianguo, Wang Dexi, and Chang Liwen (2017) A randomized, double-blind, multicenter Phase II study comparing the efficacy and safety of oral nemonoxacin with oral levofloxacin in the treatment of community-acquired pneumonia. Journal of microbiology, immunology, and and infection = Wei mian yu gan ran za zhi 50(6), 811-820	Low relevance to UK practice (nemonoxacin is not available in the UK)
Lodha Rakesh, Randev Shivani, and Kabra Sushil K (2016) Oral Antibiotics for Community acquired Pneumonia with Chest indrawing in Children Aged Below Five Years: A Systematic Review. Indian pediatrics 53(6), 489-95	A higher quality systematic review has been prioritised in this area (Lodha et al. 2013; all comparisons and 3 of 4 RCTs in Lodha et al. 2016 are included in Lodha et al. 2013 which includes more data and analysis)
Lodise Thomas P, Anzueto Antonio R, Weber David J, Shorr Andrew F, Yang Min, Smith Alexander, Zhao Qi, Huang Xingyue, and File Thomas M (2015) Assessment of time to clinical response, a proxy for discharge readiness, among hospitalized patients with community-acquired pneumonia who received either ceftaroline fosamil or ceftriaxone in two phase III FOCUS trials. Antimicrobial agents and chemotherapy 59(2), 1119-26	Secondary analysis of 2 RCTs included in an included systematic review (El Hajj et al. 2017)
Low Donald E, File Thomas M, Jr , Eckburg Paul B, Talbot George H, David Friedland, H , Lee Jon, Llorens Lily, Critchley Ian A, Thye Dirk A, and investigators Focus (2011) FOCUS 2: a randomized, double-blinded, multicentre, Phase III trial of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in community-acquired pneumonia. The Journal of antimicrobial chemotherapy 66 Suppl 3, iii33-44	RCT included in prioritised systematic review (El Hajj et al. 2017)
Mokabberi R, Haftbaradaran A, and Ravakhah K (2010) Doxycycline vs. levofloxacin in the treatment of community-acquired pneumonia. Journal of clinical pharmacy and therapeutics 35(2), 195-200	RCT included in prioritised systematic review (Nemeth et al. 2015)
Montassier E, Goffinet N, Potel G, and Batard E (2013) How to reduce antibiotic consumption for community-acquired pneumonia?. Medecine et maladies infectieuses 43(2), 52-9	A higher quality systematic review has been prioritised in this area (Li et al. 2007; Montassier et al. 2013 has fewer RCTs than Li et al. 2007 and unclear and limited reporting)
Oldach David, Clark Kay, Schranz Jennifer, Das Anita, Craft J Carl, Scott Drusilla, Jamieson Brian D, and Fernandes Prabhavathi (2013) Randomized, double-blind, multicenter phase 2 study comparing the efficacy and safety of oral solithromycin (CEM-101) to those of oral levofloxacin in the treatment of patients with community-acquired bacterial pneumonia. Antimicrobial agents and chemotherapy 57(6), 2526-34	Low relevance to UK practice (solithromycin is not available in the UK)

Study reference	Reason
Oosterheert Jan Jelrik, Bonten Marc J. M, Schneider Margriet M. E, Buskens Erik, Lammers Jan-Willem J, Hustinx Willem M. N, Kramer Mark H. H, Prins Jan M, Slee Peter H. Th J, Kaasjager Karin, and Hoepelman Andy I. M (2006) Effectiveness of early switch from intravenous to oral antibiotics in severe community acquired pneumonia: multicentre randomised trial. BMJ (Clinical research ed.) 333(7580), 1193	RCT included in prioritised systematic review (Athanassa et al. 2008)
Paladino Joseph A, Eubanks David A, Adelman Martin H, and Schentag Jerome J (2007) Once-daily cefepime versus ceftriaxone for nursing home-acquired pneumonia. Journal of the American Geriatrics Society 55(5), 651-7	Low relevance to UK practice (cefeprime is not available in the UK)
Postma Douwe F, van Werkhoven , Cornelis H, van Elden , Leontine J R, Thijsen Steven F. T, Hoepelman Andy I. M, Kluytmans Jan A. J. W, Boersma Wim G, Compaijen Clara J, van der Wall , Eva , Prins Jan M, Oosterheert Jan J, Bonten Marc J. M, and Group Cap-Start Study (2015) Antibiotic treatment strategies for community-acquired pneumonia in adults. The New England journal of medicine 372(14), 1312-23	RCT included in prioritised systematic review (Raz-Pasteur et al. 2015)
Rajesh Shimoga Mahabala, and Singhal Vikram (2013) Clinical Effectiveness of Co-trimoxazole vs. Amoxicillin in the Treatment of Non-Severe Pneumonia in Children in India: A Randomized Controlled Trial. International journal of preventive medicine 4(10), 1162-8	A systematic review has been prioritised on this area over this RCT (Lodha et al. 2013)
Ribeiro Cristiane Franco, Ferrari Giesela Fleisher, and Fioretto Jose Roberto (2011) Antibiotic treatment schemes for very severe community-acquired pneumonia in children: a randomized clinical study. Revista panamericana de salud publica = Pan American journal of public health 29(6), 444-50	RCT included in prioritised systematic review (Lodha et al. 2013)
Rojas M X, and Granados C (2006) Oral antibiotics versus parenteral antibiotics for severe pneumonia in children. The Cochrane database of systematic reviews (2), CD004979	A higher quality systematic review has been prioritised in this area (Lodha et al. 2013; Lodha et al. 2013 is also more recent than Rojas et al. 2006 and includes more RCTs)
Seki Masafumi, Higashiyama Yasuhito, Imamura Yoshifumi, Nakamura Shigeki, Kurihara Shintaro, Izumikawa Koichi, Kakeya Hiroshi, Yamamoto Yoshihiro, Yanagihara Katsunori, Tashiro Takayoshi, and Kohno Shigeru (2009) A clinical comparative study of piperacillin and sulbactam/ampicillin in patients with community-acquired bacterial pneumonia. Internal medicine (Tokyo, and Japan) 48(1), 49-55	Low relevance to UK practice (piperacillin is not available in the UK)
Shorr Andrew F, Khashab Mohammed M, Xiang Jim X, Tennenberg Alan M, and Kahn James B (2006) Levofloxacin 750-mg for 5 days for the treatment of hospitalized Fine Risk Class III/IV community-acquired pneumonia patients. Respiratory medicine 100(12), 2129-36	Secondary analysis of an RCT published before search date; comparison covered by prioritised study (Zhao et al. 2016)
Shorr Andrew F, Kollef Marin, Eckburg Paul B, Llorens Lily, and Friedland H David (2013) Assessment of ceftaroline fosamil in the treatment of community-acquired bacterial pneumonia due to Streptococcus pneumoniae: insights from two randomized trials. Diagnostic microbiology and infectious disease 75(3), 298-303	Secondary analysis of 2 RCTs included in an included systematic review (El Hajj et al. 2017)

Study reference	Reason
Sutijono Darrell, Hom Jeffrey, and Zehtabchi Shahriar (2011) Efficacy of 3-day versus 5-day antibiotic therapy for clinically diagnosed nonsevere pneumonia in children from developing countries. European journal of emergency medicine : official journal of the European Society for Emergency Medicine 18(5), 244-50	A higher quality systematic review has been prioritised in this area (Haider et al. 2008; Sutijono et al. 2011 is a lower quality systematic reivew with 3 of 4 RCTs included in Haider et al. 2008 and the 1 additional RCT covering an antibiotic not available in the UK)
Tanaseanu Cristina, Milutinovic Slobodan, Calistru Petre I, Strausz Janos, Zolubas Marius, Chernyak Valeriy, Dartois Nathalie, Castaing Nathalie, Gandjini Hassan, Cooper C Angel, and Study Group (2009) Efficacy and safety of tigecycline versus levofloxacin for community-acquired pneumonia. BMC pulmonary medicine 9, 44	RCT included in prioritised systematic review (Nemeth et al. 2015)
Torres Antoni, Garau Javier, Arvis Pierre, Carlet Jean, Choudhri Shurjeel, Kureishi Amar, Le Berre , Marie-Aude , Lode Hartmut, Winter John, Read Robert C, and Group Motiv Study (2008) Moxifloxacin monotherapy is effective in hospitalized patients with community-acquired pneumonia: the MOTIV study--a randomized clinical trial. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 46(10), 1499-509	RCT included in prioritised systematic review (Raz-Pasteur et al. 2015)
Udupa A, and Gupta P (2011) Antibiotic therapy in pneumonia: A comparative study of oral antibiotics in a rural healthcare centre. International Journal of Pharmacy and Pharmaceutical Sciences 3(SUPPL. 3), 156-158	RCT included in prioritised systematic review (Pakhale et al. 2014)
van Rensburg , Dirkie J J, Perng Reury-Perng, Mitha Ismail H, Bester Andre J, Kasumba Joseph, Wu Ren-Guang, Ho Ming-Lin, Chang Li-Wen, Chung David T, Chang Yu-Ting, King Chi-Hsin R, and Hsu Ming-Chu (2010) Efficacy and safety of nemonoxacin versus levofloxacin for community-acquired pneumonia. Antimicrobial agents and chemotherapy 54(10), 4098-106	Low relevance to UK practice (nemonoxacin is not available in the UK)
Vardakas Konstantinos Z, Siempos Ilias I, Grammatikos Alexandros, Athanassa Zoe, Korbila Ioanna P, and Falagas Matthew E (2008) Respiratory fluoroquinolones for the treatment of community-acquired pneumonia: a meta-analysis of randomized controlled trials. CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne 179(12), 1269-77	Higher quality systematic reviews have been prioritised in this area (Eliakim-Raz et al. 2012 and Skalsky et al. 2014; Vardakas et al. 2008 provides lower quality outcome reporting and is a less recent systematic review)
Xu Shuyun, Xiong Shengdao, Xu Yongjian, Liu Jin, Liu Huiguo, Zhao Jianping, and Xiong Weining (2006) Efficacy and safety of intravenous moxifloxacin versus cefoperazone with azithromycin in the treatment of community acquired pneumonia. Journal of Huazhong University of Science and Technology. Medical sciences = Hua zhong ke ji da xue xue bao. Yi xue Ying De wen ban = Huazhong keji daxue xuebao. Yixue Yingdewen ban 26(4), 421-4	RCT included in prioritised systematic review (Raz-Pasteur et al. 2015)

