National Institute for Health and Care Excellence

Final

Chronic obstructive pulmonary disease (acute exacerbation): antimicrobial prescribing

Evidence review

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1 Context

1.1 Background

Chronic obstructive pulmonary disease (COPD) is characterised by airflow obstruction that is not fully reversible. The airflow obstruction does not change markedly over several months and is usually progressive in the long term. COPD is predominantly caused by smoking. Other factors, particularly occupational exposures, may also contribute to the development of COPD. Exacerbations often occur, where there is a rapid and sustained worsening of symptoms beyond normal day-to-day variations. COPD is the preferred term for the conditions in people with airflow obstruction who were previously diagnosed as having chronic bronchitis or emphysema (NICE guideline on COPD in over 16s).

There is no single diagnostic test for COPD. Making a diagnosis relies on clinical judgement based on a combination of history, physical examination and confirmation of the presence of airflow obstruction using spirometry. The diagnosis of COPD varies in clinical studies (particularly in older studies that refer to chronic bronchitis), or is not defined.

COPD exacerbations can affect people's health status and functional capacity with a profound impact on quality of life. As COPD progresses it can result in hospital admission and death. In the UK, an acute exacerbation of COPD is one of the most common causes of acute hospital admissions (NICE guideline on COPD in over 16s).

An acute exacerbation is a sustained worsening of the person's symptoms from their usual stable state which is beyond normal day-to-day variations, and is acute in onset. Commonly reported respiratory symptoms are (NICE clinical knowledge summary [CKS]: chronic obstructive pulmonary disease):

- increased breathlessness
- increased cough
- increased sputum production
- change in sputum colour.

Other symptoms may include increased wheeze and chest tightness, upper respiratory tract symptoms, reduced exercise tolerance, ankle swelling, increased fatigue and acute confusion (NICE clinical knowledge summary [CKS]: chronic obstructive pulmonary disease). The diagnosis of an exacerbation is made clinically and does not depend on the results of investigations; however, in certain situations, investigations may assist in ensuring appropriate treatment is given. The diagnosis varies in clinical studies, but is often based on the Anthonisen classification or a clinical evaluation of worsening symptoms and signs. It is not defined in some clinical studies which limits interpretation of the evidence.

A general classification of the severity of an acute exacerbation (NICE guideline on COPD in over 16s; Oba Y et al. [2017]) is:

- mild exacerbation: the person has an increased need for medication, which they can manage in their own normal environment
- moderate exacerbation: the person has a sustained worsening of respiratory status that requires treatment with systemic corticosteroids and/or antibiotics
- severe exacerbation: the person experiences a rapid deterioration in respiratory status that requires hospitalisation.

One widely used classification of severity is based on the Anthonisen classification of type of exacerbation, which is based on the presence of 3 cardinal exacerbation symptoms:

- increased breathlessness,
- increased sputum volume, and
- sputum purulence.

This classification has influenced the clinical management of acute exacerbations, but has not been validated against objective measures of severity, and does not take account of the severity of each symptom. The American Thoracic Society (ATS)/European Respiratory Society (ERS) guideline (2017) uses health care utilisation as a proxy to classify the severity of acute exacerbation; any exacerbation that can be managed at home is classified as mild or moderate; and any exacerbation requiring hospitalisation is classified as severe. More than 80% of acute exacerbations are managed in the community (Global Initiative for Chronic Obstructive Lung Disease guideline [2017]), and of those treated in hospital, other scoring systems have been developed to help stratify risk.

A number of factors are known to trigger an acute exacerbation of COPD, such as a respiratory tract infection (which can be viral) and environmental factors (such as smoking; see the NICE guideline on COPD in over 16s). Only about half of exacerbations are thought to be caused by a bacterial infection (Vollenweider et al. 2012). Commonly isolated bacterial pathogens are *Streptococcus pneumoniae*, *Moraxella catarrhalis* and *Haemophilus influenzae* (NICE guideline on COPD in over 16s).

1.2 Managing infections that require antibiotics

An acute exacerbation of COPD is a respiratory tract infection which may require treatment with an antibiotic, depending on the clinical presentation of the person. In some instances the condition of the patient may necessitate prompt effective antibiotic treatment within 1 hour of diagnosis (or as soon as possible) in patients who have sepsis or life threatening infection, in these patients therapy should not be delayed but urine and/or blood samples for culture should, if possible, be obtained prior to treatment**.**

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

1.2.1 Antibiotic prescribing strategies

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

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

person they were prescribed or supplied for, not keeping them for use another time and returning unused antimicrobials to the pharmacy for safe disposal and not flushing them down toilets or sinks.

1.3 Safety information

1.3.1 Safety netting

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

- how long symptoms are likely to last with and without antimicrobials
- what to do if symptoms get worse
- what to do if they experience adverse effects from the treatment
- when they should ask again for medical advice.

The NICE guideline on COPD in over 16s makes recommendations on assessing the need for hospital treatment, different investigation strategies (if appropriate) and monitoring recovery from an exacerbation.

1.3.2 Medicines safety

Antibiotic-associated diarrhoea is estimated to occur in 2 to 25% of people taking antibiotics, depending on the antibiotic used (NICE clinical knowledge summary [CKS]: diarrhoea – antibiotic associated).

About 10% of the general population claim to have a penicillin allergy; this has often been because of a skin rash that occurred during a course of penicillin in childhood. Fewer than 10% of people who think they are allergic to penicillin are truly allergic. People with a history of immediate hypersensitivity to penicillins may also react to cephalosporins and other beta lactam antibiotics (BNF October 2018). See the NICE guideline on drug allergy (2014) for more information.

Macrolides, including clarithromycin and erythromycin, are an alternative to penicillins in people with penicillin allergy. They should be used with caution in people with a predisposition to QT interval prolongation. Nausea, vomiting, abdominal discomfort, and diarrhoea are the most common side effects of macrolides. These are less frequent with clarithromycin than with erythromycin (BNF October 2018).

Tetracyclines, including doxycycline, can deposit in growing bone and teeth (by binding to calcium) causing staining and occasionally dental hypoplasia. They should not be given to children under 12 years, or to pregnant or breast-feeding women. The absorption of tetracyclines is reduced by antacids, milk, and aluminium, calcium, iron, magnesium and zinc salts. Common side effects include nausea, vomiting, diarrhoea, dysphagia, and oesophageal irritation (BNF October 2018).

Cholestatic jaundice can occur either during or shortly after the use of co-amoxiclav. It is more common in people above the age of 65 years and in men; and has only rarely been reported in children. Jaundice is usually self-limiting and very rarely fatal (BNF October 2018).

Fluoroquinolones, including ciprofloxacin, cause arthropathy in the weight-bearing joints of immature animals and are generally not recommended in children or young people who are

growing (BNF October 2018). Following a review of disabling and potentially long-lasting side effects mainly involving muscles, tendons, bones and the nervous system, the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (press release October 2018) has recommended restricting the use of fluoroquinolone antibiotics.

Co-trimoxazole is currently under restriction for use in the UK. It is advised that it only be considered for use in acute exacerbations of COPD when there is bacteriological evidence of sensitivity to co-trimoxazole and good reason to prefer this combination to a single antibiotic (BNF October 2018).

1.4 Antimicrobial resistance

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

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

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

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

The ESPAUR report 2017 reported that antimicrobial prescribing declined significantly between 2012 and 2016, with community prescribing from general practice decreasing by 13% and dental practice dispensing 1 in 5 fewer antibiotics in this period. The ESPAUR report 2016 stated that antibiotic prescribing in primary care in 2015 is at the lowest level since 2011, with broad-spectrum antibiotic use (antibiotics that are effective against a wide range of bacteria) continuing to decrease in primary care, this has decreased by another 2% in 2015 to 2016 largely driven by reductions in use of penicillin's. Overall, there have been year-on-year reductions in the use of antibiotics for respiratory tract infections in primary care, mainly driven by reductions in amoxicillin prescribing. Macrolide prescribing as a class is relatively unchanged.

In a bacterial acute exacerbation of chronic obstructive pulmonary disease, the most common causative pathogens are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. Since the introduction of the pneumococcal conjugate vaccine, the most common bacterial pathogen may be changing from *Streptococcus pneumoniae* to *Haemophilus influenzae* and *Moraxella catarrhalis* (Canadian Pediatric Society position statement [2016]). Data from the ESPAUR report 2016 on the antibiotic susceptibility of pathogens causing bacteraemia show that for *Streptococcus pneumoniae* the proportion of bloodstream isolates that are not susceptible to penicillin was about 5% in 2015, with a corresponding 8% not susceptible to macrolides. These figures have stayed relatively stable for the past 5 years.

1.5 Other considerations

1.5.1 Medicines adherence

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

1.5.2 Resource impact

Antibiotics

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

2 Evidence selection

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

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

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

2.1 Literature search

The literature search was developed to identify evidence for the effectiveness and safety of interventions for managing acute exacerbations of chronic obstructive pulmonary disease (COPD; see appendix C: literature search strategy for full details). The literature search identified 6,806 references. These references were screened using their titles and abstracts and 121 full text references were obtained and assessed for relevance. Full text references of systematic reviews and randomised controlled trials (RCTs) were assessed as relevant to the guideline review question (see appendix B: review protocol). Ten percent of studies were screened to establish inter-rater reliability, and this was within the required threshold of 90%.

The methods for identifying, selecting and prioritising the best available evidence are described in the interim process guide. Nine of the 45 references were prioritised by the committee as the best available evidence and were included in this evidence review (see appendix F: included studies).

The 36 references that were not prioritised for inclusion are listed in appendix I: not prioritised studies, with reasons for not prioritising the studies. Studies that assessed. Also see appendix E: evidence prioritisation for more information on study selection.

The remaining 76 references were excluded. These are listed in appendix J: excluded studies with reasons for their exclusion.

See also appendix D: study flow diagram.

2.2 Summary of included studies

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

Table 1: Summary of included studies: antimicrobials

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
Antibiotics versus placebo					
Vollenweider et al. (2012) Cochrane review and meta-analysis (multiple countries).	N=2,068 (16 RCTs including 10 double-blinded RCTs)	People with acute exacerbations of COPD	Antibiotics including: • Amoxicillin • Chloramphenicol • Co-amoxiclav • Co-trimoxazole • Doxycycline • Ofloxacin • Oxytetracycline • Penicillin and streptomycin • Tetracycline	Placebo	No resolution or deterioration of symptoms after treatment
Antibiotics versus other antibiotics					
Korbila et al. (2009) systematic review and meta-analysis (multiple countries).	N=262 (5 RCTs including 2 double blinded RCTs)	People with acute exacerbation of chronic bronchitis (method of diagnosis unclear)	Penicillins including: • Amoxicillin • Ampicillin • Pivampicillin	Trimethoprim (with or without a sulphonamide)	Treatment success
Dimopoulos et al. (2007) systematic review and meta-analysis (multiple countries included 2 UK studies)	N=2,261 (12 RCTs including 9 double-blinded RCTs)	People with acute exacerbations of chronic bronchitis, which was based on a history of cough and expectoration for 2 consecutive years	First-line antibiotics: • Amoxicillin • Ampicillin • Pivampicillin • Co-trimoxazole • Doxycycline	Second-line antibiotics: • Co-amoxiclav • Macrolides • 2nd or 3rd generation cephalosporins • fluoroquinolones	The remission or amelioration of symptoms of acute infection
Siempos et al. (2007) systematic review and meta-analysis (multiple countries)	N=7,045 (19 RCTs including 10 double-blinded)	People with acute exacerbations of chronic bronchitis which was defined a medical history of cough and expectoration on most days during at least 3 consecutive months in each	Macrolide versus fluoroquinolone Co-amoxiclav versus macrolide Co-amoxiclav versus fluoroquinolone		The remission or amelioration of symptoms of acute infection

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
		of 2 or more consecutive years			
Yoon et al. (2013) (South Korea), an open label RCT	N=137	People with acute exacerbations of COPD (exacerbation was defined as recently increased cough or dyspnoea, recent change in colour or amount of sputum, and a diagnosis of COPD on spirometry)	Levofloxacin 500 mg once daily for 7 days	Cefuroxime 250 mg twice daily (mild to moderate exacerbation) or 500 mg twice daily (severe exacerbation)	The resolution or the improvement of symptoms after treatment
Nouira et al. (2010) (Tunisia), double-blind RCT	N=170	People with severe acute exacerbation of COPD (clinical history) requiring mechanical ventilation	Co-trimoxazole 160/800 mg twice daily for 10 days	Ciprofloxacin 750 mg twice daily for 10 days	Death in hospital; need for additional antibiotics
Petitpretz et al. (2007) (multiple countries), an open label RCT	N=585	People with acute bacterial exacerbations of chronic obstructive bronchitis (method of diagnosis unclear)	Levofloxacin 500 mg once daily for 10 days	Cefuroxime 250 mg twice daily for 10 days	The resolution or the improvement of signs or symptoms after treatment
Urueta-Roblendo et al. (2006) (multiple countries), double-blind RCT	N=561	People with a diagnosis of chronic bronchitis with exacerbation characterised by increased cough, increased sputum production with changes in sputum colour and consistency, and mild to moderate dyspnoea	Levofloxacin 500 mg once daily for 7 days	Moxifloxacin 400 mg once daily for 5 days	The resolution or the improvement of symptoms after treatment
Antibiotic course length					
Stolbrink et al. (2017) systematic review and meta-analysis (multiple countries including 1 UK study)	N=3,979 (10 RCTs)	People with acute exacerbations of COPD (method of diagnosis unclear)	Short-course antibiotic[1] duration (<6 days)	Long-course antibiotic (≥7 days)	Clinical response was defined as the resolution of clinical signs or symptoms of acute exacerbation, and was evaluated within 6 days, 7-14 days and more than 20

Study	Number of participants	Population	Intervention	Comparison	Primary outcome
					days after treatment completion

Abbreviations: RCT, Randomised controlled trial

[1] Antibiotics included in the review: amoxicillin, moxifloxacin, grepafloxacin, gatifloxacin, clarithromycin, cefixime, levofloxacin, co-amoxiclav.

3 Evidence summary

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

The main results are summarised below for antimicrobials in people with an acute exacerbation of chronic obstructive pulmonary disease (COPD). Other interventions are covered in the NICE guideline on COPD in over 16s.

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

3.1 Antimicrobials in adults

3.1.1 Back-up antibiotics

No systematic reviews or RCTs were identified on back-up antibiotic prescribing for people with an acute exacerbation of COPD.

3.1.2 Antibiotics compared with placebo

The evidence review for antibiotics compared with placebo is based on 1 systematic review of 16 placebo-controlled RCTs of 2,068 adults aged 40 years or over (mean age range 52 to 72 years) with an acute exacerbation of COPD (Vollenweider et al. 2012). The diagnosis of COPD was either based on physicians' evaluation of participants' symptoms or was confirmed by spirometry. Participants were included if their previous stable COPD was worsening, with symptoms such as increased dyspnoea, increased cough, increased sputum volume or change in sputum colour. In the review, the care setting was used a marker of the severity of the acute exacerbation in the review: people treated in the community as mild to moderate exacerbation (6 RCTs); and people treated in hospitals as severe exacerbation (9 RCTs).

Antibiotics used in the RCTs included: co-amoxiclav, co-trimoxazole, amoxicillin, doxycycline, oxytetracycline, cefaclor, ofloxacin, chloramphenicol, benzylpenicillin and tetracycline. The duration of antibiotic course ranged from 5 to 17 days, and doses varied by antibiotics. Of these, some antibiotics are no longer widely used for COPD due to changing antimicrobial resistance patterns including oxytetracycline, tetracycline and chloramphenicol. In 2 studies all participants also received prednisolone (oral or intravenous [IV]).

Up to 1 month after treatment starting, significantly fewer people in the antibiotics group failed to resolve or have improved exacerbation symptoms compared with the placebo group (12 RCTs, n=1,636: 28.4% versus 37.4%; NICE analysis[1] relative risk [RR] 0.64, 95% CI 0.50 to 0.84; number needed to treat [NNT] 12, 95% CI 8 to 23; very low quality evidence). This analysis included a heterogeneous population of people treated in the community, in hospital or in intensive care, and the result was influenced by the large positive effect observed in 1 RCT in an intensive care population. When this study was removed from the analysis, the benefit of antibiotics compared with placebo was reduced (11 RCTs, n=1,543: 29.4% versus 36.1%; NICE

[1] A fixed effect model was used in the Cochrane analysis, and NICE analysis was based on random effect model due to heterogeneity (I^2>50%).

analysis[2] RR 0.76, 95% CI 0.66 to 0.87; NNT 15, 95% CI 9 to 50; moderate quality of evidence).

In a subgroup analysis, the efficacy of antibiotics was assessed by the person's care setting[3]. Significantly fewer people who were treated with antibiotics failed treatment (no resolution or deterioration of exacerbation symptoms) compared with the placebo group across all care settings, and the benefit was greatest in people who required intensive care in hospital:

- people treated in the community (classified as a mild or moderate exacerbation): 7 RCTs, n=931: 19.9% versus 27.5%; RR 0.75 95% CI 0.60 to 0.94; NNT 14, 95% CI 8 to 46; moderate quality evidence;
- people treated in hospital (classified as a severe exacerbation): 4 RCTs, n=612; 41.8% versus 52.0%; RR 0.77 95% CI 0.65 to 0.91; NNT 10, 95% CI 6 to 45; moderate quality evidence;
- people admitted to an intensive care unit in hospital (classified as a very severe exacerbation): 1 RCT, n=93; 10.6% versus 56.5%; RR 0.19 95% CI 0.08 to 0.45; NNT 3, 95% CI 2 to 4; high quality evidence.

The review also restricted the analysis to antibiotics that the authors considered to be in current use (including co-amoxiclav, co-trimoxazole, doxycycline and amoxicillin). Studies assessing oxytetracycline, tetracycline and chloramphenicol were excluded from the analysis. There remained a significant difference in treatment failures with antibiotics compared with placebo (8 RCTs, n=1,175: 24.5% versus 34.5%; RR 0.76, 95%CI 0.64 to 0.91; NNT 11 95% CI 7 to 21; low quality evidence). However, in a subgroup analysis based on care setting, there were no significant differences between treatment groups:

- people treated in hospital: 3 RCTs, n=383: 28.9% versus 45.9%; NICE analysis[4] RR 0.56, 95% CI 0.31 to 1.03; low quality evidence;
- people treated in the community: 5 RCTs, n=790: 22.2% versus 29.1%; RR 0.80, 95% CI 0.63 to 1.01; low quality evidence.

Three studies reported the length of hospital stay, and no significant difference was found between treatment groups (3 RCTs, n=202: 11.1 days [standard deviation SD 4.25] versus 17.6 days [SD 5.75]; mean difference [MD] 3.04 fewer, 95% CI 8.83 fewer to 2.76 more; very low quality evidence). When observing days off work during study follow-up, people treated in the community with antibiotics had significantly fewer days off work compared with the placebo group, although this was based on relatively small numbers of participants in an old study (1 RCT, n=86: 4.25 days [SD 0.96] versus 9.43 [SD 2.96]; MD 5.18 fewer, 95% CI 6.08 fewer to 4.28 fewer; high quality evidence; Vollenweider et al. [2012]). Only 1 study reported health-related quality of life and no significant difference between treatment groups was found (1 RCT, n=35; very low quality evidence).

[2] In the sensitivity analysis, the analysis excluded the study which involved people who were admitted to intensive care, and I^2<50%.

[3] Five RCTs were conducted in a hospital setting. Two RCTs stated that hospital admission was judged by the receiving clinician (no admission criteria were given). In 1 RCT, people were admitted to the intensive care unit with a need for mechanical ventilation. In 1 RCT, the hospital admission criteria were adapted from the GOLD workshop summary (2001) and included marked increase in intensity of symptoms such as sudden development of resting dyspnoea, severe background of COPD, onset of new physical signs, failure of the exacerbation to respond to initial medical management, significant co-morbidities, newly occurring arrhythmias, diagnostic uncertainty, older age and insufficient home support. In 1 RCT people were admitted to hospital with an acute exacerbation with increasing symptoms, such as dyspnoea, sputum volume or cough.

