Cochrane Library

Cochrane Database of Systematic Reviews

Short-course versus long-course therapy of the same antibiotic for community-acquired pneumonia in adolescent and adult outpatients (Review)

López-Alcalde J, Rodriguez-Barrientos R, Redondo-Sánchez J, Muñoz-Gutiérrez J, Molero García JM, Rodríguez-Fernández C, Heras-Mosteiro J, Marin-Cañada J, Casanova-Colominas J, Azcoaga-Lorenzo A, Hernandez Santiago V, Gómez-García M

López-Alcalde J, Rodriguez-Barrientos R, Redondo-Sánchez J, Muñoz-Gutiérrez J, Molero García JM, Rodríguez-Fernández C, Heras-Mosteiro J, Marin-Cañada J, Casanova-Colominas J, Azcoaga-Lorenzo A, Hernandez Santiago V, Gómez-García M.

Short-course versus long-course therapy of the same antibiotic for community-acquired pneumonia in adolescent and adult outpatients.

Cochrane Database of Systematic Reviews 2018, Issue 9. Art. No.: CD009070.

DOI: 10.1002/14651858.CD009070.pub2.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Short-course versus long-course therapy of the same antibiotic for community-acquired pneumonia in adolescent and adult outpatients

Jesús López-Alcalde[1,2], Ricardo Rodriguez-Barrientos[3], Jesús Redondo-Sánchez[4], Javier Muñoz-Gutiérrez[5], José María Molero García[6], Carmen Rodríguez-Fernández[7], Julio Heras-Mosteiro[8], Jaime Marin-Cañada[9], Jose Casanova-Colominas[10], Amaya Azcoaga-Lorenzo[11], Virginia Hernandez Santiago[12], Manuel Gómez-García[13]

[1]Faculty of Medicine, Universidad Francisco de Vitoria (UFV) Madrid, Madrid, Spain. [2]Clinical Biostatistics Unit, Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid, Spain. [3]Unidad de apoyo a la Investigación, Gerencia Asistencial de Atención Primaria, Red de Investigación en Servicios de Salud en Enfermedades Crónicas (REDISSEC), Madrid, Spain. [4]Centro de Salud Ramon y Cajal, Gerencia Asistencial Atención Primaria, Madrid, Spain. [5]Centro de Salud Buenos Aires, Gerencia Asistencial Atención Primaria, Madrid, Spain. [6]Centro de Salud San Andrés, Gerencia Asistencial Atención Primaria, Madrid, Spain. [7]Centro de Salud San Cristóbal, Gerencia Asistencial Atención Primaria, Madrid, Spain. [8]Department of Preventive Medicine and Public Health & Immunology and Microbiology, Rey Juan Carlos University, Madrid, Spain. [9]Centro de Salud Villarejo de Salvanes, Gerencia Asistencial Atencion Primaria de Madrid, Villarejo de Salvanes, Spain. [10]Centro de Salud Ciudad de los Periodistas, Gerencia Asistencial de Atención Primaria, Madrid, Spain. [11]Centro de Salud Los Pintores, Gerencia Asistencial Atención Primaria, Parla, Spain. [12]Division of Population and Behavioural Sciences, School of Medicine, University of St Andrews, Dundee, UK. [13]Centro de Salud Mirasierra, Gerencia Asistencial Atención Primaria, Madrid, Spain

Contact address: Jesús López-Alcalde, Faculty of Medicine, Universidad Francisco de Vitoria (UFV) Madrid, Ctra. Pozuelo-Majadahonda km. 1,800, Madrid, Spain. cochrane.madrid@ufv.es, suso77@gmail.com.

Editorial group: Cochrane Acute Respiratory Infections Group.
Publication status and date: New, published in Issue 9, 2018.

Citation: López-Alcalde J, Rodriguez-Barrientos R, Redondo-Sánchez J, Muñoz-Gutiérrez J, Molero García JM, Rodríguez-Fernández C, Heras-Mosteiro J, Marin-Cañada J, Casanova-Colominas J, Azcoaga-Lorenzo A, Hernandez Santiago V, Gómez-García M. Short-course versus long-course therapy of the same antibiotic for community-acquired pneumonia in adolescent and adult outpatients. *Cochrane Database of Systematic Reviews* 2018, Issue 9. Art. No.: CD009070. DOI: 10.1002/14651858.CD009070.pub2.

ABSTRACT

Background

Community-acquired pneumonia (CAP) is a lung infection that can be acquired during day-to-day activities in the community (not while receiving care in a hospital). Community-acquired pneumonia poses a significant public health burden in terms of mortality, morbidity, and costs. Shorter antibiotic courses for CAP may limit treatment costs and adverse effects, but the optimal duration of antibiotic treatment is uncertain.

Objectives

To evaluate the efficacy and safety of short-course versus longer-course treatment with the same antibiotic at the same daily dosage for CAP in non-hospitalised adolescents and adults (outpatients). We planned to investigate non-inferiority of short-course versus longer-term course treatment for efficacy outcomes, and superiority of short-course treatment for safety outcomes.

Search methods

We searched CENTRAL, which contains the Cochrane Acute Respiratory Infections Group Specialised Register, MEDLINE, Embase, five other databases, and three trials registers on 28 September 2017 together with conference proceedings, reference checking, and contact with experts and pharmaceutical companies.

Selection criteria

Randomised controlled trials (RCTs) comparing short- and long-courses of the same antibiotic for CAP in adolescent and adult outpatients.

Data collection and analysis

We planned to use standard Cochrane methods.

Main results

Our searches identified 5260 records. We did not identify any RCTs that compared short- and longer-courses of the same antibiotic for the treatment of adolescents and adult outpatients with CAP.

We excluded two RCTs that compared short courses (five compared to seven days) of the same antibiotic at the same daily dose because they evaluated antibiotics (gemifloxacin and telithromycin) not commonly used in practice for the treatment of CAP. In particular, gemifloxacin is no longer approved for the treatment of mild-to-moderate CAP due to its questionable risk-benefit balance, and reported adverse effects. Moreover, the safety profile of telithromycin is also cause for concern.

We found one ongoing study that we will assess for inclusion in future updates of the review.

Authors' conclusions

We found no eligible RCTs that studied a short-course of antibiotic compared to a longer-course (with the same antibiotic at the same daily dosage) for CAP in adolescent and adult outpatients. The effects of antibiotic therapy duration for CAP in adolescent and adult outpatients remains unclear.

PLAIN LANGUAGE SUMMARY

Short- versus longer-course antibiotics for community-acquired pneumonia in non-hospitalised adolescents and adults

Review question

We investigated short- and longer-courses of antibiotics for adolescents and adults with community-acquired pneumonia (CAP) who did not require admission to hospital.

Background

Community-acquired pneumonia is a common lung infection that can be acquired during day-to-day activities in the community (not while receiving care in a hospital). Community-acquired pneumonia can be serious, and among older people and those with other health problems it can cause death. Community-acquired pneumonia is treated with antibiotics. Short-course antibiotic treatment may be effective, cheaper, and safer than longer treatment, but this needs to be demonstrated.

Search date

The evidence is current to 28 September 2017.

Key results

Our searches identified 5260 records, but no completed studies compared short- and longer-courses of the same antibiotic for treatment of adolescents and adults in the community with CAP. The effect of length of antibiotic therapy on adolescents and adults with CAP who are treated in the community remains unclear.

We excluded two studies that compared short courses (five versus seven days) of the same antibiotic at the same daily dose because they evaluated antibiotics (gemifloxacin and telithromycin) that are not commonly used for people with CAP. Gemifloxacin is no longer used because its risks do not appear be balanced with treatment benefit, and adverse treatment effects have been reported. The safety of telithromycin has also raised concerns.

We found one ongoing study that we will assess for inclusion in future updates of the review.

BACKGROUND

Description of the condition

Pneumonia is an acute lung infection. Community-acquired pneumonia (CAP) usually refers to pneumonia acquired outside the hospital setting or that develops within 48 hours of hospital admission. This contrasts with healthcare-associated pneumonia, which is defined as pneumonia that develops after 48 hours of hospital admission, or pneumonia that develops in hospital after intubation (Kalil 2016; NICE 2014). Common clinical features of CAP include cough, fever, painful breathing, fatigue, shortness of breath, and night sweats (Broulette 2013). The diagnostic criteria for pneumonia vary widely; some guidelines require the presence of dense areas of the lung on a chest x-ray or other imaging technique (Torres 2013a), while others require the presence of respiratory signs (abnormal breath sounds, such as localised crackles) or symptoms only (Lim 2015).

Community-acquired pneumonia can be caused by different micro-organisms. The most common infective organism among outpatients with non-severe pneumonia is *Streptococcus pneumoniae* (Cillóniz 2012; Torres 2013a; Welte 2012).

Several factors are associated with increased risk of CAP, including smoking, alcoholism, underlying medical conditions, nursing home residency, or regular contact with children (Sahuquillo-Arce 2016; Torres 2013b).

Community-acquired pneumonia poses a high burden of mortality, morbidity, and healthcare-associated costs worldwide (Broulette 2013). Community-acquired pneumonia incidence varies by country, age, and gender; the highest rates occur in older people (34 per 1000 adults aged 75 years and over). The overall annual incidence among adults in Europe ranges from 1.54 to 1.7 per 1000 population (Torres 2013b; Welte 2012; Woodhead 1987).

Lower respiratory tract infections, including pneumonia, are the fourth most common cause of death globally (Lim 2012; Torres 2013b). The cost associated with hospital treatment of CAP is 5 to 10 times greater than outpatient treatment (Tichopad 2013; Welte 2012).

Several studies have estimated an increase in antibiotic resistance in CAP-related pathogens worldwide (Spellberg 2008; Welte 2012; WHO 2014), which has important clinical and economic implications. The failure of antibiotic treatment due to resistance or an inappropriate treatment choice may increase treatment cost if a more expensive antibiotic class or longer hospital stay is required.

Description of the intervention

Adults diagnosed with CAP require effective antibiotic therapy. Frequently used antibiotics are beta-lactams, cephalosporins, macrolides, and fluoroquinolones (Torres 2013a). The choice of antibiotic is commonly empirical, and individual study results have not shown significant differences in efficacy among antibiotics or antibiotic groups (Pakhale 2014). Some factors implicated with empirical treatment choices include potential aetiological pathogens and their regional resistance profiles, the efficacy and safety of individual antibiotics, and the treatment schedule and its effect on adherence to treatment (Mandell 2007).

The duration of antibiotic therapy may be relevant in the management of people with CAP. Currently, there is a myriad of recommendations regarding the duration of treatment, but in most cases, treatment courses are 5 to 14 days (Li 2007; Lim 2015; Mandell 2007; Torres 2013a). People managed in the community usually have less severe pneumonia, fewer comorbidities, and may be younger, and so may not need prolonged courses of antibiotic treatment (Holter 2016; NICE 2014). Administration of short-course antibiotics has been proposed to avoid unnecessary pharmacy costs (less antibiotic consumed) and complications (Bernal-Vargas 2016; Dinh 2016). Moreover, short-course antibiotic therapy has been associated with better patient compliance and symptom resolution, without increased mortality or readmission rates (Uranga 2016).

How the intervention might work

The duration of antibiotic therapy is important in the management of people with CAP. If the course of therapy is too short, it may lead to treatment failure. Conversely, prolonged courses of antibiotics contribute significantly to antibiotic overuse, which is associated with substantial costs, and may lead to increasing rates of antibiotic resistance, Costelloe 2010; File 2004b; Karchmer 2004; Segreti 2005, and potentially severe side effects, such as *Clostridium difficile* infection (Li 2007). Prolonged treatment also makes treatment compliance more challenging (Kardas 2002).

Why it is important to do this review

Increased guideline adherence among prescribers can lead to significant reductions in morbidity and mortality (Julián-Jiménez 2012; Welte 2012). Recommendations for antibiotic treatment are based on illness severity, frequency of specific pathogens, local microbial resistance patterns, and drug safety profiles. However, the optimal length of antibiotic treatment for CAP remains unclear (Dinh 2016).

Several studies have aimed to determine the effects of antibiotic treatment duration on people with CAP. It has been suggested that shorter regimens are as effective as longer courses, and are safer, limiting the spread of drug-resistant bacteria, reducing adverse effects (including *C difficile* infection), limiting treatment costs, and improving compliance (Bernal-Vargas 2016; Chalmers 2016; Dimopoulos 2008; Dinh 2016; Dunbar 2003; El Moussaoui 2006; File 2004c; Garau 2008; Hopkins 1995; Kolditz

2005; Li 2007; Mandell 2003; Pugh 2015; Socan 1998). Current guidelines suggest courses of treatment that range from 5 days to 14 days (Eccles 2014; File 2003; File 2004c; Li 2007; Lim 2009; Lim 2015; Mandell 2000; Mandell 2007; Restrepo 2005; Uranga 2016). However, most guidelines that suggest short courses were developed for hospital inpatients, and there is a lack of evidence with respect to treating CAP in community or outpatient settings. This could explain the marked variability seen in clinical practice regarding the length of antibiotic treatment for outpatients with CAP (Lim 2009; Woodhead 2000).

There are several systematic reviews on the effects of the length of treatment for people with CAP (Dimopoulos 2008; Li 2007), including some Cochrane Reviews (Haider 2011; Lassi 2017). However, these reviews compare different antibiotic regimens; no Cochrane Review has explicitly addressed the effects of antibiotic therapy duration with the same antibiotic for treating CAP in adolescent or adult outpatients. We conducted this systematic review to compare short- versus long-course of the same antibiotic.

OBJECTIVES

To evaluate the efficacy and safety of short-course versus longer-course treatment with the same antibiotic at the same daily dosage for CAP in non-hospitalised adolescents and adults (outpatients). We planned to investigate non-inferiority of short-course versus longer-term course treatment for efficacy outcomes, and superiority of short-course treatment for safety outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs), regardless of study hypothesis (superiority, non-inferiority, or equivalence), were eligible for inclusion. A superiority trial aims to determine whether one intervention is superior to another (Piaggio 2012). A non-inferiority trial aims to determine whether one (typically new) intervention is no worse than a reference treatment (Piaggio 2012). An equivalence trial aims to determine whether one (typically new) intervention is therapeutically similar to another, usually an existing treatment (Piaggio 2012). We included studies reported as full text, those published as abstract only, and unpublished data. (See Differences between protocol and review.)

Types of participants

Adolescent and adult non-hospitalised patients (also defined as outpatients for this review) with community-acquired pneumonia (CAP) of any severity initially treated in the community were eligible for inclusion. We considered a study to be eligible for inclusion when most participants were aged over 10 years. We defined participants aged from 10 years to 19 years as adolescents, and those aged over 19 years as adults (WHO 2010). However, we planned to accept other definitions provided by the trial authors.

We planned to accept any definition of pneumonia so long as it was based on explicit criteria. Some trial authors did not consider chest x-ray as a valid diagnostic tool for pneumonia due to its low sensitivity and consistency; moreover, interpretation of x-ray images to conclude that a person has pneumonia can be quite subjective (Albaum 1996; Hemilä 2009; Hopstaken 2004; Lim 2009). Other diagnostic techniques, such as high-resolution computed tomography (CT) scan, sputum cultures, or blood counts, may be more sensitive, but they are rarely available in low-income countries (Syrjala 1998), and are not considered as first-line diagnostic tools by guidelines in high-income countries (Braman 2006; Lim 2009). We planned to assess the potential effects of diagnostic techniques used in the heterogeneity of the review results in a subgroup analysis. We considered pneumonia as 'community-acquired' when acquired in the community, as opposed to acquired in a healthcare facility, or if the participant had not recently been in a healthcare facility or in contact with someone who had recently been in a healthcare facility (MeSH Browser 2018).