Study reference	Reason
Yahav D, Lador A, Paul M, and Leibovici L (2011) Efficacy and safety of tigecycline: A systematic review and meta-analysis. Journal of Antimicrobial Chemotherapy 66(9), 1963-1971	A higher quality systematic review has been prioritised in this area (Nemeth et al. 2015; 2 relevant RCTs included in Yahav et al. 2011 are included in Nemeth et al. 2015)
Yanagihara Katsunori, Fukuda Yuichi, Seki Masafumi, Izumikawa Koichi, Higashiyama Yasuhito, Miyazaki Yoshitsugu, Hirakata Yoichi, Tomono Kazunori, Mizuta Yohei, Tsukamoto Kazuhiro, and Kohno Shigeru (2006) Clinical comparative study of sulbactam/ampicillin and imipenem/cilastatin in elderly patients with community-acquired pneumonia. Internal medicine (Tokyo, and Japan) 45(17), 995-9	Low relevance to UK practice (sulbactam is not available in the UK)
Zhao Xu, Wu Ju-Fang, Xiu Qing-Yu, Wang Chen, Zhang De-Ping, Huang Jian-An, Xie Can-Mao, Sun Sheng-Hua, Lv Xiao-Ju, Si Bin, Xiao Zu-Ke, and Zhang Ying-Yuan (2014) A randomized controlled clinical trial of levofloxacin 750 mg versus 500 mg intravenous infusion in the treatment of community-acquired pneumonia. Diagnostic microbiology and infectious disease 80(2), 141-7	A higher quality RCT has been prioritised in this area (Zhao et al. 2014; Zhao et al. 2014 is a more recent RCT including more participants)
Zhong Nan Shan, Sun Tieying, Zhuo Chao, D'Souza George, Lee Sang Haak, Lan Nguyen Huu, Chiang Chi-Huei, Wilson David, Sun Fang, Iaconis Joseph, and Melnick David (2015) Ceftaroline fosamil versus ceftriaxone for the treatment of Asian patients with community-acquired pneumonia: a randomised, controlled, double-blind, phase 3, non-inferiority with nested superiority trial. The Lancet. Infectious diseases 15(2), 161-71	RCT included in prioritised systematic review (El Hajj et al. 2017)

Appendix J: Excluded studies

Study reference	Reason for exclusion
Anheyer Dennis, Cramer Holger, Lauche Romy, Saha Felix Joyonto, and Dobos Gustav (2017) Herbal Medicine in Children With Respiratory Tract Infection: Systematic Review and Meta-Analysis. Academic pediatrics ,	Excluded on population
Bansal Vikas, Mangi Muhammad A, Johnson Margaret M, and Festic Emir (2015) Inhaled corticosteroids and incident pneumonia in patients with asthma: Systematic review and meta-analysis. Acta medica academica 44(2), 135-58	Excluded on population
(2012) Dexamethasone reduces length of stay in patients with community-acquired pneumonia. Journal of the national medical association 104(1-2), 119	Excluded on publication/study type
Aabenhus Rune, Jensen Jens-Ulrik S, Jorgensen Karsten Juhl, Hrobjartsson Asbjorn, and Bjerrum Lars (2014) Biomarkers as point-of-care tests to guide prescription of antibiotics in patients with acute respiratory infections in primary care. The Cochrane database of systematic reviews (11), CD010130	Excluded on intervention
Albertson T E, Dean N C, El Solh , A A, Gotfried M H, Kaplan C, and Niederman M S (2010) Fluoroquinolones in the management of community-acquired pneumonia. International journal of clinical practice 64(3), 378-88	Excluded on publication/study type

Study reference	Reason for exclusion
Al-Dorzi Hasan M, Al Harbi, Shmylan A, and Arabi Yaseen M (2014) Antibiotic therapy of pneumonia in the obese patient: dosing and delivery. Current opinion in infectious diseases 27(2), 165-73	Excluded on publication/study type
Aliberti Stefano, Giuliani Fabio, Ramirez Julio, Blasi Francesco, and Group Duration Study (2015) How to choose the duration of antibiotic therapy in patients with pneumonia. Current opinion in infectious diseases 28(2), 177-84	Excluded on publication/study type
Alves Galvao, M G, Rocha Crispino Santos, M A, Alves Da Cunha, and A J L (2009) Antibiotics for undifferentiated acute respiratory tract infections in children under five years of age. Cochrane Database of Systematic Reviews (3), CD007880	Excluded on publication/study type
Ambrose Paul G (2008) Use of pharmacokinetics and pharmacodynamics in a failure analysis of community-acquired pneumonia: implications for future clinical trial study design. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 47 Suppl 3, S225-31	Excluded on publication/study type
Anonymous (2006) Azithromycin extended-release (Zmax) for sinusitis and pneumonia. Obstetrics and gynecology 107(1), 180-2	Excluded on publication/study type
Anonymous (2006) Pneumonia: 3 days of antibiotics for uncomplicated course. Journal of hospital medicine 1(6), 387	Excluded on publication/study type
Anonymous (2007) Incorrect antibiotic choice doesn't affect CAP outcome. Journal of Family Practice 56(3), 180	Excluded on publication/study type
Anonymous (2008) Pneumonia can be treated with 3-5 days of ABX. Journal of the National Medical Association 100(1), 151	Excluded on publication/study type
Arguedas Adriano, Cespedes Jaime, Botet Francesc Aseni, Blumer Jeffrey, Yogev Ram, Gesser Richard, Wang Jean, West Joseph, Snyder Theresa, Wimmer Wendy, Protocol 036 Study, and Group (2009) Safety and tolerability of ertapenem versus ceftriaxone in a double-blind study performed in children with complicated urinary tract infection, community-acquired pneumonia or skin and soft-tissue infection. International journal of antimicrobial agents 33(2), 163-7	Excluded on population
Attridge Russell T, and Frei Christopher R (2011) Health care-associated pneumonia: an evidence-based review. The American journal of medicine 124(8), 689-97	Excluded on population
Avni Tomer, Shiver-Ofer Shahaf, Leibovici Leonard, Tacconelli Evelina, DeAngelis Giulia, Cookson Barry, Pagani Leonardo, and Paul Mical (2015) Participation of elderly adults in randomized controlled trials addressing antibiotic treatment of pneumonia. Journal of the American Geriatrics Society 63(2), 233-43	Excluded on outcomes reported
Awad Samir S, Rodriguez Alejandro H, Chuang Yin-Ching, Marjanek Zsuszanna, Pareigis Alex J, Reis Gilmar, Scheeren Thomas W. L, Sanchez Alejandro S, Zhou Xin, Saulay Mikael, and Engelhardt Marc (2014) A phase 3 randomized double-blind comparison of ceftobiprole medocaril versus ceftazidime plus linezolid for the treatment of hospital-acquired pneumonia. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 59(1), 51-61	Excluded on population
Bao H, Lv Y, Wang D, Xue J, and Yan Z (2017) Clinical outcomes of extended versus intermittent administration of	Excluded on population