[4] A fixed effect model was used in the Cochrane analysis, and the NICE analysis was based on a random effect model due to heterogeneity (I^2>50%).

When observing adverse events between 5 and 28 days after treatment, significantly more people treated with antibiotics reported adverse events compared with people in the placebo group (5 RCTs, n=1,243: 10.6% versus 7.4%; RR 1.46, 95%CI 1.03 to 2.09;]; low quality evidence), although there is considerable uncertainly in this result as the frequency of adverse events was low. More people on antibiotics reported diarrhoea than people treated with placebo (3 RCTs, n=698, 4.4% versus 1.8%; RR 2.62, 95%CI 1.11 to 6.17; low quality evidence), although the incidence was low in both groups. There was no difference in adverse events such as dyspepsia and exanthema and rash (very low quality evidence).

See GRADE profile 1 (Table 4).

3.1.3 Choice of antibiotic

The evidence review for choice of antibiotic in adults is based on 3 systematic reviews (Dimopoulos et al. 2007; Korbila et al. 2009; Siempos et al. 2007;) and 4 RCTs [Petitpretz et al. 2007; Nouira et al. 2010, Yoon et al. 2013; Urueta-Robledo et al. 2006], which all cover different comparisons of antibiotic regimens.

3.1.3.1 First-line antibiotics compared with second-line antibiotics

The review by Dimopoulos et al (2007) included 12 RCTs (n=2,261) comparing antibiotics that were considered to be first-line (amoxicillin, ampicillin, pivampicillin, co-trimoxazole and doxycycline) with second-line antibiotics (co-amoxiclav, macrolides, cefaclor and fluoroquinolones). Dose regimens varied by antibiotics, and antibiotic course length ranged from 5 to 14 days. Three studies permitted the use of corticosteroids before an acute exacerbation of chronic bronchitis (details about doses and duration were not provided in the review). The efficacy of antibiotics was assessed up to 7 days after the end of treatment.

Adults aged over 18 years (range 49 to 71 years) were included if they experienced an acute exacerbation of chronic bronchitis. Six RCTs included people treated in the community, and 6 RCTs included people treated in hospital, of these 6, 4 included a mixed of people treated in the community and in hospital but admission criteria were not specified in Dimopoulos et al. (2007). The diagnosis of chronic bronchitis was based on a history of cough and expectoration on most days during a period of at least 3 consecutive months for 2 consecutive years, and an exacerbation was classified by exacerbation symptoms based on the Anthonisen classification. The severity of participants' acute exacerbation varied across studies, and was not specified in 2 RCTs.

In Dimopoulos et al. (2007) first-line antibiotics were significantly less effective in resolving or improving exacerbation symptoms compared with second-line antibiotics (12 RCTs, n=1,166: 81.8% versus 91.3%; NICE analysis[5] RR 0.92, 95%CI 0.85 to 0.99; NNT 11, 95% CI 8 to 16; moderate quality evidence).

In a subgroup analysis by the person's care setting (community or hospital [no hospital admission criteria stated]), significantly fewer people who were treated in both care settings had resolved or improved symptoms with first-line antibiotics compared with second-line antibiotics (people treated in the community, 4 RCTs, n=605: 90.3% versus 95.5%; NNT 20, 95% CI 9 to 371; NICE analysis[5] RR 0.94, 95%CI 0.89 to 0.99; moderate quality evidence). However, there was no difference in

[5] The review reported odds ratios as an estimation of the treatment effect, and the NICE analysis used relative risk to evaluate the treatment effect. A fixed effect model was used when $I^2 \leq 50\%$, and a random effect model was used when there was heterogeneity ($I^2 > 50\%$).

people treated in hospital (6 RCTs, n=561; 74.0% versus 87.5%; NICE analysis[5] RR 0.86, 95% CI 0.73 to 1.02; low quality evidence).

When sputum samples were examined up to 7 days after antibiotic treatment, there was no significant difference in the absence of pathogens that were initially isolated in participants' sputum samples between treatment groups (9 RCTs, n=608: 82.3% versus 91.9%; NICE analysis[5] RR 0.95, 95% CI 0.85 to 1.06; moderate quality evidence).

No significant difference was found in all-cause mortality among treatment groups during the observation period (5 RCTs, n=1,392: 1.0% versus 1.6%; NICE analysis[5] RR 0.66, 95% CI 0.27 to 1.63; moderate quality evidence). When observing antibiotic-related adverse events up to 7 days after treatment, there was no significant difference between first-line antibiotics and second-line antibiotics (9 RCTs, n=1,670: 14.6% versus 20.6%; NICE analysis[5] RR 0.79, 95% CI 0.47 to 1.33; very low quality evidence). Common adverse events reported included diarrhoea, nausea, abdominal pain, vomiting, skin rashes, insomnia and dizziness.

See GRADE profile 2 (Table 5).

3.1.3.2 Macrolides compared with fluoroquinolones

A systematic review (Siempos et al. 2007) included 19 RCTs (n=7,045) that compared the effectiveness of broader-spectrum antibiotics: macrolides, fluoroquinolones and co-amoxiclav (course duration range from 3 to 10 days) when treating adults (18 years or over) with an acute exacerbation of chronic bronchitis. Diagnosis of chronic bronchitis was based on a medical history of cough and expectoration on most days during at least 3 consecutive months in each of 2 or more consecutive years. All participants were treated in the community during study enrolment except for 1 RCT in which both people treated in the community and in hospital were included. An acute exacerbation was classified by the number of symptoms based on the Anthonisen classification. The severity of the exacerbation varied across studies.

Based on all participants who were randomised (intention to treat [ITT] analysis), Siempos et al. (2007) found no significant difference between macrolides and fluoroquinolones for resolving or improving symptoms in people with acute exacerbations of chronic bronchitis (5 RCTs[6], n=3,326; 88.1% versus 89.3%; NICE analysis[5] RR 1.00, 95% CI 0.97 to 1.02; high quality evidence). Similar results were reported when the analysis was based on participants whose response to antibiotics could be measured and determined (clinically evaluable [CE] population; high quality evidence).

In a subgroup analysis of people with moderate or severe exacerbations, there was also no significant difference between treatment groups in the resolution or the improvement in exacerbation symptoms (2 RCTs[7], n=1,454: 80.7% versus 80.1%; NICE analysis[5] RR 1.01, 95% CI 0.96 to 1.06, ITT analysis; high quality evidence). Similar results were reported in the analysis based on clinically evaluation population (high quality evidence).

[6] Three of 5 RCTs permitted the use of systemic corticosteroid before an acute exacerbation of chronic bronchitis, range from 21% to 39% in macrolide group, and from 21% to 50% in fluoroquinolone group. Of 2 of 3 studies that permitted the use of corticosteroid, studies included people with moderate to severe exacerbation of chronic bronchitis based on the Anthonisen classification.

[7] Both studies permitted the use of systemic corticosteroid before an acute exacerbation of chronic bronchitis

When sputum samples were examined up to 18 days after antibiotic treatment, significantly fewer people in the macrolide group had eradication of the pathogen that caused the acute exacerbation compared with people in the fluoroquinolone group (7 RCTs, n=1,308: 83.1% versus 91.8%; NICE analysis[5] RR 0.92, 95% CI 0.87 to 0.98; NNT 12, 95% CI 8 to 19; moderate quality evidence).

There was no significant difference between groups in all-cause mortality, with 4 deaths in the macrolide group and 2 deaths in the fluoroquinolone group (4 RCTs, n=2,627; moderate quality evidence).

No significant difference in adverse events was reported with macrolides compared with fluoroquinolones (7 RCTs, n=4,081: 20.3% versus 20.0%; NICE analysis[5] RR 1.09, 95% CI 0.97 to 1.24; high quality evidence).

See GRADE profile 3 (Table 6).

3.1.3.3 Co-amoxiclav compared with macrolides

Eight RCTs included in Siempos et al. (2007) compared the efficacy and safety of co-amoxiclav with macrolides. Dose regimens of co-amoxiclav were 500/125 mg or 875/125 mg (for 5 to 14 days). In the macrolide group, the following regimens were included: clarithromycin 500 mg or 1000 mg once daily (7-day course), azithromycin 250 mg or 500 mg once or twice daily (3-day course), or other macrolides not available in the UK (dirithromycin [5-day course] and roxithromycin [14-day course]).

There was no significant difference between co-amoxiclav and macrolides in the resolution or improvement of exacerbation symptoms (5 RCTs[8], n=869: 86.4% versus 85.1%; RR 1.02, 95% CI 0.88 to 1.17, ITT population; moderate quality evidence). The result was consistent in clinically evaluable population (moderate quality evidence).

Between 6 and 21 days following the onset of acute exacerbation, eradication of the pathogen that caused the acute exacerbation was not significantly different between treatment groups (4 RCTs, n=502; 78% versus 71%; RR 1.08, 95% CI 0.86 to 1.37; low quality evidence).

There was also no significant difference in adverse events observed between co-amoxiclav and macrolides (2 RCTs, n=437: 23.1% versus 16.7%; RR 1.38, 95% CI 0.96 to 1.94; moderate quality evidence).

See GRADE profile 4 (Table 7).

3.1.3.4 Co-amoxiclav compared with fluoroquinolones

Four RCTs included in Siempos et al. (2007) compared the efficacy and safety of co-amoxiclav with fluoroquinolones. Dose regimens of co-amoxiclav were 500/125 mg or 875/125 mg twice or three times daily (range, 7 to 10-day course). Fluoroquinolone regimens included moxifloxacin 400 mg once daily (5-day course), levofloxacin 750 mg once daily (5-day course) and gemifloxacin 320 mg once daily (5-day course).

In the ITT analysis, significantly fewer people had resolved or improved exacerbation symptoms with co-amoxiclav compared with a fluoroquinolone (1 RCT, n=575: 85.2% versus 92.5%; NICE analysis[5] RR 0.92, 95% CI 0.87 to 0.98; NNT 14, 95% CI 8 to 45; moderate quality evidence). However, in the analysis based on clinically

[8] Two of 5 RCTs permitted the use of systemic corticosteroid before an acute exacerbation of chronic bronchitis (details were not reported in the review)

evaluable participants, there was no significant difference between treatment groups (4 RCTs[9], n=1,445: 90.4% versus 90.0%; RR 0.99, 95% CI 0.96 to 1.03; moderate quality evidence).

Between 6 and 21 days following the onset of the acute exacerbation, there was no significant difference in the eradication of pathogens that caused the acute exacerbation between co-amoxiclav and fluoroquinolones (4 RCTs, n=444: 83.6% versus 86.6%; NICE analysis[5] RR 0.97, 95% CI 0.90 to 1.05; moderate quality evidence).

Significantly more people treated with co-amoxiclav had adverse events compared with fluoroquinolones (4 RCTs, n=1,699: 16.6% versus 12.8%; NICE analysis[5] RR 1.30, 95% CI 1.03 to 1.64; NNH 27 [95% CI 13 to 207]; moderate quality evidence).

See GRADE profile 5 (Table 8).

3.1.3.5 Co-trimoxazole compared with fluoroquinolone

One double-blind RCT (Nouira et al. 2010; n=170) assessed the effectiveness and safety of co-trimoxazole compared with ciprofloxacin in adults aged 40 years or over (mean 67 years) with an acute exacerbation of COPD being admitted to an intensive care unit in hospital. The diagnosis of acute exacerbation of COPD was based on a history of COPD with clinical evidence of a purulent bronchitis in addition to acute respiratory failure requiring mechanical ventilation within the first 24 hours after hospital admission. Participants were randomised to either co-trimoxazole 160/800 mg twice daily (for 10 days) or ciprofloxacin 750 mg twice daily (for 10 days).

Up to 6 months after antibiotic treatment, there were no significant differences between co-trimoxazole and ciprofloxacin in the rates of hospital deaths (8.2% versus 9.4%; NICE analysis RR 0.88, 95% CI 0.33 to 2.31; low quality evidence), the need for additional antibiotics (8.2% versus 5.9%; NICE analysis[10] RR 1.40, 95% CI 0.46 to 4.24; moderate quality evidence) or the duration of hospital stay (12.9 days [SD 7.4] versus 13.1 days [SD 8.4]; MD 0.2 fewer, 95% CI 2.6 fewer to 2.2 more; high quality evidence).

There were also no significant differences in adverse events between co-trimoxazole and fluoroquinolone (5.9% versus 7.0%; NICE analysis RR 0.83, 95% CI 0.26 to 2.63; moderate quality evidence).

See GRADE profile 6 (Table 9).

3.1.3.6 Fluoroquinolones compared with cephalosporins

Two open-label RCTs (Petitpretz et al. 2007 and Yoon et al. 2013) compared levofloxacin with cefuroxime for treating people with an acute exacerbation of COPD.

Petitpretz et al. (2007) compared the efficacy and safety of a fluoroquinolone versus a cephalosporin with follow-up over a 6-month period. The study included adults aged 45 years and over with a diagnosis of an acute exacerbation of chronic obstructive bronchitis. Participants were enrolled if they had a history of cough and sputum production on most days for 3 consecutive months and for more than 2 consecutive years with the presence of recent increase in sputum volume, sputum

[9] Two of 4 RCTs permitted the use of systemic corticosteroids before an acute exacerbation of chronic bronchitis, which ranged from 14% to 43% in the co-amoxiclav group and 17% to 48% in the fluoroquinolone group.

[10] The study author reported mean differences of the outcome, and the NICE analysis reported relative risk based on the number that reported in the study.

purulence and dyspnoea. There was no stratification by severity of chronic obstructive bronchitis.

All participants (n=585) were treated in the community during the study, and were randomised to receive oral levofloxacin 500 mg once daily (10-day course) or oral cefuroxime 250 mg twice daily (10-day course). The mean age of study participants was 64 years, and the majority were men (81.4%). All participants presented with a severe exacerbation with increased purulence and volume of expectoration, and increased dyspnoea.

There was no significant difference between levofloxacin and cefuroxime in the number of people who resolved or had improved exacerbation symptoms (95% versus 92%; RR 1.02, 95% CI 0.98 to 1.07; moderate quality evidence). There was no significant difference in adverse events between levofloxacin and cefuroxime (5.9% versus 3.4%; RR 1.74, 95% CI 0.81 to 3.74; very low quality evidence).

A further RCT by Yoon et al. (2013) also compared the efficacy and safety of levofloxacin with cefuroxime (n=137). The study included adults over 18 years (mean age 70 years) with an acute exacerbation of COPD (recently increased cough or dyspnoea, recent change in colour or amount of sputum, and a diagnosis of COPD on spirometry). The severity of participants' exacerbation varied from mild to severe, with the majority of people having a mild or moderate exacerbation based on clinicians' evaluation. Participants were randomised to levofloxacin 500 mg once daily for 7 days or cefuroxime for 7 days (250 mg twice daily for a mild to moderate exacerbation or 500 mg twice daily for a severe exacerbation).

No significant difference in the resolution or the improvement of symptoms was reported with levofloxacin compared with cefuroxime (n=137: 81.5% versus 80.6%; RR 1.01, 95% CI 0.86 to 1.19; moderate quality evidence).

See GRADE profile 7 (Table 10).

3.1.3.7 Fluoroquinolones compared with another fluoroquinolone

One double-blind RCT (Urueta-Robledo et al. 2006) (n=563) assessed the efficacy and safety of levofloxacin compared with moxifloxacin in adults aged 18 years or over (mean 60 years) with an acute exacerbation of chronic bronchitis (history of cough and sputum on most days during at least 3 consecutive months and for more than 2 consecutive years, with exacerbation within the previous 14 days characterised by increased cough, increased sputum production combined with change in colour and consistency of sputum, and mild to moderate dyspnoea). The severity of participants' exacerbation was not specified in the study.

Participants were randomised to either levofloxacin 500 mg once daily (for 7 days) or moxifloxacin 400 mg once daily (for 5 days). The treatment groups were similar in their baseline demographics and medical history, such as smoking history.

Up to 14 days after antibiotic treatment, there was no significant difference in the resolution of exacerbation symptoms with levofloxacin compared with moxifloxacin group (n=561: 83.7% versus 80.9%; RR 1.03, 95%CI 0.96 to 1.12; moderate quality evidence).

No significant difference was found in adverse events between levofloxacin and moxifloxacin (n=561: 26.9% versus 23.7%; RR 1.13, 95% CI 0.85 to 1.50; low quality evidence).

See GRADE profile 8 (Table 11).

3.1.3.8 Penicillins compared with trimethoprim (with or without a sulphonamide)

One systematic review by Korbila et al. (2009) included 5 RCTs that compared penicillins with trimethoprim alone (or in combination with a sulphonamide) for treating adults over 18 years with an acute exacerbation of chronic bronchitis. All included studies were published in or before 1995. Penicillins included: amoxicillin 7 to 10-day courses and pivampicillin with pivmecillinam hydrochloride 10-day course. Trimethoprim regimens included: trimethoprim 7-day course, co-trimoxazole 7 to 10-day course, trimethoprim/sulfadiazine 7-day course. The use of systemic corticosteroids was not reported in the review.

All participants (n=262) were diagnosed with an acute bacterial exacerbation (mild, moderate or severe) of chronic bronchitis, and 4 RCTs included people treated in hospital. The criteria for the diagnosis of chronic bronchitis were not specified in the review and the severity of the acute exacerbation was based on the Anthonisen classification.

Korbila et al. (2009) found no significant difference between penicillins and trimethoprim (with or without a sulphonamide) for the resolution or the improvement of exacerbation symptoms after 7 or 10 days of antibiotic treatment (5 RCTs, n=262: 83.5% versus 74.4%; NICE analysis[5] RR 1.11, 95% CI 0.98 to 1.26; moderate quality evidence).

No significant difference was found between penicillin and trimethoprim regimens in adverse events (3 RCTs, n=186: 3.2% versus 6.5%; NICE analysis[5] RR 0.55, 95%CI 0.16 to 1.92; very low quality evidence) and all-cause mortality (1 RCT, n=37: 5.6% versus 10.5%; NICE analysis[5] RR 0.53, 95% CI 0.05 to 5.33; low quality evidence).

See GRADE profile 9 (Table 12).

3.1.1 Antibiotic dosage, duration and route of administration

The evidence review for antibiotic duration of treatment in adults is based on 1 systematic review of 10 RCTs (Stolbrink et al. 2017; n=3,979). No systematic reviews or RCTs were identified that compared the frequency of antibiotic dosing or the route of antibiotic administration.

Short-course antibiotic (less than 6 days) compared with long-course antibiotic (7 days or more)

Stolbrink et al (2017) compared a short-course antibiotic (for less than 6 days) with a long-course antibiotic (for 7 days or more) of the same antibiotic for treating adults aged 18 years or over with an acute exacerbation of COPD. A diagnosis of COPD was based on the participants' smoking history and their airway obstruction. The diagnosis of an acute exacerbation was based on clinical evaluation in all studies except 1 RCT that used microscopically confirmed purulent sputum. The severity of exacerbation ranged from mild to severe, and 4 studies used the Anthonisen classification for assessing severity. Participants were recruited from outpatients (4 RCTs), hospital (3 RCTs) and primary care (3 RCTs).