We planned to include participants with additional infections if the trial reported data specifically for CAP or if most (more than 50%) of the study population had CAP.

We planned to include participants attending or living in healthcare facilities where the risk of exposure to multidrug-resistant organisms was high (such as haemodialysis outpatients or people living in nursing homes or residential facilities) if participants living in the community constituted most (more than 50%) of the study population. We planned to assess the potential effects of including participants attending or living in healthcare facilities where the risk of exposure to multidrug-resistant organisms was high in a subgroup analysis. On the other hand, participants with CAP who initially attended hospital emergency departments, but did not require further hospital admission, were not considered to be eligible.

Studies that included participants who were immunocompromised or immunocompetent HIV-positive were eligible for inclusion.

Types of interventions

We planned to include RCTs that assessed the effects of the duration of antibiotic monotherapy for CAP, that is comparing short- versus long-courses of the same antibiotic administered by the same route and the same daily dose. There was no restriction on

the type of antibiotic used, the daily dose, or the frequency of administration. We planned to include the following co-interventions provided they were not part of the randomised treatment: antitussives, antipyretics, bronchodilators, mucolytics, or any other non-antibiotic agent.

Taking into account the variety of antibiotics used for CAP, it was difficult to establish a cut-off point for defining an antibiotic course as 'short' or 'long'. Considering similar systematic reviews and guidelines on the topic (Dimopoulos 2008; Li 2007; Lim 2009; Mandell 2007), we defined an antibiotic course as 'short' if it lasted seven days or less, and 'long' if it lasted more than seven days. When comparing two short courses or two long courses (e.g. three days versus five days), we considered the shortest one to be the 'short' course. We decided we would not stratify the analysis by antibiotic type. (See Differences between protocol and review.)

Types of outcome measures

Primary outcomes

Efficacy outcomes

1. **Clinical response** (reported as dichotomous data when possible).

i) Defined as 'resolution or improvement' of baseline symptoms and clinical signs related to pneumonia without the need for additional or alternative antibiotic therapy. However, we accepted any definition of clinical response as long as it was based on explicit criteria reported by the trial authors. If data for the combined outcome 'resolution or improvement' were not reported, we considered data for resolution or improvement alone.

ii) We assessed 'clinical response' at two time points: at the end-of-therapy evaluation visit, and at the latest follow-up evaluation visit. For the latter time point, the follow-up from the beginning of treatment should have been at least 14 days. (See Differences between protocol and review.)

2. **Overall mortality rate** (reported as dichotomous data when possible). Defined as death due to any cause occurring until the end of the follow-up period. The follow-up period from the beginning of treatment should have lasted at least 14 days.

Safety outcomes

1. **All adverse effects** (dichotomous data, no minimum follow-up defined).

2. **Serious adverse effects** (as reported by the study authors, dichotomous data, no minimum follow-up defined). We did not define death as a serious adverse event, as we considered mortality as an efficacy outcome (see above). We followed the terminology suggested by the *Cochrane Handbook for Systematic Reviews of Interventions* for harms (Loke 2011):

i) adverse event: an unfavourable outcome that occurs during or after the use of a drug or other intervention but is not necessarily caused by it;

ii) adverse effect: an adverse event for which the causal relation between the intervention and the event is at least a reasonable possibility;

iii) adverse drug reaction: an adverse effect specific to a drug;

iv) side effect: any unintended effect, adverse or beneficial, of a drug that occurs at doses normally used for treatment;

v) complications: adverse events or effects following surgical and other invasive interventions.

We anticipated that various types of adverse effects and adverse events would be reported. We thus planned to narrow the focus, as suggested by the *Cochrane Handbook for Systematic Reviews of Interventions* (Loke 2011). We attempted to prepare a table describing all the safety outcomes of the included studies, and based on our judgement about the relevance of the outcome for participants, we would subsequently have grouped the outcomes.

We did not consider withdrawals or dropouts as surrogate markers for safety or tolerability because of the potential for bias (Loke 2011). However, if this had been the only safety information reported, we would have extracted these data.

Secondary outcomes

1. **Mortality attributable to pneumonia** (reported as dichotomous data when possible). Defined as death due to pneumonia occurring until the end of the follow-up period. The follow-up period from the beginning of treatment should have been at least 14 days.

2. **Hospitalisation due to pneumonia** (reported as dichotomous data when possible). Defined as the need for hospital admission until the end of the follow-up period. We preferably considered hospital admissions due to pneumonia. However, if this outcome was not reported, we considered hospital admission for any cause.

3. **Relapse rate** defined as the reappearance of signs and symptoms of pneumonia in participants deemed clinically cured or improved (follow-up period not defined).

4. **Radiological response** (reported as dichotomous data when possible). Defined as reaching resolution or improvement of radiographic findings after antibiotic therapy. The follow-up period from the beginning of treatment should have been at least 14 days.

5. **Patient satisfaction with treatment** (measured using a validated tool).

Reporting one of more of the outcomes listed here in the trial was not an inclusion criterion of the review.

Search methods for identification of studies

See Differences between protocol and review for this section.

Electronic searches

We searched the following databases up to 28 September 2017:

1. Cochrane Acute Respiratory Infections Group Specialised Register (searched 28 September 2017);
2. Cochrane Central Register of Controlled Trials (CENTRAL; 2017, Issue 9) in the Cochrane Library (searched 28 September 2017) (Appendix 1);
3. Database of Abstracts of Reviews of Effects (DARE; the Cochrane Library, Issue 9, 2017) and NHS Economic Evaluation Database (NHS EED; the Cochrane Library, Issue 9, 2017) (Appendix 1). These databases ceased publication in March 2015 and have now been searched completely.
4. MEDLINE (Ovid) (1946 to 28 September 2017) (Appendix 1);
5. Embase (Elsevier) (1974 to 28 September 2017) (Appendix 2);
6. Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCO) (1981 to 28 September 2017) (Appendix 3);
7. Latin American and Caribbean Health Sciences Literature Database (LILACS) via Virtual Health Library (VHL) (1982 to 28 September 2017) (Appendix 4);
8. OpenGrey (www.opengrey.eu) (accessed 28 September 2017) (Appendix 5);
9. ProQuest Dissertations & Theses Database (1734 to 28 September 2017) (Appendix 6); and
10. Web of Science Conference Proceedings Citation Index Science (WoS CPCI-S) (1990 to 28 September 2017) (Appendix 7).

The MEDLINE search was used to search CENTRAL, DARE, and NHS EED, and was combined with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision); Ovid format to search MEDLINE (Lefebvre 2011).

We searched the following trials registries on 25 September 2017 (Appendix 8):

1. US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (clinicaltrials.gov);
2. ISRCTN registry (www.isrctn.com); and
3. WHO International Clinical Trials Registry Platform (apps.who.int/trialsearch).

We did not restrict results by language or publication status.

Searching other resources

We checked reference lists of potentially eligible studies (File 2007; Tellier 2004), review articles (Afshar 2009; Biondi 2014; Cordero 2013; Dawson-Hahn 2017; Marras 2004; Migliori 2012; Sazawal 2003; Simpson 2005; Troitino 2013; Vardakas 2008; Yu 2008), and clinical guidelines for additional references (Aliberti 2010; Mandell 2007; Woodhead 2011). We also used the Web of Science (WoS) citation map to track articles that had cited File 2007 and Tellier 2004. We did not handsearch journals, because all journals that appeared to have a high yield of relevant studies had been handsearched on behalf of Cochrane.

We contacted experts to identify additional unpublished materials.

We contacted the following pharmaceutical companies to identify further published or unpublished studies eligible for inclusion: Abbott, AstraZeneca, Aventis, Boehringer-Ingelheim, Bristol-Myers Squibb, Chiesi, Faes Farma, GlaxoSmithKline Beecham, Hoffmann-LaRoche, Lilly, Merck, Merck Sharp & Dohme, Novartis, Pfizer, Pharmacia, Sanofi, and Yamanouchi.

We checked abstracts presented at the following conferences (from 2004 onward): European Respiratory Society (ERS) (2004 to 2017); American Association for Respiratory Care (AARC) (2004 to 2016); British Thoracic Society (BTS) winter and summer meetings (2004 to 2016); Primary Care Respiratory Society (PCRS) - UK National Primary Care Conference (2004 to 2009; 2012 to 2017); Sociedad Española de Medicina de Familia y Comunitaria (semFYC) (2004 to 2017); Sociedad Española de Médicos de Atención Primaria (SEMERGEN) (2004 to 2017); Sociedad Española de Medicina Interna (SEMI) (2004 to 2016); Sociedad Española de Neumología y Cirugía Torácica (SEPAR) (2004 to 2017); and Sociedad Española de Neumología Pediátrica (NEUMOPED) (2005; 2007 to 2012; 2014 to 2017).

Data collection and analysis

Selection of studies

Two review authors (RRB or JRS or JMG or JMMG or CRF or JMC or JCC or MGG or JHM or AAL or VHS) independently screened titles and abstracts for inclusion. We retrieved the full-text study reports/publications of potentially relevant studies, and two review authors (RRB or JRS or JMG or JMMG or CRF or JMC or JCC or MGG or JHM or AAL or VHS) independently screened the full-texts and identified studies for inclusion and identified and recorded reasons for exclusion of ineligible studies. Any disagreements were resolved through discussion or by consulting a third review author (JLA) if necessary. We identified and excluded duplicates and collated multiple reports of the same study so that each study, rather than each report, was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and Characteristics of excluded studies tables (Moher 2009).

Data extraction and management

We planned to use a data collection form for study characteristics and outcome data that had been piloted on one study in the review. Two review authors (JLA, RRB or JHM) planned to extract

study characteristics from included studies in duplicate. We would have extracted the following study characteristics using Covidence software (Covidence 2017).

1. Verification of study eligibility.
2. Data sources.
3. Study details: sponsorship source, country, setting, author's contact details.
4. Methods:
   i) unit and method of allocation;
   ii) design: parallel/cross-over/factorial/other;
   iii) study phase: I; II; III; IV;
   iv) number of arms and allocation ratio;
   v) study aim; and
   vi) interim analyses and stopping rules.
5. Population:
   i) inclusion criteria;
   ii) exclusion criteria;
   iii) total sample size and number of participants allocated per group; and
   iv) baseline characteristics.
6. Interventions:
   i) intervention characteristics: antibiotics used, doses, duration, and frequency;
   ii) intervention fidelity;
   iii) co-interventions; and
   iv) feasibility.
7. Equity: exclusion of disadvantaged groups.
8. Outcomes:
   i) time frame;
   ii) study hypothesis: superiority/non-inferiority/equivalence;
   iii) margin of non-inferiority or equivalence;
   iv) outcome measurement;
   v) assumed risk and sample estimate; and
   vi) results per outcome: results, measure of effect, statistical significance, follow-up duration.
9. 'Risk of bias' tool domains.

We planned that two review authors (JLA, RRB or JHM) would independently extract outcome data from the included studies. We planned to note in the Characteristics of included studies table if outcome data had not been reported in a usable way. Any disagreements would have been resolved by consensus or by involving a third review author (JLA or RRB). One review author (JLA) would have transferred the data into Review Manager 5 (Review Manager 2014). We planned to double-check that data were entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (RRB or JHM) would have spot-checked study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

We planned to independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). Any disagreements would have been resolved by discussion or by involving another review author. We would have assessed the risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

We planned to assess the following domains for each study as a whole (therefore by a single entry in the 'Risk of bias' tool for each study): random sequence generation; allocation concealment; baseline imbalance; blinding of participants and personnel; and selective outcome reporting. We planned to assess blinding of outcome assessment and incomplete outcome data separately for each outcome (and each time point if several time points were considered). We would have classified susceptibility to lack of blinding of the outcome assessment as low for overall mortality and all-cause hospitalisations, and high for the remaining outcomes.

In trials attempting to establish non-inferiority, per-protocol (PP) analysis may be desirable as a protection from the tendency of intention-to-treat (ITT) analyses to bias the results towards no difference (falsely concluding non-inferiority) (Higgins 2011a; Piaggio 2012). For outcomes testing non-inferiority, we therefore planned to consider the domain 'incomplete outcome data' to be at low risk of bias if results from both analyses (PP and ITT) were consistent.

However, many consider that available-case and ITT analyses are not appropriate when assessing adverse effects, as it is wrong to attribute these to a treatment that somebody did not receive (Higgins 2011a). For this reason, for safety outcomes, we planned to consider the domain 'incomplete outcome data' to be at low risk of bias if the results from both analyses (PP and ITT) were consistent.

When considering treatment effects, we planned to take into account the risk of bias for the studies that contributed to that outcome.

See Differences between protocol and review.

Assessment of bias in conducting the systematic review

We conducted the review according to the published protocol and reported deviations in Differences between protocol and review.

Measures of treatment effect

We planned to enter outcome data for the included studies into data tables in Review Manager 5 to calculate treatment effects

(Review Manager 2014). We planned to use odds ratio (OR) for dichotomous outcomes, and to perform available-case analyses of the PP populations (re-analysed by the review authors if needed). We planned to perform meta-analyses only where this was meaningful, that is if the treatments, participants, and the underlying clinical question were similar enough for pooling to make sense.

Unit of analysis issues

We planned to obtain data considering the participant (rather than the event) as the unit of analysis. If we found unit of analysis errors, we planned to apply recommendations provided in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011).

Dealing with missing data

We planned to contact study investigators to verify key study characteristics and to obtain missing numerical outcome data where possible (e.g. when a study was available only as an abstract). Where this was not possible, we planned to describe missing participant data by reporting proportions of randomised participants for whom no outcome data were obtained (with reasons) by outcome and randomised group in the 'Risk of bias' tables. We planned to address the potential impact of missing outcomes on the results of the included studies in a sensitivity analysis. For all outcomes (benefits and harms), we planned to repeat the analysis carrying out analyses on the ITT principle; if there were missing data, and we could not obtain additional information, we planned to perform an available-case analysis. We also planned to perform sensitivity analyses to assess how sensitive results were to changes in assumptions made in the available-case analysis (see Sensitivity analysis). We planned to establish non-inferiority for potential benefit outcomes. We defined the primary analysis to be PP, because this is the most sensitive approach to detect any difference in efficacy between groups (EMEA 2004). Per-protocol analysis considers results only from those participants who completed the trial and who complied with or received some of the allocated intervention (Higgins 2011b). On the other hand, ITT or available-case analyses may not be the most appropriate analyses when attempting to establish non-inferiority of a treatment (CRD 2009; Higgins 2011b), as they may tend to bias results towards no difference. Intention-to-treat analysis fulfils the following principles: 1) keeps participants in the intervention groups to which they were randomised, regardless of the intervention they actually received; 2) there is a measurement of outcome data on all participants; and 3) includes all randomised participants in the analysis (Higgins 2011a). Available-case analysis includes data only for those participants whose results are known, using the total number of people who had data recorded for the particular outcome in question as a denominator (Higgins 2011a).