Study reference	Reason for exclusion
piperacillin/tazobactam for the treatment of hospital-acquired pneumonia: a randomized controlled trial. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology 36(3), 459-466	
Bari Abdul, Sadruddin Salim, Khan Attaullah, Khan Ibad ul Haque, Khan Amanullah, Lehri Iqbal A, Macleod William B, Fox Matthew P, Thea Donald M, and Qazi Shamim A (2011) Community case management of severe pneumonia with oral amoxicillin in children aged 2-59 months in Haripur district, Pakistan: a cluster randomised trial. Lancet (London, and England) 378(9805), 1796-803	Excluded on intervention
Barriere Steven L (2014) The ATTAIN trials: efficacy and safety of telavancin compared with vancomycin for the treatment of hospital-acquired and ventilator-associated bacterial pneumonia. Future microbiology 9(3), 281-9	Excluded on publication/study type
Barriere Steven L, Stryjewski Martin E, Corey G Ralph, Genter Fredric C, and Rubinstein Ethan (2014) Effect of vancomycin serum trough levels on outcomes in patients with nosocomial pneumonia due to Staphylococcus aureus: a retrospective, post hoc, subgroup analysis of the Phase 3 ATTAIN studies. BMC infectious diseases 14, 183	Excluded on population
Bassetti M, Righi E, Rosso R, Mannelli S, Di Biagio , A , Fasce R, Pallavicini F Bobbio, Marchetti F, and Viscoli C (2006) Efficacy of the combination of levofloxacin plus ceftazidime in the treatment of hospital-acquired pneumonia in the intensive care unit. International journal of antimicrobial agents 28(6), 582-5	Excluded on publication/study type
Bhavnani Sujata M, and Ambrose Paul G (2008) Cost-effectiveness of oral gemifloxacin versus intravenous ceftriaxone followed by oral cefuroxime with/without a macrolide for the treatment of hospitalized patients with community-acquired pneumonia. Diagnostic microbiology and infectious disease 60(1), 59-64	Excluded on outcomes reported
Bhutta Zulfiqar A, Das Jai K, Walker Neff, Rizvi Arjumand, Campbell Harry, Rudan Igor, Black Robert E, Lancet Diarrhoea, Pneumonia Interventions Study, and Group (2013) Interventions to address deaths from childhood pneumonia and diarrhoea equitably: what works and at what cost?. Lancet (London, and England) 381(9875), 1417-29	Excluded on publication/study type
Bi Jirui, Yang Jin, Wang Ying, Yao Cijiang, Mei Jing, Liu Ying, Cao Jiyu, and Lu Youjin (2016) Efficacy and Safety of Adjunctive Corticosteroids Therapy for Severe Community-Acquired Pneumonia in Adults: An Updated Systematic Review and Meta-Analysis. PloS one 11(11), e0165942	Excluded on intervention
Biondi Eric, McCulloh Russell, Alverson Brian, Klein Andrew, Dixon Angela, and Ralston Shawn (2014) Treatment of mycoplasma pneumonia: a systematic review. Pediatrics 133(6), 1081-90	Excluded on publication/study type
Bjerre Lise M, Verheij Theo Jm, and Kochen Michael M (2009) Antibiotics for community acquired pneumonia in adult outpatients. The Cochrane database of systematic reviews (4), CD002109	Duplicate

Study reference	Reason for exclusion
Blasi F, Cazzola M, Tarsia P, Aliberti S, Baldessari C, and Valenti V (2006) Telithromycin in lower respiratory tract infections. Future microbiology 1(1), 7-16	Excluded on publication/study type
Blondeau Joseph M, and Tillotson Glenn (2008) Role of gemifloxacin in the management of community-acquired lower respiratory tract infections. International journal of antimicrobial agents 31(4), 299-306	Excluded on publication/study type
Bradley John S, and McCracken George H (2008) Unique considerations in the evaluation of antibacterials in clinical trials for pediatric community-acquired pneumonia. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 47 Suppl 3, S241-8	Excluded on publication/study type
Briel Matthias, Spoorenberg Simone M. C, Snijders Dominic, Torres Antoni, Fernandez-Serrano Silvia, Meduri G Umberto, Gabarrus Albert, Blum Claudine A, Confalonieri Marco, Kasenda Benjamin, Siemieniuk Reed A. C, Boersma Wim, Bos Willem Jan W, Christ-Crain Mirjam, Ovidius study, group , Capisce study, group , and group Step study (2017) Corticosteroids in patients hospitalized with community-acquired pneumonia: systematic review and individual patient data meta-analysis. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America ,	Excluded on intervention
Buege Michael J, Brown Jack E, and Aitken Samuel L (2017) Solithromycin: A novel ketolide antibiotic. American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists 74(12), 875-887	Excluded on publication/study type
Carballo Nuria, De Antonio-Cusco , Marta , Echeverria-Esnal Daniel, Luque Sonia, Salas Esther, and Grau Santiago (2017) Community-acquired pneumonia caused by methicillin-resistant Staphylococcus aureus in critically-ill patients: systematic review. Neumonia comunitaria por Staphylococcus aureus resistente a meticilina en paciente critico: revision sistematica. 41(2), 187-203	Excluded on publication/study type
Carbon C, van Rensburg , D , Hagberg L, Fogarty C, Tellier G, Rangaraju M, and Nusrat R (2006) Clinical and bacteriologic efficacy of telithromycin in patients with bacteremic community-acquired pneumonia. Respiratory medicine 100(4), 577-85	Excluded on publication/study type
Cardoso Teresa, Almeida Monica, Carratala Jordi, Aragao Irene, Costa-Pereira Altamiro, Sarmento Antonio E, and Azevedo Luis (2015) Microbiology of healthcare-associated infections and the definition accuracy to predict infection by potentially drug resistant pathogens: a systematic review. BMC infectious diseases 15, 565	Excluded on population
Carreno Joseph J, and Lodise Thomas P (2014) Ceftaroline Fosamil for the Treatment of Community-Acquired Pneumonia: from FOCUS to CAPTURE. Infectious diseases and therapy 3(2), 123-32	Excluded on publication/study type
Ceccato A, Ferrer M, Gabarrus A, Sibilla O, Polverino E, Cilloniz C, Agusti C, Lopez F, Niederman M, and Torres A (2016) Benefits of co-administration of macrolides and glucocorticosteroids in the treatment of severe community acquired pneumonia. European respiratory journal. Conference: european respiratory society annual congress 2016. United kingdom. Conference start: 20160903. Conference end: 20160907 48(no pagination),	Excluded on publication/study type

Study reference	Reason for exclusion
Ceccato Adrian, Cilloniz Catia, Ranzani Otavio T, Menendez Rosario, Agusti Carles, Gabarrus Albert, Ferrer Miquel, Sibila Oriol, Niederman Michael S, and Torres Antoni (2017) Treatment with macrolides and glucocorticosteroids in severe community-acquired pneumonia: A post-hoc exploratory analysis of a randomized controlled trial. PloS one 12(6), e0178022	Excluded on intervention
Chalmers James D, and Rutherford Julia (2012) Can we use severity assessment tools to increase outpatient management of community-acquired pneumonia?. European journal of internal medicine 23(5), 398-406	Excluded on intervention
Chalumeau Martin, and Duijvestijn Yvonne C. M (2013) Acetylcysteine and carbocysteine for acute upper and lower respiratory tract infections in paediatric patients without chronic broncho-pulmonary disease. The Cochrane database of systematic reviews (5), CD003124	Excluded on population
Chang Christina C, Cheng Allen C, and Chang Anne B (2014) Over-the-counter (OTC) medications to reduce cough as an adjunct to antibiotics for acute pneumonia in children and adults. The Cochrane database of systematic reviews (3), CD006088	Excluded on intervention
Chang Jh (2011) Levofloxacin 750 mg versus conventional treatment of ceftriaxone and macrolide in community acquired pneumonia: a randomized, open label study. Respirology (carlton, and vic.) 16(Suppl 2), 67 [1204]	Excluded on publication/study type
Chaudhary Manu, Shrivastava Sanjay Mohan, and Sehgal Rajesh (2009) Evaluation of efficacy and safety of fixed dose combination of ceftazidime-tobramycin in comparison with ceftazidime in lower respiratory tract infections. Current clinical pharmacology 4(1), 62-6	Excluded on population
Chaudhary Manu, Shrivastava Sanjay Mohan, Varughese Lallu, and Sehgal Rajesh (2008) Efficacy and safety evaluation of fixed dose combination of cefepime and amikacin in comparison with cefepime alone in treatment of nosocomial pneumonia patients. Current clinical pharmacology 3(2), 118-22	Excluded on population
Chen Li-Ping, Chen Jun-Hui, Chen Ying, Wu Chao, and Yang Xiao-Hong (2015) Efficacy and safety of glucocorticoids in the treatment of community-acquired pneumonia: A meta-analysis of randomized controlled trials. World journal of emergency medicine 6(3), 172-8	Excluded on intervention
Chen P, Huang S, Tian J, Yang J, Gou W, and Ma Z (2016) The clinical observation of azithromycin with montelukast in the treatment of pneumonia in children. Respirology. Conference: 21st congress of the asian pacific society of respirology, and APSR 2016. Thailand. Conference start: 20161112. Conference end: 20161115 21, 91	Excluded on publication/study type
Chen Qf, and Zhang Yw (2018) Clinical effect of Saccharomyces boulardii powder combined with azithromycin sequential therapy in treatment of children with diarrhea secondary to Mycoplasma pneumoniae pneumonia. Zhongguo dang dai er ke za zhi [Chinese journal of contemporary pediatrics] 20(2), 116-120	Excluded on non-English language
Chen Yuanjing, Li Ka, Pu Hongshan, and Wu Taixiang (2011) Corticosteroids for pneumonia. The Cochrane database of systematic reviews (3), CD007720	Excluded on intervention