Quinolones were the most commonly studied antibiotics (5 RCTs), and dose regimens included: levofloxacin 500 mg once daily, moxifloxacin 400 mg once daily, grepafloxacin 400 mg once daily, and gatifloxacin 400 mg once daily. The other studies included amoxicillin 500 mg three times daily or 3 g twice daily (1 RCT), clarithromycin 500 mg twice daily or 1 g once daily (1 RCT), cefixime 400 mg once daily (1 RCT) and co-amoxiclav 500/125 mg or 2000/125 mg twice daily (2 RCTs),

No significant difference was found between short-course antibiotics and long-course antibiotics in the resolution of exacerbation symptoms (clinical success) after completing treatment, regardless of the length of follow-up or the care setting (3 of the 10 RCTs were in hospital):

- within 6 days – 5 RCTs, n=2,650: 81.2% versus 81.5%; RR 1.00, 95%CI 0.96 to 1.03; moderate quality evidence
- between 7 and 14 days – 4 RCTs, n=1,915: 80.1% versus 82%; RR 0.98, 95% CI 0.94 to 1.02, moderate quality evidence
- more than 20 days – 4 RCTs, n=2,012: 67.4% versus 68.3%; RR 0.99, 95% CI 0.94 to 1.05; moderate quality evidence

During the study period, there were significantly fewer adverse events with short-course antibiotics compared with long-course antibiotics (8 RCTs, n=3,371: 20.9% versus 24.9%; RR 0.84, 95% CI 0.75 to 0.95; NNH 25, 95% CI 14 to 100; low quality evidence).

See GRADE profile 10 (Table 13).

4 Terms used in the guideline

4.1.1 Acute exacerbation

An acute exacerbation is defined as sustained worsening of the person's symptoms from their usual stable state which is beyond normal day-to-day variations, and is acute in onset (NICE guideline on COPD in over 16s). Common symptoms of exacerbation include worsening breathlessness, cough, increased sputum production and change in sputum colour.

A generalised classification of the severity of an exacerbation (NICE guideline on COPD in over 16s; Oba Y et al. [2017]) as following:

- Mild: the person has an increased need for medication, which they can manage in their own normal environment;
- Moderate: the person has a sustained worsening of respiratory status that requires treatment with systemic corticosteroids and/or antibiotics
- Severe: the person experiences a rapid deterioration in respiratory status that requires hospitalisation

4.1.2 Anthonisen classification

Anthonisen et al. (1987) classified the type of an exacerbation based on 3 cardinal exacerbation symptoms:

- increased dyspnoea
- increased sputum volume and
- sputum purulence.

The presence all 3 symptoms was defined as type 1 exacerbation; 2 of the 3 symptoms was defined as type 2 exacerbation; and 1 of the 3 symptoms with the presence of 1 or more supporting symptoms and signs was defined as type 3 exacerbation. Supporting symptoms were cough, wheezing, fever without an obvious source, upper respiratory tract infection in the past 5 days, respiratory rate increase and/or heart rate increase 20% above baseline.

Appendices

Appendix A: Evidence sources

Key area	Key question(s)	Evidence sources
Background	• What is the natural history of the infection? • What is the expected duration and severity of symptoms with or without antimicrobial treatment? • What are the most likely causative organisms? • What are the usual symptoms and signs of the infection? • What are the known complication rates of the infection, with and without antimicrobial treatment? • Are there any diagnostic or prognostic factors to identify people who may or may not benefit from an antimicrobial?	• NICE clinical knowledge summary on chronic obstructive pulmonary disease • NICE guideline NG115: NICE guideline on COPD in over 16s (2018) • ERS/ATS guideline: Management of COPD exacerbation (2017) • Committee experience
Safety netting	• What safety netting advice is needed for managing the infection?	• NICE guideline NG63: NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population (2017) • NICE clinical knowledge summary on chronic obstructive pulmonary disease • Committee experience
Red flags	• What symptoms and signs suggest a more serious illness or condition (red flags)?	• NICE guideline NG115: NICE guideline on COPD in over 16s (2018) • Committee experience
Antimicrobial prescribing strategies	• What is the clinical effectiveness and safety of antimicrobial prescribing strategies (including back-up prescribing) for managing the infection or symptoms?	• Evidence review – see appendix F for included studies
Antimicrobials	• What is the clinical effectiveness and safety of antimicrobials for managing the infection or symptoms?	• Evidence review – see appendix F for included studies • BNF (October 2018)

Key area	Key question(s)	Evidence sources
	• Which people are most likely to benefit from an antimicrobial?	• Evidence review – see appendix F for included studies
	• Which antimicrobial should be prescribed if one is indicated (first, second and third line treatment, including people with drug allergy)?	• Evidence review – see appendix F for included studies
	• What is the optimal dose, duration and route of administration of antimicrobials?	• Evidence review – see appendix F for included studies
Antimicrobial resistance	• What resistance patterns, trends and levels of resistance exist both locally and nationally for the causative organisms of the infection • What is the need for broad or narrow spectrum antimicrobials? • What is the impact of specific antimicrobials on the development of future resistance to that and other antimicrobials?	• NICE guideline NG15: Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) • Chief medical officer (CMO) report (2011) • ESPAUR report (2016)
Resource impact	• What is the resource impact of interventions (such as escalation or de-escalation of treatment)?	• Drug tariff (October 2018)
Medicines adherence	• What are the problems with medicines adherence (such as when longer courses of treatment are used)?	• NICE guideline NG76: Medicines adherence: involving patients in decisions about prescribed medicines and supporting adherence (2009)

Appendix B: Review protocol

I	Review question	What antimicrobial interventions are effective in treating acute exacerbations of chronic obstructive pulmonary disease (COPD)?	• Antimicrobial interventions include antibiotics • Search will include terms for acute exacerbation of COPD.
II	Types of review question	Intervention questions will primarily be addressed through the search.	These will, for example, also identify natural history in placebo groups and causative organisms in studies that use laboratory diagnosis, and relative risks of differing management options.
III	Objective of the review	To determine the effectiveness of antimicrobial prescribing in managing an acute exacerbation of COPD, in line with the major goals of antimicrobial stewardship. This includes interventions that lead prescribers to: • optimise outcomes for individuals • reduce overuse, misuse or abuse of antimicrobials All of the above will be considered in the context of national antimicrobial resistance patterns where available, if not available committee expertise will be used to guide decision-making.	The secondary objectives of the review of studies will include: • indications for no or back-up antimicrobials • antimicrobial choice, optimal dose, duration and route for specified antimicrobial(s) • the natural history of the infection • identifying sub-groups of people who are more likely to benefit from antimicrobials.
IV	Eligibility criteria – population/ disease/ condition/ issue/domain	Population: Adults with an acute exacerbation of COPD of any severity. People diagnosed with COPD (by any means including Global Strategy for the Diagnosis, Management and Prevention of COPD, GOLD, guideline; American Thoracic Society criteria for COPD; European Respiratory Society criteria)	Subgroups of interest are those: • with protected characteristics under the Equality Act 2010. • with chronic conditions (such as high blood pressure, diabetes or heart disease).

		An acute exacerbation is defined as a sustained worsening of the person's symptoms from their usual stable state which is beyond normal day-to-day variations, and is acute in onset (NICE guideline on chronic obstructive pulmonary disease in over 16s). Commonly reported symptoms are worsening breathlessness, cough, increased sputum production and change in sputum colour. The change in these symptoms often necessitates a change in medication. A moderate acute exacerbation is a sustained worsening of respiratory status that requires treatment with systemic corticosteroids and/or antibiotics. A severe acute exacerbation is a rapid deterioration in respiratory status that requires hospitalisation.	• at high risk of serious complications because of pre-existing comorbidity[11] • with symptoms and signs suggestive of serious illness and/or complications[12] • older than 65 years and older than 80 years[13] • with purulent sputum and acute exacerbation • with moderate or severe acute exacerbation • with increased frequency of acute exacerbations • with asthma • with alpha 1-antitrypsin deficiency • who are smokers.
V	Eligibility criteria – intervention(s)/ exposure(s)/ prognostic factor(s)	The review will include studies which include: • Antimicrobial pharmacological interventions[14]. • Back-up antibiotic prescribing strategies. For the treatment of acute exacerbation of COPD as outlined above, in primary, secondary or other care settings (for example urgent care) either by prescription or by any other legal means of supply of medicine (for example patient group direction).	Limited to those antimicrobial interventions commonly in use (as agreed by the committee)
VI	Eligibility criteria – comparator(s	• Placebo. • Back-up antibiotic prescribing strategies.	

[11] significant heart, lung, renal, liver or neuromuscular disease, immunosuppression, cystic fibrosis, and young children who were born prematurely
[12] Including pneumonia, heart, lung, kidney, liver or neuromuscular disease, or immunosuppression
[13] hospitalisation in previous year; type 1 or type 2 diabetes, history of congestive heart failure, current use of oral glucocorticoids.
[14] Antimicrobial pharmacological interventions include: back-up antibiotic prescribing, standby or rescue therapy, narrow or broad spectrum, single, dual or triple therapy, escalation or de-escalation of treatment. Antibiotics included in the search include those named in current guidance (plus the class to which they belong) plus other antibiotics agreed by the committee

	)/ control or reference (gold) standard	• Non-pharmacological interventions. • Non-antimicrobial pharmacological interventions, for example oral corticosteroids. • Other antimicrobial pharmacological interventions.	
VII	Outcomes and prioritisation	a) Clinical outcomes such as: • mortality • infection cure rates (number or proportion of people with resolution of symptoms at a given time point, incidence of escalation of treatment) • time to clinical cure (mean or median time to resolution of illness) • reduction in symptoms (duration or severity) • rate of complications with or without treatment • safety, tolerability, and adverse effects. b) Thresholds or indications for antimicrobial treatment (which people are most, or least likely to benefit from antimicrobials) c) Changes in antimicrobial resistance patterns, trends and levels as a result of treatment. d) Patient-reported outcomes, such as medicines adherence, patient experience and patient satisfaction. e) Ability to carry out activities of daily living. f) Service user experience. g) Health and social care related quality of life, including long-term harm or disability.	The committee have agreed that the following outcomes are critical: • reduction in symptoms (duration or severity) for example difference in time to substantial improvement • time to clinical cure (mean or median time to resolution of illness) • rate of complications[15] (including mortality) with or without treatment, including escalation of treatment • health and social care utilisation (including length of stay, ITU stays, planned and unplanned contacts). • thresholds or indications for antimicrobial treatment (which people are most, or least likely to benefit from antimicrobials) The committee have agreed that the following outcomes are important: • patient-reported outcomes, such as medicines adherence, patient experience, sickness absence

[15] These would include but are not limited to more common complications e.g. chronic bacterial colonization

		h) Health and social care utilisation (including length of stay, planned and unplanned contacts). The Committee considered which outcomes should be prioritised when multiple outcomes are reported (critical and important outcomes). Additionally, the Committee were asked to consider what clinically important features of study design may be important for this condition (for example length of study follow-up, treatment failure/recurrence, important outcomes of interest such as sequela or progression to more severe illness).	• changes in antimicrobial resistance patterns, trends and levels as a result of treatment
VIII	Eligibility criteria – study design	The search will look for: • Systematic review of randomised controlled trials (RCTs) • RCTs If insufficient evidence is available progress to: • Controlled trials • Systematic reviews of non-randomised controlled trials • Non-randomised controlled trials • Observational and cohort studies • Pre and post intervention studies (before and after) • Time series studies	Committee to advise the NICE project team on the inclusion of information from other condition specific guidance and on whether to progress due to insufficient evidence.
IX	Other inclusion exclusion criteria	The scope sets out what the guidelines will and will not include (exclusions). Further exclusions specific to this guideline include: • non-English language papers, studies that are only available as abstracts • in relation to antimicrobial resistance, non-UK papers	

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

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

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

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

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

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Appendix C: Literature search strategy

Key to search operators

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

Number of hits to be retrieved

	No. of hits in MEDLINE	Position in the strategy
Search with limits and Systematic Reviews	1780	Line 146
Search with limits and RCTs (not SRs)	427	Line 163
Search with limits and Observational Studies (not SRs or RCTs)	411	Line 186
Search with limits (without SRs, RCTs, Observational)	436	Line 187
Total for screening	3054	

MEDLINE strategy
Database(s): **Ovid MEDLINE(R) 1946 to Present with Daily Update, Ovid MEDLINE(R) Epub Ahead of Print** January 03, 2018**, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations** January 03, 2018

#	Searches	Results
1	exp Pulmonary Disease, Chronic Obstructive/	51962
2	Lung Diseases, Obstructive/	19183
3	(chronic* adj4 (bronchit* or tracheobronchit*)).ti,ab.	11517
4	(obstruct* adj4 (pulmonary* or lung* or airway* or airflow* or bronch* or respirat*)).ti,ab.	83196
5	(copd or coad or cobd).ti,ab.	40799
6	(AECOPD* or AE-COPD* or "AE COPD*" or AECB* or AE-CB* or "AE CB*").ti,ab.	1123
7	Emphysema*.ti,ab.	25653
8	or/1-7	139285
9	limit 8 to yr="2006 -Current"	66677
10	limit 9 to english language	60122
11	Animals/ not (Animals/ and Humans/)	4777642
12	10 not 11	57479

13	limit 12 to (letter or historical article or comment or editorial or news or case reports)	9190
14	12 not 13	48289
15	anti-infective agents/ or exp anti-bacterial agents/ or exp anti-infective agents, local/	932312
16	(antibacter* or anti-bacter* or "anti bacter*" or antimicrobial or anti-microbial or "anti microbial" or antibiot* or anti-biot* or "anti biot*").ti,ab.	449234
17	or/15-16	1126498
18	Amoxicillin/	9630
19	(Amoxicillin* or Amoxycillin* or Amoxil*).ti,ab.	17041
20	Ampicillin/	13960
21	Ampicillin*.ti,ab.	22590
22	Azithromycin/	4942
23	(Azithromycin* or Azithromicin* or Zithromax*).ti,ab.	7531
24	Aztreonam/	1450
25	(Aztreonam* or Azactam*).ti,ab.	3024
26	Penicillin G/	9438
27	(Benzylpenicillin* or "Penicillin G").ti,ab.	8355
28	Cefaclor/	898
29	(Cefaclor* or Distaclor* or Keftid*).ti,ab.	1781
30	Cefixime/	789
31	(Cefixime* or Suprax*).ti,ab.	1615
32	Cefotaxime/	5660
33	Cefotaxime*.ti,ab.	8347
34	(Ceftaroline* or Zinforo*).ti,ab.	602
35	Ceftazidime/	3909
36	(Ceftazidime* or Fortum* or Tazidime*).ti,ab.	8640
37	(Ceftobiprole* or Zevtera*).ti,ab.	271
38	(Ceftolozane* or Tazobactam* or Zerbaxa*).ti,ab.	4076
39	Ceftriaxone/	5882
40	(Ceftriaxone* or Rocephin* or Rocefin*).ti,ab.	9980
41	Cefuroxime/	2268
42	(Cefuroxime* or Cephuroxime* or Zinacef* or Zinnat* or Aprokam*).ti,ab.	4387

43	Chloramphenicol/	20387
44	(Chloramphenicol* or Cloranfenicol* or Kemicetine* or Kloramfenikol*).ti,ab.	27095
45	Ciprofloxacin/	13081
46	(Ciprofloxacin* or Ciproxin*).ti,ab.	24481
47	Clarithromycin/	6263
48	(Clarithromycin* or Clarie* or Klaricid* or Xetinin*).ti,ab.	8855
49	Clindamycin/	5767
50	(Clindamycin* or Dalacin* or Zindaclin*).ti,ab.	10186
51	Amoxicillin-Potassium Clavulanate Combination/	2589
52	(Co-amoxiclav* or Coamoxiclav* or Amox-clav* or Amoxicillin-Clavulanic Acid* or Amoxicillin-Potassium Clavulanate Combination* or Amoxi-Clavulanate* or Clavulanate Potentiated Amoxycillin Potassium* or Clavulanate-Amoxicillin Combination* or Augmentin*).ti,ab.	15335
53	Trimethoprim, Sulfamethoxazole Drug Combination/	7016
54	(Septrin* or Co-trimoxazole* or Cotrimoxazole* or Sulfamethoxazole Trimethoprim Comb* or Trimethoprim Sulfamethoxazole Comb*).ti,ab.	6223
55	Colistin/	3555
56	(Colistin* or Colistimethate* or Colimycin* or Coly-Mycin* or Colymycin* or Colomycin* or Promixin*).ti,ab.	5142
57	Doxycycline/	9508
58	(Doxycycline* or Efracea* or Periostat* or Vibramycin*).ti,ab.	12764
59	(Ertapenem* or Invanz*).ti,ab.	1317
60	Erythromycin/	14436
61	Erythromycin Estolate/	155
62	Erythromycin Ethylsuccinate/	527
63	(Erythromycin* or Erymax* or Tiloryth* or Erythrocin* or Erythrolar* or Erythroped*).ti,ab.	21132
64	Fosfomycin/	1893
65	(Fosfomycin* or Phosphomycin* or Fosfocina* or Monuril* or Monurol* or Fomicyt*).ti,ab.	2747
66	Floxacillin/	758
67	(Floxacillin* or Flucloxacillin*).ti,ab.	871
68	Gentamicins/	18910
69	(Gentamicin* or Gentamycin* or Cidomycin*).ti,ab.	26602
70	Imipenem/	4116

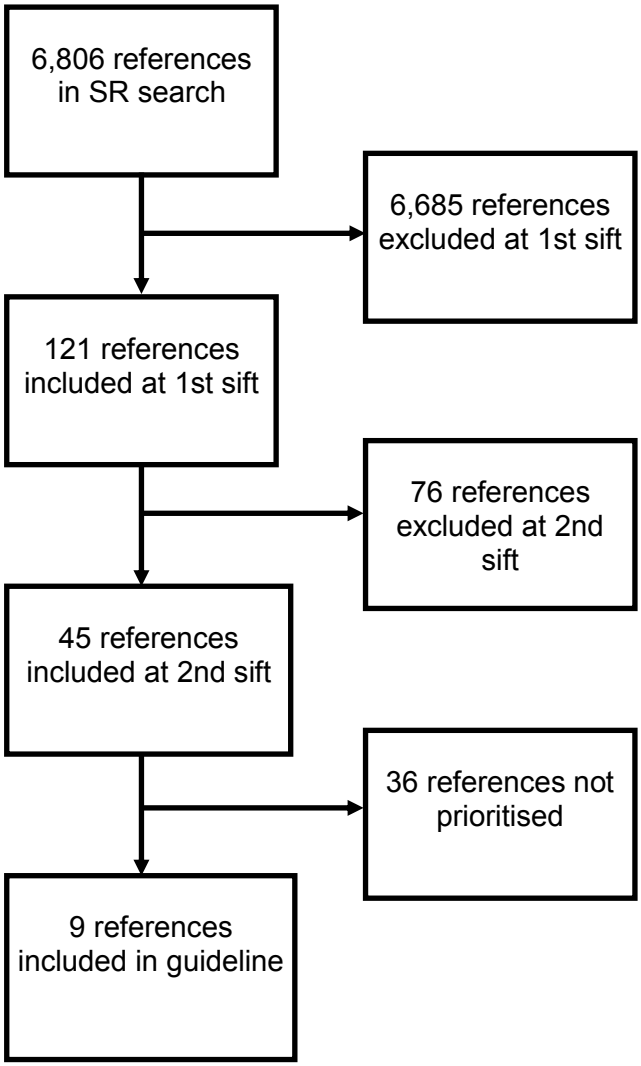
71	(Imipenem* or Primaxin*).ti,ab.	10011
72	Levofloxacin/	3116
73	(Levofloxacin* or Evoxil* or Tavanic*).ti,ab.	6960
74	Linezolid/	2704
75	(Linezolid* or Zyvox*).ti,ab.	5131
76	Meropenem*.ti,ab.	5477
77	(Moxifloxacin* or Avelox*).ti,ab.	4274
78	Ofloxacin/	6408
79	(Ofloxacin* or Tarivid*).ti,ab.	7052
80	Piperacillin/	2791
81	(Piperacillin* or Tazobactam* or Tazocin*).ti,ab.	7076
82	Rifampin/	17660
83	(Rifampicin* or Rifampin* or Rifadin* or Rimactane*).ti,ab.	23292
84	Teicoplanin/	2299
85	(Teicoplanin* or Targocid*).ti,ab.	3587
86	(Telavancin* or Vibativ*).ti,ab.	382
87	(Temocillin* or Negaban*).ti,ab.	311
88	(Tigecycline* or Tygacil*).ti,ab.	2701
89	Vancomycin/	13325
90	(Vancomycin* or Vancomicin* or Vancocin*).ti,ab.	25335
91	or/18-90	284126
92	exp Aminoglycosides/	158208
93	Aminoglycoside*.ti,ab.	18680
94	exp Penicillins/	82448
95	Penicillin*.ti,ab.	55081
96	exp beta-Lactamase inhibitors/	7711
97	(("beta Lactamase*" or betaLactamase*) adj3 (antagonist* or agonist* or agent* or inhibitor* or blocker*)).ti,ab.	2997
98	beta-Lactams/	6335
99	("beta-Lactam" or betaLactam or "beta Lactam " or "beta-Lactams" or betaLactams or "beta Lactams").ti,ab.	20432
100	exp Carbapenems/	9973
101	Carbapenem*.ti,ab.	11501