We planned to establish superiority and defined the primary analysis to be PP for potential harms. Intention-to-treat analysis may not be appropriate when assessing harms, because it is wrong to attribute these to a treatment that somebody did not receive (Higgins 2011a).

If the trials reported ITT or PP results exclusively (and it was not possible to re-analyse data), we planned to perform the analysis using the results provided in the studies.

Assessment of heterogeneity

We planned to check for heterogeneity for each outcome by examining:

1. the characteristics of the studies;
2. the forest plot of results of the studies. We planned to display study results graphically and check symmetry of the results visually;
3. the results of the Chi² test for statistical heterogeneity (we considered a significant P value to be $P < 0.10$); and
4. the results of the I^2 statistic for quantification of statistical heterogeneity. The I^2 statistic describes the percentage total variation across studies due to heterogeneity rather than chance. We planned to judge the importance of the observed value of the I^2 statistic depending on the magnitude and direction of effects and the strength of evidence for heterogeneity (we defined moderate-to-high heterogeneity as $I^2 > 50\%$) (Deeks 2011).

Assessment of reporting biases

We planned to assess publication bias by means of a funnel plot for each outcome. We planned to assess funnel plot asymmetry statistically. If there was evidence of asymmetry, we planned to consider publication bias as only one of a number of possible explanations.

Data synthesis

We planned to combine outcome measures from individual trials in a meta-analysis to provide a pooled effect estimate for each outcome only if there were enough studies (at least two studies), and if they were clinically and methodologically similar. If we detected statistical heterogeneity ($I^2 > 50\%$ or by observation), or if we deemed the meta-analysis inappropriate for other reasons, we planned not to combine results but to undertake a narrative analysis of studies, providing a descriptive presentation of results with supporting tables. If we conducted a meta-analysis, and the number of trials for each outcome measure was greater than three, we planned to use a random-effects model; if there were two trials, we would use the fixed-effect model (Deeks 2011). We planned to assess the influence of the statistical model used to pool data on the effects being evaluated in a sensitivity analysis (see Sensitivity analysis). We planned to perform statistical analyses using Review Manager 5, and to present results with 95% confidence interval (CI) (Review Manager 2014).

Hypotheses tested

We planned to investigate non-inferiority for efficacy outcomes, and superiority for harms. For non-inferiority we predefined a margin (Δ) of 10% (i.e. relative differences of 10 percentage points). We selected this margin as suggested by the European Medicines Agency (EMEA 2004). However, we acknowledge that it is difficult to justify this choice, because our review could have included different types of antibiotics (each with different efficacy against placebo) and outcomes.

Non-inferiority for efficacy outcomes

We planned to classify short antibiotic courses as superior, non-inferior, inconclusive, or inferior, according to definitions from the extension of the CONSORT statement for non-inferiority trials (Piaggio 2012). We considered the short antibiotic course according to the following classification.

a. Desirable outcomes (Δ: OR = 0.9)

Desirable outcomes included clinical cure at the end-of-therapy evaluation visit; clinical cure at the latest follow-up evaluation visit; radiological response; and patient satisfaction with treatment. We classified the findings as explained below (adapted from Piaggio 2012).

- The short course is superior **(A)**: the whole 95% CI lies to the right of OR = 1.
- The short course is non-inferior.
  - Non-inferior but not shown to be superior **(B** and**C)**: the whole 95% CI lies to the right of Δ (OR = 0.9) and includes OR = 1.
  - Non-inferior and also shown to be inferior **(D):** the whole 95% CI lies wholly to the right of Δ (OR = 0.9) and wholly to the left of OR = 1. It is also inferior in the sense that a null treatment difference is excluded. This circumstance is rare: it requires a very large sample size and can also result from a non-inferiority margin that is too wide.
- The result regarding non-inferiority of the short course is inconclusive.
  - The result regarding non-inferiority of the short course is inconclusive, and the difference is non-significant (**E** and **F**): the 95% CI includes Δ (OR = 0.9) and OR = 1.
  - The result regarding non-inferiority of the short course is inconclusive, but the difference is statistically significant (**G**): the 95% CI includes Δ (OR = 0.9) and is wholly to the left of OR = 1. This CI is inconclusive in that it is still plausible that the true treatment difference is more than Δ, but the new treatment is significantly worse than the standard.
- The short course is inferior **(H)**: the whole 95% CI is to the left of Δ (OR = 0.9).

b. Undesirable outcomes (Δ: OR = 1.1)

Undesirable outcomes: overall mortality; mortality attributable to pneumonia; hospitalisation due to pneumonia; all-cause hospitalisations; and relapse rate. We classified the findings as explained below (adapted from Piaggio 2012).

- The short course is superior **(A)**: the whole 95% CI lies to the left of OR = 1.
- The short course is non-inferior.
  - Non-inferior but not shown to be superior **(B** and**C)**: the whole 95% CI lies to the left of Δ (OR = 1.1) and includes OR = 1.
  - Non-inferior and also shown to be inferior **(D):** the whole 95% CI lies wholly to the left of Δ (OR = 1.1) and wholly to the right of OR = 1. It is also inferior in the sense that a null treatment difference is excluded. This circumstance is rare: it requires a very large sample size and can also result from a non-inferiority margin that is too wide.
- The result regarding non-inferiority of the short course is inconclusive.
  - The result regarding non-inferiority of the short course is inconclusive, and the difference is non-significant (**E** and **F**): the 95% CI includes Δ (OR = 1.1) and OR = 1.
  - The result regarding non-inferiority of the short course is inconclusive, but the difference is statistically significant (**G**): the 95% CI includes Δ (OR = 1.1) and is wholly to the right of OR = 1. This CI is inconclusive in that it is still plausible that the true treatment difference is less than Δ, but the new treatment is significantly worse than the standard.
- The short course is inferior **(H)**: the whole 95% CI is to the right of Δ (OR = 1.1).

GRADE and 'Summary of findings' tables

We planned to create a 'Summary of findings' table using the following outcomes: clinical cure (at the end of therapy evaluation visit); clinical cure (at the latest follow-up evaluation visit); overall mortality; all adverse effects; serious adverse effects; mortality attributable to pneumonia; and hospitalisations due to pneumonia. We planned to use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias) to assess the quality of a body of evidence as it related to the studies that contributed data to the analyses for the prespecified outcomes (Atkins 2004). We planned to use methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011c), employing GRADEpro GDT software (GRADEpro GDT 2014). We planned to justify all decisions to down- or upgrade study quality using footnotes, and provide comments to aid the reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We planned to undertake the following subgroup analyses.

1. Age of participants: more than 50% of participants were aged 10 to 18 years versus more than 50% of participants were adults (aged 19 to 74 years) versus more than 50% of participants were aged 75 years or over.
2. Diagnosis of pneumonia: exclusively based on clinical signs and symptoms versus also based on radiographic (or other image techniques) findings.
3. Presence of relevant comorbidity: studies including participants with relevant comorbidity (e.g. chronic pulmonary disease, congestive heart failure, myocardial disease, cerebrovascular disease, smokers) versus studies excluding these participants.
4. Risk of exposure to multidrug-resistant organisms: studies excluding participants living in healthcare facilities where the risk of exposure to multidrug-resistant organisms is high (such as nursing homes or residential facilities) versus studies including these participants.
5. Severity of pneumonia: measured with a validated scale, such as the pneumonia severity index (PSI) or CURB-65.
6. The degree of missing outcome data across studies: outcomes with levels of missing data described during the 'Risk of bias' assessment stage as enough to induce clinically relevant bias in the intervention effect estimate versus outcomes with levels of missing data described as not enough to induce clinically relevant bias in the intervention effect estimate.
7. Population sets: trials with PP analysis versus trials with ITT analysis.
8. Study hypothesis: non-inferiority versus equivalence versus superiority.

Sensitivity analysis

If there were sufficient included studies (at least two), we planned to undertake sensitivity analyses to explore the influence of the following factors on the robustness of results.

1. Allocation concealment: we planned to exclude studies with inadequate or unclear allocation concealment from the meta-analysis.
2. Statistical model chosen for meta-analysis: we planned to use a fixed-effect model for meta-analyses performed with a random-effects model, and to use a random-effects model for meta-analyses based on a fixed-effect model in the first place.
3. Population sets: we planned to repeat the analysis carrying out analyses based on the ITT principle.
4. Assumptions taken in the available-case analysis: we planned to perform an analysis with imputation of missing data.

i) For dichotomous outcomes, we planned to consider best-case and worst-case scenarios (Gamble 2005). We defined the best-case scenario as all participants with missing outcomes in the experimental intervention group having good outcomes, and all those with missing outcomes in the control intervention group having poor outcomes. The worst-case scenario would be the converse (Higgins 2011b).

ii) For continuous data, we planned to conduct a sensitivity analysis assuming a fixed difference between the actual mean for the missing data and the mean assumed by the analysis (Higgins 2011b).

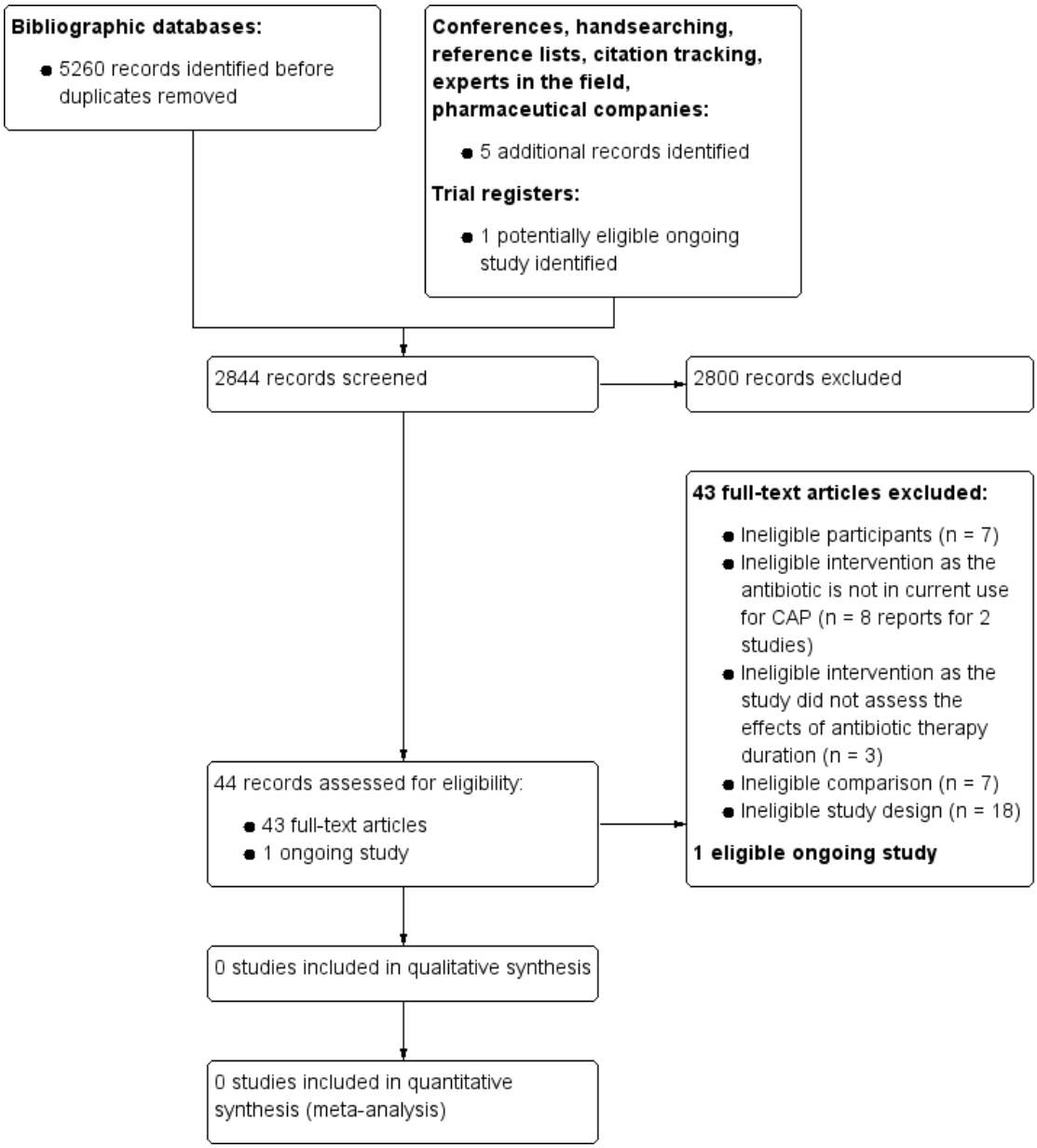
RESULTS

Description of studies

Results of the search

We searched electronic databases to 28 September 2017 and identified 5260 records. Our searches of other sources identified six additional records. Following removal of duplicates, we assessed 2844 records by title and abstract, and excluded 2800 records that did not match our inclusion criteria. We retrieved 44 full-text reports for further assessment and excluded 43 full-text articles that did not meet the eligibility criteria (Excluded studies; Characteristics of excluded studies; Figure 1). We did not identify any trials for inclusion. However, we identified one ongoing trial (NCT02903836).

Figure 1. Study flow diagram.



Included studies

We did not identify any trials for inclusion.

Excluded studies

We excluded 43 publications for the following reasons (Characteristics of excluded studies; Figure 1).

1. Ineligible participants. The initial CAP treatment was provided at a hospital for inpatients (CAP not initially treated in the community) (n = 7; Aliberti 2017; Demartini 2004; El Moussaoui 2006; Lagler 2012; Marti 2017; McCabe 1989; Van den Brande 1997).
2. Ineligible intervention. The antibiotic is not in current use for CAP (File 2007, reported in three publications; Tellier 2004, reported in five publications).
3. Ineligible intervention. The study did not assess the effects of antibiotic therapy duration (n = 3; Donowitz 1997; Hammerschlag 2003; Rovira 1999).
4. Ineligible comparison. There were differences between study arms in antibiotic dose (n = 7; Dunbar 2003; Dunbar 2004; File 2004a; Oldach 2015; Schonwald 1999; Zhao 2015; Zhao 2016).
5. Ineligible study design (n = 18). Studies were based on pooled data from other RCTs (Niederman 2004a; Van Rensburg 2005); presented a subgroup analysis (Shorr 2005); presented post hoc analysis (Niederman 2004b); or were not randomised designs (n = 14; Coley 2000; Darkes 2003; Fekete 2016; File 2005; Fogarty 2001; Hagberg 2003; Hammerschlag 2007; Hammerschlag 2008; Hemenway 2014; Khashab 2006; Li 2007; Lorenz 2003; Queen 2014; Rasche 2015).

Two RCTs compared short courses of the same antibiotic at the same daily dose (File 2007; Tellier 2004). The studies compared a five-day course versus a seven-day course of telithromycin (800 mg/day), Tellier 2004, or gemifloxacin (320 mg/day), File 2007, for the treatment of CAP in adults. These studies did not compare short- (seven days or less) and long- (more than seven days) antibiotic courses (File 2007; Tellier 2004). Regarding effectiveness, these studies could not rule out whether or not the shorter course was superior to the longer course. Following the suggestion of the Cochrane Acute Respiratory Infections editorial team, we excluded these studies because they evaluated antibiotics not commonly used in clinical practice for treatment of CAP. Moreover, according to the European Medicines Agency, gemifloxacin, File 2007, is no longer approved for the treatment of mild-to-moderate CAP due to its questionable risk-benefit relationship (EMEA 2009). The safety profile of telithromycin, Tellier 2004, is also cause for concern (Brinker 2006; Dore 2007; Ross 2007; Wilde Mathews 2006). Further details are provided in Overall completeness and applicability of evidence.