Study reference	Reason for exclusion
Cheng A C, Stephens D P, and Currie B J (2007) Granulocyte-colony stimulating factor (G-CSF) as an adjunct to antibiotics in the treatment of pneumonia in adults. The Cochrane database of systematic reviews (2), CD004400	Excluded on intervention
Cheng Ming, Pan Zhi-Yong, Yang Jiong, and Gao Ya-Dong (2014) Corticosteroid therapy for severe community-acquired pneumonia: a meta-analysis. Respiratory care 59(4), 557-63	Excluded on intervention
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Gorman Sean K, Slavik Richard S, and Marin Judith (2007) Corticosteroid treatment of severe community-acquired pneumonia. The Annals of pharmacotherapy 41(7), 1233-7	Excluded on publication/study type
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Jung Young Ju, Koh Younsuck, Hong Sang-Bum, Chung Joo Won, Ho Choi, Sang , Kim Nam Joong, Kim Mi-Na, Choi Ik Su, Han Song Yi, Kim Won-Dong, Yun Sung-Cheol, and Lim Chae-Man (2010) Effect of vancomycin plus rifampicin in the treatment of nosocomial methicillin-resistant Staphylococcus aureus pneumonia. Critical care medicine 38(1), 175-80	Excluded on population
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Kamath Ajay V, and Myint Phyo K (2006) Recognizing and managing severe community-acquired pneumonia. British journal of hospital medicine (London, and England : 2005) 67(4), M76-8	Excluded on publication/study type
Kim Jong Wook, Chung Joowon, Choi Sang-Ho, Jang Hang Jea, Hong Sang-Bum, Lim Chae-Man, and Koh Younsuck (2012) Early use of imipenem/cilastatin and vancomycin followed by de-escalation versus conventional antimicrobials without de-escalation for patients with hospital-acquired pneumonia in a medical ICU: a randomized clinical trial. Critical care (London, and England) 16(1), R28	Excluded on population
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Kola A, and Gastmeier P (2007) Efficacy of oral chlorhexidine in preventing lower respiratory tract infections. Meta-analysis of randomized controlled trials. The Journal of hospital infection 66(3), 207-16	Excluded on intervention
Kolditz Martin, Halank Michael, and Hoffken Gert (2006) Monotherapy versus Combination Therapy in Patients Hospitalized with Community-Acquired Pneumonia. Treatments in respiratory medicine 5(6), 371-83	Excluded on publication/study type
Koulenti Despoina, and Rello Jordi (2006) Gram-negative bacterial pneumonia: aetiology and management. Current opinion in pulmonary medicine 12(3), 198-204	Excluded on publication/study type
Koulenti Despoina, and Rello Jordi (2006) Hospital-acquired pneumonia in the 21st century: a review of existing treatment options and their impact on patient care. Expert opinion on pharmacotherapy 7(12), 1555-69	Excluded on publication/study type
Kulkarni N S (2015) Beta-lactam not as effective as beta-lactam plus macrolide for treating CAP in the hospital. American Family Physician 91(10), 720	Excluded on publication/study type
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Laterre Pierre-Francois (2008) Beyond antibiotics in severe community-acquired pneumonia: the role and rationale for tissue	Excluded on publication/study type

Study reference	Reason for exclusion
factor pathway inhibition. Critical care (London, and England) 12 Suppl 6, S4	
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Lee Jonathan S, Giesler Daniel L, Gellad Walid F, and Fine Michael J (2016) Antibiotic Therapy for Adults Hospitalized With Community-Acquired Pneumonia: A Systematic Review. JAMA 315(6), 593-602	Excluded on publication/study type
Lee Jong Hoo, Kim Hyun Jung, and Kim Yee Hyung (2017) Is beta-Lactam Plus Macrolide More Effective than beta-Lactam Plus Fluoroquinolone among Patients with Severe Community-Acquired Pneumonia?: a Systemic Review and Meta-Analysis. Journal of Korean medical science 32(1), 77-84	Excluded on publication/study type
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Liu Dong, Zhang Jing, Liu Hai-Xia, Zhu Ying-Gang, and Qu Jie-Ming (2015) Intravenous combined with aerosolised polymyxin versus intravenous polymyxin alone in the treatment of pneumonia caused by multidrug-resistant pathogens: a systematic review and	Excluded on publication/study type

Study reference	Reason for exclusion
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Loeb Mark (2010) Community-acquired pneumonia. BMJ clinical evidence 2010,	Excluded on publication/study type
Lopez-Vejar Ce, Castellanos-De La Cruz L, Meraz-Ortega R, Roman-Flores A, Geuguer-Chavez L, Pedro-Gonzalez A, Lozano-Nuevo Jj, and Rubio-Guerra A (2013) Efficacy of levofloxacin in the treatment of community-acquired pneumonia. Medicina interna de mexico 29(6), 587-594	Excluded on non-English language
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Lü Y, Yan Z, Wang Dh, Dong Wl, Yang Y, and Xia R (2013) Treatment study of hospital acquired pneumonia by optimizing dosing regimen of piperacillin/tazobactam: prolonged vs. regular infusion. Zhonghua wei zhong bing ji jiu yi xue 25(8), 479-483	Excluded on non-English language
Ludlam H A, and Enoch D A (2008) Doxycycline or moxifloxacin for the management of community-acquired pneumonia in the UK?. International journal of antimicrobial agents 32(2), 101-5	Excluded on publication/study type
Lynch Joseph P, 3rd , File Thomas M, Jr , and Zhanel George G (2006) Levofloxacin for the treatment of community-acquired pneumonia. Expert review of anti-infective therapy 4(5), 725-42	Excluded on publication/study type
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Maeurer Markus, Rao Martin, and Zumla Alimuddin (2016) Host-directed therapies for antimicrobial resistant respiratory tract infections. Current opinion in pulmonary medicine 22(3), 203-11	Excluded on publication/study type
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Mandell L A, and Waterer G W (2015) Empirical therapy of community-acquired pneumonia: Advancing evidence or just more doubt?. JAMA - Journal of the American Medical Association 314(4), 396-397	Excluded on publication/study type
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Maraqa Nizar F (2014) Pneumococcal infections. Pediatrics in review 35(7), 299-310	Excluded on publication/study type
Marquet K, Liesenborgs A, Bergs J, Vleugels A, and Claes N (2015) Incidence and outcome of inappropriate in-hospital empiric antibiotics for severe infection: A systematic review and meta-analysis. Critical Care 19(1), 63	Excluded on population
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Mathew Joseph L, Patwari Ashok K, Gupta Piyush, Shah Dheeraj, Gera Tarun, Gogia Siddhartha, Mohan Pavitra, Panda Rajmohan, and Menon Subhadra (2011) Acute respiratory infection and pneumonia in India: a systematic review of literature for advocacy and action: UNICEF-PHFI series on newborn and child health, India. Indian pediatrics 48(3), 191-218	Excluded on publication/study type
Matsuda Shuichi, Ogasawara Takashi, Sugimoto Shunsuke, Kato Shinpei, Umezawa Hiroki, Yano Toshiaki, and Kasamatsu Norio (2016) Prospective open-label randomized comparative, non-inferiority study of two initial antibiotic strategies for patients with nursing- and healthcare-associated pneumonia: Guideline-concordant therapy versus empiric therapy. Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy 22(6), 400-6	Excluded on population
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Meijvis Sabine C. A, Hardeman Hans, Remmelts Hilde H. F, Heijligenberg Rik, Rijkers Ger T, van Velzen-Blad , Heleen , Voorn G Paul, van de Garde , Ewoudt M W, Endeman Henrik, Grutters	Excluded on intervention

Study reference	Reason for exclusion
Jan C, Bos Willem Jan W, and Biesma Douwe H (2011) Dexamethasone and length of hospital stay in patients with community-acquired pneumonia: a randomised, double-blind, placebo-controlled trial. Lancet (London, and England) 377(9782), 2023-30	
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Miravitlles Marc, and Anzueto Antonio (2008) Moxifloxacin: a respiratory fluoroquinolone. Expert opinion on pharmacotherapy 9(10), 1755-72	Excluded on publication/study type
Morton Ben, Pennington Shaun Harry, and Gordon Stephen B (2014) Immunomodulatory adjuvant therapy in severe community-acquired pneumonia. Expert review of respiratory medicine 8(5), 587-96	Excluded on publication/study type
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Nannini Esteban C, Corey G Ralph, and Stryjewski Martin E (2012) Telavancin for the treatment of hospital-acquired pneumonia: findings from the ATTAIN studies. Expert review of anti-infective therapy 10(8), 847-54	Excluded on publication/study type
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Ni J, Hu G, and Sun R (2012) Clinical evaluation of ertapenem as empirical treatment of severe community-acquired pneumonia in elderly patients. Chinese Journal of Infection and Chemotherapy 12(6), 424-427	Excluded on non-English language
Ni J, Sun R, and Hu G-P (2011) Clinical effect of ertapenem in the treatment of severe community-acquired pneumonia in elderly patients. Respirology (carlton, and vic.) 16(Suppl 2), 57 [617]	Excluded on publication/study type
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Study reference	Reason for exclusion
Nie Wei, Li Bing, and Xiu Qingyu (2014) beta-Lactam/macrolide dual therapy versus beta-lactam monotherapy for the treatment of community-acquired pneumonia in adults: a systematic review and meta-analysis. The Journal of antimicrobial chemotherapy 69(6), 1441-6	Excluded on publication/study type
Nie Wei, Zhang Yi, Cheng Jinwei, and Xiu Qingyu (2012) Corticosteroids in the treatment of community-acquired pneumonia in adults: a meta-analysis. PloS one 7(10), e47926	Excluded on intervention
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Okimoto Niro, Kawai Yasuhiro, Katoh Tadashi, Hayashi Toshikiyo, Kurihara Takeyuki, and Miyashita Naoyuki (2015) Clinical effect of biapenem on nursing and healthcare-associated pneumonia (NHCAP). Journal of infection and chemotherapy : official journal of the Japan Society of Chemotherapy 21(8), 592-5	Excluded on publication/study type
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Oldach Dw, Barrera Cm, Metev H, Dvoretskiy Li, Mykietiuk A, Mitha I, Salvo Mc, Tanaseanu Cm, Szabo P, Clark K, Jamieson B, Das A, Keedy K, and Fernandes P (2015) Oral solithromycin versus oral moxifloxacin for treatment of adult community-acquired bacterial pneumonia (CABP): results of the global phase-3 trial solitaire-oral. American journal of respiratory and critical care medicine 191(no pagination),	Excluded on publication/study type
Opal S M (2012) Review: Short-course antibiotics in hospital-acquired pneumonia do not affect mortality. Annals of Internal Medicine 156(6), JC3-JC13	Excluded on publication/study type
Opmeer B C, El Moussaoui , R , Bossuyt P M. M, Speelman P, Prins J M, de Borgie , and C A J. M (2007) Costs associated with shorter duration of antibiotic therapy in hospitalized patients with	Excluded on publication/study type