102	exp Cephalosporins/	43294
103	Cephalosporin*.ti,ab.	21807
104	exp Fluoroquinolones/	32423
105	Fluoroquinolone*.ti,ab.	15468
106	exp Macrolides/	109212
107	Macrolide*.ti,ab.	15161
108	exp Polymyxins/	8842
109	Polymyxin*.ti,ab.	6935
110	exp Quinolones/	46563
111	Quinolone*.ti,ab.	13539
112	exp Tetracyclines/	48277
113	Tetracycline*.ti,ab.	35003
114	or/92-113	511550
115	watchful waiting/	2954
116	"no intervention*".ti,ab.	7237
117	(watchful* adj2 wait*).ti,ab.	2442
118	(wait adj2 see).ti,ab.	1407
119	(active* adj2 surveillance*).ti,ab.	6880
120	(expectant* adj2 manage*).ti,ab.	3139
121	or/115-120	22437
122	Inappropriate prescribing/	2315
123	((delay* or defer*) adj3 (treat* or therap* or interven*)).ti,ab.	30325
124	((prescription* or prescrib*) adj3 ("red flag" or strateg* or appropriat* or inappropriat* or unnecessary or defer* or delay* or no or non or behaviour* or behavior* or optimal or optimi* or reduc* or decreas* or declin* or rate* or improv* or back-up* or backup* or immediate* or rapid* or short* or long* or standby or "stand by" or rescue or escalat* or "de-escalat*" or misuse* or "mis-use*" or overuse* or "over-use*" or "over-prescri*" or abuse*)).ti,ab.	25823
125	((bacter* or antibacter* or anti-bacter* or "anti bacter*" or antimicrobial or anti-microbial or "anti microbial" or antibiot* or anti-biot* or "anti biot*") adj3 ("red flag" or strateg* or appropriat* or inappropriat* or unnecessary or defer* or delay* or no or non or behaviour* or behavior* or optimal or optimi* or reduc* or decreas* or declin* or rate* or improv* or back-up* or backup* or immediate* or rapid* or short* or long* or standby or "stand by" or rescue or escalat* or "de-escalat*" or misuse* or "mis-use*" or overuse* or "over-use*" or "over-prescri*" or abuse*)).ti,ab.	107614

126	or/122-125	161305
127	17 or 91 or 114 or 121 or 126	1414602
128	14 and 127	3033
129	Meta-Analysis.pt.	98161
130	Network Meta-Analysis/	288
131	Meta-Analysis as Topic/	17993
132	Review.pt.	2551942
133	exp Review Literature as Topic/	10626
134	(metaanaly* or metanaly* or (meta adj3 analy*)).ti,ab.	139310
135	(review* or overview*).ti.	455833
136	(systematic* adj5 (review* or overview*)).ti,ab.	139504
137	((quantitative* or qualitative*) adj5 (review* or overview*)).ti,ab.	8912
138	((studies or trial*) adj2 (review* or overview*)).ti,ab.	42682
139	(integrat* adj3 (research or review* or literature)).ti,ab.	10397
140	(pool* adj2 (analy* or data)).ti,ab.	27217
141	(handsearch* or (hand adj3 search*)).ti,ab.	8730
142	(manual* adj3 search*).ti,ab.	5525
143	or/129-142	2844101
144	128 and 143	816
145	91 or 114 or 121 or 126	775765
146	14 and 145	1780
147	Randomized Controlled Trial.pt.	515637
148	Controlled Clinical Trial.pt.	101734
149	Clinical Trial.pt.	561578
150	exp Clinical Trials as Topic/	346490
151	Placebos/	37117
152	Random Allocation/	103148
153	Double-Blind Method/	162482
154	Single-Blind Method/	27772
155	Cross-Over Studies/	46942
156	((random* or control* or clinical*) adj3 (trial* or stud*)).ti,ab.	1163863
157	(random* adj3 allocat*).ti,ab.	33102

158	placebo*.ti,ab.	216889
159	((singl* or doubl* or trebl* or tripl*) adj (blind* or mask*)).ti,ab.	173217
160	(crossover* or (cross adj over*)).ti,ab.	84826
161	or/147-160	1972717
162	146 and 161	682
163	162 not 144	427
164	Observational Studies as Topic/	3142
165	Observational Study/	51701
166	Epidemiologic Studies/	8310
167	exp Case-Control Studies/	1000586
168	exp Cohort Studies/	1909508
169	Cross-Sectional Studies/	284820
170	Controlled Before-After Studies/	337
171	Historically Controlled Study/	164
172	Interrupted Time Series Analysis/	423
173	Comparative Study.pt.	1962555
174	case control*.ti,ab.	119983
175	case series.ti,ab.	62263
176	(cohort adj (study or studies)).ti,ab.	164599
177	cohort analy*.ti,ab.	6605
178	(follow up adj (study or studies)).ti,ab.	48699
179	(observational adj (study or studies)).ti,ab.	86114
180	longitudinal.ti,ab.	219621
181	prospective.ti,ab.	531121
182	retrospective.ti,ab.	452406
183	cross sectional.ti,ab.	291845
184	or/164-183	4500766
185	146 and 184	711
186	185 not (144 or 163)	411
187	146 not (144 or 163 or 186)	436

Appendix D: Study flow diagram



Appendix E: Evidence prioritisation

Key questions	Included studies[1]		Studies not prioritised[2]	
	Systematic reviews	RCTs	Systematic reviews	RCTs
Is an antibiotic effective?				
Antibiotics versus placebo	Vollenweider et al. (2012)		Zhang et al. (2017) Puhan et al. (2007) Puhan et al. (2008)	Van Velzen et al. (2017) Soltaninejad et al. (2016) Wang et al. (2016) Hassan et al. (2015) Brusse-Keizer. (2014) Llor et al. (2012) Daniels et al. (2010)
Which antibiotic is most effective?				
Antibiotics versus different antibiotics	Krobila et al. (2009) Siempos et al. (2007) Dimopoulos et al. (2007)	Yoon et al. (2013) Nouira et al. (2010) Petitpretz et al. (2007) Urueta-Robledo et al. (2006)	Zhang et al. (2017) Liu et al. (2013) Zhang et al. (2012) Miravitlles et al. (2007) Niederman. (2006) Fogarty et al. (2006)	Giusti et al. (2016) Rhee et al. (2015) Blasi et al. (2013) Blasi et al. (2013) Wilson et al. (2012) Chatterjee et al. (2011) Wang et al. (2010) Llor et al. (2009) Renuka et al. (2017) Ruiz-Gonzalez et al. (2007) Zervos et al. (2007) Alvare-Sala et al. (2006) Andre-Alves et al. (2006) Grossman et al. (2006) Wilson et al. (2006)
What is the optimal dosage, duration and route of administration of antibiotic?				

Key questions	Included studies[1]		Studies not prioritised[2]	
	Systematic reviews	RCTs	Systematic reviews	RCTs
Dosage, course length and route of administration studies	Stolbrink et al. (2017)		Gotfried et al. (2010) El Moussaoui et al. (2008) Falagas et al. (2008)	Gotfried et al. (2007) Roede et al. (2006)

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

Appendix F: Included studies

Dimopoulos George, Siempos Ilias I, Korbila Ioanna P, Manta Katerina G, and Falagas Matthew E (2007) Comparison of first-line with second-line antibiotics for acute exacerbations of chronic bronchitis: a metaanalysis of randomized controlled trials. Chest 132(2), 447-55

Korbila Ioanna P, Manta Katerina G, Siempos Ilias I, Dimopoulos George, and Falagas Matthew E (2009) Penicillins vs trimethoprim-based regimens for acute bacterial exacerbations of chronic bronchitis: meta-analysis of randomized controlled trials. Canadian family physician Medecin de famille canadien 55(1), 60-7

Nouira Semir, Marghli Soudani, Besbes Lamia, Boukef Riadh, Daami Monia, Nciri Noureddine, Elatrous Souheil, and Abroug Fekri (2010) Standard versus newer antibacterial agents in the treatment of severe acute exacerbation of chronic obstructive pulmonary disease: a randomized trial of trimethoprim-sulfamethoxazole versus ciprofloxacin. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America 51(2), 143-9

Petitpretz Patrick, Chone Claudie, Tremolieres Francois, Investigator Study, and Group (2007) Levofloxacin 500 mg once daily versus cefuroxime 250 mg twice daily in patients with acute exacerbations of chronic obstructive bronchitis: clinical efficacy and exacerbation-free interval. International journal of antimicrobial agents 30(1), 52-9

Siempos I I, Dimopoulos G, Korbila I P, Manta K, and Falagas M E (2007) Macrolides, quinolones and amoxicillin/clavulanate for chronic bronchitis: a meta-analysis. The European respiratory journal 29(6), 1127-37

Stolbrink Marie, Amiry Jack, and Blakey John D (2017) Does antibiotic treatment duration affect the outcomes of exacerbations of asthma and COPD? A systematic review. Chronic respiratory disease, 1479972317745734

Urueta-Robledo Juan, Ariza Horacio, Jardim Jose R, Caballero Andres, Garcia-Calderon Andres, Amabile-Cuevas Carlos F, Hernandez-Oliva Gerardo, Vivar-Orozco Raul, and Group Mox-Cb Study (2006) Moxifloxacin versus levofloxacin against acute exacerbations of chronic bronchitis: the Latin American Cohort. Respiratory medicine 100(9), 1504-11

Vollenweider Daniela J, Jarrett Harish, Steurer-Stey Claudia A, Garcia-Aymerich Judith, and Puhan Milo A (2012) Antibiotics for exacerbations of chronic obstructive pulmonary disease. The Cochrane database of systematic reviews 12, CD010257

Yoon Ho Ii, Lee Chang-Hoon, Kim Deog Kyeom, Park Geun Min, Lee Sang-Min, Yim Jae-Joon, Kim Jae-Yeol, Lee Jae Ho, Lee Choon-Taek, Chung Hee Soon, Kim Young Whan, Han Sung Koo, and Yoo Chul-Gyu (2013) Efficacy of levofloxacin versus cefuroxime in treating acute exacerbations of chronic obstructive pulmonary disease. International journal of chronic obstructive pulmonary disease 8, 329-34

Appendix G: Quality assessment of included studies

Table 2: Overall risk of bias/quality assessment – systematic reviews (SR checklist)

Study reference	Vollenweider et al. (2012)	Siempos et al. (2007)	Dimopoulos et al. (2007)	Korbila et al. (2009)	Stolbrink et al. (2017)
Did the review address a clearly focused question?	Yes	Yes	Yes	Yes	Yes
Did the authors look for the right type of papers?	Yes	Yes	Yes	Yes	Yes
Do you think all the important, relevant studies were included?	Yes	Yes	Yes	Yes	Yes
Did the review's authors do enough to assess the quality of the included studies?	Yes	Yes	Yes	Yes	Yes
If the results of the review have been combined, was it reasonable to do so?	Yes	Yes	Yes	Yes	Yes
What are the overall results of the review?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles
How precise are the results?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles
Can the results be applied to the local population?	Yes	Yes	Yes	Yes	Yes
Were all important outcomes considered?	Yes	Yes	Yes	Yes	Yes
Are the benefits worth the harms and costs?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles

Table 3: Overall risk of bias/quality assessment – randomised controlled trials (RCT checklist)

Study reference	Yoon et al. (2013)	Nouira et al. (2010)	Petitpretz et al. (2007)	Urueta-Robledo et al. (2006)
Did the trial address a clearly focused issue?	Yes	Yes	Yes	Yes
Was the assignment of patients to treatments randomised?	Yes	Yes	Yes	Yes
Were patients, health workers and study personnel blinded?	No[1]	Yes	No[1]	Yes

Study reference	Yoon et al. (2013)	Nouira et al. (2010)	Petitpretz et al. (2007)	Urueta-Robledo et al. (2006)
Were the groups similar at the start of the trial?	Yes	Yes	Yes	Yes
Aside from the experimental intervention, were the groups treated equally?	Yes	Yes	Yes	Yes
Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes	Yes	Yes	Yes
How large was the treatment effect?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles
How precise was the estimate of the treatment effect?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles
Can the results be applied in your context? (or to the local population)	Yes	Yes	Yes	Yes
Were all clinically important outcomes considered?	See GRADE profiles	See GRADE profiles	See GRADE profiles	See GRADE profiles
Are the benefits worth the harms and costs?				
Footnote 1. Open label study				

Appendix H: GRADE profiles

H.1 Antibiotics compared with placebo

Table 4: GRADE profile 1 – antibiotics versus placebo

Quality assessment							No of people[1]		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic[2]	Placebo	Relative (95% CI)	Absolute		
Treatment failure[3], follow-up 7 to 30 days												
12[4]	randomised trials	serious[5]	serious[6]	no serious indirectness	serious[7]	none	251/884 (28.4%)	281/752 (37.4%)	NICE analysis[8] RR 0.64 (0.50 to 0.84)	135 fewer per 1000 (from 60 fewer to 187 fewer)	⊕OOO VERY LOW	CRITICAL
Adverse event												
5[4]	randomised trials	serious[10]	no serious inconsistency	no serious indirectness	serious[7]	none	67/634 (10.6%)	45/609 (7.4%)	NICE analysis[9] RR 1.46 (1.03 to 2.09)	34 more per 1000 (from 2 more to 81 more)	⊕⊕OO LOW	CRITICAL
All-cause mortality												
5[4]	randomised trials	no serious risk of bias[11]	no serious inconsistency	no serious indirectness	serious[10]	none	10/351 (2.8%)	18/273 (6.6%)	NICE analysis[9] RR 0.57 (0.28 to 1.16)	28 fewer per 1000 (from 47 fewer to 11 more)	⊕⊕⊕O MODERATE	CRITICAL
Duration of hospital stay (days)												
3[4]	randomised trials	serious[12]	serious[6]	no serious indirectness	serious[13]	none	119	83	MD 3.04 fewer (8.83 fewer to 2.76 more)	-	⊕OOO VERY LOW	IMPORTANT
Days off work (days)												
1[4]	randomised trials	no serious risk of bias	not applicable	no serious indirectness	no serious imprecision	Short study follow-up (mean=17 days); people were instructed to take antibiotics or placebo without a doctor visit as soon as new or aggravated respiratory symptoms were present.	42	46	MD 5.18 fewer (6.08 fewer to 4.29 fewer)	-	⊕⊕⊕⊕ HIGH	IMPORTANT

Quality assessment							No of people[1]		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic[2]	Placebo	Relative (95% CI)	Absolute		
Health related quality of life (for functional status)												
1[4]	randomised trials	serious[14]	not applicable	no serious indirectness	very serious[15]	none	18	17	MD 0.0 (1.79 fewer to 1.79 more)	-	⊕OOO VERY LOW	IMPORTANT
Subgroup analyses												
Treatment failure: all people in the community and in hospital except those in the intensive care unit												
11[4]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[7]	none	246/847 (29.4%)	255/706 (36.1%)	RR 0.76 (0.66 to 087)	87 fewer per 1000 (from 47 fewer to 123 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Treatment failure: outpatients (adults who were treated in the community)												
7[4]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[7]	none	94/473 (19.9%)	126/458 (27.5%)	RR 0.75 (0.60 to 0.94)	69 fewer per 1000 (from 17 fewer to 110 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Treatment failure: inpatients (adults who were treated in hospital)												
4[4]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[7]	none	152/364 (41.8%)	129/248 (52.0%)	RR 0.77 (0.65 to 0.91)	120 fewer per 1000 (from 47 fewer to 182 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Treatment failure: inpatients (adults who were treated in hospital, in intensive care unit)												
1[4]	randomised trial	no serious risk of bias	not applicable	no serious indirectness	no serious imprecision	none	5/47 (10.6%)	26/46 (56.5%)	RR 0.19 (0.08 to 0.45)	458 fewer per 1000 (from 311 fewer to 520 fewer)	⊕⊕⊕⊕ HIGH	CRITICAL
Treatment failure: antibiotics in current use[16]												
8[4]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[7]	none	149/609 (24.5%)	195/566 (34.5%)	RR 0.76 (0.64 to 0.91)	83 fewer per 1000 (from 31 fewer to 124 fewer)	⊕⊕OO LOW	CRITICAL
Treatment failure: antibiotics in current use (adults who were treated in the community)												
5[4]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[7]	none	90/405 (22.2%)	112/385 (29.1%)	RR 0.8 (0.63 to 1.01)	58 fewer per 1000 (from 108 fewer to 3 more)	⊕⊕OO LOW	CRITICAL
Treatment failure: antibiotics in current use (adults who were treated in hospital)												

Quality assessment							No of people[1]		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Antibiotic[2]	Placebo	Relative (95% CI)	Absolute		
3[4]	randomised trials	no serious risk of bias	serious[6]	no serious indirectness	serious[7]	none	59/204 (28.9%)	83/181 (45.9%)	NICE analysis[17] RR 0.56 (0.31 to 1.03)	202 fewer per 1000 (from 316 fewer to 14 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: COPD- chronic obstructive pulmonary disease; CI – confidence interval; RR – relative risk												

[1] People with acute exacerbation of COPD. An acute exacerbation of COPD was defined as a worsening of a previous stable situation with 1 or more symptoms such as increased dyspnoea, increased cough, increased sputum volume or change in sputum colour

[2] Sixteen RCTs included antibiotics dose regimens: amoxicillin 1 or 1.5 g/day, ranged from 7 to 10-days course; co-amoxiclav,1.5 or 2 g/day ranged from 5 to 8-days course; co-trimoxazole 1.9 g/day ranged from 7 to 10 days course; cefaclor 1.5 g/day for 8-day course; Chloramphenicol 2g/day, ranged from 10 to 12-day course; doxycycline 0.1 to 0.2/day, ranged from 7 to 10-days course; Ofloxacin 400 mg/day for 10 days course; oxytetracycline 1 g/day, ranged 5 to 7 days course; penicillin 1 g/day for 14 days. 2 of 16 RCTs allowed corticosteroid treatment (one study included people treated in the community and another study included people treated in hospital, antibiotics +IV steroid taper).

[3] Treatment failure as observed between 7 days and 1 month after treatment initiation (no resolution or deterioration of symptoms after intervention of any duration or death when explicitly stated due to exacerbation or additional course of antibiotics or other medication)

[4] Vollenweider et al. (2012),

[5] Downgraded 1 level: >50% included studies did not provide enough information regarding allocation concealment, and/or blinding of outcome assessment

[6] Downgraded 1 level: I^2>50%

[7] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction, effect estimate is consistent with no meaningful difference or appreciable benefit with antibiotic

[8] The review author reported the estimated effect (RR 0.71, 95% CI 0.62 to 0.81) using a fixed-effects model when there was considerable heterogeneity between the studies (I2>50%); NICE analysis used a random effect model for the estimation as reported in the GRADE table.

[9] The review author reported the estimated effect (OR 1.53, 95% CI 1.03 to 2.27) using Peto odds ratios; NICE analysis used the relative risk for the estimation of the effect.