Ongoing trials

We identified one ongoing trial from ClinicalTrials.gov (NCT02903836). The estimated study completion date was September 2017.

Risk of bias in included studies

No studies fulfilled the review inclusion criteria. We could not assess risk of bias.

Effects of interventions

No studies fulfilled the review inclusion criteria.

DISCUSSION

Summary of main results

We did not identify any studies that compared short- and longer-courses of the same antibiotic for the treatment of adolescents and adult outpatients with CAP.

We excluded two RCTs that compared short courses (five compared to seven days) of the same antibiotic at the same daily dose because they evaluated antibiotics not commonly used in practice for the treatment of CAP (File 2007; Tellier 2004). In particular, gemifloxacin, File 2007, is no longer approved for the treatment of mild-to-moderate CAP due to its questionable risk-benefit balance and reported adverse effects (EMEA 2009). Moreover, the safety profile of telithromycin, Tellier 2004, is also cause for concern (Brinker 2006; Dore 2007; Ross 2007; Wilde Mathews 2006). Furthers details are provided in Overall completeness and applicability of evidence.

Overall completeness and applicability of evidence

Because no studies fulfilled the review inclusion criteria, we could not compare short- and longer-courses of antibiotics for the treatment of CAP. Randomised controlled trial evidence comparing different durations of antibiotic treatment for CAP is therefore incomplete.

We were surprised by the absence of RCTs because CAP is a relevant health problem; antibiotics are interventions commonly

used in practice; and this research area is not new. This absence may be explained by the following reasons. First, we defined as eligible people with CAP of any severity, initially treated in the community; we therefore excluded seven RCTs because initial CAP treatment was provided to hospital inpatients (Aliberti 2017; Demartini 2004; El Moussaoui 2006; Lagler 2012; Marti 2017; McCabe 1989; Van den Brande 1997). Second, we attempted to disentangle the effects of the duration of the treatment. As a consequence, we excluded studies in which the antibiotic treatment duration was not the only difference between study arms (Donowitz 1997; Hammerschlag 2003). Third, we found difficulties associated with evaluation of non-inferiority or equivalence, which present a number of methodological challenges, in addition to the methodological problems that any superiority study must overcome (Piaggio 2012). Fourth, we restricted our review to RCTs and excluded studies that used data gathered retrospectively, or studies that made use of subgroup analyses of RCTs. Finally, we decided to exclude two RCTs that were otherwise eligible for inclusion in the review because the antibiotics evaluated (gemifloxacin in File 2007 and telithromycin in Tellier 2004) are not commonly used in practice for the treatment of CAP (File 2007; Tellier 2004). Neither gemifloxacin nor telithromycin is recommended by guidelines as a first-line option for the treatment of CAP (Mandell 2007; NICE 2014), and their risk-benefit balance is unclear.

Gemifloxacin is no longer approved for the treatment of mild-to-moderate CAP due to its questionable risk-benefit balance (EMEA 2009). Similarly, the safety profile of telithromycin is cause for concern. Although we identified relevant information, we did not include this evidence in the review because the corresponding studies did not fulfil our eligibility criteria. We found that an initial analysis of 12 cases provided evidence for a rare, unusual form of hepatotoxicity associated with telithromycin and characterised by short latency, systemic symptoms and, in some cases, significant ascites (Brinker 2006). Telithromycin was also the subject of two investigations in the USA relating to potentially fraudulent safety data and inappropriate trial methodology when submitted for US Food and Drug Administration (FDA) approval. The FDA did not include a warning until 16 months after the first cases of liver injury were reported (Ross 2007). An analysis of the FDA's post-marketing database showed that the rate of reporting of acute liver failure was 3.5 to 11 times higher for telithromycin compared to other antibiotics marketed for similar indications. This implies a reporting rate of 167 cases of acute liver failure per 1 million person-years of telithromycin use, against the expected rate of 1 case per 1 million person-years (Wilde Mathews 2006). The FDA Adverse Event Reporting System showed that the risk of hepatotoxicity is 82% greater with telithromycin than with other agents (Dore 2007).

Quality of the evidence

We found no evidence that compared short- and longer-courses (more than seven days) of the same antibiotic for the treatment of adolescent and adult outpatients with CAP. This review did not identify any RCTs that studied this question.

Potential biases in the review process

We attempted to minimise bias by following Cochrane standard methods. In particular, we would like to discuss the following items.

Selection criteria

When writing the protocol for this review, we were not aware of the existence of core outcomes sets for clinical trials, that is agreed standardised sets of outcomes, such as those proposed by the Core Outcome Measures in Effectiveness Trials (COMET) Initiative (COMET 2010). We therefore did not select our review outcomes according to those proposed by Barlow 2003. We did not consider some of the outcomes as defined in this set, in particular symptoms measured as Community-Acquired Pneumonia Symptom Questionnaire (CAP-Sym) (Lamping 2002), time to clinical stability (Halm 2002), and 30-day post-admission mortality (Mortensen 2002). We did consider some of the proposed outcomes, such as adverse effects, and we think that the review outcomes addressed endpoints relevant to patients.

We excluded studies that analysed selected subgroups of the randomised participants, for example those that made use of subgroup analyses. We consider this to be a strength of our review, because we attempted to maximise the external validity of our review results to unselected patients presenting to their physician (Pakhale 2014).

Two RCTs fulfilled our eligibility criteria (File 2007; Tellier 2004). However, we decided to exclude these trials due to the worrying safety profiles of the antibiotics evaluated, gemifloxacin and telithromycin (Dore 2007; EMEA 2009; Brinker 2006; Ross 2007; Wilde Mathews 2006). We are aware of the possibility of introducing bias by the post hoc exclusion of these two studies, but we made this decision based on advice from the Cochrane Acute Respiratory Infections editorial team.

Search methods for identification of studies

We performed our searches as comprehensively as possible according to our resources. We aimed to reduce the risk of publication bias and to identify as much relevant evidence as possible. A healthcare librarian designed the searches adapted to existing terminology. We also contacted experts in the field and pharmaceutical companies, and handsearched conference abstracts. We did not limit the searches by language of publication. However, it is possible that we missed some trials not published in mainstream journals.

We did not search for data reported in drug regulatory material because we had neither the resources nor the expertise within our team to do so. Moreover, we felt there was no methodological guidance to accomplish this task. Searching for drug regulatory material seems important because, due to the absence of included studies, it is possible that the consideration of this information may change review conclusions, especially for harms.

Equity, sex and gender issues

We did not assess equity or sex and gender issues in an explicit way. Future updates of this review will follow the guidance proposed by the Campbell and Cochrane Equity Methods Group, Equity Checklist 2012, and the sex and gender in systematic reviews planning tool (Doull 2011).

Synthesising non-inferiority

There is no Cochrane guidance to synthesise evidence of non-inferiority or equivalence. This guidance is needed for several key steps of the review process, such as the analysis strategy (ITT principle or PP), or the meta-analysis itself (Witte 2004). We anticipate that systematic reviews addressing non-inferiority or equivalence will be more frequent due to non-inferiority trials having become common place in recent years, so that this guidance is urgently needed (Witte 2004).

Agreements and disagreements with other studies or reviews

No studies fulfilled the inclusion criteria of this review.

We found two systematic reviews that compared the effects of antibiotic treatment duration for CAP (Dimopoulos 2008; Li 2007) . However, no study included in these reviews met all the eligibility criteria for our review. Li 2007, which included RCTs comparing courses of antibiotic of seven days or less with longer periods, did not find differences in effectiveness or safety. An important limitation of these findings is the under-representation of some types of commonly used antibiotics, such as doxycycline. Moreover, most included participants had mild or moderate pneumonia. Dimopoulos 2008 included seven clinical trials, two of which were File 2007 and Tellier 2004, already discussed in our review; the other trials were not eligible for our review because they included children, hospitalised patients, or because the study arms considered the same antibiotic in different dosages. Dimopoulos 2008 did not find differences regarding clinical effectiveness, mortality, or adverse effects between short and long antibiotic cycles, although the number of participants assessed was small.

A recent RCT evaluated the use of shorter antibiotic regimens versus standard care for treating CAP (Uranga 2016). The researchers found that shorter courses could be as effective, if not more so, than conventional therapy with regard to patient recovery, without an increase in adverse outcomes such as mortality and readmission. However, this study was based on hospital inpatients, therefore the findings may not extrapolate to outpatient settings.

AUTHORS' CONCLUSIONS

Implications for practice

We found no eligible randomised controlled trials (RCTs) that studied short- versus longer-course antibiotic therapy (the same antibiotic at the same daily dosage) for adolescent and adult outpatients with community-acquired pneumonia (CAP). We concluded that the effects of antibiotic therapy duration for adolescent and adult outpatients with CAP remain unclear.

Implications for research

The optimal duration of antibiotic therapy for people with CAP is uncertain. There is a need for rigorous RCTs to determine the efficacy and safety of short- versus long-course antibiotic therapy (the same antibiotic at the same daily dosage) for adolescent and adult outpatients with CAP. In particular, studies evaluating the non-inferiority of short-course antibiotic therapy for efficacy, and its superiority for safety are required.

A rigorous evaluation is relevant because short courses of antibiotics would reduce unnecessary antibiotic treatment, which may limit the spread of drug-resistant bacteria, reduce treatment costs and associated adverse events (including *Clostridium difficile* infection), and improve treatment compliance (Bernal-Vargas 2016; Chalmers 2016; Dinh 2016; Dunbar 2003; El Moussaoui 2006; File 2004c; Garau 2008; Hopkins 1995; Kolditz 2005; Li 2007; Mandell 2003; Pugh 2015; Socan 1998). Moreover, unnecessary variability in clinical practice may be minimised because at present there is no consensus on the minimum duration of antibiotic treatment for adolescent or adult outpatients with CAP (Lim 2009; Woodhead 2000).

Appendix 9 details the research that would be most desirable according to the Evidence Population(s) Intervention Comparison Outcomes Time stamp (EPICOT) format (Brown 2006). Future trials should be rigorous in design and delivery, with adequate reporting to enable appraisal and interpretation of results. Researchers should report the studies in a standardised and informative format according to the following guidelines, among others: CONSORT statement (Schulz 2010); extension of the CONSORT 2010 statement to non-inferiority and equivalence randomised trials (Piaggio 2012); Template for Intervention Description and Replication (TIDieR) checklist (Hoffmann 2014); and reporting guideline for health equity concerns in randomised controlled trials (Welch 2017).

There is an ongoing RCT that we will assess for inclusion in an update of this review (NCT02903836).

ACKNOWLEDGEMENTS

Marta García Solano (Consejería de Sanidad de la Comunidad de Madrid, Spain), who contributed to the co-ordination of the protocol of this review. Madrid Cochrane Associate Centre and Sociedad Madrileña de Medicina Familiar y Comunitaria (Somamfyc) for its support and locations. Biblioteca Virtual (Consejería de Sanidad de la Comunidad de Madrid) and the American Society for Microbiology for the full texts provided.

Nieves Plana (Cochrane Associate Centre of Madrid, Hospital Universitario Ramón y Cajal/Universidad Fancisco de Vitoria-Madrid) for her methodological support.

We thank the following referees for commenting on the draft protocol and review: Durhane Wong-Rieger, Ekpereonne Esu, Mark Jones, Janet Wale, Richard Pugh, Zulfiqar Bhutta, Robert Ware, and Roger Damoiseaux.

REFERENCES

References to studies excluded from this review

Aliberti 2017 *{published data only}*
Aliberti S, Ramirez J, Giuliani F, Wiemken T, Sotgiu G, Tedeschi S, et al. Individualizing duration of antibiotic therapy in community-acquired pneumonia. *Pulmonary Pharmacology & Therapeutics* 2017;**45**:191–201. PUBMED: 28666965]

Coley 2000 *{published data only}*
Coley KC, Skledar SJ, Fine MJ, Yealy DM, Gleason PP, Ryan ML, et al. Changing physician prescribing behavior: the community-acquired pneumonia intervention trial. *American Journal of Health-System Pharmacy* 2000;**57**(16): 1506–10.

Darkes 2003 *{published data only}*
Darkes MJ, Perry CM. Clarithromycin extended-release tablet: a review of its use in the management of respiratory tract infections. *American Journal of Respiratory Medicine* 2003;**2**(2):175–201.

Demartini 2004 *{published data only}*
Demartini G, Esposti D, Marthyn P, Lapidari A, Fraschini F, Scaglione F. Effect of multiple doses of clarithromycin and amoxicillin on IL-6, IFNgamma and IL-10 plasma levels in patients with community acquired pneumonia. *Journal of Chemotherapy* 2004;**16**(1):82–5.

Donowitz 1997 *{published data only}*
Donowitz GR, Brandon ML, Salisbury JP, Harman CP, Tipping DM, Urick AE, et al. Sparfloxacin versus cefaclor in the treatment of patients with community-acquired pneumonia: a randomized, double-masked, comparative, multicenter study. *Clinical Therapeutics* 1997;**19**(5): 936–53.

Dunbar 2003 *{published data only}*
Dunbar LM, Wunderink RG, Habib MP, Smith LG, Tennenberg AM, Khashab MM, et al. High-dose, short-course levofloxacin for community-acquired pneumonia: a new treatment paradigm. *Clinical Infectious Diseases* 2003; **37**(6):752–60.

Dunbar 2004 *{published data only}*
Dunbar LM, Khashab MM, Kahn JB, Zadeikis N, Xiang JX, Tennenberg AM. Efficacy of 750-mg, 5-day levofloxacin in the treatment of community-acquired pneumonia caused by atypical pathogens. *Current Medical Research and Opinion* 2004;**20**(6):555–63.

El Moussaoui 2006 *{published data only}*
El Moussaoui R, de Borgie CAJ, van den Broek P, Hustinx WN, Bresser P, Poley J, et al. Effectiveness of discontinuing antibiotic treatment after three days versus eight days in mild to moderate-severe community acquired pneumonia: randomised, double blind study. *BMJ* 2006;**332**(7554): 1355.

Fekete 2016 *{published data only}*
Fekete T. Stopping antibiotics after 5 days in clinically stable community-acquired pneumonia was noninferior to usual care. *ACP Journal Club* 2016;**165**(10):1.

File 2004a *{published data only}*
File TM Jr, Milkovich G, Tennenberg AM, Xiang JX, Khashab MM, Zadeikis N. Clinical implications of 750 mg, 5-day levofloxacin for the treatment of community-acquired pneumonia. *Current Medical Research and Opinion* 2004;**20** (9):1473–81.

File 2005 *{published data only}*
File TM, Garau J, Jacobs MR, Wynne B, Twynholm M, Berkowitz E. Efficacy of a new pharmacokinetically enhanced formulation of amoxicillin/clavulanate (2000/125 mg) in adults with community-acquired pneumonia caused by Streptococcus pneumoniae, including penicillin-resistant strains. *International Journal of Antimicrobial Agents* 2005; **25**(2):110–9.