Study reference	Reason for exclusion
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Ouchi K, Takayama S, Fujioka Y, Sunakawa K, and Iwata S (2017) A phase III, randomized, open-label study on 15% tosufloxacin granules in pediatric mycoplasma pneumoniae pneumonia. Japanese journal of chemotherapy 65(4), 585-596	Excluded on non-English language
Pascale G, Fortuna S, Montini L, Occhionero A, Festa R, Marsili S, Biancone M, Antonicelli F, Santis P, Tanzarella Es, Cutuli Sl, Pennisi Ma, Navarra P, and Antonelli M (2013) Linezolid continuous infusion in obese patients with nosocomial pneumonia. Intensive care medicine. 39, S270	Excluded on publication/study type
Patel Archana B, Bang Akash, Singh Meenu, Dhande Leena, Chelliah Luke Ravi, Malik Ashraf, Khadse Sandhya, and Group Ispot Study (2015) A randomized controlled trial of hospital versus home based therapy with oral amoxicillin for severe pneumonia in children aged 3 - 59 months: The IndiaCLEN Severe Pneumonia Oral Therapy (ISPOT) Study. BMC pediatrics 15, 186	Excluded on intervention
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Paul Mical, Daikos George L, Durante-Mangoni Emanuele, Yahav Dafna, Carmeli Yehuda, Benattar Yael Dishon, Skiada Anna, Andini Roberto, Eliakim-Raz Noa, Nutman Amir, Zusman Oren, Antoniadou Anastasia, Pafundi Pia Clara, Adler Amos, Dickstein Yaakov, Pavleas Ioannis, Zampino Rosa, Daitch Vered, Bitterman Roni, Zayyad Hiba, Koppel Fidi, Levi Inbar, Babich Tanya, Friberg Lena E, Mouton Johan W, Theuretzbacher Ursula, and Leibovici Leonard (2018) Colistin alone versus colistin plus meropenem for treatment of severe infections caused by carbapenem-resistant Gram-negative bacteria: an open-label, randomised controlled trial. The Lancet. Infectious diseases 18(4), 391-400	Excluded on population
Pei Guangsheng, Yin Weijiao, Zhang Yongmei, Wang Tongsheng, Mao Yimin, and Sun Yuxia (2016) Efficacy and safety of biapenem in treatment of infectious disease: a meta-analysis of randomized controlled trials. Journal of chemotherapy (Florence, and Italy) 28(1), 28-36	Excluded on population
Peterson Janet, Yektashenas Behin, and Fisher Alan C (2009) Levofloxacin for the treatment of pneumonia caused by Streptococcus pneumoniae including multidrug-resistant strains: pooled analysis. Current medical research and opinion 25(3), 559-68	Excluded on publication/study type
Peyrani P, and Ramirez J A (2008) Fluoroquinolones in hospitalized patients with CAP: An evidence-based review. Infections in Medicine 25(4), 161-170	Excluded on publication/study type
Phua Jason, Dean Nathan C, Guo Qi, Kuan Win Sen, Lim Hui Fang, and Lim Tow Keang (2016) Severe community-acquired	Excluded on intervention

Study reference	Reason for exclusion
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Pineda Lilibeth A, Saliba Ranime G, El Solh , and Ali A (2006) Effect of oral decontamination with chlorhexidine on the incidence of nosocomial pneumonia: a meta-analysis. Critical care (London, and England) 10(1), R35	Excluded on intervention
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Pooley N, Chadda S, Madrigal Am, Kuessner D, and Posthumus J (2014) A network meta-analysis comparing the efficacy and safety of ceftobiprole and selected comparators in the treatment of hospital-acquired pneumonia. Value in health. 17(7), A588	Excluded on publication/study type
Poon Henry, Chang Mei H, and Fung Horatio B (2012) Ceftaroline fosamil: a cephalosporin with activity against methicillin-resistant Staphylococcus aureus. Clinical therapeutics 34(4), 743-65	Excluded on publication/study type
Pothirat C, Champunot R, and Inchai J (2006) The optimal duration of antibiotic treatment for hospital acquired pneumonia a comparative study between the two antibiotic discontinuation policies. Chest 130(4 Suppl), 106s	Excluded on publication/study type
Prabhudesai P P, Jain S, Keshvani A, and Kulkarni Kp (2011) The efficacy and safety of amoxicillin-clavulanic acid 1000/125 mg twice daily extended release (XR) tablet for the treatment of bacterial community-acquired pneumonia in adults. Journal of the Indian Medical Association 109(2), 124-127	Excluded on publication/study type
Prina Elena, Ranzani Otavio T, and Torres Antoni (2015) Community-acquired pneumonia. Lancet (London, and England) 386(9998), 1097-108	Excluded on publication/study type
Principi N, Bianchini S, Baggi E, and Esposito S (2013) No evidence for the effectiveness of systemic corticosteroids in acute pharyngitis, community-acquired pneumonia and acute otitis media. European journal of clinical microbiology & infectious diseases : official publication of the European Society of Clinical Microbiology 32(2), 151-60	Excluded on publication/study type
Pugh Richard, Grant Chris, Cooke Richard P. D, and Dempsey Ged (2015) Short-course versus prolonged-course antibiotic therapy for hospital-acquired pneumonia in critically ill adults. The Cochrane database of systematic reviews (8), CD007577	Excluded on population
Punpanich Warunee, Groome Michelle, Muhe Lulu, Qazi Shamim A, and Madhi Shabir A (2011) Systematic review on the etiology and antibiotic treatment of pneumonia in human immunodeficiency virus-infected children. The Pediatric infectious disease journal 30(10), e192-202	Excluded on population

Study reference	Reason for exclusion
Qiang Li, Di Yunfei , Jiang Zhilan, and Xu Juanjuan (2018) Resveratrol improves efficacy of oral amoxicillin against childhood fast breathing pneumonia in a randomized placebo-controlled double blind clinical trial. Microbial pathogenesis 114, 209-212	Excluded on intervention
Qu Xiao-Yu, Hu Ting-Ting, and Zhou Wei (2015) A meta-analysis of efficacy and safety of doripenem for treating bacterial infections. The Brazilian journal of infectious diseases : an official publication of the Brazilian Society of Infectious Diseases 19(2), 156-62	Excluded on population
Ramirez Julio A, Cooper Angel C, Wiemken Timothy, Gardiner David, Babinchak Timothy, and Study Group (2012) Switch therapy in hospitalized patients with community-acquired pneumonia: tigecycline vs. levofloxacin. BMC infectious diseases 12, 159	Excluded on publication/study type
Ramirez Julio, Dartois Nathalie, Gandjini Hassan, Yan Jean Li, Korth-Bradley Joan, and McGovern Paul C (2013) Randomized phase 2 trial to evaluate the clinical efficacy of two high-dosage tigecycline regimens versus imipenem-cilastatin for treatment of hospital-acquired pneumonia. Antimicrobial agents and chemotherapy 57(4), 1756-62	Excluded on population
Rea-Neto Alvaro, Niederman Michael, Lobo Suzana Margareth, Schroeder Eric, Lee Michael, Kaniga Kone, Ketter Nzeera, Prokocimer Philippe, and Friedland Ian (2008) Efficacy and safety of doripenem versus piperacillin/tazobactam in nosocomial pneumonia: a randomized, open-label, multicenter study. Current medical research and opinion 24(7), 2113-26	Excluded on population
Remmelts H H. F, Meijvis S C. A, Heijligenberg R, Rijkers G T, Oosterheert J J, Bos W J. W, Endeman H, Grutters J C, Hoepelman A I. M, and Biesma D H (2012) Biomarkers define the clinical response to dexamethasone in community-acquired pneumonia. Journal of Infection 65(1), 25-31	Excluded on intervention
Restrepo M I (2009) Efficacy of intravenous infusion of doripenem. Clinical Infectious Diseases 49(SUPPL. 1), S17-S27	Excluded on publication/study type
Reyes B, Tomas , Ortega G, Marcos , Saldias P, and Fernando (2016) Are new antibiotics better than beta-lactams for non-critical inpatients with community-acquired pneumonia?. ?Son los nuevos antibioticos superiores a los betalactamicos para los pacientes hospitalizados, no criticos, and con neumonia adquirida en la comunidad? 16 Suppl 3, e6499	Excluded on lack of relevance to the review question
Rice Dennis A. K, Kaniga Kone, Lee Michael, and Redman Rebecca (2013) Activity of doripenem versus comparators in subjects with baseline bacteraemia in six pooled phase 3 clinical trials. International journal of antimicrobial agents 41(4), 388-92	Excluded on population
Roh Yh, and Lee Bj (2013) Treatment of elderly patients with community-acquired pneumonia with the guidance of procalcitonin. Chest 144(4 meeting abstract),	Excluded on publication/study type
Rubinstein E, Corey Gr, Boucher Hw, and Niederman Ms (2009) Telavancin for the treatment of hospital-acquired pneumonia in severely ill and older patients: the ATTAIN studies. Critical care (london, and england) ume 13 Suppl 1P310 (Abstract number),	Excluded on publication/study type
Rubinstein Ethan, Corey G Ralph, Stryjewski Martin E, and Kanafani Zeina A (2011) Telavancin for the treatment of serious	Excluded on publication/study type