[10] Downgraded 1 level: non-significant effect, 95%CI RR cross 1.

[11] Downgraded 1 level: >50% included studies did not provide details regarding allocation concealment, blinding of participants and outcome assessment

[12] No downgrade: 3 of 5 included studies were with low risk of bias.

[13] Downgrade 1 level: at a default minimal important difference (MID) of 25% or 0.5 SD for continuous data, (approximately 3 days) data are consistent with no meaningful difference or appreciable benefit with antibiotics

[14] Downgraded 1 level: the study did not provide sufficient information regarding allocation concealment and blinding of outcome assessment.

[15] Downgraded 2 levels: at a default minimal important difference (MID) of 25% or 0.5 SD for continuous data, (approximately 1.35) data are consistent with no meaningful difference or appreciable benefit with antibiotics or consistent with no meaningful difference or appreciable benefit with placebo.

[16] In the sensitivity analysis: the analysis included trials that evaluated antibiotics that are used in in current practice including co-amoxiclav, co-trimoxazole, doxycycline, penicillin.

[17] The review author reported the estimated effect (RR 0.71, 95% CI 0.55 to 0.92) using a fixed-effects model when there was considerable heterogeneity between the studies (I2>50%); NICE analysis used a random effect model for the estimation as reported in the GRADE table

H.2 Antibiotics compared with other antibiotics

Table 5: GRADE profile 2 – first-line antibiotics versus second-line antibiotics

Quality assessment							No of people[1]		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	First-line antibiotics[2]	Second-line antibiotics[2]	Relative (95% CI)	Absolute		
Treatment success[3]: clinical evaluable participants[4], 1 to 7 days after the end of treatment												
12[5]	randomised trials	no serious risk of bias	serious[6]	no serious indirectness	no serious imprecision	none	462/565 (81.8%)	549/601 (91.3%)	NICE analysis[7] RR 0.92 (0.87 to 0.98)	73 fewer per 1000 (from 18 fewer to 119 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Treatment success in microbiological evaluable participants[8], 1 to 7 days after the end of treatment												
9[5]	randomised trials	no serious risk of bias	serious[6]	no serious indirectness	no serious imprecision	none	251/305 (82.3%)	306/333 (91.9%)	RR 0.95 (0.85 to 1.06)	46 fewer per 1000 (from 138 fewer to 55 more)	⊕⊕⊕O MODERATE	IMPORTANT
Adverse event												
8[5]	randomised trials	no serious risk of bias[9]	serious[6]	no serious indirectness	very serious[10]	none	118/787 (15.0%)	178/844 (21.9%)	RR 0.79 (0.47 to 1.33)	43 fewer per 1000 (from 109 fewer to 68 more)	⊕OOO VERY LOW	CRITICAL
All-cause mortality												
5[5]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[11]	none	7/698 (1%)	11/694 (1.6%)	RR 0.66 (0.27 to 1.63)	5 fewer per 1000 (from 12 fewer to 10 more)	⊕⊕⊕O MODERATE	CRITICAL
Subgroup analyses												
Treatment success: adults were treated in the community[12]												
4[5]	randomised trials	serious[13]	no serious inconsistency	no serious indirectness	no serious imprecision	none	177/196 (90.3%)	232/243 (95.5%)	RR 0.94 (0.89 to 0.99)	57 fewer per 1000 (from 10 fewer to 105 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Treatment success: adults were treated to in hospital [12]												
6[5]	randomised trials	no serious risk of bias	serious[6]	no serious indirectness	serious[14]	none	214/289 (74%)	238/272 (87.5%)	NICE analysis[15] RR 0.86 (0.73 to 1.02)	122 fewer per 1000 (from 236 fewer to 17 more)	⊕⊕OO LOW	CRITICAL
Pathogen eradication[16]: *H influenzae*												
7[4]	randomised trials	no serious risk of bias	serious[6]	no serious indirectness	serious[14]	none	95/113 (84.1%)	117/128 (91.4%)	RR 0.97 (0.83 to 1.12)	27 fewer per 1000 (from 155 fewer to 110 more)	⊕⊕OO LOW	IMPORTANT
Pathogen eradication: *M catarrhalis*												
6[4]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[13]	none	40/43 (93%)	54/55 (98.2%)	RR 0.94 (0.83 to 1.07)	59 fewer per 1000 (from 167 fewer to 69 more)	⊕⊕⊕O MODERATE	IMPORTANT
Pathogen eradication: *S pneumoniae*												
7[4]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	73/79 (92.4%)	51/58 (87.9%)	RR 1.07 (0.94 to 1.23)	62 more per 1000 (from 53 fewer to 202 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Abbreviations: CI – confidence interval; RR – relative risk												

[1] People with acute exacerbation of chronic bronchitis. The diagnosis of chronic bronchitis in all RCTs was based on the history of cough and expectoration on most days during at least 3 consecutive months in each of 2 or more consecutive years. Acute bacterial exacerbation of chronic bronchitis had to be classified according to symptoms described by Anthonisen et al. (1987) as follows: type I who met all the following criteria: increase in amount of sputum; purulence of sputum; and dyspnoea; type II who met who of the above 3 criteria; type III who met only one of the above 3 criteria

[2] First-line antibiotics included: amoxicillin 500 mg three times daily (7 or 10 day-course), ampicillin 250 mg or 500 mg three or four times daily (7 to 14-day course), pivampicillin/pivmecillinam 250/200 mg twice daily (10-day course), co-trimoxazole 80/400 mg once daily for 7 day course, and doxycycline 200 mg once daily (7-14 day course); second-line antibiotics included: co-amoxiclav 250/125 mg three times daily for 10 day course, macrolides (Azithromycin 250 mg or 500 mg once daily for 3 day course; clarithromycin 250 mg twice daily 7-14 day course; roxithromycin 300 mg once daily 7-14 day course) , cephalosporins (cefaclor 500 mg three times daily for 7 day course) and fluoroquinolones (fleroxacin 400 mg once daily for 7 day course). 3 included studies permitted the use of corticosteroid before an acute exacerbation of chronic bronchitis (details about doses and duration were not provided in the review).

[3] Treatment success defined as remission of all baseline symptoms of acute infection (clinical cure) or amelioration of symptoms without their complete disappearance (improvement).

[4] Clinically evaluable participants: participants who included and randomised, and who follow important components of the trial protocol as specified (e.g., administration of a specified minimum amount of an antibiotic). Participants considered as clinically evaluable in the individual RCTs who had an indeterminate clinical outcome at the follow-up visit were deemed unevaluable for the analysis.

[5] Dimopoulos et al (2007)

[6] Downgraded 1 level: I^2>50%.

[7] The review author reported the estimated effect (OR 0.51, 95% CI 0.34 to 0.75) using a fixed-effects model when there was considerable heterogeneity between the studies (I2>50%); NICE analysis used a random effect model for the estimation (relative risk) as reported in the GRADE table

[8] The absence of a baseline pathogen or the absence of adequate culturable material from a person exhibiting clinical cure (the resolution) or improvement among participants who have a baseline bacterial pathogen known to cause exacerbation.

[9] No downgrade: >50% included studies were rated as good quality

[10] Downgraded 2 levels: at a default minimal important difference of 25% relative risk reduction, effect estimate is consistent with no meaningful difference or appreciable harm with first-line antibiotics, and no meaningful difference or appreciable harm with second-line antibiotics.

[11] Downgraded 1 level: non-significant effect, 95%CI RR cross 1.

[12] In the subgroup analysis, the analyses were conducted by including trials that enrolled hospitalised patients and trials that enrolled outpatients.

[13] Downgraded 1 level: 2 included studies were single-blinded, although 3 of 4 studies were considered as a quality study by the author's assessment.

[14] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction, effect estimate is consistent with no meaningful difference or appreciable benefit with first-line antibiotics

[15] The review author reported the estimated effect (OR 0.55, 95% CI 0.34 to 0.90) using a fixed-effects model when there was considerable heterogeneity between the studies (I2>50%); NICE analysis used a random effect model for the estimation (relative risk) as reported in the GRADE table

[16] Pathogen eradication rate was calculated as the number of isolated eradicated pathogen is divided by total number of isolated for each pathogen at baseline.

Table 6: GRADE profile 3 – macrolides versus fluoroquinolones

Quality assessment							No of people[1]		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Macrolides[2]	Quinolones[3]	Relative (95% CI)	Absolute		
Treatment success[4]: intention to treat population[5], 6-21 days after the onset of exacerbation												
5[6, 7]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1298/1530 (84.8%)	1556/1796 (86.6%)	RR 1.00 (0.97 to 1.02)	0 fewer per 1000 (from 26 fewer to 17 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Treatment success: clinically evaluable population[8], 6-21 days after the onset of exacerbation												
8[6]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	1289/1463 (88.1%)	1409/1577 (89.3%)	RR 0.99 (0.97 to 1.02)	9 fewer per 1000 (from 27 fewer to 18 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Treatment success in microbiological evaluable participants[9], 6 to 21 days after the onset of exacerbation												

Quality assessment							No of people[1]		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Macrolides[2]	Quinolones[3]	Relative (95% CI)	Absolute		
7[6]	randomised trials	no serious risk of bias	serious[10]	no serious indirectness	no serious imprecision	none	487/586 (83.1%)	663/722 (91.8%)	RR 0.92 (0.87 to 0.98)	73 fewer per 1000 (from 18 fewer to 119 fewer)	⊕⊕⊕O MODERATE	IMPORTANT
Adverse event												
7[6]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	386/1900 (20.3%)	437/2181 (20%)	RR 1.09 (0.97 to 1.24)	18 more per 1000 (from 6 fewer to 48 more)	⊕⊕⊕⊕ HIGH	CRITICAL
All-cause mortality												
4[6]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[11]	none	4/1166 (0.34%)	2/1461 (0.14%)	RR 2.23 (0.46 to 10.75)	2 more per 1000 (from 1 fewer to 13 more)	⊕⊕⊕O MODERATE	CRITICAL
Subgroup analyses												
Treatment success: people with Anthonisen type 1, 2[12] exacerbation, intention to treat population[5]												
2[6,13]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	588/729 (80.7%)	581/725 (80.1%)	RR 1.01 (0.96 to 1.06)	8 more per 1000 (from 32 fewer to 48 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Treatment success: people with Anthonisen type 1, 2[12] exacerbation, clinical evaluable participants[8]												
5[6]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	781/898 (87%)	762/863 (88.3%)	RR 0.99 (0.95 to 1.02)	9 fewer per 1000 (from 44 fewer to 18 more)	⊕⊕⊕⊕ HIGH	CRITICAL
Pathogen eradication[14]: *H influenzae*												
5[6]	randomised trials	no serious risk of bias	Serious[9]	no serious indirectness	serious[15]	none	124/158 (78.5%)	174/180 (96.7%)	RR 0.85 (0.73 to 1.00)	145 fewer per 1000 (from 261 fewer to 0 more)	⊕⊕OO LOW	IMPORTANT
Pathogen eradication: *M catarrhalis*												
5[5]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	92/95 (96.8%)	123/127 (96.9%)	RR 1.01 (0.95 to 1.07)	0 fewer per 1000 (from 39 fewer to 48 more)	⊕⊕⊕⊕ HIGH	IMPORTANT
Pathogen eradication: *S pneumoniae*												
5[6]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	no serious imprecision	none	86/90 (95.6%)	98/105 (93.3%)	RR 1.02 (0.94 to 1.11)	19 more per 1000 (from 56 fewer to 103 more)	⊕⊕⊕⊕ HIGH	IMPORTANT

Abbreviations: CI – confidence interval; RR – relative risk

[1] People with acute exacerbation of chronic bronchitis. The criterion used for the diagnosis of chronic bronchitis in all RCTs was a medical history of cough and expectoration on most days during at least 3 consecutive months in each of 2 or more consecutive years. Acute bacterial exacerbation of chronic bronchitis had to be classified according to symptoms described by Anthonisen et al. (1987) as follows: type I who met all the following criteria: increase in amount of sputum; purulence of sputum; and dyspnoea; type II who met who of the above 3 criteria; type III who met only one of the above 3 criteria.

[2] Macrolide regimens included azithromycin 500 mg once daily for 1 day then 250 mg once daily for 4 day; clarithromycin 500 mg twice daily for 7-10 day course.

[3] Fluoroquinolone regimens included levofloxacin 500 mg or 750 mg once daily for 3-7 day; moxifloxacin 400 mg once daily for 5-day course; gemifloxacin 320 mg once daily for 5-day course.

[4] Treatment success defined as remission of all baseline symptoms of acute infection (clinical cure) or amelioration of symptoms without their complete disappearance (improvement).

[5] Intention to treat participants: participants were randomised in the trial to be considered to be part of the trial regardless of their completion of the trial.
[6] Siempos et al (2007)
[7] Three of 5 RCTs permitted the use of systemic corticosteroid before acute exacerbation of chronic bronchitis, range from 21% to 39% in macrolide group, and from 21% to 50% in fluoroquinolone group. Of 2 of 3 studies that permitted the use of corticosteroid, studies included people with moderate to severe exacerbation of chronic bronchitis based on the Anthonisen classification.
[8] Clinically evaluable participants: participants who included and randomised, and who follow important components of the trial protocol as specified (e.g., administration of a specified minimum amount of an antibiotic). Participants considered as clinically evaluable in the individual RCTs who had an indeterminate clinical outcome at the follow-up visit were deemed unevaluable for the analysis.
[9] The absence of a baseline pathogen or the absence of adequate culturable material from a person exhibiting clinical cure (the resolution) or improvement among participants who have a baseline bacterial pathogen known to cause exacerbation.
[10] Downgraded 1 level: I^2 >50%
[11] Downgraded 1 level: non-significant effect, 95%CI RR cross 1.
[12] In the subgroup analysis, the analysis were conducted by including trials that enrolled patients with an Anthonisen type 1 or type 2 acute exacerbation of chronic bronchitis (macrolides versus fluoroquinolones)
[13] Both studies permitted the use of systemic corticosteroid before acute exacerbation of chronic bronchitis.
[14] Pathogen eradication rate was calculated as the number of isolated eradicated pathogen is divided by total number of isolated for each pathogen at baseline.
[15] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction, effect estimate is consistent with no meaningful difference or appreciable benefit with macrolides

Table 7: GRADE profile 4 – co-amoxiclav versus macrolide

Quality assessment							No of people[1]		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Co-amoxiclav[2]	Macrolides[3]	Relative (95% CI)	Absolute		
Treatment success[4] , intention to treat population[5], 6-21 days after the onset of exacerbation												
5[6, 7]	randomised trials	no serious risk of bias	serious[8]	no serious indirectness	no serious imprecision	none	356/412 (86.4%)	389/457 (85.1%)	RR 1.02 (0.88 to 1.17)	17 more per 1000 (from 102 fewer to 145 more)	⊕⊕⊕O MODERATE	CRITICAL
Treatment success[4], clinical evaluable population[9], 6-21 days after the onset of exacerbation												
8[6]	randomised trials	no serious risk of bias	serious[8]	no serious indirectness	no serious imprecision	none	570/622 (91.6%)	617/695 (88.8%)	RR 1.02 (0.95 to 1.10)	27 more per 1000 (from 9 fewer to 62 more)	⊕⊕⊕O MODERATE	CRITICAL
Treatment success in microbiological evaluable participants[10], 6 to 21 days after the onset of exacerbation												
4[6]	randomised trials	no serious risk of bias	serious[8]	no serious indirectness	serious[10]	none	192/247 (77.7%)	180/255 (70.6%)	RR 1.08 (0.86 to 1.37)	56 more per 1000 (from 99 fewer to 261 more)	⊕⊕OO LOW	IMPORTANT
Adverse event												
2[6]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[11]	none	62/268 (23.1%)	45/269 (16.7%)	RR 1.38 (0.98 to 1.94)	64 more per 1000 (from 3 fewer to 157 more)	⊕⊕⊕O MODERATE	CRITICAL
Subgroup analyses												
Pathogen eradication[12] : *H influenzae*												
4[6]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[11]	none	57/69 (82.6%)	60/105 (57.1%)	RR 1.41 (1.16 to 1.71)	240 more per 1000 (from 40 more to 503 more)	⊕⊕⊕O MODERATE	IMPORTANT
Pathogen eradication : *M catarrhalis*												

Quality assessment							No of people[1]		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Co-amoxiclav[2]	Macrolides[3]	Relative (95% CI)	Absolute		
4[6]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[13]	none	35/38 (92.1%)	39/42 (92.9%)	RR 0.97 (0.84 to 1.12)	28 fewer per 1000 (from 149 fewer to 111 more)	⊕⊕⊕O MODERATE	IMPORTANT
Pathogen eradication: *S pneumoniae*												
4[6]	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[11]	none	60/66 (90.9%)	51/67 (76.1%)	RR 1.19 (1.01 to 1.41)	240 more per 1000 (from 40 more to 490 more)	⊕⊕⊕O MODERATE	IMPORTANT

Abbreviations: CI – confidence interval; RR – relative risk

[1] People with acute exacerbation of chronic bronchitis. The criterion used for the diagnosis of chronic bronchitis in all RCTs was a medical history of cough and expectoration on most days during at least 3 consecutive months in each of 2 or more consecutive years. Acute bacterial exacerbation of chronic bronchitis had to be classified according to symptoms described by Anthonisen et al. (1987) as follows: type I who met all the following criteria: increase in amount of sputum; purulence of sputum; and dyspnoea; type II who met who of the above 3 criteria; type III who met only one of the above 3 criteria.

[2] Dose regimens of co-amoxiclav were 500 mg/125 mg or 875 mg/125 mg (for 5 to 14 days).

[3] In the macrolide group, the following regimens were included: clarithromycin 500 mg or 1000 mg once daily (7-day course), azithromycin 250 mg or 500mg twice or once daily (3-day course), dirithromycin 500 mg once daily (5-day course); and roxithromycin 150 mg twice daily (14-day course

[4] Treatment success defined as remission of all baseline symptoms of acute infection (clinical cure) or amelioration of symptoms without their complete disappearance (improvement).

[5] Intention to treat participants: participants were randomised in the trial to be considered to be part of the trial regardless of their completion of the trial.

[6] Siempos et al (2007)

[7] Two of 5 RCTs permitted the use of systemic corticosteroid before acute exacerbation of chronic bronchitis (details were not reported in the review)

[8] Downgraded 1 level: I^2>50%.

[9] Clinically evaluable participants: participants who included and randomised, and who follow important components of the trial protocol as specified (e.g., administration of a specified minimum amount of an antibiotic). Participants considered as clinically evaluable in the individual RCTs who had an indeterminate clinical outcome at the follow-up visit were deemed unevaluable for the analysis.

[10] The absence of a baseline pathogen or the absence of adequate culturable material from a person exhibiting clinical cure (the resolution) or improvement among participants who have a baseline bacterial pathogen known to cause exacerbation

[11] Downgraded 1 level: at a default minimal important difference of 25% relative risk increase, effect estimate is consistent with no meaningful difference or appreciable benefit with co-amoxiclav.