File 2007 *{published data only (unpublished sought but not used)}*
* File TM Jr, Mandell LA, Tillotson G, Kostov K, Georgiev O. Gemifloxacin once daily for 5 days versus 7 days for the treatment of community-acquired pneumonia: a randomized, multicentre, double-blind study. *Journal of Antimicrobial Chemotherapy* 2007;**60**(1):112–20.
File TM, Mandell LA, Tillotson G. Gemifloxacin once daily for 5 days versus 7 days for the treatment of community-acquired pneumonia: a randomized, multicentre, double-

blind study - authors' response. *Journal of Antimicrobial Chemotherapy* 2007;**60**(4):903.

Hammerschlag MR. Comment on: Gemifloxacin once daily for 5 days versus 7 days for the treatment of community-acquired pneumonia: a randomized, multicentre, double-blind study. Journal of Antimicrobial Chemotherapy 2007; Vol. 60, issue 4:902-3; author reply.

Fogarty 2001 *{published data only}*

Fogarty CM, Greenberg RN, Dunbar L, Player R, Marrie TJ, Kojak CM, et al. Effectiveness of levofloxacin for adult community-acquired pneumonia caused by macrolide-resistant Streptococcus pneumoniae: integrated results from four open-label, multicenter, phase III clinical trials. *Clinical Therapeutics* 2001;**23**(3):425–9.

Hagberg 2003 *{published data only}*

Hagberg L, Carbon C, van Rensburg DJ, Fogarty C, Dunbar L, Pullman J. Telithromycin in the treatment of community-acquired pneumonia: a pooled analysis. *Respiratory Medicine* 2003;**97**(6):625–33.

Hammerschlag 2003 *{published data only}*

Hammerschlag MR, Reznik T, Roblin PM, Ramirez J, Summersgill J, Bukofzer S. Microbiological efficacy of ABT-773 (cethromycin) for the treatment of community-acquired pneumonia due to Chlamydia pneumoniae. *Journal of Antimicrobial Chemotherapy* 2003;**51**(4):1025–8.

Hammerschlag 2007 *{published data only}*

Hammerschlag MR. Comment on: Gemifloxacin once daily for 5 days versus 7 days for the treatment of community-acquired pneumonia: a randomized, multicentre, double-blind study. *Journal of Antimicrobial Chemotherapy* 2007;**60**(4):902–3.

Hammerschlag 2008 *{published data only}*

Hammerschlag MR, Sharma R. Use of cethromycin, a new ketolide, for treatment of community-acquired respiratory infections. *Expert Opinion on Investigational Drugs* 2008;**17**(3):387–400.

Hemenway 2014 *{published data only}*

Hemenway A, Naretta M. Impact of antibiotic choice on pneumonia readmission rates. *Pharmacotherapy* 2014;**34**(10):E206–7.

Khashab 2006 *{published data only}*

Khashab MM, Xiang J, Kahn JBC. Comparison of the adverse event profiles of levofloxacin 500 mg and 750 mg in clinical trials for the treatment of respiratory infections. *Current Medical Research and Opinion* 2006;**22**(10):1997–2006.

Lagler 2012 *{published data only}*

Lagler H, Gattringer R, Derler V, Wlazny D, Graninger W, Burgmann H. Intravenous azithromycin - single dose 1.5 g vs. 500 mg once daily for 3 days in patients with community-acquired pneumonia: a prospective and randomised study. *Clinical Microbiology and Infection* 2012;**18**:137–8.

Li 2007 *{published data only}*

Li JZ, Winston LG, Moore DH, Bent S. Efficacy of short-course antibiotic regimens for community-acquired pneumonia: a meta-analysis. *American Journal of Medicine* 2007;**120**(9):783–90.

Lorenz 2003 *{published data only}*

Lorenz J. Telithromycin: the first ketolide antibacterial for the treatment of community-acquired respiratory tract infections. *International Journal of Clinical Practice* 2003;**57**(6):519–29.

Marti 2017 *{published data only}*

Marti C, John G, Genne D, Prendki V, Rutschmann OT, Stirnemann J, et al. Time to antibiotics administration and outcome in community-acquired pneumonia: secondary analysis of a randomized controlled trial. *European Journal of Internal Medicine* 2017;**43**:58–61. PUBMED: 28648477]

McCabe 1989 *{published data only}*

McCabe RE, Schlossberg D, Donowitz GR, Scheld WM, Zellner SR, Lindenberg LB, et al. Comparison of once-daily cephalosporin regimens for community-acquired lower respiratory tract infections in patients with chronic lung disease. *Clinical Therapeutics* 1989;**11**(3):304–14.

Niederman 2004a *{published data only}*

Niederman MS, Chang JR, Stewart J, Asche CV, Lavin B, Nusrat R, et al. Hospitalization rates among patients with community-acquired pneumonia treated with telithromycin vs clarithromycin: results from two randomized, double-blind, clinical trials. *Current Medical Research and Opinion* 2004;**20**(7):969–80.

Niederman 2004b *{published data only}*

Niederman MS, Chang JR, Stewart J, Nusrat R, Nieman RB. Comparison of hospitalization rates in patients with community-acquired pneumonia treated with 10 days of telithromycin or clarithromycin. *Current Medical Research and Opinion* 2004;**20**(5):749–56.

Oldach 2015 *{published data only}*

Oldach D, Barrera C, Rowe B, Nitu FM, Mykietiuk A, Metev H. Results from a phase 3 trial in moderate to moderately severe community acquired bacterial pneumonia (CABP) treated as outpatients with a new oral macrolide, solithromycin. *Chest* 2015;**148**(4):78a.

Queen 2014 *{published data only}*

Queen MA, Myers AL, Hall M, Shah SS, Williams DJ, Auger KA, et al. Comparative effectiveness of empiric antibiotics for community-acquired pneumonia. *Pediatrics* 2014;**133**(1):e23–9.

Rasche 2015 *{published data only}*

Rasche K, Nitschmann S. Community-acquired pneumonia. New treatment concepts. *Internist* 2015;**56**(12):1458–62.

Rovira 1999 *{published data only}*

Rovira E, Martinez-Moragon E, Belda A, Gonzalvo F, Ripolles F, Pascual JM. Treatment of community-acquired pneumonia in outpatients: randomized study of clarithromycin alone versus clarithromycin and cefuroxime. *Respiration; International Review of Thoracic Diseases* 1999;**66**(5):413–8.

Schonwald 1999 *{published data only}*
Schonwald S, Kuzman I, Oreskovic K, Burek V, Skerk V, Car V, et al. Azithromycin: single 1.5 g dose in the treatment of patients with atypical pneumonia syndrome - a randomized study. *Infection* 1999;**27**(3):198–202.

Shorr 2005 *{published data only}*
Shorr AF, Zadeikis N, Xiang JX, Tennenberg AM, Wes Ely E. A multicenter, randomized, double-blind, retrospective comparison of 5- and 10-day regimens of levofloxacin in a subgroup of patients aged > or = 65 years with community-acquired pneumonia. *Clinical Therapeutics* 2005;**27**(8): 1251–9.

Tellier 2004 *{published data only (unpublished sought but not used)}*
Cifaldi MA. Comments on: Comparison of hospitalization rates in patients with community-acquired pneumonia treated with 10 days of telithromycin or clarithromycin and comparison of hospitalization rates in patients with community-acquired pneumonia treated with telithromycin for 5 or 7 days or clarithromycin for 10 days. *Current Medical Research and Opinion* 2004;**20**(12):1895-6; author reply 6-7.
Tellier G, Chang JR, Asche CV, Lavin B, Stewart J, Sullivan SD. Comparison of hospitalization rates in patients with community-acquired pneumonia treated with telithromycin for 5 or 7 days or clarithromycin for 10 days. *Current Medical Research and Opinion* 2004;**20**(5):739–47.
Tellier G, Chang JR, Carl V. Corrections to: Tellier G, Chang JR, Carl V. Comparison of hospitalization rates in patients with community acquired pneumonia treated with telithromycin for 5 or 7 days or clarithromycin for 10 days. *Current Medical Research and Opinion* 2004;**20**(8):1331.
Tellier G, Isakov T, Petermann W, Patel M, Lavin B. Efficacy and safety of telithromycin for 5 or 7 days vs clarithromycin for 10 days in the treatment of patients with community acquired pneumonia. Abstracts - 42nd Interscience Conference on Antimicrobial Agents and Chemotherapy: ASM's annual meeting on infectious diseases; 2002 September 27 - 30; San Diego, California, USA. Washington DC: American Society for Microbiology, 2002:L373.
* Tellier G, Niederman MS, Nusrat R, Patel M, Lavin B. Clinical and bacteriological efficacy and safety of 5 and 7 day regimens of telithromycin once daily compared with a 10 day regimen of clarithromycin twice daily in patients with mild to moderate community-acquired pneumonia. *Journal of Antimicrobial Chemotherapy* 2004;**54**(2):515–23.

Van den Brande 1997 *{published data only}*
Van den Brande P, Vondra V, Vogel F, Schlaeffer F, Staley H, Holmes C. Sequential therapy with cefuroxime followed by cefuroxime axetil in community-acquired pneumonia. *Chest* 1997;**112**(2):406–15.

Van Rensburg 2005 *{published data only}*
Van Rensburg DJ, Fogarty C, Kohno S, Dunbar L, Rangaraju M, Nusrat R. Efficacy of telithromycin in community-acquired pneumonia caused by pneumococci with reduced susceptibility to penicillin and/or erythromycin. *Chemotherapy* 2005;**51**(4):186–92.

Zhao 2015 *{published data only}*
Zhao T. A multicentre randomized study of levofloxacin 750mg IV short-course versus 500mg IV/PO sequential convention-course for the treatment of community-acquired pneumonia in mainland China. *Respirology* 2015; **20**(Suppl 3):128.

Zhao 2016 *{published data only}*
Zhao T, Chen LA, Wang P, Tian G, Ye F, Zhu H, et al. A randomized, open, multicenter clinical study on the short course of intravenous infusion of 750 mg of levofloxacin and the sequential standard course of intravenous infusion/ oral administration of 500 mg of levofloxacin for treatment of community-acquired pneumonia. *Journal of Thoracic Disease* 2016;**8**(9):2473–84.

References to ongoing studies

NCT02903836 *{unpublished data only}*
NCT02903836. Phase II study of oral nafithromycin in CABP [A phase II, randomized, double–blind, multicenter, comparative study to determine the safety, tolerability, pharmacokinetics and efficacy of oral nafithromycin versus oral moxifloxacin in the treatment of community–acquired bacterial pneumonia (CABP) in adults]. clinicaltrials.gov/ct2/show/NCT02903836 (first received 16 September 2016).

Additional references

Afshar 2009
Afshar N, Tabas J, Afshar K, Silbergleit R. Blood cultures for community-acquired pneumonia: are they worthy of two quality measures: a systematic review. *Journal of Hospital Medicine* 2009;**4**(2):112–23.

Albaum 1996
Albaum MN, Hill LC, Murphy M, Li YH, Fuhrman CR, Britton CA, et al. Interobserver reliability of the chest radiograph in community-acquired pneumonia. PORT Investigators. *Chest* 1996;**110**(2):343–50.

Aliberti 2010
Aliberti S, Blasi F, Zanaboni AM, Peyrani P, Tarsia P, Gaito S, et al. Duration of antibiotic therapy in hospitalised patients with community-acquired pneumonia. *European Respiratory Journal* 2010;**36**(1):128–34.

Atkins 2004
Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, et al. GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ* 2004; **328**(7454):1490.

Barlow 2003
Barlow GD, Lamping DL, Davey PG, Nathwani D. Evaluation of outcomes in community-acquired pneumonia: a guide for patients, physicians, and policy-makers. *Lancet Infectious Diseases* 2003;**3**(8):476–88.

Bernal-Vargas 2016
Bernal-Vargas MA, Cortes JA. Duration of treatment and oral administration of antibiotics in community acquired

pneumonia [Duración del tratamiento y administración oral de antimicrobianos en neumonía adquirida en la comunidad]. *Revista Chilena de Infectologia* 2016;**33**(2): 177–86.

Biondi 2014
Biondi E, McCulloh R, Alverson B, Klein A, Dixon A, Ralston S. Treatment of mycoplasma pneumonia: a systematic review. *Pediatrics* 2014;**133**(6):1081–90.

Braman 2006
Braman SS. Chronic cough due to acute bronchitis: ACCP evidence-based clinical practice guidelines. *Chest* 2006;**129** (Suppl 1):95–103.

Brinker 2006
Brinker A. Telithromycin-associated hepatotoxicity. Presentation to the Joint meeting of the Anti-Infective Drugs Advisory Committee and the Drug Safety and Risk Management Committee, US Food and Drug Administration; 2006 December 14-15; Silver Spring (MD) 2006.

Broulette 2013
Broulette J, Yu H, Pyenson B, Iwasaki K, Sato R. The rate and economic burden of community-acquired pneumonia in a working-age population. *American Health Drug Benefits* 2013;**6**(8):494-503.

Brown 2006
Brown P, Brunnhuber K, Chalkidou K, Chalmers I, Clarke M, Fenton M, et al. How to formulate research recommendations. *BMJ (Clinical Research Ed.)* 2006;**333** (7572):804–6.

CCCG 2013
Cochrane Consumers and Communication Group. Study design guide for review authors, 2013. https://figshare.com/articles/Study_design_guide/6818900 (accessed 3 September 2018).

Chalmers 2016
Chalmers JD, Akram AR, Singanayagam A, Wilcox MH, Hill AT. Risk factors for Clostridium difficile infection in hospitalized patients with community-acquired pneumonia. *Journal of Infection* 2016;**73**(1):45–53.

Cillóniz 2012
Cillóniz C, Ewing S, Polverino E, Marcos MA, Prina E, Sellares J, et al. Community-acquired pneumonia in outpatients: aetiology and outcomes. *European Respiratory Journal* 2012;**40**(4):931–8.

COMET 2010
COMET Initiative. Database. www.comet-initiative.org/resources. (accessed 3 September 2018) 2010.

Cordero 2013
Cordero PM, Ruiz-Aragon J, Linde JMM, Marquez-Pelaez S, Sanchez VM. Evaluation of the efficacy and safety of tigecycline for treatment of respiratory tract infections. Systematic review of literature [Evaluación de la eficacia y seguridad de tigeciclina en el tratamiento de infecciones del tracto respiratorio: Revisión sistemática de la literatura científica]. Revista Chilena de Infectología 2013; Vol. 60, issue 6:591–7.

Costelloe 2010
Costelloe C, Metcalfe C, Lovering A, Mant D, Hay AD. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ* 2010;**340**:c2096.

Covidence 2017 [Computer program]
Veritas Health Innovation. Covidence. Version (accessed 3 September 2018). Melbourne, Australia: Veritas Health Innovation, 2017.

CRD 2009
Centre for Reviews and Dissemination. *Systematic Reviews. CRD's Guidance for Undertaking Reviews in Health Care*. Layerthorpe (York): CRD, University of York, 2009.

Dawson-Hahn 2017
Dawson-Hahn EE, Mickan S, Onakpoya I, Roberts N, Kronman M, Butler CC, et al. Short-course versus long-course oral antibiotic treatment for infections treated in outpatient settings: a review of systematic reviews. *Family Practice* 2017;**34**(5):511–9.