Study reference	Reason for exclusion
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Rubinstein Ethan, Lalani Tahaniyat, Corey G Ralph, Kanafani Zeina A, Nannini Esteban C, Rocha Marcelo G, Rahav Galia, Niederman Michael S, Kollef Marin H, Shorr Andrew F, Lee Patrick C, Lentnek Arnold L, Luna Carlos M, Fagon Jean-Yves, Torres Antoni, Kitt Michael M, Genter Fredric C, Barriere Steven L, Friedland H David, Stryjewski Martin E, and Group Attain Study (2011) Telavancin versus vancomycin for hospital-acquired pneumonia due to gram-positive pathogens. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 52(1), 31-40	Excluded on population
Rubinstein Ethan, Stryjewski Martin E, and Barriere Steven L (2014) Clinical utility of telavancin for treatment of hospital-acquired pneumonia: focus on non-ventilator-associated pneumonia. Infection and drug resistance 7, 129-35	Excluded on publication/study type
Rubio Fernando G, Cunha Clovis A, Lundgren Fernando L. C, Lima Maria P. J. S, Teixeira Paulo J. Z, Oliveira Julio C. A, Golin Valdir, Mattos Waldo L. L. D, Mahlmann Herbert K, Moreira Edson D, Jardim Jose R, Silva Rodney L. F, and Silva Patricia H. B (2008) Intravenous azithromycin plus ceftriaxone followed by oral azithromycin for the treatment of inpatients with community-acquired pneumonia: an open-label, non-comparative multicenter trial. The Brazilian journal of infectious diseases : an official publication of the Brazilian Society of Infectious Diseases 12(3), 202-9	Excluded on publication/study type
Sader Helio S, and Jones Ronald N (2007) Cefdinir: an oral cephalosporin for the treatment of respiratory tract infections and skin and skin structure infections. Expert review of anti-infective therapy 5(1), 29-43	Excluded on publication/study type
Saito A, Watanabe A, Aoki N, Niki Y, Kohno S, Kaku M, and Hori S (2008) Phase III double-blind comparative study of sitafloxacin versus tosufloxacin in patients with community-acquired pneumonia. Japanese journal of chemotherapy 56(Suppl. 1), 49-62	Excluded on non-English language
Salluh Jorge I. F, Povoa Pedro, Soares Marcio, Castro-Faria-Neto Hugo C, Bozza Fernando A, and Bozza Patricia T (2008) The role of corticosteroids in severe community-acquired pneumonia: a systematic review. Critical care (London, and England) 12(3), R76	Excluded on intervention
Sandrock Christian E, and Shorr Andrew F (2015) The role of telavancin in hospital-acquired pneumonia and ventilator-associated pneumonia. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 61 Suppl 2, S79-86	Excluded on publication/study type
Scalera Nikole M, File Thomas M, and Jr (2007) How long should we treat community-acquired pneumonia?. Current opinion in infectious diseases 20(2), 177-81	Excluded on publication/study type
Scalera Nikole M, File Thomas M, and Jr (2013) Determining the duration of therapy for patients with community-acquired pneumonia. Current infectious disease reports 15(2), 191-5	Excluded on publication/study type

Study reference	Reason for exclusion
Schapowal Andreas (2013) Efficacy and safety of Echinaforce in respiratory tract infections. Wiener medizinische Wochenschrift (1946) 163(3-4), 102-5	Excluded on publication/study type
Schmitt D V, Leitner E, Welte T, and Lode H (2006) Piperacillin/tazobactam vs imipenem/cilastatin in the treatment of nosocomial pneumonia--a double blind prospective multicentre study. Infection 34(3), 127-34	Excluded on population
Scott Lesley J (2013) Telavancin: a review of its use in patients with nosocomial pneumonia. Drugs 73(16), 1829-39	Excluded on publication/study type
Scott Lesley J (2016) Ceftaroline Fosamil: A Review in Complicated Skin and Soft Tissue Infections and Community-Acquired Pneumonia. Drugs 76(17), 1659-1674	Excluded on publication/study type
Serra A, Schito G C, Nicoletti G, and Fadda G (2007) A therapeutic approach in the treatment of infections of the upper airways: thiamphenicol glycinate acetylcysteinate in sequential treatment (systemic-inhalatory route). International journal of immunopathology and pharmacology 20(3), 607-17	Excluded on population
Shafiq M, Mansoor M S, Khan A A, Sohail M R, and Murad M H (2013) Adjuvant steroid therapy in community-acquired pneumonia: A systematic review and meta-analysis. Journal of Hospital Medicine 8(2), 68-75	Excluded on intervention
Shah D (2008) 3-Day or 5-day oral antibiotics for non-severe pneumonia in children?. Indian Pediatrics 45(7), 577-578	Excluded on publication/study type
Shankar P K, Devi V, Bairy K L, and Nair S (2007) Antibiotics for Staphylococcus aureus pneumonia in adults. Cochrane Database of Systematic Reviews (1), CD006337	Excluded on publication/study type
Shao C-Z, He L-X, Wang G-F, Zhou X, Shen C, Li H-P, Xiu Q-Y, Chen B-Y, Zhou J-Y, Shi Y, Feng Y-L, Wu G-M, Chen P, and Dai L-M (2008) A randomized controlled multicentre clinical trial of levofloxacin sequential therapy compared with combination therapy with cefuroxime and azithromycin in patients with community-acquired pneumonia. Chinese journal of infection and chemotherapy 8(2), 102-106	Excluded on non-English language
Shmelev Ei, Stepanian Ie, Za?tseva As, Sokolova Lb, Mazaeva La, Tumanova Nf, and Sternin Iul (2009) The effectiveness and safety of accessory treatment with vobenzyme in patients with community-acquired pneumonia. Problemy tuberkuleza i boleznei legkikh (4), 14-18	Excluded on non-English language
Shrikant Kulkarni, and Nita (2016) Steroids Beneficial As Adjunctive Treatment for Community-Acquired Pneumonia. American family physician 93(3), 227	Excluded on publication/study type
Siemieniuk R A. C, Meade M O, Alonso-Coello P, Briel M, Evaniew N, Prasad M, Alexander P E, Fei Y, Vandvik P O, Loeb M, and Guyatt G H (2015) Corticosteroid therapy for patients hospitalized with community-acquired pneumonia: A systematic review and metaanalysis. Annals of Internal Medicine 163(7), 519-528	Excluded on intervention
Siemieniuk Reed A. C, and Guyatt Gordon H (2015) Corticosteroids in the treatment of community-acquired pneumonia: an evidence summary. Polskie Archiwum Medycyny Wewnetrznej 125(7-8), 570-5	Excluded on publication/study type

Study reference	Reason for exclusion
Siempos I I, Dimopoulos G, and Falagas M E (2009) Meta-analyses on the Prevention and Treatment of Respiratory Tract Infections. Infectious Disease Clinics of North America 23(2), 331-353	Excluded on publication/study type
Siempos I I, Vardakas K Z, Manta K G, and Falagas M E (2007) Carbapenems for the treatment of immunocompetent adult patients with nosocomial pneumonia. The European respiratory journal 29(3), 548-60	Excluded on population
Siempos Ilias I, Vardakas Konstantinos Z, Kopterides Petros, and Falagas Matthew E (2008) Adjunctive therapies for community-acquired pneumonia: a systematic review. The Journal of antimicrobial chemotherapy 62(4), 661-8	Excluded on intervention
Silvestri L, Weir I, Gregori D, Taylor N, Zandstra D, Van Saene , J J, Van Saene , and H K (2014) Effectiveness of oral chlorhexidine on nosocomial pneumonia, causative micro-organisms and mortality in critically ill patients: a systematic review and meta-analysis. Minerva anestesiologica 80(7), 805-20	Excluded on intervention
Simoens Steven, and Decramer Marc (2008) A pharmacoeconomic review of the management of respiratory tract infections with moxifloxacin. Expert opinion on pharmacotherapy 9(10), 1735-44	Excluded on publication/study type
Sligl Wendy I, Asadi Leyla, Eurich Dean T, Tjosvold Lisa, Marrie Thomas J, and Majumdar Sumit R (2014) Macrolides and mortality in critically ill patients with community-acquired pneumonia: a systematic review and meta-analysis. Critical care medicine 42(2), 420-32	Excluded on publication/study type
Snijders D, Daniels J M. A, De Graaff , C S, Van Der Werf , T S, and Boersma W G (2010) Efficacy of corticosteroids in community-acquired pneumonia: A randomized double-blinded clinical trial. American Journal of Respiratory and Critical Care Medicine 181(9), 975-982	Excluded on intervention
Song Y, Yao C, Shang H, Yao X, and Bai C (2017) Intravenous infusion of Chinese medicine Xuebijing for patients with severe pneumonia: a multicenter, randomised, double-blind controlled trial. The lancet. Conference: chinese academy of medical sciences health summit, and CAMS 2017. China 390(Spec.iss 1), 34	Excluded on publication/study type
Sorbello A, Komo S, and Valappil T (2010) Noninferiority margin for clinical trials of antibacterial drugs for nosocomial pneumonia. Drug Information Journal 44(2), 165-176	Excluded on outcomes reported
Spurling Geoffrey K. P, Del Mar , Chris B, Dooley Liz, Foxlee Ruth, and Farley Rebecca (2013) Delayed antibiotics for respiratory infections. The Cochrane database of systematic reviews (4), CD004417	Excluded on population
Steinmetz T, Eliakim-Raz N, Goldberg E, Leibovici L, and Yahav D (2015) Association of vancomycin serum concentrations with efficacy in patients with MRSA infections: a systematic review and meta-analysis. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases 21(7), 665-73	Excluded on publication/study type