[12] Pathogen eradication rate was calculated as the number of isolated eradicated pathogen is divided by total number of isolated for each pathogen at baseline

[13] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction, effect estimate is consistent with no meaningful difference or appreciable benefit with co-amoxiclav

Table 8: GRADE profile 5 – co-amoxiclav versus fluoroquinolones

Quality assessment							No of people[1]		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Co-amoxiclav[2]	Fluoroquinolones[3]	Relative (95% CI)	Absolute		
Treatment success[4], intention to treat population[5], 6-21 days after the onset of exacerbation												
1[6]	randomised trials	serious[7]	not applicable	no serious indirectness	no serious imprecision	none	241/283 (85.2%)	270/292 (92.5%)	RR 0.92 (0.87 to 0.98)	74 fewer per 1000 (from 18 fewer to 120 fewer)	⊕⊕⊕O MODERATE	CRITICAL
Treatment success[4], clinical evaluable population[8], 6-21 days after the onset of exacerbation												

Quality assessment							No of people[1]		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Co-amoxiclav[2]	Fluoroquinolones[3]	Relative (95% CI)	Absolute		
4[6,9]	randomised trials	Serious[10]	no serious inconsistency	no serious indirectness	no serious imprecision	none	647/716 (90.4%)	663/729 (90.9%)	RR 0.99 (0.96 to 1.03)	9 fewer per 1000 (from 36 fewer to 27 more)	⊕⊕⊕O MODERATE	CRITICAL
Treatment success in microbiological evaluable participants[11], 6 to 21 days after the onset of exacerbation												
4[6]	randomised trials	serious[12]	no serious inconsistency	no serious indirectness	no serious imprecision	none	184/220 (83.6%)	194/224 (86.6%)	RR 0.97 (0.90 to 1.05)	26 fewer per 1000 (from 87 fewer to 43 more)	⊕⊕⊕O MODERATE	IMPORTANT
Adverse event												
4[4]	randomised trials	no serious risk of bias[13]	no serious inconsistency	no serious indirectness	serious[14]	none	139/837 (16.6%)	110/862 (12.8%)	RR 1.3 (1.03 to 1.64)	38 more per 1000 (from 4 more to 82 more)	⊕⊕⊕O MODERATE	CRITICAL
All-cause mortality												
2[6]	randomised trials	serious[15]	no serious inconsistency	no serious indirectness	serious[16]	none	0/475 (0%)	3/487 (0.62%)	RR 0.15 (0.01 to 2.83)	5 fewer per 1000 (from 6 fewer to 11 more)	⊕⊕OO LOW	CRITICAL
Subgroup analyses												
Pathogen eradication[17] : *H influenzae*												
1[6]	randomised trial	serious[17]	not applicable	no serious indirectness	serious[14]	none	20/20 (100%)	25/30 (83.3%)	RR 1.19 (0.99 to 1.42)	158 more per 1000 (from 8 fewer to 350 more)	⊕⊕OO LOW	IMPORTANT
Pathogen eradication : *M catarrhalis*												
1[6]	randomised trial	serious[18]	not applicable	no serious indirectness	very serious[19]	none	16/19 (84.2%)	10/12 (83.3%)	RR 1.01 (0.73 to 1.39)	8 more per 1000 (from 225 fewer to 325 more)	⊕⊕⊕O VERY LOW	IMPORTANT
Pathogen eradication : *S pneumoniae*												
1[6]	randomised trial	Serious[20]	not applicable	no serious indirectness	serious[21]	none	10/13 (76.9%)	16/18 (88.9%)	RR 0.87 (0.62 to 1.22)	116 fewer per 1000 (from 338 fewer to 196 more)	⊕⊕OO LOW	IMPORTANT
Abbreviations: CI – confidence interval; RR – relative risk												

[1] People with acute exacerbation of chronic bronchitis. The criterion used for the diagnosis of chronic bronchitis in all RCTs was a medical history of cough and expectoration on most days during at least 3 consecutive months in each of 2 or more consecutive years. Acute bacterial exacerbation of chronic bronchitis had to be classified according to symptoms described by Anthonisen et al. (1987) as follows: type 1 who met all the following criteria: increase in amount of sputum; purulence of sputum; and dyspnoea; type 2 who met who of the above 3 criteria; type 3 who met only one of the above 3 criteria.
[2] Dose regimens of co-amoxiclav were 500 mg/125 mg or 875 mg/125 mg twice or three times daily (range, 7 to 10-day course).
[3] Fluoroquinolones regimens included moxifloxacin 400 mg once daily (5-day course), levofloxacin 750 mg once daily (5-day course) and gemifloxacin 320 mg once daily (5-day course).
[4] Treatment success defined as remission of all baseline symptoms of acute infection (clinical cure) or amelioration of symptoms without their complete disappearance (improvement).
[5] Intention to treat participants: participants were randomised in the trial to be considered to be part of the trial regardless of their completion of the trial.
[6] Siempos et al (2007)
[7] Downgraded 1 level: the study was rated as low quality (study quality score<3)

[8] Clinically evaluable participants: participants who included and randomised, and who follow important components of the trial protocol as specified (e.g., administration of a specified minimum amount of an antibiotic). Participants considered as clinically evaluable in the individual RCTs who had an indeterminate clinical outcome at the follow-up visit were deemed unevaluable for the analysis.
[9] Two of 4 RCTs permitted the use of systemic corticosteroid before acute exacerbation of chronic bronchitis, ranged from 14% to 43% in co-amoxiclav group and ranged from 17% to 48% in fluoroquinolone group
[10] Downgraded 1 level: 3 of 4 included were rated as low quality (study quality score <3)
[11] The absence of a baseline pathogen or the absence of adequate culturable material from a person exhibiting clinical cure (the resolution) or improvement among participants who have a baseline bacterial pathogen known to cause exacerbation
[12] Downgraded 1 level: >50% included studies were rated as low quality (study quality study<3).
[13] No downgrade: >50% included studies were rated as good quality
[14] Downgraded 1 level: at a default minimal important difference of 25% relative risk increase, effect estimate is consistent with no meaningful difference or appreciable harm with co-amoxiclav.
[15] Downgraded 1 level: both included studies were rated as low quality (study quality score<3).
[16] Downgraded 1 level: non-significant effect, 95%CI RR cross 1.
[17] Pathogen eradication rate was calculated as the number of isolated eradicated pathogen is divided by total number of isolated for each pathogen at baseline
[18] Downgraded 1 level: the study was rated as low quality (study quality score<3)
[19] Downgraded 1 level: at a default minimal important difference of 25% relative risk increase, effect estimate is consistent with no meaningful difference or appreciable benefit with co-amoxiclav and no meaningful difference or appreciable benefit with fluoroquinolones.
[20] Downgraded 1 level: the study was rated as low quality (study quality score<3)
[21] Downgrade 1 level: at a default minimal important difference of 25% relative risk reduction, effect estimate is consistent with no meaningful difference or appreciable benefit with co-amoxiclav

Table 9: GRADE profile 6– co-trimoxazole versus fluoroquinolone

Quality assessment							No of people[1]		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Co-trimoxazole[2]	Ciprofloxacin[3]	Relative (95% CI)	Absolute		
Need for an additional antibiotics (up to 6 months after the completion of treatment)												
1[4]	randomised trial	no serious risk of bias	not applicable	no serious indirectness	very serious[5]	none	7/85 (8.2%)	5/85 (9.4%)	NICE analysis[6] RR 1.40 (0.46 to 4.24)	23 more per 1000 (from 54 fewer to 100 more)	⊕⊕⊕O MODERATE	IMPORTANT
Adverse events												
1[4]	randomised trial	no serious risk of bias	not applicable	no serious indirectness	very serious[5]	none	5/85 (5.9%)	6/85 (7.0%)	NICE analysis[7] RR 0.83 (0.26 to 2.63)	11 fewer per 1000 (from 85 fewer to 63 more)	⊕⊕⊕O MODERATE	IMPORTANT
All-cause mortality, hospital												
1[4]	randomised trial	no serious risk of bias	not applicable	no serious indirectness	serious[8]	none	7/85 (8.2%)	8/19 (9.4%)	NICE analysis[9] RR 0.88 (0.33 to 2.31)	12 fewer per 1000 (from 97 fewer to 73 more)	⊕⊕⊕O MODERATE	CRITICAL
Duration of hospital stay (days)												
1[4]	randomised trial	no serious risk of bias	not applicable	no serious indirectness	no serious imprecision	None	85	85	MD 0.2 fewer (2.6 fewer to 2.2 more)	-	⊕⊕⊕⊕ HIGH	IMPORTANT
Abbreviations: CI – confidence interval; RR – relative risk												

[1]People with an acute exacerbation of COPD. The diagnosis of an acute exacerbation of COPD required a history of COPD with clinical evidence of a purulent bronchitis in addition to acute respiratory failure requiring medical ventilation within the first 24 hour after intensive care unit admission. Acute respiratory failure was defined characteristics: respiratory rate>30 breaths/min; arterial partial pressure of carbon dioxide >6k Pa and arterial pH<7.3 just before the initiation of mechanical ventilation.

[2] Co-trimoxazole dose regimen: 160/800 mg twice daily for 10 days.
[3] Ciprofloxacin dose regimen: 750 mg twice daily for 10 days.
[4] Nouira et al 2010.
[5] Downgraded 2 levels: at a default minimal important difference of 25% relative risk reduction, effect estimate is consistent with no meaningful difference or appreciable harm with co-trimoxazole, and no meaningful difference or appreciable harm with ciprofloxacin.
[6] The study author reported the difference in the rate of additional antibiotic prescription, 2.3% (95% CI 5.4% fewer to 10.0% more), p=0.549; NICE analysis used relative risk estimating the effect between treatment groups as reported in GRADE table.
[7] The study author reported the difference in the rate of additional antibiotic prescription, -1.1% (95% CI 8.5% fewer to 6.3% more), p=0.75; NICE analysis used relative risk estimating the effect between treatment groups as reported in GRADE table.
[8] Downgraded 1 level: non-significant effect, 95%CI RR cross 1.
[9] The study author reported the difference in the rate of additional antibiotic prescription, -1.2% (95% CI 9.7% fewer to 7.3% more), p=0.99; NICE analysis used relative risk estimating the effect between treatment groups as reported in GRADE table.

Table 10: GRADE profile 7 – fluoroquinolones versus cephalosporin

Quality assessment							No of people[1]		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Levofloxacin[2]	Cefuroxime[3]	Relative (95% CI)	Absolute		
Clinical success[4], intention to treat population[5], 11 days after the completion of treatment												
1[6]	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	273/289 (94.4%)	273/296 (92.2%)	RR 1.02 (0.98 to 1.07)	18 more per 1000 (from 18 fewer to 63 more)	⊕⊕⊕O MODERATE	CRITICAL
1[8]	randomised trials	serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	53/65 (81.5%)	58/72 (80.6%)	RR 1.01 (0.86 to 1.19)	17 more per 1000 (from 17 fewer to 60 more)	⊕⊕⊕O MODERATE	CRITICAL
Microbiological response[9], intention to treat population[5], 5 to 7 days after the completion of treatment												
1[8]	randomised trial	serious[7]	not applicable	no serious indirectness	very serious[10]	none	6/7 (85.7%)	11/16 (68.8%)	RR 1.25 (0.8 to 1.95)	172 more per 1000 (from 137 fewer to 653 more)	⊕⊕⊕O VERY LOW	IMPORTANT
Adverse events												
1[6]	randomised trial	serious[7]	not applicable	no serious indirectness	very serious[11]	none	17/289 (5.9%)	10/296 (3.4%)	RR 1.74 (0.81 to 3.74)	25 more per 1000 (from 6 fewer to 93 more)	⊕OOO VERY LOW	CRITICAL
Abbreviations: CI – confidence interval; RR – relative risk												

[1] People with acute exacerbation of chronic bronchitis or COPD. Exacerbation of COPD was defined as recently increased cough or dyspnoea, recent change in colour or amount of sputum and a diagnosis of COPD on spirometry (Yoon et al. 2013)
[2] Levofloxacin 500 mg once daily (7 or 10-day course)
[3] Cefuroxime 250 mg twice daily (7 or 10-day course).
[4] Clinical success: cure if all infection-related signs and symptoms disappeared or improved to an extent that represented normal infection clearance and no subsequent antibiotics therapy was indicated.
[5] Intention to treat participants: participants were randomised in the trial to be considered to be part of the trial regardless of their completion of the trial.
[6] Petitpretz et al (2007); the use of corticosteroid was not reported in the review
[7] Downgraded 1 level: open label design
[8] Yoon et al (2013); the use of corticosteroid was not reported in the review

[9] A microbiological response of eradication, presumed eradication, or superinfection was defined as effective. Microbiological response was graded as eradication (disappearance of pathogenic bacteria on the second visit), presumed eradication (inability to produce sputum due to improvement), persistence (persistence of initial pathogenic bacteria), presumed persistence (detection of pathogenic bacteria only on the second visit with clinical evidence of persistence), or superinfection (appearance of pathogenic bacteria other than initial ones) at the second visit (5-7 days after the final dose of antibiotics)
[10] Downgraded 2 levels: at a default minimal important difference of 25% relative risk increase, effect estimate is consistent with no meaningful difference or appreciable benefit with levofloxacin, or no meaningful difference or appreciable benefit with the cefuroxime.
[11] Downgraded 2 levels: at a default minimal important difference of 25% relative risk increase, effect estimate is consistent with no meaningful difference or appreciable harm with levofloxacin, or no meaningful difference or appreciable harm with the cefuroxime.

Table 11: GRADE profile 8 – fluoroquinolone versus another fluoroquinolone

Quality assessment							No of people[1]		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Levofloxacin[2]	Moxifloxacin[3]	Relative (95% CI)	Absolute		
Clinical cure[4], intention to treat population[5], 7 to 14 days after completion of treatment												
1[6]	randomised trials	serious[7]	not applicable	no serious indirectness	no serious imprecision	none	237/284 (83.7%)	225/278 (80.9%)	RR 1.03 (0.96 to 1.12)	24 more per 1000 (from 32 fewer to 97 more)	⊕⊕⊕O MODERATE	CRITICAL
Bacteriological success[8], intention to treat population[5], 7 to 14 days after completion of treatment												
1[6]	randomised trial	serious[7]	not applicable	no serious indirectness	very serious[9]	none	121/129 (93.8%)	128/138 (92.8%)	RR 1.18 (0.45 to 3.09)	10 more per 1000 (from 75 fewer to 48 more)	⊕⊕⊕O VERY LOW	IMPORTANT
Adverse events												
1[6]	randomised trial	serious[7]	not applicable	no serious indirectness	serious[10]	none	76/283 (26.9%)	66/278 (23.7%)	RR 1.13 (0.85 to 1.5)	31 more per 1000 (from 36 fewer to 119 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI – confidence interval; RR – relative risk												

[1] People with chronic bronchitis A diagnosis of chronic bronchitis was defined a history of cough and sputum on most days during at least 3 consecutive months and for more than 2 successive years, with exacerbation within the previous 14 days characterised by increased cough, increased sputum production with change in colour and consistency, and mild to moderate dyspnoea.
[2] Levofloxacin 500 mg once daily (for 7 days).
[3] Moxifloxacin 400 mg once daily (for 5 days).
[4] Clinical cure, resolution was defined as total resolution of signs and symptoms related to the acute exacerbation to such an extent that no additional or alternative therapy was necessary.
[5] Intention to treat participants: participants were randomised in the trial to be considered to be part of the trial regardless of their completion of the trial.
[6] Urueta-Robledo et al (2006); the use of corticosteroid was not reported in the study.
[7] Downgraded 1 level: the study did not provide detailed regarding allocation concealment, blinding of participants and outcome assessment, and the selection of outcome reporting.
[8] Bacteriological success was assessed by eradication or presumed eradication (clinical cure in the absence of a repeat sputum culture) of bacterial in sputum.
[9] Downgraded 2 levels: at a default minimal important difference of 25% relative risk increase, effect estimate is consistent with no meaningful difference or appreciable benefit with levofloxacin, or no meaningful difference or appreciable benefit with moxifloxacin
[10] Downgraded 1 level: at a default minimal important difference of 25% relative risk increase, effect estimate is consistent with no meaningful difference or appreciable harm with levofloxacin

Table 12: GRADE profile 9 penicillins versus trimethoprim (with or without a sulphonamide)

Quality assessment							No of people[1]		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Penicillins[2]	Trimethoprim within or without sulphonamide[3]	Relative (95% CI)	Absolute		
Treatment success[4]: intention-to-treat participants[5], 6 to 34 days from onset of exacerbations												
5[6]	randomised trials	Serious[7]	no serious inconsistency	no serious indirectness	no serious imprecision	none	111/133 (83.5%)	96/129 (74.4%)	RR 1.11 (0.98 to 1.26)	82 more per 1000 (from 15 fewer to 193 more)	⊕⊕⊕O MODERATE	CRITICAL
Adverse event												
3[6]	randomised trials	Serious[8]	no serious inconsistency	no serious indirectness	very serious[9]	none	3/93 (3.2%)	6/93 (6.5%)	RR 0.55 (0.16 to 1.92)	29 fewer per 1000 (from 54 fewer to 59 more)	⊕OOO VERY LOW	CRITICAL
All-cause mortality												
1[6]	randomised trial	no serious risk of bias	not applicable	no serious indirectness	very serious[10]	none	1/18 (5.6%)	2/19 (10.5%)	RR 0.53 (0.05 to 5.33)	49 fewer per 1000 (from 100 fewer to 456 more)	⊕⊕OO LOW	CRITICAL
Abbreviations: CI – confidence interval; RR – relative risk												

[1]People with acute exacerbation of chronic bronchitis. The criterion used for the diagnosis of chronic bronchitis in all RCTs was a medical history of cough and expectoration on most days during at least 3 consecutive months in each of 2 or more consecutive years. Acute bacterial exacerbation of chronic bronchitis had to be classified according to symptoms described by Anthonisen et al. (1987) as follows: type 1 who met all the following criteria: increase in amount of sputum; purulence of sputum; and dyspnoea; type 2 who met who of the above 3 criteria; type 3 who met only one of the above 3 criteria

[2] Penicillins dose regimens included: amoxicillin 250 mg or 500 mg three or four times a day (7 to 10-day courses) and pivampicillin 375 mg with pivmecillinam hydrochloride 300 mg twice daily (10-day course). The use of corticosteroid was not reported in the review

[3] Trimethoprim dose regimens included: trimethoprim 200 mg twice daily (7-day course), trimethoprim/sulfamethoxazole 160/800 mg or 240/1200 mg twice or three times day (7 to 10-day course), trimethoprim/sulfadiazine 150/450 mg twice daily (7-day course)

[4] Treatment success defined as remission of all baseline symptoms of acute infection (clinical cure) or amelioration of symptoms without their complete disappearance (improvement)

[5] Intention to treat participants: participants were randomised in the trial to be considered to be part of the trial regardless of their completion of the trial.

[6]Korbila et al (2009)

[7] Downgraded 1 level: of 5 included studies, 2 included studies were rated as low quality (study quality score<3); 1 included study was single-blinded trial.

[8] Downgraded 1 level: only 1 included study was double blinded

[9] Downgraded 2 levels: at a default minimal important difference of 25% relative risk reduction, effect estimate is consistent with no meaningful difference or appreciable harm with penicillins, and no meaningful difference or appreciable harm with trimethoprim regimens

[10] Downgraded 2 levels: non-significant effect, 95%CI RR cross 1, wide confidence interval (sample size=35)

H.3 Antibiotics course length

Table 13: GRADE profile 10 – short-course antibiotic (less than 6 days) versus long-course antibiotic (7 days or more)

Quality assessment	No of people[1]	Effect	Quality	Importance

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Short-course antibiotic[2] (<6 days)	Long-course antibiotic[2] (≥7 days)	Relative (95% CI)	Absolute		
Early clinical success[3] (<6 days)												
5[4]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1120/1380 (81.2%)	1117/1370 (81.5%)	RR 1 (0.96 to 1.03)	0 fewer per 1000 (from 33 fewer to 24 more)	⊕⊕⊕O MODERATE	CRITICAL
Medium clinical success[3] (7-14 days)												
4[4]	randomised trials	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	763/952 (80.1%)	788/963 (81.8%)	RR 0.98 (0.94 to 1.02)	16 fewer per 1000 (from 49 fewer to 16 more)	⊕⊕⊕O MODERATE	CRITICAL
Late clinical success[3] (>20 days)												
4[4]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	679/1007 (67.4%)	686/1005 (68.3%)	RR 0.99 (0.94 to 1.05)	7 fewer per 1000 (from 41 fewer to 34 more)	⊕⊕⊕O MODERATE	CRITICAL
Bacteriological response[7]: early clinical success (<6 days)												
3[4]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	247/288 (85.8%)	245/279 (87.8%)	RR 0.99 (0.93 to 1.05)	9 fewer per 1000 (from 61 fewer to 44 more)	⊕⊕⊕O MODERATE	IMPORTANT
Bacteriological response: medium clinical success (7-23 days)												
5[4]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	327/395 (82.8%)	324/376 (86.2%)	RR 0.97 (0.92 to 1.03)	26 fewer per 1000 (from 69 fewer to 26 more)	⊕⊕⊕O MODERATE	IMPORTANT
Adverse events												
8[4]	randomised trials	serious[5]	no serious inconsistency	no serious indirectness	serious[8]	none	353/1687 (20.9%)	420/1684 (24.9%)	RR 0.84 (0.75 to 0.95)	40 fewer per 1000 (from 12 fewer to 62 fewer)	⊕⊕OO LOW	CRITICAL

Abbreviations: CI – confidence interval; RR – relative risk

[1] People with acute exacerbations of chronic obstructive pulmonary disease

[2] Dose regimens included: levofloxacin 500 mg once daily, moxifloxacin 400 mg once daily grepafloxacin 400 mg once daily, and gatifloxacin 400 mg once daily. The other studies included amoxicillin 500 mg three times daily or 3 g twice daily (1 RCT), clarithromycin 500 mg twice daily or 1 g once daily (1 RCT), cefixime 400 mg once daily (1 RCT) and co-amoxiclav 500/125 mg or 2000/125 mg twice daily (2 RCTs). The use of corticosteroid was not reported in the review.