Deeks 2011
Deeks JJ, Higgins JP, Altman DG (editors). Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JP, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Dimopoulos 2008
Dimopoulos G, Matthaiou DK, Karageorgopoulos DE, Grammatikos AP, Athanassa Z, Falagas ME. Short- versus long-course antibacterial therapy for community-acquired pneumonia: a meta-analysis. *Drugs* 2008;**68**(13):1841–54.

Dinh 2016
Dinh A, Bouchand F, Salomon J, Bernard L. Short-course antibiotic regimens: up-to-date. *La Revue de Medecine Interne* 2016;**37**(7):466–72.

Dore 2007
Dore DD, DiBello JR, Lapane KL. Telithromycin use and spontaneous reports of hepatotoxicity. *Drug Safety* 2007;**30** (8):697–703.

Doull 2011
Doull M, Runnels V, Tudiver S, Boscoe M. Sex and gender in systematic reviews: planning tool. methods.cochrane.org/sites/methods.cochrane.org.equity/files/public/uploads/SRTool_PlanningVersionSHORTFINAL.pdf. (accessed 3 September 2018) 2011.

Eccles 2014
Eccles S, Pincus C, Higgins B, Woodhead M, Guideline Development Group. Diagnosis and management of community and hospital acquired pneumonia in adults: summary of NICE guidance. *BMJ* 2014;**349**:g67.

EMEA 2004
European Agency for the Evaluation of Medicinal Products (EMEA). Note for guidance on evaluation of medicinal products indicated for treatment of bacterial infections, 2004. ema.europa.eu/docs/en_GB/document_library/

Scientific_guideline/2009/09/WC500003417.pdf. (accessed 3 September 2018) 2004.

EMEA 2009
European Agency for the Evaluation of Medicinal Products (EMEA). Withdrawal assessment report for FACTIVE (International Nonproprietary Name: Gemifloxacin) Procedure No. EMEA/H/C/995. www.ema.europa.eu/docs/en_GB/document_library/Application_withdrawal_assessment_report/2010/01/WC500060988.pdf. (accessed 3 September 2018) 2009.

Equity Checklist 2012
Campbell & Cochrane Equity Methods Group. Equity checklist for systematic review authors. methods.cochrane.org/sites/methods.cochrane.org.equity/files/public/uploads/EquityChecklist2012.pdf. (accessed 3 September 2018) 2012.

File 2003
File TM. Community-acquired pneumonia. *Lancet* 2003; **362**(9400):1991–2001.

File 2004b
File TM Jr, Niederman MS. Antimicrobial therapy of community-acquired pneumonia. *Infectious Disease Clinics of North America* 2004;**18**(4):993-1016, xi.

File 2004c
File TM Jr. Clinical efficacy of newer agents in short-duration therapy for community-acquired pneumonia. *Clinical Infectious Diseases* 2004;**39**(Suppl 3):159–64.

Gamble 2005
Gamble C, Hollis S. Uncertainty method improved on best-worst case analysis in a binary meta-analysis. *Journal of Clinical Epidemiology* 2005;**58**(6):579–88.

Garau 2008
Garau J, Calbo E. Community-acquired pneumonia. *Lancet* 2008;**371**(9611):455–8.

GRADEpro GDT 2014 [Computer program]
GRADE Working Group, McMaster University. GRADEpro GDT. Version (accessed 3 September 2018). Hamilton (ON): GRADE Working Group, McMaster University, 2014.

Haider 2011
Haider BA, Saeed MA, Bhutta ZA. Short-course versus long-course antibiotic therapy for non-severe community-acquired pneumonia in children aged 2 months to 59 months. *Cochrane Database of Systematic Reviews* 2011, Issue 4. DOI: 10.1002/14651858.CD005976.pub2

Halm 2002
Halm EA, Fine MJ, Kapoor WN, Singer DE, Marrie TJ, Siu AL. Instability on hospital discharge and the risk of adverse outcomes in patients with pneumonia. *Archives of Internal Medicine* 2002;**162**(11):1278–84.

Hemilä 2009
Hemilä H, Louhiala P. Vitamin C for preventing and treating pneumonia. *Cochrane Database of Systematic Reviews* 2013, Issue 8. DOI: 10.1002/14651858.CD005532.pub3

Higgins 2003
Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557–60.

Higgins 2011a
Higgins JP, Altman DG, Sterne JAC (editors). Chapter 8: Assessing risk of bias in included studies. In: Higgins JP, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Higgins 2011b
Higgins JP, Deeks JJ, Altman DG (editors). Chapter 16: Special topics in statistics. In: Higgins JP, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Higgins 2011c
Higgins JP, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Hoffmann 2014
Hoffmann TC, Glasziou PP, Boutron I, Milne R, Perera R, Moher D, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *BMJ (Clinical Research Ed.)* 2014;**348**: g1687.

Holter 2016
Holter JC, Ueland T, Jenum PA, Müller F, Brunborg C, Frøland SS, et al. Risk factors for long-term mortality after hospitalization for community-acquired pneumonia: a 5-year prospective follow-up study. *PLoS ONE* 2016;**11**(2): e0148741.

Hopkins 1995
Hopkins S, Williams D. Five-day azithromycin in the treatment of patients with community-acquired pneumonia. *Current Therapeutic Research, Clinical and Experimental* 1995;**56**(9):915–25.

Hopstaken 2004
Hopstaken RM, Witbraad T, van Engelshoven JM, Dinant GJ. Inter-observer variation in the interpretation of chest radiographs for pneumonia in community-acquired lower respiratory tract infections. *Clinical Radiology* 2004;**59**(8): 743–52.

Julián-Jiménez 2012
Julián-Jiménez A, Palomo de los Reyes MJ, Parejo Miguez R, Laín-Terés N, Cuena-Boy R, Lozano-Ancín A. Improved management of community-acquired pneumonia in the emergency department. *Archivos de Bronconeumologia* 2013; **49**(6):230–40.

Kalil 2016
Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, et al. Management of adults with hospital-

acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. *Clinical Infectious Diseases* 2016;**63**(5):e61–111.

Karchmer 2004
Karchmer AW. Increased antibiotic resistance in respiratory tract pathogens: PROTEKT US - an update. *Clinical Infectious Diseases* 2004;**39**(Suppl 3):142–50.

Kardas 2002
Kardas P. Patient compliance with antibiotic treatment for respiratory tract infections. *Journal of Antimicrobial Chemotherapy* 2002;**49**(6):897–903.

Kolditz 2005
Kolditz M, Halank M, Hoffken G. Short-course antimicrobial therapy for community-acquired pneumonia. *Treatments in Respiratory Medicine* 2005;**4**(4):231–9.

Lamping 2002
Lamping DL, Schroter S, Marquis P, Marrel A, Duprat-Lomon I, Sagnier PP. The community-acquired pneumonia symptom questionnaire: a new, patient-based outcome measure to evaluate symptoms in patients with community-acquired pneumonia. *Chest* 2002;**122**(3):920–9.

Lassi 2017
Lassi Z, Imdad A, Bhutta ZA. Short-course versus long-course intravenous therapy with the same antibiotic for severe community-acquired pneumonia in children aged two months to 59 months. *Cochrane Database of Systematic Reviews* 2017, Issue 10. DOI: 10.1002/14651858.CD008032.pub3

Lefebvre 2011
Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JP, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Lim 2009
Lim WS, Baudouin SV, George RC, Hill AT, Jamieson C, Le Jeune I, et al. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. *Thorax* 2009;**64**(Suppl 3):iii1–55.

Lim 2012
Lim SS, Vos T, Flaxman AD, Danaei G, Shibuya K, Adair-Rohani H, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012;**380**(9859):2224–60.

Lim 2015
Lim WS, Smith D, Wise M, Welham S. 2015 - Annotated BTS Guideline for the management of CAP in adults (2009) - Summary of recommendations. www.brit-thoracic.org.uk/document-library/clinical-information/pneumonia/adult-pneumonia/annotated-bts-cap-guideline-summary-of-recommendations/. (accessed 3 September 2018) 2015.

Loke 2011
Loke YK, Price D, Herxheimer A. Chapter 14: Adverse effects. In: Higgins JP, Green S (editors), Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Mandell 2000
Mandell LA, Marrie TJ, Grossman RF, Chow AW, Hyland RH. Canadian guidelines for the initial management of community-acquired pneumonia: an evidence-based update by the Canadian Infectious Diseases Society and the Canadian Thoracic Society. The Canadian Community-Acquired Pneumonia Working Group. *Clinical Infectious Diseases* 2000;**31**(2):383–421.

Mandell 2003
Mandell LA, File TM Jr. Short-course treatment of community-acquired pneumonia. Clinical Infectious Diseases 2003; Vol. 37, issue 6:761–3.

Mandell 2007
Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clinical Infectious Diseases* 2007;**44**(Suppl 2):27–72.

Marras 2004
Marras TK, Nopmaneejumruslers C, Chan CK. Efficacy of exclusively oral antibiotic therapy in patients hospitalized with nonsevere community-acquired pneumonia: a retrospective study and meta-analysis. American Journal of Medicine 2004; Vol. 116, issue 6:385–93.

MeSH Browser 2018
US National Library of Medicine. MeSH Browser 2018. www.ncbi.nlm.nih.gov/mesh/ (accessed 3 September 2018).

Migliori 2012
Migliori GB, Langendam MW, D'Ambrosio L, Centis R, Blasi F, Huitric E, et al. Protecting the tuberculosis drug pipeline: stating the case for the rational use of fluoroquinolones. European Respiratory Journal 2012; Vol. 40, issue 4:814–22.

Moher 2009
Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *BMJ* 2009;**339**: 2535.

Mortensen 2002
Mortensen EM, Coley CM, Singer DE, Marrie TJ, Obrosky DS, Kapoor WN, et al. Causes of death for patients with community-acquired pneumonia: results from the Pneumonia Patient Outcomes Research Team cohort study. *Archives of Internal Medicine* 2002;**162**(9):1059–64.

NICE 2014
National Institute for Health and Care Excellence (NICE). Clinical guideline [CG191] - Pneumonia in adults: diagnosis and management. www.nice.org.uk/guidance/cg191. (accessed 3 September 2018) 2014.

Pakhale 2014
Pakhale S, Mulpuru S, Verheij TJ, Kochen MM, Rohde GG, Bjerre LM. Antibiotics for community-acquired pneumonia in adult outpatients. *Cochrane Database of Systematic Reviews* 2014, Issue 10. DOI: 10.1002/14651858.CD002109.pub4

Piaggio 2012
Piaggio G, Elbourne DR, Pocock SJ, Evans SJ, Altman DG. Reporting of noninferiority and equivalence randomized trials: extension of the CONSORT 2010 statement. *JAMA* 2012;**308**(24):2594–604.

Pugh 2015
Pugh R, Grant C, Cooke RP, Dempsey G. Short-course versus prolonged-course antibiotic therapy for hospital-acquired pneumonia in critically ill adults. *Cochrane Database of Systematic Reviews* 2015, Issue 8. DOI: 10.1002/14651858.CD007577.pub3

Restrepo 2005
Restrepo MI, Anzueto A. Antimicrobial treatment of community-acquired pneumonia. *Clinics in Chest Medicine* 2005;**26**(1):65–73.

Review Manager 2014 [Computer program]
Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager 5 (RevMan 5). Version 5.3. Copenhagen: Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Ross 2007
Ross DB. The FDA and the case of Ketek. *New England Journal of Medicine* 2007;**356**(16):1601–4.

Sahuquillo-Arce 2016
Sahuquillo-Arce JM, Menéndez R, Méndez R, Amara-Elori I, Zalacain R, Capelastegui A, et al. Age-related risk factors for bacterial aetiology in community-acquired pneumonia. *Respirology* 2016;**21**(8):1472–9.

Sazawal 2003
Sazawal S, Black RE. Effect of pneumonia case management on mortality in neonates, infants, and preschool children: a meta-analysis of community-based trials. Lancet Infectious Diseases 2003; Vol. 3, issue 9:547–56.

Schulz 2010
Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. *Annals of Internal Medicine* 2010;**152**(11):726–32.

Segreti 2005
Segreti J, House HR, Siegel RE. Principles of antibiotic treatment of community-acquired pneumonia in the outpatient setting. *American Journal of Medicine* 2005;**118**(Suppl 7A):S21–8.

Simpson 2005
Simpson SH, Marrie TJ, Majumdar SR. Do guidelines guide pneumonia practice: a systematic review of interventions and barriers to best practice in the management of community-acquired pneumonia. Respiratory Care Clinics of North America 2005; Vol. 11, issue 1:1–13.

Socan 1998
Socan M. Treatment of atypical pneumonia with azithromycin: comparison of a 5-day and a 3-day course. *Journal of Chemotherapy* 1998;**10**(1):64–8.

Spellberg 2008
Spellberg B, Guidos R, Gilbert D, Bradley J, Boucher HW, Scheld WM, et al. Infectious Diseases Society of America. The epidemic of antibiotic-resistant infections: a call to action for the medical community from the Infectious Diseases Society of America. *Clinical Infectious Diseases* 2008;**46**(2):155–64.

Syrjala 1998
Syrjala H, Broas M, Suramo I, Ojala A, Lahde S. High-resolution computed tomography for the diagnosis of community-acquired pneumonia. *Clinical Infectious Diseases* 1998;**27**(2):358–63.

Tichopad 2013
Tichopad A, Roberts C, Gembula I, Hajek P, Skoczynska A, Hryniewicz W, et al. Clinical and economic burden of community-acquired pneumonia among adults in the Czech Republic, Hungary, Poland and Slovakia. *PLoS ONE* 2013;**8**(8):e7137.

Torres 2013a
Torres A, Barberán J, Falguera M, Menéndez R, Molina J, Olaechea P, et al. Multidisciplinary guidelines for the management of community-acquired pneumonia [Grupo de la guía multidisciplinar para el manejo de la neumonía adquirida en la comunidad]. *Medicina Clinica* 2013;**140**(5):223.e1–19.

Torres 2013b
Torres A, Peetermans WE, Viegi G, Blasi F. Risk factors for community-acquired pneumonia in adults in Europe: a literature review. *Thorax* 2013;**68**(11):1057–65.

Troitino 2013
Troitino AX, Porhomayon J, El-Solh AA. Guideline-concordant antimicrobial therapy for healthcare-associated pneumonia: a systematic review and meta-analysis. Lung 2013; Vol. 191, issue 3:229–37.

Uranga 2016
Uranga A, España PP, Bilbao A, Quintana JM, Arriaga I, Intxausti M, et al. Duration of antibiotic treatment in community-acquired pneumonia: a multicenter randomized clinical trial. *JAMA Internal Medicine* 2016;**176**(9):1257–65.

Vardakas 2008
Vardakas KZ, Siempos IL, Grammatikos A, Athanassa Z, Korbila IP, Falagas ME. Respiratory fluoroquinolones for the treatment of community-acquired pneumonia: a meta-analysis of randomized controlled trials. CMAJ: Canadian Medical Association Journal 2008; Vol. 179, issue 12:1269–77.

Welch 2017
Welch VA, Norheim OF, Jull J, Cookson R, Sommerfelt H, Tugwell P. CONSORT-Equity 2017 extension and elaboration for better reporting of health equity in

randomised trials. *BMJ (Clinical Research Ed.)* 2017;**359**: j5085.

Welte 2012
Welte T, Torres A, Nathwani D. Clinical and economic burden of community-acquired pneumonia among adults in Europe. *Thorax* 2012;**67**(1):71–9.