Study reference	Reason for exclusion
Stern Anat, Skalsky Keren, Avni Tomer, Carrara Elena, Leibovici Leonard, and Paul Mical (2017) Corticosteroids for pneumonia. The Cochrane database of systematic reviews 12, CD007720	Excluded on intervention
Steurer J (2015) Steroids in addition to antibiotics improve outcome in patients with "community acquired" pneumonia. Praxis 104(13), 705-706	Excluded on non-English language
Sun L, Dong H, Wang Y, Shi W, Zhao X, and Wu J (2014) Effects and Safety of Ceftriaxone Versus Levofloxacin in Treating Community-Acquired Pneumonia: A Sysytematic Review. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 17(7), A665	Excluded on publication/study type
Sun S G, Shi Y F, Yan H, Li Y, Wang R, Wang S H, and Sun X D (2015) Xiyanping Injection in Treatment of Viral Pneumonia in Children: A Meta-analysis of Random Control Trials. Chinese Herbal Medicines 7(2), 173-178	Excluded on population
Sun Tieying, Sun Li, Wang Rongmei, Ren Xiaoping, Sui Dong-Jiang, Pu Chun, Ren Yajuan, Liu Ying, Yang Zhuo, and Li Fengzhi (2014) Clinical efficacy and safety of moxifloxacin versus levofloxacin plus metronidazole for community-acquired pneumonia with aspiration factors. Chinese medical journal 127(7), 1201-5	Excluded on population
Syed Yahiya Y (2014) Ceftobiprole medocaril: a review of its use in patients with hospital- or community-acquired pneumonia. Drugs 74(13), 1523-42	Excluded on publication/study type
Taboada M, Melnick D, Iaconis J P, Sun F, Zhong N S, File T M, Llorens L, David Friedland, H , and Wilson D (2016) Erratum to Ceftaroline fosamil versus ceftriaxone for the treatment of community-acquired pneumonia: Individual patient data meta-analysis of randomized controlled trials [J Antimicrob Chemother 2016; 71: 862-70]. Journal of Antimicrobial Chemotherapy 71(6), 1748-1749	Excluded on publication/study type
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Taboada Maria, Melnick David, Iaconis Joseph P, Sun Fang, Zhong Nan Shan, File Thomas M, Llorens Lily, Friedland H David, and Wilson David (2016) Ceftaroline fosamil versus ceftriaxone for the treatment of community-acquired pneumonia: individual patient data meta-analysis of randomized controlled trials. The Journal of antimicrobial chemotherapy 71(4), 862-70	Duplicate
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Study reference	Reason for exclusion
primary care: subgroup analysis. The european respiratory journal 47(1), 327-330	
Terblanche A J, Green R J, Rheeder P, and Wittenberg D F (2008) Adjunctive corticosteroid treatment of clinical Pneumocystis jiroveci pneumonia in infants less than 18 months of age - A randomised controlled trial. South African Medical Journal 98(4), 287-290	Excluded on publication/study type
Theodoratou Evropi, Al-Jilaihawi Sarah, Woodward Felicity, Ferguson Joy, Jhass Arnoupe, Balliet Manuela, Kolcic Ivana, Sadruddin Salim, Duke Trevor, Rudan Igor, and Campbell Harry (2010) The effect of case management on childhood pneumonia mortality in developing countries. International journal of epidemiology 39 Suppl 1, i155-71	Excluded on publication/study type
Thompson A M, Thomas S E, Schafers S J, Hartmann A P, Call W B, Bushwitz J, and Deal E N (2015) The role of azithromycin in healthcare-associated pneumonia treatment. Journal of clinical pharmacy and therapeutics ,	Excluded on population
Tie Hong-Tao, Tan Qi, Luo Ming-Zhu, Li Qiang, Yu Jia-Lin, and Wu Qing-Chen (2016) Zinc as an adjunct to antibiotics for the treatment of severe pneumonia in children <5 years: a meta-analysis of randomised-controlled trials. The British journal of nutrition 115(5), 807-16	Excluded on intervention
Tillotson Glenn S (2008) Role of gemifloxacin in community-acquired pneumonia. Expert review of anti-infective therapy 6(4), 405-18	Exclude on publication/study type
Tleyjeh Imad M, Tlaygeh Haytham M, Hejal Rana, Montori Victor M, and Baddour Larry M (2006) The impact of penicillin resistance on short-term mortality in hospitalized adults with pneumococcal pneumonia: a systematic review and meta-analysis. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 42(6), 788-97	Excluded on publication/study type
Todisco T, Dal Farra, F , Ciliberti G, Pirina P, Guelfi R, Serra G, Paris R, Mancuso I, and Cepparulo M (2008) An Italian experience of sequential intravenous and oral azithromycin plus intravenous ampicillin/sulbactam in hospitalized patients with community-acquired pneumonia. Journal of chemotherapy (Florence, and Italy) 20(2), 225-32	Excluded on publication/study type
Tokuyasu H, Harada T, Watanabe E, Okazaki R, Touge H, Kawasaki Y, and Shimizu E (2009) Effectiveness of meropenem for the treatment of aspiration pneumonia in elderly patients. Internal Medicine 48(3), 129-135	Excluded on population
Tolentino Ac, Seabra E, and Tanaka E (2016) Cost analysis of levofloxacin 750mg during 5 days vs levofloxacin 500mg during 10 days for the treatment of comunity-acquired pneumonia under the Brazilian public hospital perspective. Value in health. Conference: ISPOR 19th annual european congress. Austria. Conference start: 20161029. Conference end: 20161102 19(7), A910	Excluded on publication/study type
Torres A, Berre M, Choudhri S, and Arvis P (2007) Moxifloxacin vs ceftriaxone/levofloxacin in hospitalized patients with community-acquired pneumonia (CAP), PSI class IV and V: a MOTIV Study subanalysis. American thoracic society international conference, may 18-23, 2007, san francisco, california, and USA , Poster #J70	Excluded on publication/study type

Study reference	Reason for exclusion
Torres A, Niederman M S, Chastre J, Ewig S, Fernandez-Vandellos P, Hanberger H, Kollef M, Bassi G L, Luna C M, Martin-Loeches I, Paiva J A, Read R C, Rigau D, Timsit J F, Welte T, and Wunderink R (2017) International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia. European Respiratory Journal 50(3), 00582	Excluded on publication/study type
Torres A, Zhong N, Pachl J, Timsit J F, Kollef M, Chen Z, Song J, Taylor D, Laud P J, Stone G G, and Chow J W (2017) Ceftazidime-avibactam versus meropenem in nosocomial pneumonia, including ventilator-associated pneumonia (REPROVE): A randomised, double-blind, phase 3 non-inferiority trial. The Lancet Infectious Diseases ,	Excluded on population
Torres Antoni, and Liapikou Adamantia (2012) Levofloxacin for the treatment of respiratory tract infections. Expert opinion on pharmacotherapy 13(8), 1203-12	Not available
Trupka Tracy, Fisher Kristen, Micek Scott T, Juang Paul, and Kollef Marin H (2017) Enhanced antimicrobial de-escalation for pneumonia in mechanically ventilated patients: a cross-over study. Critical care (London, and England) 21(1), 180	Excluded on population
Valavi E, Hakimzadeh M, Shamsizadeh A, Aminzadeh M, and Alghasi A (2011) The efficacy of zinc supplementation on outcome of children with severe pneumonia. A randomized double-blind placebo-controlled clinical trial. Indian Journal of Pediatrics 78(9), 1079-1084	Excluded on intervention
Valentiner-Branth Palle, Shrestha Prakash S, Chandyo Ram K, Mathisen Maria, Basnet Sudha, Bhandari Nita, Adhikari Ramesh K, Sommerfelt Halvor, and Strand Tor A (2010) A randomized controlled trial of the effect of zinc as adjuvant therapy in children 2-35 mo of age with severe or nonsevere pneumonia in Bhaktapur, Nepal. The American journal of clinical nutrition 91(6), 1667-74	Excluded on intervention
Van Bambeke , Francoise , and Tulkens Paul M (2016) The role of solithromycin in the management of bacterial community-acquired pneumonia. Expert review of anti-infective therapy 14(3), 311-24	Excluded on publication/study type
van Hecke , Oliver , Wang Kay, Lee Joseph J, Roberts Nia W, and Butler Chris C (2017) Implications of Antibiotic Resistance for Patients' Recovery From Common Infections in the Community: A Systematic Review and Meta-analysis. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 65(3), 371-382	Excluded on publication/study type
van Zanten , A R H, Oudijk M, Nohlmans-Paulssen M K. E, van der Meer , Y G, Girbes A R. J, and Polderman K H (2007) Continuous vs. intermittent cefotaxime administration in patients with chronic obstructive pulmonary disease and respiratory tract infections: pharmacokinetics/pharmacodynamics, bacterial susceptibility and clinical efficacy. British journal of clinical pharmacology 63(1), 100-9	Excluded on population
Vardakas K Z, Trigkidis K K, and Falagas M E (2017) Fluoroquinolones or macrolides in combination with beta-lactams in adult patients hospitalized with community acquired pneumonia: a systematic review and meta-analysis. Clinical microbiology and	Excluded on publication/study type