[3] Clinical success was defined as the resolution of clinical signs or symptoms of acute exacerbations. It was presented as early clinical success (within 6 days of treatment completion), middle clinical success (7-14 days after treatment completion) or late clinical success (more than 20 days after treatment completion).

[4] Stolbrink et al (2017)

[5] Downgraded 1 level: >50% included studies did not provide details regarding allocation concealment, blinding of participants, outcome assessment and selecting outcome reporting.

[6] Downgraded 1 level: 2 included studies accounted for 75% weight in the meta-analysis, did not provide detailed information regarding allocation concealment, blinding of participants, outcome assessment and selecting outcome reporting.

[7] Bacteriological response was assessed eradication or presumed eradication of pathogens which were present in pre-treatment sputum samples. Presumed eradication was defined as improvement in clinical symptoms without sputum that could be cultured at follow-up. It was assess within 6 days of treatment completion, and 7 to 23 days after treatment completion.

[8] Downgraded 1 level: at a default minimal important difference of 25% relative risk reduction, effect estimate is consistent with no meaningful difference or appreciable harm with shorter treatment duration.

Appendix I: Studies not-prioritised

Study reference	Reason
Alvarez-Sala Jose-Luis, Kardos Peter, Martinez-Beltran Jesus, Coronel Pilar, and Aguilar Lorenzo (2006) Clinical and bacteriological efficacy in treatment of acute exacerbations of chronic bronchitis with cefditoren-pivoxil versus cefuroxime-axetil. Antimicrobial agents and chemotherapy 50(5), 1762-7	Low relevance to current UK practice
Andre-Alves Mara Rubia, Jardim Jose Roberto, Frare e Silva, Rodney , Fiss Elie, Freire Denison Noronha, and Teixeira Paulo Jose Zimermann (2007) Comparison between azithromycin and amoxicillin in the treatment of infectious exacerbation of chronic obstructive pulmonary disease. Jornal brasileiro de pneumologia : publicacao oficial da Sociedade Brasileira de Pneumologia e Tisilogia 33(1), 43-50	Systematic review has been prioritised (Dimpolous et al 2007)
Blasi F, Tarsia P, Mantero M, Morlacchi L C, and Piffer F (2013) Cefditoren versus levofloxacin in patients with exacerbations of chronic bronchitis: Serum inflammatory biomarkers, clinical efficacy, and microbiological eradication. Therapeutics and Clinical Risk Management 9(1), 55-64	Low relevance to current UK practice (cefditoren)
Blasi F, Schaberg T, Centanni S, Del Vecchio , A , Rosignoli M T, and Dionisio P (2013) Prulifloxacin versus levofloxacin in the treatment of severe COPD patients with acute exacerbations of chronic bronchitis. Pulmonary pharmacology & therapeutics 26(5), 609-16	Low relevance to current UK practice (prulifloxacin)
Brusse-Keizer Marjolein, VanderValk Paul, Hendrix Ron, Kerstjens Huib, van der Palen , and Job (2014) Necessity of amoxicillin clavulanic acid in addition to prednisolone in mild-to-moderate COPD exacerbations. BMJ open respiratory research 1(1), e000052	RCT does not add additional information (on population, comparison or outcome) to the evidence included in a systematic review that has been prioritised (Vollenweider et al 2012)
Chatterjee S, Biswas T, Dutta A, Sengupta G, Mitra A, and Kundu S (2011) Clinical effectiveness and safety of gemifloxacin versus cefpodoxime in acute exacerbation of chronic bronchitis: A randomized, controlled trial. Indian journal of pharmacology 43(1), 40-4	Low relevance to current UK practice (gatifloxacin)
Daniels Johannes M. A, Snijders Dominic, de Graaff , Casper S, Vlaspolder Fer, Jansen Henk M, and Boersma Wim G (2010) Antibiotics in addition to systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. American journal of respiratory and critical care medicine 181(2), 150-7	RCT included in a systematic review that has been prioritised (Volleoweider et al 2012)
El Moussaoui , R , Roede B M, Speelman P, Bresser P, Prins J M, and Bossuyt P M. M (2008) Short-course antibiotic treatment in acute exacerbations of chronic bronchitis and COPD: a meta-analysis of double-blind studies. Thorax 63(5), 415-22	Systematic review has been prioritised (Stolbrink et al 2017)

Study reference	Reason
Falagas Matthew E, Avgeri Sofia G, Matthaiou Dimitrios K, Dimopoulos George, and Siempos Ilias I (2008) Short- versus long-duration antimicrobial treatment for exacerbations of chronic bronchitis: a meta-analysis. The Journal of antimicrobial chemotherapy 62(3), 442-50	Systematic review has been prioritised, and low relevance to current UK practice (gatifloxacin)
Fogarty Charles M, Buchanan Patricia, Aubier Michel, Baz Malik, van Rensburg , Dirkie , Rangaraju Manickam, and Nusrat Roomi (2006) Telithromycin in the treatment of pneumococcal community-acquired respiratory tract infections: a review. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases 10(2), 136-47	Low relevance to current UK practice (telithromycin)
Giusti Massimo, Blasi Francesco, Iori Ido, Mazzone Antonino, Sgambato Francesco, Politi Cecilia, Colagrande Paola, Casali Annamaria, Valerio Antonella, Gussoni Gualberto, Bonizzoni Erminio, and Campanini Mauro (2016) Prulifloxacin vs Levofloxacin for Exacerbation of COPD after Failure of Other Antibiotics. COPD 13(5), 555-60	Low relevance to current UK practice (prulifloxacin)
Gotfried Mark, Busman Todd A, Norris Sandra, and Notario Gerard F (2007) Role for 5-day, once-daily extended-release clarithromycin in acute bacterial exacerbation of chronic bronchitis. Current medical research and opinion 23(2), 459-66	This study does not add additional information (on population, comparison or outcome) to the evidence included in a systematic review that has been prioritised (Stolbrik et al 2017)
Gotfried Mark H, and Grossman Ronald F (2010) Short-course fluoroquinolones in acute exacerbations of chronic bronchitis. Expert review of respiratory medicine 4(5), 661-72	Systematic review has been prioritised, and low relevance to current UK practice (gemitfloxacin)
Grossman Ronald F, Ambrusz Mary E, Fisher Alan C, Khashab Mohammed M, and Kahn James B (2006) Levofloxacin 750 mg QD for five days versus amoxicillin/clavulanate 875 mg/125 mg BID for ten days for treatment of acute bacterial exacerbation of chronic bronchitis: a post hoc analysis of data from severely ill patients. Clinical therapeutics 28(8), 1175-80	This RCT (secondary analysis) did not add additional information (no population, comparison or outcome to the evidence included in included in a systematic review that has been prioritised (Simpos et al 2007)
Hassan W A, Shalan I, and Elsobhy M (2015) Impact of antibiotics on acute exacerbations of COPD. Egyptian Journal of Chest Diseases and Tuberculosis 64(3), 579-585	Systematic review has been prioritised (Vollenweider et al 2012)
Llor Carl, Hernandez Silvia, Ribas Anna, Alvarez Carmen, Cots Josep Maria, Bayona Carolina, Gonzalez Isabel, Miravitlles Marc, and Group Bramox Study (2009) Efficacy of amoxycillin versus amoxycillin/clavulanate in acute exacerbations of chronic pulmonary obstructive disease in primary care. International journal of chronic obstructive pulmonary disease 4, 45-53	Systematic review has been prioritised ((Dimpolous et al 2007)
Llor Carl, Moragas Ana, Hernandez Silvia, Bayona Carolina, and Miravitlles Marc (2012) Efficacy of antibiotic therapy for acute exacerbations of mild to moderate chronic obstructive pulmonary disease. American journal of respiratory and critical care medicine 186(8), 716-23	RCT included in a systematic review that has been prioritised

Study reference	Reason
Liu Kai-Xiong, Xu Bing, Wang Jie, Zhang Jing, Ding Hai-Bo, Ariani Felinda, Qu Jie-Ming, and Lin Qi-Chang (2014) Efficacy and safety of moxifloxacin in acute exacerbations of chronic bronchitis and COPD: a systematic review and meta-analysis. Journal of thoracic disease 6(3), 221-9	Systematic review has been prioritised (Simpos et al 2007)
Milstone Aaron P (2008) Use of azithromycin in the treatment of acute exacerbations of COPD. International journal of chronic obstructive pulmonary disease 3(4), 515-20	Systematic review has been prioritised (Dimopoulos et al. 2007; Simpos et al 2007)
Miravitlles M, Molina J, and Brosa M (2007) Clinical efficacy of moxifloxacin in the treatment of exacerbations of chronic bronchitis: a systematic review and meta-analysis. Archivos de Bronconeumologia 43(1), 22-28	Systematic review has been prioritised (Simpos et al 2007)
Niederman M S, Anzueto A, Sethi S, Choudhri S, Kureishi A, Haverstock D, and Perroncel R (2006) Eradication of H. influenzae in AECB: A pooled analysis of moxifloxacin phase III trials compared with macrolide agents. Respiratory medicine 100(10), 1781-90	Systematic review has been prioritised (Simpos et al 2007)
Puhan Milo A, Vollenweider Daniela, Latshang Tsogyal, Steurer Johann, and Steurer-Stey Claudia (2007) Exacerbations of chronic obstructive pulmonary disease: when are antibiotics indicated? A systematic review. Respiratory research 8, 30	Systematic review has been prioritised (Vollenweider et al 2012)
Puhan Milo A, Vollenweider Daniela, Steurer Johann, Bossuyt Patrick M, Ter Riet, and Gerben (2008) Where is the supporting evidence for treating mild to moderate chronic obstructive pulmonary disease exacerbations with antibiotics? A systematic review. BMC medicine 6, 28	Systematic review has been prioritised (Vollenweider et al 2012)
Renuka A, Vasanthi C, and Chellathai D (2017) A randomised open label parallel group study on evaluation of efficacy and safety of Gemifloxacin versus Cefpodoxime in Chronic Obstructive Pulmonary Disease patients. International Journal of Pharma and Bio Sciences 8(2), P324-P331	Low relevance to current UK practice (gemifloxacin)
Rhee Chin Kook, Chang Jung Hyun, Choi Eu Gene, Kim Hyun Kuk, Kwon Yong-Soo, Kyung Sun Young, Lee Ji-Hyun, Park Myung Jae, Yoo Kwang Ha, and Oh Yeon Mok (2015) Zabofloxacin versus moxifloxacin in patients with COPD exacerbation: a multicenter, double-blind, double-dummy, randomized, controlled, Phase III, non-inferiority trial. International journal of chronic obstructive pulmonary disease 10, 2265-75	Low relevance to current UK practice (zabofloxacin)
Roede B M, Bresser P, El Moussaoui , R , Krouwels F H, van den Berg , B T J, Hooghiemstra P M, de Borgie , C A J. M, Speelman P, Bossuyt P M. M, and Prins J M (2007) Three vs. 10 days of amoxycillin-clavulanic acid for type 1 acute exacerbations of chronic obstructive pulmonary disease: a randomised, double-blind study. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases 13(3), 284-90	Systematic review has been prioritised (Stolbrink et al 2017)

Study reference	Reason
Ruiz-Gonzalez Agustin, Gimenez Antonio, Gomez-Arbones Xavier, Soler-Gonzalez Jorge, Sanchez Virginia, Falguera Miquel, and Porcel Jose M (2007) Open-label, randomized comparison trial of long-term outcomes of levofloxacin versus standard antibiotic therapy in acute exacerbations of chronic obstructive pulmonary disease. Respirology (Carlton, and Vic.) 12(1), 117-21	Systematic review has been prioritised (Dimopolous 2007 and Siempos 2007)
Soltaninejad Forogh, Kheiri Soleiman, Habibian Roya, Amra Arshia, and Asgari-Savadjani Shahin (2016) Evaluation effects of nebulized gentamicin in exacerbation of chronic obstructive lung disease. Journal of research in medical sciences : the official journal of Isfahan University of Medical Sciences 21, 56	Low relevance to current UK practice (gentamicin)
van Velzen , Patricia , Ter Riet, Gerben , Bresser Paul, Baars Jeroen J, van den Berg , Bob T J, van den Berg , Jan W K, Brinkman Paul, Dagelet Jennece W. F, Daniels Johannes M. A, Groeneveld-Tjiong Dewi R. G. L, Jonkers Rene E, van Kan , Coen , Krouwels Frans H, Pool Karin, Rudolphus Arjan, Sterk Peter J, and Prins Jan M (2017) Doxycycline for outpatient-treated acute exacerbations of COPD: a randomised double-blind placebo-controlled trial. The Lancet. Respiratory medicine 5(6), 492-499	This study does not add additional information (on population, comparison or outcome) to the evidence which is included in a systematic review that has been prioritised (Vollenweider et al 2012)
Wang Jin, Xiao Yonghong, Huang Wenxiang, Xu Nan, Bai Chunxue, Xiu Qingyu, Mei Changlin, and Zheng Qingshan (2010) A phase II study of antofloxacin hydrochloride, a novel fluoroquinolone, for the treatment of acute bacterial infections. Chemotherapy 56(5), 378-85	Low relevance to current UK practice (antofloxacin hydrochloride)
Wang Jin-Xiang, Zhang Shu-Ming, Li Xiao-Hui, Zhang Yao, Xu Zhen-Yang, and Cao Bin (2016) Acute exacerbations of chronic obstructive pulmonary disease with low serum procalcitonin values do not benefit from antibiotic treatment: a prospective randomized controlled trial. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases 48, 40-5	Systematic review has been prioritised (Vollenweider et al 2012)
Wilson R, Jones P, Schaberg T, Arvis P, Duprat-Lomon I, Sagnier P P, and Group Mosaic Study (2006) Antibiotic treatment and factors influencing short and long term outcomes of acute exacerbations of chronic bronchitis. Thorax 61(4), 337-42	Systematic review has been prioritised (Dimopolous et al 2007)
Wilson Robert, Anzueto Antonio, Miravitlles Marc, Arvis Pierre, Alder Jeff, Haverstock Daniel, Trajanovic Mila, and Sethi Sanjay (2012) Moxifloxacin versus amoxicillin/clavulanic acid in outpatient acute exacerbations of COPD: MAESTRAL results. The European respiratory journal 40(1), 17-27	Systematic review has been prioritised (Siempos et al 2007)
Zervos Marcus, Martinez Fernando J, Amsden Guy W, Rothermel Constance D, and Treadway Glenda (2007) Efficacy and safety of 3-day azithromycin versus 5-day moxifloxacin for the treatment of acute bacterial exacerbations of chronic bronchitis. International journal of antimicrobial agents 29(1), 56-61	Systematic review has been prioritised (Siempos 2007)
Zhang Lei, Wang Rui, Falagas Matthew E, Chen Liang-an, and Liu You-ning (2012) Gemifloxacin for the treatment of community-acquired pneumonia and acute exacerbation of chronic bronchitis: a meta-analysis of randomized controlled trials. Chinese medical journal 125(4), 687-95	Low relevance to current UK practice (gemifloxacin)

Study reference	Reason
Zhang Hai-Lin, Tan Min, Qiu Ai-Min, Tao Zhang, and Wang Chang-Hui (2017) Antibiotics for treatment of acute exacerbation of chronic obstructive pulmonary disease: a network meta-analysis. BMC pulmonary medicine 17(1), 196	Lower quality systematic review (early studies were not included and interventions included antibiotic prophylaxis)

Appendix J: Excluded studies

Study reference	Reason for exclusion
Andrijevi I, Povazan D, Andrijevi L, Povazan A, and Milutinov S (2011) Treatment effects of co-amoxiclav (Amoxiclav 2x) in acute exacerbation of severe chronic obstructive pulmonary disease: clinical evaluation. Medicinski pregled 64(3-4), 178-182	Non-English language
Anzueto Antonio, Bishai William R, and Pottumarthy Sudha (2007) Role of oral extended-spectrum cephems in the treatment of acute exacerbation of chronic bronchitis. Diagnostic microbiology and infectious disease 57(3 Suppl), 31S-38S	Not a systematic view
Anzueto Antonio, and Miravitlles Marc (2010) Short-course fluoroquinolone therapy in exacerbations of chronic bronchitis and COPD. Respiratory medicine 104(10), 1396-403	Not a systematic view
Astaf'ev Av, Styrt Ea, and Sinopal'nikov Ai (2013) Infectious exacerbation of chronic obstructive pulmonary disease: prospects for high-dose levofloxacin therapy. Klinicheskaia meditsina 91(3), 44-50	Non-English language
Balser Emily, Neher Jon O, Safranek Sarah, and Taraday Julie (2006) Clinical inquiries: When are antibiotics indicated for acute COPD exacerbations?.The Journal of family practice 55(12), 1079-80	Not a systematic view
Balter M, and Weiss K (2006) Treating acute exacerbations of chronic bronchitis and community-acquired pneumonia: how effective are respiratory fluoroquinolones? Canadian family physician Medecin de famille canadien 52(10), 1236-42	Study population included people with acute exacerbations of chronic bronchitis and community-acquired pneumonia
Barclay Laurie (2007) Second-line antibiotics more effective than first line in acute exacerbation of chronic bronchitis. Journal of the National Medical Association 99(12), 1421-1422	Not a systematic view
Barry H C (2013) Amoxicillin/clavulanate during COPD exacerbations decreases symptoms and delays subsequent exacerbations. American Family Physician 87(7), 512	Abstract only
Blasi Francesco, Ewig Santiago, Torres Antoni, and Huchon Gerard (2006) A review of guidelines for antibacterial use in acute exacerbations of chronic bronchitis. Pulmonary pharmacology & therapeutics 19(5), 361-9	Not a systematic view
Blasi F, Aliberti S, and Tarsia P (2007) Clinical applications of azithromycin microspheres in respiratory tract infections. International Journal of Nanomedicine 2(4), 551-559	Not a clinical trial
Butorac-Petanjek B, Parnham M J, and Popovic-Grle S (2010) Antibiotic therapy for exacerbations of chronic obstructive pulmonary disease (COPD). Journal of chemotherapy (Florence, and Italy) 22(5), 291-7	Not a systematic view
Cazzola M, Rogliani P, Puxeddu E, Ora J, and Matera M G (2018) An overview of the current management of chronic obstructive pulmonary disease: can we go beyond the GOLD recommendations?. Expert Review of Respiratory Medicine 12(1), 43-54	Not a systematic view
Cazzola Mario, Salvatori Enrica, Dionisio Paolo, and Allegra Luigi (2006) Prulifloxacin: a new fluoroquinolone for the treatment of acute exacerbation of chronic bronchitis. Pulmonary pharmacology & therapeutics 19 Suppl 1, 30-7	Not a systematic view