WHO 2010
World Health Organization. Health topics - adolescent health. www.who.int/topics/adolescent_health/en/. (accessed 3 September 2018) 2010.

WHO 2014
World Health Organization. Antimicrobial resistance: global report on surveillance 2014. www.who.int/drugresistance/documents/surveillancereport/en/. (accessed 3 September 2018). WHO, 2014.

Wilde Mathews 2006
Wilde Mathews A. FDA panel urges prominent warning label for antibiotic. Wall Street Journal. 19 May 2006. www.wsj.com/articles/SB114799677462757266 (accessed 3 September 2018).

Witte 2004
Witte S, Victor N. Some problems with the investigation of noninferiority in meta-analysis. *Methods of Information in Medicine* 2004;**43**(5):470–4.

Woodhead 1987
Woodhead MA, Macfarlane JT, McCracken JS, Rose DH, Finch RG. Prospective study of the aetiology and outcome of pneumonia in the community. *Lancet* 1987;**1**(8534): 671–4.

Woodhead 2000
Woodhead M, Macfarlane J. Local antibiotic guidelines for adult community-acquired pneumonia (CAP): a survey of UK hospital practice in 1999. *Journal of Antimicrobial Chemotherapy* 2000;**46**(1):141–3.

Woodhead 2011
Woodhead M, Blasi F, Ewig S, Garau J, Huchon G, Ieven M, et al. Guidelines for the management of adult lower respiratory tract infections - summary. *Clinical Microbiology and Infection* 2011;**17**(Suppl 6):1–24.

Yu 2008
Yu KT, Wyer PC. Evidence-based emergency medicine/critically appraised topic. Evidence behind the 4-hour rule for initiation of antibiotic therapy in community-acquired pneumonia. *Annals of Emergency Medicine* 2008;**51**(5):651-62, 662.e1-2.

References to other published versions of this review

Rodriguez-Barrientos 2011
Rodriguez-Barrientos R, López-Alcalde J, Rodríguez-Fernández C, Muñoz-Gutiérrez J, Gómez-García M, Molero-García JM, et al. Short-course versus long-course therapy of the same antibiotic for community-acquired pneumonia in adolescent and adult outpatients. *Cochrane Database of Systematic Reviews* 2011, Issue 4. DOI: 10.1002/14651858.CD009070

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aliberti 2017	RCT; ineligible participants. Initial CAP treatment was provided for inpatients at hospital
Coley 2000	CCT; ineligible participants. Initial CAP treatment was provided for inpatients at hospital
Darkes 2003	Ineligible design: review
Demartini 2004	RCT; ineligible participants. Initial CAP treatment was provided for inpatients at hospital
Donowitz 1997	RCT; ineligible intervention. Study did not assess the effects of antibiotic monotherapy duration
Dunbar 2003	RCT; ineligible comparison. Differences between study arms in antibiotic dose
Dunbar 2004	RCT; ineligible comparison. Differences between study arms in antibiotic dose
El Moussaoui 2006	RCT; ineligible participants. Initial CAP treatment was provided for inpatients at hospital
Fekete 2016	CCT; ineligible participants. Initial CAP treatment was provided for inpatients at hospital
File 2004a	RCT; ineligible comparison. Differences between study arms in antibiotic dose
File 2005	CCT; ineligible intervention. Study did not assess the effects of antibiotic monotherapy duration
File 2007	RCT; ineligible intervention. The antibiotic is not in current use for CAP
Fogarty 2001	CCT; ineligible intervention. Study did not assess the effects of antibiotic monotherapy duration
Hagberg 2003	CCT; ineligible intervention. Study did not assess the effects of antibiotic monotherapy duration
Hammerschlag 2003	RCT; ineligible intervention. Study did not assess the effects of antibiotic monotherapy duration
Hammerschlag 2007	CCT; ineligible design. Allocation sequence was not random.
Hammerschlag 2008	CCT; ineligible intervention. Study did not assess the effects of antibiotic monotherapy duration
Hemenway 2014	CCT; ineligible participants. Initial CAP treatment was provided for inpatients at hospital
Khashab 2006	CCT; ineligible intervention. Study did not assess the effects of antibiotic monotherapy duration
Lagler 2012	RCT; ineligible participants. Initial CAP treatment was provided for inpatients at hospital
Li 2007	Ineligible design: review

(*Continued*)

Lorenz 2003	Ineligible design: review
Marti 2017	RCT; ineligible participants. Initial CAP treatment was provided for inpatients at hospital
McCabe 1989	RCT; ineligible participants. Initial CAP treatment was provided for inpatients at hospital
Niederman 2004a	RCT; ineligible design. Pooled data from 2 RCTs
Niederman 2004b	RCT; ineligible design. Post hoc analysis to investigate whether there were differences in overall healthcare resource utilisation associated with 10 days of oral telithromycin 800 mg once daily versus 10 days of clarithromycin twice daily in adults with CAP
Oldach 2015	RCT; ineligible comparison. Differences between study arms in antibiotic dose
Queen 2014	CCT; ineligible design. Observational study
Rasche 2015	CCT; ineligible design. Review
Rovira 1999	RCT; ineligible intervention. Did not consider antibiotic as monotherapy
Schonwald 1999	RCT; ineligible comparison. Differences between study arms in antibiotic dose
Shorr 2005	RCT; ineligible design. Subgroup analysis of an RCT
Tellier 2004	RCT; ineligible intervention. The antibiotic is not in current use for CAP
Van den Brande 1997	RCT; ineligible participants. Initial CAP treatment was provided for inpatients at hospital
Van Rensburg 2005	RCT; ineligible design. Pooled data from RCTs
Zhao 2015	RCT; ineligible comparison. Differences between study arms in antibiotic dose
Zhao 2016	RCT; ineligible comparison. Differences between study arms in antibiotic dose

CAP: community-acquired pneumonia
CCT: controlled clinical trial
RCT: randomised controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

NCT02903836

Trial name or title	Phase II study of oral nafithromycin in CABP
Methods	Phase II Randomised clinical trial Blinding of participants, caregivers, investigators, and outcomes assessors
Participants	**Inclusion criteria:** Male and female Aged 18 years or over Clinical criteria for CABP based on the following: 1. clinical symptoms (new or worsening); 2. vital sign abnormalities; 3. laboratory abnormalities; 4. radiographic evidence of CABP; 5. PORT score. **Exclusion criteria:** People with any of the following confirmed or suspected types of pneumonia: 1. aspiration pneumonia; 2. hospital-acquired bacterial pneumonia; 3. healthcare-associated bacterial pneumonia; 4. ventilator-associated bacterial pneumonia; 5. pneumonia that may be caused by pathogen(s) resistant to either study drug; 6. receipt of 1 or more dose(s) of a potentially effective systemic antibacterial treatment for treatment of the current CABP; 7. suspected or confirmed non-infectious causes of pulmonary infiltrates; 8. people requiring concomitant adjunctive or additional potentially effective systemic antibacterial treatment for management of CABP.
Interventions	**Arm 1:** nafithromycin 800 mg 3 days **Arm 2:** nafithromycin 800 mg 5 days **Arm 3:** moxifloxacin 400 mg
Outcomes	**Primary outcome:** 1. clinical response in the ITT population (time frame: day 4) **Secondary outcomes:** 1. clinical response in the micro-ITT population (time frame: day 4) 2. safety evaluation: number of participants with treatment-emergent adverse events, abnormal clinical laboratory evaluation, abnormal vital signs, abnormal physical examination findings, and abnormal ECGs during the treatment and follow-up phase (time frame: 31 days)
Starting date	September 2016
Contact information	Rakesh Chugh; rchugh@wockhardt.com
Notes	This study compares oral nafithromycin versus oral moxifloxacin, a comparison not eligible for this review. However, we hope that we will be able to extract the data of the comparison nafithromycin 800 mg 3 days versus nafithromycin 800 mg 5 days

CABP: community-acquired bacterial pneumonia
ECG: electrocardiogram
ITT: intention-to-treat
PORT: pneumonia patient outcomes research team

APPENDICES

Appendix 1. CENTRAL, MEDLINE, DARE search strategy

MEDLINE ALL (Ovid)

1 (communit* adj5 pneumon*).tw.
2 cap.tw.
3 Community-Acquired Infections/
4 (community-acquired or community acquired).tw.
5 3 or 4
6 exp pneumonia/
7 pneumon*.tw.
8 6 or 7
9 5 and 8
10 1 or 2 or 9
11 exp Anti-Bacterial Agents/
12 antibiotic*.tw.
13 exp Macrolides/
14 exp beta-Lactams/
15 exp Quinolones/
16 exp Tetracyclines/
17 (macrolide* or erythromycin* or azithromycin* or clarithromycin* or ketolides* or telithromycin* or beta-lactam* or amoxicillin* or clavulanic* or co-amoxiclav* or cephalosporin* or cefuroxime* or cefotaxime* or ceftriaxone* or ceftibuten* or cefditoren*or cefpodoxim* or quinolone* or fluoroquinalone* or moxifloxacin* or levofloxacin* or ampicillin* or trimethoprim* or oxytetracycline* or doxycycline*).tw,nm.
18 or/11-17
19 10 and 18
The MEDLINE search was used to search CENTRAL, DARE and NHS EED.

Appendix 2. Embase search strategy

Embase (Elsevier)

#1. 'community acquired pneumonia'/de
#2. (communit* NEAR/5 pneumon*):ab,ti
#3. cap:ab,ti
#4. 'communicable disease'/de
#5. 'community acquired':ab,ti OR 'community-acquired':ab,ti
#6. #4 OR #5
#7. 'pneumonia'/exp
#8. pneumon*:ab,ti
#9. #7 OR #8
#10. #6 AND #9
#11. #1 OR #2 OR #3 OR #10
#12. 'antibiotic agent'/exp
#13. antibiotic*:ab,ti
#14. 'macrolide'/exp OR 'beta lactam'/de OR 'quinolone derivative'/exp OR 'tetracycline derivative'/exp
#15. macrolide*:ab,ti OR erythromycin*:ab,ti OR azithromycin*:ab,ti OR clarithromycin*:ab,ti OR ketolide*:ab,ti OR telithromycin*:ab,ti OR 'beta-lactam':ab,ti OR 'beta-lactams':ab,ti OR
amoxycillin*:ab,ti OR amoxicillin*:ab,ti OR clavulanic*:ab,ti OR 'co-amoxiclavulanate':ab,ti OR cephalosporin*:ab,ti OR cefuroxime*:ab,ti OR cefotaxime*:ab,ti OR ceftriaxone*:ab,ti OR
ceftibuten*:ab,ti OR cefditoren*:ab,ti OR cefpodoxin*:ab,ti OR quinolone*:ab,ti OR fluoroquinolone*:ab,ti OR moxifloxacin*:ab,ti OR levofloxacin*:ab,ti OR ampicillin*:ab,ti OR trimethoprim*:ab,ti OR oxytetracycline*:ab,ti OR doxycycline*:ab,ti
#16. #12 OR #13 OR #14 OR #15
#17. #11 AND #16
#18. 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp
#19. random*:ab,ti OR placebo*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR 'cross over':ab,ti OR 'cross-over':ab,ti OR volunteer*:ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR ((singl* OR doubl*) NEAR/1 blind*):ab,ti
#20. #18 OR #19
#21. #17 AND #20

Appendix 3. CINAHL search strategy

CINAHL (EBSCO)

S1: (MH "Community-Acquired Pneumonia")
S2: TI communit* N5 pneumon* or AB communit* N5 pneumon*
S3: TI CAP or AB CAP
S4: (MH "Community-Acquired Infections")
S5: TI (community acquired or community-acquired) or AB (community acquired or community-acquired)
S6: S4 or S5
S7 (MH "Pneumonia+")
S8 TI pneumon* or AB pneumon*
S9 S7 or S8
S10 S6 and S9
S11: S1 or S2 or S3 or S10
S12: (MH "Antibiotics+")
S13: TI antibiotic* or AB antibiotic*
S14: (MH "Antibiotics, Macrolide+")
S15: (MH "Antiinfective Agents, Fluoroquinolone")

S16: (MH "Tetracyclines+")
S17: TI (macrolide* or azithromycin* or clarithromycin* or beta-lactam* or amoxicillin* or cephalosporin* or cefuroxime* or cefotaxime* or ceftriaxone* or quinolone* or fluoroquinalone* or moxifloxacin* or ampicillin* or trimethoprim*) or AB (macrolide* or azithromycin* or clarithromycin* or beta-lactam* or amoxicillin* or cephalosporin* or cefuroxime* or cefotaxime* or ceftriaxone* or quinolone* or fluoroquinalone* or moxifloxacin* or ampicillin* or trimethoprim*)
S18: S12 or S13 or S14 or S15 or S16 or S17
S19: S11 and S18
S20: (MH "Clinical Trials+")
S21: PT clinical trial
S22: TI clinical* trial* or AB clinical* trial*
S23: TI (singl* blind* or doubl* blind* or tripl* blind* or trebl* blind* or singl* mask* or doubl* mask* or tripl* mask* or trebl* mask*) or AB (singl* blind* or doubl* blind* or tripl* blind* or trebl* blind* or singl* mask* or doubl* mask* or tripl* mask* or trebl* mask*)
S24: TI random* or AB random*
S25: (MH "Placebos")
S26: TI placebo* or AB placebo*
S27: (MH "Quantitative Studies")
S28: S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27
S29: S19 and S28

Appendix 4. LILACS search strategy

LILACS

> Search > (((MH:pneumonia OR MH:C08.381.677$ OR MH:C08.730.610$ OR Neumonía OR pneumon$ OR "Inflamación del Pulmón" OR "Neumonía Lobar" OR Neumonitis OR "Inflamación Pulmonar" OR Pneumonía OR Pulmonía OR "Inflamação do Pulmão" OR "Pneumonia Lobar" OR Pneumonite OR "Inflamação Pulmonar" OR Pulmonia) AND (MH:"Community-Acquired Infections" OR "Infecciones Comunitarias Adquiridas" OR "Infecções Comunitárias Adquiridas" OR community OR Comunitarias OR Comunitárias)) OR cap OR "community-acquired pneumonia" OR "community acquired pneumonia") AND (MH: "Anti-Bacterial Agents" OR antibiotic$ OR Antibacterianos OR MH:D27.505.954.122.085$ OR Antibióticos OR MH:macrolides OR Macrólidos OR Macrolídeos OR macrolid$ OR MH:D02.540.505$ OR MH:"beta-Lactams" OR "beta-Lactamas" OR MH: D02.065.589.099$ OR MH:D02.886.108$ OR MH:D04.075.080.875.099.221$ OR betalactam$ OR "beta-lactam" OR "beta-lactams" OR MH:quinolones OR Quinolonas OR MH: D03.438.810.835$ OR quinolon$ OR MH:Tetracyclines OR Tetracyclin$ OR Tetraciclinas OR MH: D02.455.426.559.847.562.900$ OR MH:D04.615.562.900$ OR erythromycin$ OR azithromycin$ OR clarithromycin$ OR ketolid$ OR telithromycin$ OR amoxicillin$ OR clavulanic$ OR "co-amoxiclavulanic" OR "co amoxicavulanic" OR coamoxyclavulanic$ OR cephalosporin$ OR cefuroxim$ OR cefotaxim$ OR ceftriaxon$ OR ceftibuten$ OR cefditoren$ OR cefpodoxim$ OR fluoroquinalone$ OR moxifloxacin$ OR levofloxacin$ OR ampicillin$ OR trimethoprim$ OR oxytetracyclin$ OR doxycyclin$) > trials filter

Appendix 5. Search strategy OpenGrey

OpenGrey

Pneumonia

Appendix 6. ProQuest Dissertations & Theses search strategy

ProQuest Dissertations & Theses

ab(Antibiotic or antibiotics or macrolides or macrolide or beta-lactams or beta-lactam or betalactam or betalactams or quinolines or quinoline or tetracyclines or tetracycline or erythromycin or azithromycin or clarithromycin or ketolides or ketolide or telithromycin or amoxicillin or amoxicillin or clavulanic or co-amoxiclav or cephalosporin or cephalosporins or cefuroxime or cefotaxime or ceftriaxone or ceftibuten or cefditoren or cefpodoxim or fluoroquinoline or fluoroquinolines or moxifloxacin or levofloxacin or ampicillin or trimethoprim or oxytetracycline or doxycline) AND ab(pneumonia)

Appendix 7. Web of Science Conference Proceedings Citation Index Science search strategy

Web of Science CPCI-S

Topic=(Antibiotic or antibiotics or macrolides or macrolide or beta-lactams or beta-lactam or betalactam or betalactams or quinolones or quinolone or tetracylines or tetracycline or erythromycin or azithromycin or clarithromycin or ketolides or ketolide or telithromycin or amoxicillin or amoxycillin or clavulanic or co-amoxiclav or cephalosporin or cephalosporins or cefuroxime or cefotaxime or ceftriaxone or ceftibuten or cefditoren or cefpodoxim or fluoroquinolone or fluoroquinolones or moxifloxacin or levofloxacin or ampicillin or trimethoprim or oxytetracycline or doxycline) AND Topic=(pneumonia)
Refined by: Topic=(random* or placebo* or singl* blind* or doubl* blind* or clinical trial*)
Timespan=All Years. Databases=CPCI-S.