Study reference	Reason for exclusion
infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases 23(4), 234-241	
Vardakas K Z, Trigkidis K K, and Falagas M E (2017) Fluoroquinolones or macrolides in combination with beta-lactams in adult patients hospitalized with community acquired pneumonia: a systematic review and meta-analysis. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases 23(4), 234-241	Excluded on publication/study type
Vardakas Konstantinos Z, Trigkidis Kyriakos K, Apiranthiti Katerina N, and Falagas Matthew E (2017) The dilemma of monotherapy or combination therapy in community acquired pneumonia. European journal of clinical investigation ,	Excluded on outcomes reported
Vardakas Konstantinos Z, Trigkidis Kyriakos K, Apiranthiti Katerina N, and Falagas Matthew E (2017) The dilemma of monotherapy or combination therapy in community acquired pneumonia. European journal of clinical investigation ,	Excludde on publication/study type
Vidal L, Borok S, Gafter-Gvili A, Fraser A, Leibovici L, and Paul M (2007) Aminoglycosides as a single antibiotic versus other (non-aminoglycosides) antibiotics for the treatment of patients with infection. Cochrane Database of Systematic Reviews (2), CD006485	Excluded on population
Vilas-Boas A-L, Nascimento-Carvalho Cm, Matutino Ar, Barreto Bb, Silva Cc, Braga Da, Oliveira F, Nogueira Gv, Oliveira Is, Lorgetto I, Costa In, Araripe J, Vieira Jr, Neiva Lb, Santana Mc, Nobre-Bastos M, Santos Pm, Camara Sf, Carneiro S, Sirmos Ur, Araujo Vf, Vilas-Boas C, Gantois D, Azevedo F, Maia J-R, Piraja L, Jesus Ps, Fonseca T, Vilar T, Fontoura M-Sh, Xavier-Souza G, Araujo-Neto Ca, Andrade Sc, Brim Rv, Noblat L, Barral A, and Cardoso M-Ra (2015) Comparison of oral amoxicillin given thrice or twice daily to children between 2 and 59 months old with non-severe pneumonia: a randomized controlled trial-authors' response. Journal of antimicrobial chemotherapy 70(2), 636-638	Excluded on publication/study type
Vines-Douglas Greta (2008) Diagnosing and treating CAP in immunocompetent adults. JAAPA : official journal of the American Academy of Physician Assistants 21(1), 26-30	Excluded on publication/study type
Wadhwa Nitya, Chandran Aruna, Aneja Satinder, Lodha Rakesh, Kabra Sushil K, Chaturvedi Mona K, Sodhi Jitender, Fitzwater Sean P, Chandra Jagdish, Rath Bimbadhar, Kainth Udaypal S, Saini Savita, Black Robert E, Santosham Mathuram, and Bhatnagar Shinjini (2013) Efficacy of zinc given as an adjunct in the treatment of severe and very severe pneumonia in hospitalized children 2-24 mo of age: a randomized, double-blind, placebo-controlled trial. The American journal of clinical nutrition 97(6), 1387-94	Excluded on intervention
Walkey Allan J, O'Donnell Max R, and Wiener Renda Soylemez (2011) Linezolid vs glycopeptide antibiotics for the treatment of suspected methicillin-resistant Staphylococcus aureus nosocomial pneumonia: a meta-analysis of randomized controlled trials. Chest 139(5), 1148-1155	Excluded on population
Walkey Allan J, O'Donnell Max R, and Wiener Renda Soylemez (2011) Linezolid vs glycopeptide antibiotics for the treatment of suspected methicillin-resistant Staphylococcus aureus nosocomial	Excluded on publication/study type

Study reference	Reason for exclusion
pneumonia: a meta-analysis of randomized controlled trials. Chest 139(5), 1148-1155	
Wan You-Dong, Sun Tong-Wen, Liu Zi-Qi, Zhang Shu-Guang, Wang Le-Xin, and Kan Quan-Cheng (2016) Efficacy and Safety of Corticosteroids for Community-Acquired Pneumonia: A Systematic Review and Meta-Analysis. Chest 149(1), 209-19	Excluded on intervention
Wang Linlin, and Song Yuanlin (2017) Efficacy of zinc given as an adjunct to the treatment of severe pneumonia: A meta-analysis of randomized, double-blind and placebo-controlled trials. The clinical respiratory journal ,	Excluded on intervention
Wang Q, Zhu S, Zhao Yh, and Wang Hl (2015) Treatment of Intractable Pediatric Mycoplasma Pneumonia by Qingfei Huoxue Recipe Combined Azithromycin: a Random Parallel Control Study. Zhongguo zhong xi yi jie he za zhi zhongguo zhongxiyi jiehe zazhi = chinese journal of integrated traditional and western medicine 35(5), 545-548	Excluded on non-English language
Wang Yan, Zou Yamin, Xie Jiao, Wang Taotao, Zheng Xiaowei, He Hairong, Dong Weihua, Xing Jianfeng, and Dong Yalin (2015) Linezolid versus vancomycin for the treatment of suspected methicillin-resistant Staphylococcus aureus nosocomial pneumonia: a systematic review employing meta-analysis. European journal of clinical pharmacology 71(1), 107-15	Excluded on population
Wang Z, Shan T, Liu Y, Ding S, Li C, Zhai Q, Chen X, Du B, Li Y, Zhang J, Wang H, and Wu D (2014) Comparison of 3-hour and 30-minute infusion regimens for meropenem in patients with hospital acquired pneumonia in intensive care unit: a randomized controlled clinical trial. Zhonghua wei zhong bing ji jiu yi xue 26(9), 644-649	Excluded on non-English language
Watanabe A, Aoki N, Chida K, Niki Y, Saito A, Kohno S, Kadota J-I, and Shiba K (2010) Comparative phase III tazobactam/piperacillin and ceftazidime study in the treatment of community-acquired pneumonia. Japanese journal of chemotherapy 58(Suppl. 1), 29-49	Excluded on non-English language
Welte T, Scheeren Twl, Rodriguez A, Demange A, and Engelhardt M (2014) Efficacy of ceftobiprole in intensive care unit (ICU) patients with hospital-acquired pneumonia (HAP). European respiratory journal 44,	Excluded on publication/study type
Wilke Michael, and Grube Rolf (2013) Update on management options in the treatment of nosocomial and ventilator assisted pneumonia: review of actual guidelines and economic aspects of therapy. Infection and drug resistance 7, 1-7	Excluded on publication/study type
Wood G Christopher (2011) Aerosolized antibiotics for treating hospital-acquired and ventilator-associated pneumonia. Expert review of anti-infective therapy 9(11), 993-1000	Excluded on publication/study type
Wood G Christopher, and Swanson Joseph M (2007) Aerosolised antibacterials for the prevention and treatment of hospital-acquired pneumonia. Drugs 67(6), 903-14	Excluded on publication/study type
Woods Christian, and Colice Gene (2014) Methicillin-resistant Staphylococcus aureus pneumonia in adults. Expert review of respiratory medicine 8(5), 641-51	Excluded on publication/study type

Study reference	Reason for exclusion
Wu (2017) The clinical efficacy of integrated traditional chinese and western medicine treatment of hospital-acquired pneumonia. Biomedical research (india) 28(9), 3957-3961	Excluded on intervention
Wu Wei-Fang, Fang Qiang, and He Guo-Jun (2017) Efficacy of corticosteroid treatment for severe community-acquired pneumonia: A meta-analysis. The American journal of emergency medicine ,	Excluded on intervention
Wunderink Richard G, and Waterer Grant (2017) Advances in the causes and management of community acquired pneumonia in adults. BMJ (Clinical research ed.) 358, j2471	Excluded on publication/study type
Wunderink Richard G, Niederman Michael S, Kollef Marin H, Shorr Andrew F, Kunkel Mark J, Baruch Alice, McGee William T, Reisman Arlene, and Chastre Jean (2012) Linezolid in methicillin-resistant Staphylococcus aureus nosocomial pneumonia: a randomized, controlled study. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America 54(5), 621-9	Excluded on population
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