Study reference	Reason for exclusion
de la Poza Abad, Mariam , Mas Dalmau, Gemma , Moreno Bakedano, Mikel , Gonzalez Gonzalez, Ana Isabel, Canellas Criado, Yolanda , Hernandez Anadon, Silvia , Rotaeche del Campo, Rafael , Toran Monserrat, Pere , Negrete Palma, Antonio , Pera Guillem, Borrell Thio, Eulalia , Llor Carl, Little Paul, Alonso Coello, Pablo , Delayed Antibiotic Prescription Working, and Group (2013) Rationale, design and organization of the delayed antibiotic prescription (DAP) trial: a randomized controlled trial of the efficacy and safety of delayed antibiotic prescribing strategies in the non-complicated acute respiratory tract infections in general practice. BMC family practice 14, 63	This is a study protocol
De Soyza , Anthony , and Calverley Peter M. A (2015) Large trials, new knowledge: the changing face of COPD management. The European respiratory journal 45(6), 1692-703	Inappropriate or unclear methodology (intervention)
Fally M, Corti C, Fabricius-Bjerre A, Mortensen K, Jensen Bn, and Andreassen H (2015) Point-of-care procalcitonin test to reduce antibiotics in COPD exacerbation: a quasi-randomised control trial. European respiratory journal 46,	Not a clinical trial
Feng Y, Jin F, Mu S, Shen H, Yang X, Wang Y, Wang Z, Kong Y, Xiao Z, and Feng Q (2010) Greatest International ANtiinfective Trial (GIANT) with moxifloxacin in the treatment of acute exacerbation of chronic bronchitis: Subanalysis of Chinese data of a global, multicenter, noninterventional study. Clinical Epidemiology 2(1), 15-21	Not a clinical trial
Gasparic M, Penezic A, Kolumbic-Lakos A, Kovacic D, Kukuruzovic M M, and Barsic B (2015) Safety and effectiveness of azithromycin in the treatment of lower respiratory infections: An international, multicenter, non-comparative study. Acta Clinica Croatica 54(2), 149-158	Not a clinical trial
Giusti M, Valerio A, Sgambato F, Politi C, Casali A, and Pinna G (2013) Fluoroquinolones in the treatment of resistant exacerbations of COPD: preliminary results from the FADOI-FLOR study. Italian journal of medicine. 7, 60	Abstract only
Hammerschlag Margaret R, and Sharma Roopali (2008) Use of cethromycin, a new ketolide, for treatment of community-acquired respiratory infections. Expert opinion on investigational drugs 17(3), 387-400	Not a systematic view
Huang B L, Hu S L, Shen G, Wu L, Xu T J, Chen Y, and Xu W P (2011) Clarithromycin extended-release and immediate-release formulations in the treatment of patients with acute exacerbation of chronic bronchitis: A systematic review. Chinese Journal of Evidence-Based Medicine 11(6), 693-697	Non-English language
Jones P, Evers T, Haverstock D, and Sethi S (2008) Pulsed moxifloxacin therapy and health status in patients with acute exacerbations of chronic obstructive pulmonary disease (the PULSE study). European respiratory society annual congress, berlin, germany, and october 4-8 , [267]	Abstract only
Kadota J, Tokimatsu I, Hiramatsu K, Morimoto T, Imai H, Suzaki Y, Okumura K, and Stass H (2012) A randomized controlled study to investigate the safety and pharmacokinetics of multiple doses of ciprofloxacin dry powder for inhalation in Japanese patients with moderate to severe COPD. American journal of respiratory and critical care medicine 185,	Abstract only
Khanchandani R, Punera Dc, Srivastava B, and Gaur S (2015)	Not a clinical trial

Study reference	Reason for exclusion
Efficacy and safety of garenoxacin versus moxifloxacin in acute exacerbation of copd: a comparative study. Indian journal of physiology and pharmacology. 59(5 suppl. 1), 128	
Khashab Mohammed M, Xiang Jim, and Kahn James B (2006) 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 22(10), 1997-2006	Included studies were not RCT
Kim Hk, Lee Yc, Oh Y-M, Rhee Ck, Kyung Sy, and Chang Jh (2015) Zabofloxacin 367mg for five days versus moxifloxacin 400mg for seven days in patients with COPD exacerbation: a multicenter, randomized, double-blind, phase 3, non-inferiority trial. American journal of respiratory and critical care medicine 191(Meeting Abstracts), A2817	Abstract only
Kiser T, Moss M, Burnham E, Ho M, and Vandivier R (2016) Influence of macrolide antibiotics on outcomes in ICU patients with acute exacerbations of COPD. Critical care medicine. Conference: 46th critical care congress of the society of critical care medicine, and SCCM 2016. United states. Conference start: 20170121. Conference end: 20170125 44(12 Supplement 1), 100	Abstract only
Lin Q, Liu K, Liu S, Lin T, Lai G, and Hong X (2015) The efficacy and safety of moxifloxacin in the treatment of patients with acute exacerbation of chronic obstructive pulmonary disease. Zhonghua jie he he hu xi za zhi [Chinese journal of tuberculosis and respiratory diseases] 38(5), 366-369	Non-English language
Llor C, Moragas A, Hernandez S, Bayona C, and Miravitlles M (2013) Amoxicillin/clavulanate vs placebo: More exacerbation cures, fewer recurrences in mild-to-moderate COPD. Annals of Internal Medicine 158(6), JC3	Not a clinical trial
Mathew Sagi, Zeitlin Deborah, and Rickett Katherine (2012) Clinical inquiries. Do antibiotics improve outcomes for patients hospitalized with COPD exacerbations?. The Journal of family practice 61(9), 561-573	Not a systematic view
Miravitlles Marc (2007) Moxifloxacin in the management of exacerbations of chronic bronchitis and COPD. International journal of chronic obstructive pulmonary disease 2(3), 191-204	Not a systematic view
Miravitlles M, Monso E, Vila S, Roza C, Marin A, Hervas R, Esquinas C, Garcia M, Morera J, and Torres A (2007) Efficacy of moxifloxacin for treatment of bronchial colonisation in COPD patients: a randomized, double blind, placebo controlled study. European respiratory journal 30(Suppl 51), 525s [3162]	Abstract only
Miravitlles M, Marin A, Monso E, Vila S, de la Roza , C , Hervas R, Esquinas C, Garcia M, Millares L, Morera J, and Torres A (2009) Efficacy of moxifloxacin in the treatment of bronchial colonisation in COPD. The European respiratory journal 34(5), 1066-71	Inappropriate or unclear methodology (study population, not population with an acute exacerbation)
Moore M, Stuart B, Coenen S, Butler C C, Goossens H, Verheij T J. M, and Little P (2014) Amoxicillin for acute lower respiratory tract infection in primary care: Subgroup analysis of potential high-risk groups. British Journal of General Practice 64(619), e75-e80	Inappropriate or unclear methodology (study population)
Morice A, Moretti M, and Ballabio M (2007) Erdosteine in association with amoxicillin improves the outcome of acute	Abstract only

Study reference	Reason for exclusion
exacerbations compared to amoxicillin alone in COPD patients. Thorax 62(Suppl iii), A47	
Nissly T, and Prasad S (2014) Should you consider antibiotics for exacerbations of mild COPD?. Journal of Family Practice 63(4), E11-E13	Not a clinical trial
Pasqua Franco, Biscione Gianluca, Crigna Girolmina, and Cazzola Mario (2008) Prulifloxacin in the treatment of acute exacerbations of COPD in cigarette smokers. Therapeutic advances in respiratory disease 2(4), 209-14	Not a clinical trial
Patel Amit, and Wilson Robert (2006) Newer fluoroquinolones in the treatment of acute exacerbations of COPD. International journal of chronic obstructive pulmonary disease 1(3), 243-50	Not a systematic view
Puhan M A, Vollenweider D, Latshang T, Steurer J, and Steurer-Stey C (2008) Correction: Exacerbations of chronic obstructive pulmonary disease: When are antibiotics indicated? A systematic review [Respiratory Research, 8, (2007) (30)] doi: 10.1186/1465-9921-8-30. Respiratory Research 9(1), 81	Not a primary study
Quon Bradley S, Gan Wen Qi, and Sin Don D (2008) Contemporary management of acute exacerbations of COPD: a systematic review and metaanalysis. Chest 133(3), 756-66	Inappropriate or unclear methodology (interventions included steroid and antibiotics)
Rafailidis P I, Pitsounis A I, and Falagas M E (2009) Meta-analyses on the Optimization of the Duration of Antimicrobial Treatment for Various Infections. Infectious Disease Clinics of North America 23(2), 269-276	Not a systematic view
Rhee C K, Chang J H, Choi E G, Kim H K, Kwon Y S, Kyung S Y, Lee J H, Park M J, Yoo K H, and Oh Y M (2015) Zabofloxacin versus moxifloxacin in patients with COPD exacerbation: A multicenter, double-blind, double-dummy, randomized, controlled, phase III, non-inferiority trial. International Journal of COPD 10(1), 2265-2275	Not a systematic view
Rohde Gernot G. U, Koch Armin, Welte Tobias, and group Abacopd study (2015) Randomized double blind placebo-controlled study to demonstrate that antibiotics are not needed in moderate acute exacerbations of COPD--the ABACOPD study. BMC pulmonary medicine 15, 5	This is a study protocol
Romanovskikh A, Sinopalinkov A, and Ratchina S (2007) Open label randomized, comparative trial of the efficacy of levofloxacin versus clarithromycin SR therapy in complicated infectious exacerbation of COPD. European respiratory journal 30(Suppl 51), 674s [E3919]	Abstract only
Rothberg Michael B, Pekow Penelope S, Lahti Maureen, Brody Oren, Skiest Daniel J, and Lindenauer Peter K (2010) Comparative effectiveness of macrolides and quinolones for patients hospitalized with acute exacerbations of chronic obstructive pulmonary disease (AECOPD). Journal of hospital medicine 5(5), 261-7	Not a systematic view
Segal (2016) Randomised, double-blind, placebo-controlled trial with azithromycin selects for anti-inflammatory microbial metabolites in the emphysematous lung. Thorax	Inappropriate or unclear methodology (study population)
Sethi Sanjay, Jones Paul W, Theron Marlize Schmitt, Miravitlles Marc, Rubinstein Ethan, Wedzicha Jadwiga A, Wilson Robert, and group Pulse Study (2010) Pulsed moxifloxacin for the prevention	Inappropriate or unclear methodology (intervention)

Study reference	Reason for exclusion
of exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial. Respiratory research 11, 10	
Shafuddin Eskandarain, Mills Graham D, Holmes Mark D, Poole Phillippa J, Mullins Peter R, and Black Peter N (2015) A double-blind, randomised, placebo-controlled study of roxithromycin and doxycycline combination, roxithromycin alone, or matching placebo for 12 weeks in adults with frequent exacerbations of chronic obstructive pulmonary disease. Journal of negative results in biomedicine 14, 15	Inappropriate or unclear methodology (intervention)
Sharma A, Bagchi A, Gupta H, Kinagi Sb, Sharma Yb, and Baliga Vp (2007) Comparative evaluation of the efficacy, safety and tolerability of the fixed dose combinations of cefixime plus erdosteine and amoxicillin plus bromhexine in patients with acute exacerbations of chronic bronchitis. Chest 132(4), 529	Abstract only
Siempos Ilias I, Michalopoulos Argyris, and Falagas Matthew E (2009) Treatment of acute bacterial exacerbations of chronic bronchitis. Expert opinion on pharmacotherapy 10(7), 1173-82	Not a systematic view
Stass H, Badorrek P, Hohlfeld J, Krug N, Nagelschmitz J, and Welte T (2011) Safety and pharmacokinetics of multiple-dose ciprofloxacin dry powder for inhalation in patients with moderate or severe COPD. European respiratory journal 38(no pagination),	Abstract only
Stass H, Nagelschmitz J, Watz H, and Kirsten Am (2012) Safety and pharmacokinetics of two dose strengths of ciprofloxacin dry powder for inhalation (DPI) in patients with moderate to severe COPD. European respiratory journal 40,	Abstract only
Stass H, Nagelschmitz J, Weimann B, and Timmer W (2011) Safety, tolerability and pharmacokinetics of ciprofloxacin dry powder for inhalation in patients with mild to moderate chronic obstructive pulmonary disease: a randomized controlled trial. American journal of respiratory and critical care medicine 183(1 MeetingAbstracts),	Abstract only
Stolz Daiana, Christ-Crain Mirjam, Bingisser Roland, Leuppi Jorg, Miedinger David, Muller Christian, Huber Peter, Muller Beat, and Tamm Michael (2007) Antibiotic treatment of exacerbations of COPD: a randomized, controlled trial comparing procalcitonin-guidance with standard therapy. Chest 131(1), 9-19	Inappropriate or unclear methodology (intervention)
Stolz Daiana, and Tamm Michael (2009) Discriminate use of antibiotics for exacerbation of COPD. Current opinion in pulmonary medicine 15(2), 126-32	Not a systematic view
Tokimatsu I, Hiramatsu K, Morimoto T, Imai H, Suzaki Y, Stass H, Okumura K, and Kadota J (2011) Safety, tolerability and pharmacokinetics of a single dose of ciprofloxacin dry powder for inhalation in japanese patients with mild to moderate chronic obstructive pulmonary disease: a randomized controlled trial. American journal of respiratory and critical care medicine 183(1 MeetingAbstracts),	Abstract only
van Zanten , A R H, Oudijk M, Nohlmans-Paulssen M K. E, van der Meer , Y G, Girbes A R. J, and Polderman K H (2007) Continuous vs. intermittent cefotaxime administration in patients with chronic obstructive pulmonary disease and respiratory tract infections: pharmacokinetics/pharmacodynamics, bacterial	Inappropriate or unclear methodology (intervention, route of administration)

Study reference	Reason for exclusion
susceptibility and clinical efficacy. British journal of clinical pharmacology 63(1), 100-9	
Verduri Alessia, Luppi Fabrizio, D'Amico Roberto, Balduzzi Sara, Vicini Roberto, Liverani Anna, Ruggieri Valentina, Plebani Mario, Barbaro Maria Pia Foschino, Spanevello Antonio, Canonica Giorgio Walter, Papi Alberto, Fabbri Leonardo Michele, Beghe Bianca, and Group Farm J. Xh Study (2015) Antibiotic treatment of severe exacerbations of chronic obstructive pulmonary disease with procalcitonin: a randomized noninferiority trial. PloS one 10(3), e0118241	Inappropriate or unclear methodology (intervention)
Vermeersch Kristina, Gabrovska Maria, Deslypere Griet, Demedts Ingel K, Slabbynck Hans, Aumann Joseph, Ninane Vincent, Verleden Geert M, Troosters Thierry, Bogaerts Kris, Brusselle Guy G, and Janssens Wim (2016) The Belgian trial with azithromycin for acute COPD exacerbations requiring hospitalization: an investigator-initiated study protocol for a multicenter, randomized, double-blind, placebo-controlled trial. International journal of chronic obstructive pulmonary disease 11, 687-96	This is a study protocol
Vermeersch K, Everaerts S, Ninane V, Gabrovska M, Aumann J, Deslypere G, Demedts Ik, Corhay J-L, Marchand E, Slabbynck H, Haerens M, Haenebalcke C, Vincken W, Hanon S, Peche R, Fremault A, Lauwerier T, Brusselle Gg, and Janssens W (2016) Time-to-treatment failure in the Belgian randomized controlled trial with azithromycin for acute COPD exacerbations requiring hospitalization. European respiratory journal. Conference: european respiratory society annual congress 2016. United kingdom 48.	Abstract only
Vinnamala S (2007) Continuous administration of cefotaxime at exacerbation of COPD. Thorax 62(5), 461	Not a clinical trial
Vollenweider D J, Jarrett H, Steurer-Stey C A, Garcia-Aymerich J, and Puhan M A (2013) Review: Antibiotics reduce treatment failure in acute chronic obstructive pulmonary disease exacerbations. Annals of Internal Medicine 158(8), JC5	Not a systematic review
Wang Xh, and Liu Xj (2012) Moxifloxacin versus levofloxacin for acute exacerbation of chronic obstructive pulmonary diseases: a systematic review (Provisional abstract). Chinese Journal of Evidence-Based Medicine 12(6), 694-699	Non-English language
Wedzicha Jadwiga A. Ers Co-Chair, Miravitlles Marc, Hurst John R, Calverley Peter M. A, Albert Richard K, Anzueto Antonio, Criner Gerard J, Papi Alberto, Rabe Klaus F, Rigau David, Sliwinski Pawel, Tonia Thomy, Vestbo Jorgen, Wilson Kevin C, and Krishnan Jerry A. Ats Co-Chair (2017) Management of COPD exacerbations: a European Respiratory Society/American Thoracic Society guideline. The European respiratory journal 49(3),	Not a systematic review
Wilson R, Anzueto A, Miravitlles M, Arvis P, Haverstock D, Trajanovic M, Chen R, and Sethi S (2011) Moxifloxacin (MXF) vs. Amoxicillin/clavulanic acid (AMC) in acute exacerbations of COPD (AECOPD): results of a large clinical trial with a novel endpoint. Respirology. 16(Suppl 2), 109	Abstract only
Wong C, and Herath S (2014) Azithromycin for patients with frequent COPD exacerbations. The Lancet Respiratory Medicine 2(5), 340-341	Not a clinical trial

Study reference	Reason for exclusion
Wu R, Fengjie Z, Li Y, Yan S, Miao L, Tan W, and Jinchao Z (2013) Modified Dachengqi Decoction combined with conventional treatment for treating acute exacerbation of chronic obstructive pulmonary disease: A systematic review based on randomized controlled trials. Evidence-based Complementary and Alternative Medicine 2013, 323715	Unclear comparator
Xin X, Jian L, Xia X, Jia B, Huang W, Li C, Wang C, Zhou L, Sun X, Tang X, Huang Y, Zhu Y, and Zhang W (2013) A multicentre clinical study on the injection of ceftriaxone/sulbactam compared with cefoperazone/sulbactam in the treatment of respiratory and urinary tract infections. Annals of Clinical Microbiology and Antimicrobials 12(1), 38	Inappropriate or unclear methodology (study population)
Yao G Y, Ma Y L, Zhang M Q, and Gao Z C (2013) Macrolide therapy decreases chronic obstructive pulmonary disease exacerbation: A meta-analysis. Respiration 86(3), 254-260	Intervention is preventing exacerbation of COPD
Zervos M, Breen Jd, Jorgensen Dm, and Goodrich Jm (2006) Azithromycin microspheres (AZ-M) are as effective as levofloxacin (LEV) in subjects with moderate to very severe COPD. Proceedings of the american thoracic society , A121 [Poster J78]	Abstract only
Zhang M, Zhou X, Zhang X-Y, and Ding X (2007) Short-term and long-term outcomes of moxifloxacin treatment in acute exacerbations of COPD. Chinese journal of infection and chemotherapy 7(5), 313-317	Non-English language
Zhong Y, Mao B, Wang G, Fan T, Liu X, Diao X, and Fu J (2010) Tanreqing injection combined with conventional western medicine for acute exacerbations of chronic obstructive pulmonary disease: A systematic review. Journal of Alternative and Complementary Medicine 16(12), 1309-1319	Unclear comparator (western medicine is a combination of antibiotics, bronchodilators, oxygen administration)
Zykov K, Rvatcheva A, Pustovalov A, and Averyanov A (2008) Long term treatment with clarithromycin of stage II COPD patients with frequent exacerbations. European respiratory society annual congress, berlin, germany, and october 4-8 , [1770]	Abstract only