Appendix 8. Trials registers search strategy

Trials registers

1. ClinicalTrials.gov (www.clinicaltrials.gov)

"Interventional" [STUDY-TYPES] AND (Pneumonia OR Bronchopneumonia OR Pleuropneumonia) [CONDITION]

2. ISRCTN registry (www.isrctn.com/)

Condition: Pneumonia OR Bronchopneumonia OR Pleuropneumonia

3. WHO International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/Default.aspx)

Condition: Pneumonia OR Bronchopneumonia OR Pleuropneumonia
Recruitment status: Recruiting

Appendix 9. Implications for research

5 days versus 10 days of amoxicillin for community-acquired pneumonia in adult outpatients: a non-inferiority RCT		
Evidence	1. We found no eligible RCT that studied a short-course of antibiotic compared to a long-course of antibiotic (with the same antibiotic at the same daily dosage) for CAP in adolescent and adult outpatients. We have thus concluded that the effects of the duration of antibiotic therapy for CAP in adolescent and adult outpatients is still unclear. 2. Further studies are needed to determine the efficacy and safety of short-course versus long-course antibiotic therapy (with the same antibiotic at the same daily dosage) for CAP in adolescent and adult outpatients. 3. We propose here an RCT to assess the efficacy and safety of short-course (5 days) versus long-course (10 days) of amoxicillin at the same daily dosage (1 g each 8 hours) for CAP in adults managed in the outpatient setting. 4. We chose amoxicillin because it is an antibiotic commonly used in practice for the treatment of CAP. However, other frequently used antibiotics may be evaluated as well, such as other beta-lactams, macrolides, fluoroquinolones, cotrimoxazole, or tetracyclines.	
		Comments
Population(s)	**Age**: 18 to 65 years. **Gender:** any. **Condition**: CAP 1. Diagnosis of CAP (based on NICE 2014): i) Symptoms and signs of an acute lower respiratory tract infection (such as altered breath sounds, localised rales, or both) ii) Confirmed by a chest x ray showing new shadowing that is not due to any other cause (such as pulmonary oedema or infarction) iii) The pneumonia must be acquired outside the hospital setting or within 48 hours of hospital admission 2. Severity of the CAP: i) Not-severe CAP (CRB-65 score = 0) (NICE 2014). CAP with severe impairment will be excluded because it is usually managed at the hospital: impairment of consciousness, respiratory rate > 30 breaths/min, heart rate > 125 beats/min, systolic blood pressure < 90 mmHg, diastolic blood pressure < 60 mmHg, temperature > 40 °C or oxygen saturation < 92%. **Setting**:	1. The diagnosis should be as similar as possible to real practice, while still ensuring that it is valid. 2. The study will not exclude participants based on the presence comorbidities such as diabetes or COPD, in order to reflect routine clinical practice.

(*Continued*)

	1. Outpatients: CAP initially treated in the community 2. Patients recruited in urban settings 3. Patients recruited in high- as well as low- and middle-income countries	
Intervention	1. Amoxicillin 1 g each 8 hours orally during **5 days** 2. Co-interventions: the antibiotic can be used alone or in combination with other interventions, such as antitussives, antipyretics, bronchodilators, or mucolytic.	1. The study design should allow the effect of the duration of antibiotic course to be evaluated. 2. Provide details of all the interventions and co-interventions undertaken, their compliance and their acceptability. 3. In order to disentangle the effects of the duration of the antibiotic course, the same antibiotic at the same daily dosage must be administered in all the study arms. Moreover, the co-interventions must be also similar in both study groups.
Comparison	1. Amoxicillin 1 g each 8 hours orally during **10 days** 2. Co-interventions: the antibiotic can be used alone or in combination with other interventions, such as antitussives, antipyretics, bronchodilators, or mucolytic.	
Outcomes **(from** Barlow 2003**)**	Include at least the following outcomes: 1. **Symptoms and quality of life measures** i) CAP-Sym (Lamping 2002) 2. **Clinically based measures** i) Time to clinical stability (Halm 2002)* ii) 30-day postadmission mortality (Mortensen 2002)** iii) Hospitalisation due to CAP *Clinical instability, defined as fulfilling 1 or more of the following factors: temperature > 37.8 °C, pulse > 100/min, respiratory rate > 24/min, systolic blood pressure < 90 mmHg, oxygen saturation < 90%, lack of availability of the oral route, and abnormal mental status (Halm 2002). **Not validated as an outcome measure, but clearly important. 30 days' follow-up is the evidence-based time point	1. Measure, collect, and report outcomes in an objective, reliable, accurate, and actionable way. 2. Ensure blinding of participants, caregivers, and outcome assessment wherever possible to minimise performance, attrition, and detection biases. 3. Specify beforehand in the protocol and assess relevant harms related to the use of the antibiotic.
Time stamp	Date of recommendation: July 2018	
Study type	**RCT with the following study features:** 1. **Allocation procedure of participants:** concealed randomisation 2. **Adequate sample size:** calculate	RCT: type of study where the participants (or groups of participants) are assigned prospectively to an intervention or to a control group (or more than 1 control group)

(*Continued*)

	sample size using a non-inferiority or equivalence criterion and specify the margin of equivalence with the rationale for its choice 3. **Prospective parts of the study:** i) generation of hypothesis ii) identification of participants iii) assessment of baseline iv) allocation to intervention v) assessment of outcome 4. **Study hypothesis:** i) effectivenness outcomes: non-inferiority or equivalence ii) safety outcomes: superiority 5. **Blinding of participant and personnel** 6. **Blinding of outcome assessment** 7. **Strategy of analysis** i) non-inferiority or equivalence outcomes: per protocol ii) superiority outcomes: intention-to-treat	using a process of random allocation (e.g. random number generation or coin flips) . Randomisation ensures that participants in each group should, at least theoretically, differ only in their exposure to the intervention - all other measurable characteristics (such as gender, age, educational level, smoking status, etc.) and those that cannot be easily measured (such as attitude, personal beliefs, etc.) should, by chance, be distributed equally between the intervention and control groups. This theoretically ensures that the intervention and the control group differ only in the exposure to the treatment (CCCG 2013).

Abbreviations: CAP: community-acquired pneumonia; CAP-Sym: Community-Acquired Pneumonia Symptom Questionnaire; COPD: chronic obstructive pulmonary disease; CRB-65 score: confusion, respiratory rate, blood pressure, 65 years of age; RCT: randomised controlled trial

CONTRIBUTIONS OF AUTHORS

	JLA	RRB	JRS; JMG; JMMG; CRF; JMC; JCC; MGG	JHM	AAL	VHS
Protocol development	X	X	X			
Guarantor	X	X				
Contact person	X					
Piloted the selection stage	X	X				
Screened titles and abstracts		X	X	X	X	X

(*Continued*)

and assessed full texts						
Resolution of disagreements	X					
Assessed conferences		X	X	X	X	X
Designed the data extraction form	X	X				
Piloted the data extraction form	X	X				
Extracted data	X	X		X		
Resolution of disagreements	X	X				
Cross-checking extracted data		X		X		
'Risk of bias' assessment	X	X		X		
Resolution of disagreements	X	X				
Entered data into Review Manager 5	X					
Data analysis	X	X				
Checked data entered into Review Manager 5	X	X		X		
Wrote the Background			X			
Wrote the Methods sections of the review	X	X				

(*Continued*)

Wrote the Results, Discussion, and Authors' conclusions sections	X	X	X		X	
Prepared the flow chart	X			X		
Prepared 'Summary of findings' tables	X			X		
Made an intellectual contribution and provided clinical perspective	X	X	X	X	X	X
Edited the review	X	X		X		
Assessed Methodological Expectations of Cochrane Intervention Reviews (MECIR) standards	X	X		X		
Approved final version of the review prior to submission	X	X	X	X	X	X

Jesús López Alcalde (JLA); Ricardo Rodríguez Barrientos (RRB); Jesús Redondo-Sánchez (JRS); Javier Muñoz-Gutiérrez (JMG); José María Molero-García (JMMG); Carmen Rodríguez-Fernández (CRF); Julio Heras-Mosteiro (JHM); Jaime Marin-Cañada (JMC); Jose Casanova-Colominas (JCC); Amaya Azcoaga-Lorenzo (AAL); Virginia Hernandez Santiago (VHS); Manuel Gómez-García (MGG).

DECLARATIONS OF INTEREST

Jesús López-Alcalde: None known.

Ricardo Rodriguez-Barrientos: None known.

Jesús Redondo-Sánchez: 1. Grant PI10/01581, Spain: Acción Estratégica de Salud; (2010), as a part of the Plan Nacional de Investigación Científica, Desarrollo e Innovación Tecnológica 2008-2011; 2. ISCIII-Subdirección General de Evaluación and Fondo Europeo de Desarrollo Regional (FEDER); 3. Ayuda de Intensificación de la Fundación de Investigación en Atención primaria de la Comunidad de Madrid (FIIBAP).

Javier Muñoz-Gutiérrez: None known.

José María Molero-García: None known.

Carmen Rodríguez-Fernández: None known.

Julio Heras-Mosteiro: None known.

Jaime Marin-Cañada: I collaborated on lectures about viral hepatitis through my local Family Medicine Society, and Gilead sponsored these activities.

Jose Casanova-Colominas: None known.

Amaya Azcoaga-Lorenzo: I attended a meeting organised by SI-Health Institute for Health and Strategy that was paid for by ViiV Healthcare. The meeting analysed HIV epidemic status in Spain.

Virginia Hernandez Santiago: None known.

Manuel Gómez-García: None known.

SOURCES OF SUPPORT

Internal sources

- Cochrane Associated Centre of Madrid, Spain.

Hospital Universitario Ramón y Cajal (IRYCIS), Madrid / Universidad Francisco de Vitoria (UFV)-Madrid, Madrid

- Gerencia Asistencial Atención Primaria de Madrid, Spain.
- Fundación para la Investigación e Innovación Biomédica de Atención Primaria de Madrid (FIIBAP), Madrid, Spain.
- Agencia Laín Entralgo para la Formación, Investigación y Estudios Sanitarios, Madrid, Spain.

External sources

- Grant PI10/01581: "Acción Estratégica de Salud" (2010), Plan Nacional de Investigación Científica, Desarrollo e Innovación Tecnológica 2008-2011(ISCIII), Spain.
- ISCIII-Subdirección General de Evaluación and Fondo Europeo de Desarrollo Regional (FEDER), Spain.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Objectives

The original text in the protocol was "To evaluate the efficacy and safety of short-course versus long-course antibiotic therapy (with the same antibiotic at the same daily dosage) for CAP in adolescent and adult outpatients. For efficacy outcomes, we will investigate non-inferiority of short-course antibiotic treatment; for safety outcomes, we will investigate superiority". The aim was the same, but we expressed this differently in the review.

Types of studies

Following the standard text for the Methods section of the Cochrane Acute Respiratory Infections protocol, we added: "We included studies reported as full text, those published as abstract only, and unpublished data".

Types of interventions

The protocol stated that "...we anticipate that the class of antibiotic will be a relevant source of heterogeneity. Therefore, if we find enough studies we will stratify the analysis by antibiotic type." However, according to the suggestion of the Cochrane Acute Respiratory Infections editorial team, we will meta-analyse studies regardless of whether they evaluate different types of antibiotics.

Types of outcome measures

We planned to assess the outcome "clinical response at the end-of-therapy evaluation visit" with a minimum follow-up of 14 days from the beginning of treatment. However, we realised this minimum follow-up period was not compatible with certain antibiotic regimens because the end-of-therapy evaluation visit occurred before this point. We therefore decided to consider the end-of-therapy evaluation visit without a minimum follow-up.

The protocol planned to assess "patient compliance with treatment" (reported as dichotomous data where possible) as a secondary review outcome. However, we reported the compliance as part of the description of the interventions, as suggested in the TIDieR checklist and guide (Hoffmann 2014), and not as an outcome.

Search methods for identification of studies

The search strategy for MEDLINE differed slightly from the protocol, as follows.

1. We did not handsearch journals. All journals that appeared to have high yields of relevant studies had already been handsearched on behalf of Cochrane.
2. We checked abstracts presented at the predefined conferences from 2004 onward (instead of 2000, as detailed in the protocol).
3. We could not search Asociación Latinoamericana del Tórax (ALAT) because it was not available.
4. We could not search 2004, 2006, and 2013 editions of NEUMOPED because they were not available.
5. We could not search 2011 and 2012 editions of PCRS because they were not available.
6. We searched CINAHL and OpenGrey (which were not planned in the protocol).
7. We did not consult IFPMA Clinical Trials Portal (www.clinicaltrials.ifpma.org); visitors are now redirected to the WHO International Clinical Trials Registry Platform.
8. We did not consult PhRMA Clinical Study Results Database (website no longer available).

Assessment of risk of bias in included studies

- We planned to consider the tool described in the *Cochrane Handbook for Systematic Reviews of Interventions* version 5.1.0 (Higgins 2011a), rather than version 5.0.2 as proposed, because among other reasons the revised version assesses bias related to blinding of participants and personnel in a domain separately from bias related to blinding of outcome assessment.
- We did not attempt to document the interrater reliability in the 'Risk of bias' assessment using the kappa statistic or report relevant discrepancies in the assessments (Higgins 2003).
- We planned to incorporate summary assessments of risk of bias for each outcome across studies into explicit measures of evidence quality for each important outcome using the GRADE system (GRADEpro GDT 2014).

Sensitivity analysis

We could not perform sensitivity analysis.