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Vollenweider DJ, Frei A, Steurer-Stey CA, Garcia-Aymerich J, Puhan MA

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[Intervention Review]

Antibiotics for exacerbations of chronic obstructive pulmonary disease

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ABSTRACT

Background

Many patients with an exacerbation of chronic obstructive pulmonary disease (COPD) are treated with antibiotics. However, the value of antibiotics remains uncertain, as systematic reviews and clinical trials have shown conflicting results.

Objectives

To assess effects of antibiotics on treatment failure as observed between seven days and one month after treatment initiation (primary outcome) for management of acute COPD exacerbations, as well as their effects on other patient-important outcomes (mortality, adverse events, length of hospital stay, time to next exacerbation).

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library, MEDLINE, Embase, and other electronically available databases up to 26 September 2018.

Selection criteria

We sought to find randomised controlled trials (RCTs) including people with acute COPD exacerbations comparing antibiotic therapy and placebo and providing follow-up of at least seven days.

Data collection and analysis

Two review authors independently screened references and extracted data from trial reports. We kept the three groups of outpatients, inpatients, and patients admitted to the intensive care unit (ICU) separate for benefit outcomes and mortality because we considered them to be clinically too different to be summarised as a single group. We considered outpatients to have a mild to moderate exacerbation, inpatients to have a severe exacerbation, and ICU patients to have a very severe exacerbation. When authors of primary studies did not report outcomes or study details, we contacted them to request missing data. We calculated pooled risk ratios (RRs) for treatment failure, Peto odds ratios (ORs) for rare events (mortality and adverse events), and mean differences (MDs) for continuous outcomes using random-effects models. We used GRADE to assess the quality of the evidence. The primary outcome was treatment failure as observed between seven days and one month after treatment initiation.

Main results

We included 19 trials with 2663 participants (11 with outpatients, seven with inpatients, and one with ICU patients).

For outpatients (with mild to moderate exacerbations), evidence of low quality suggests that currently available antibiotics statistically significantly reduced the risk for treatment failure between seven days and one month after treatment initiation (RR 0.72, 95% confidence interval (CI) 0.56 to 0.94; I^2 = 31%; in absolute terms, reduction in treatment failures from 295 to 212 per 1000 treated participants, 95% CI 165 to 277). Studies providing older antibiotics not in use anymore yielded an RR of 0.69 (95% CI 0.53 to 0.90; I^2 = 31%). Evidence of low quality from one trial in outpatients suggested no effects of antibiotics on mortality (Peto OR 1.27, 95% CI 0.49 to 3.30). One trial reported no effects of antibiotics on re-exacerbations between two and six weeks after treatment initiation. Only one trial (N = 35) reported health-related quality of life but did not show a statistically significant difference between treatment and control groups.

Evidence of moderate quality does not show that currently used antibiotics statistically significantly reduced the risk of treatment failure among inpatients with severe exacerbations (i.e. for inpatients excluding ICU patients) (RR 0.65, 95% CI 0.38 to 1.12; I^2 = 50%), but trial results remain uncertain. In turn, the effect was statistically significant when trials included older antibiotics no longer in clinical use (RR 0.76, 95% CI 0.58 to 1.00; I^2 = 39%). Evidence of moderate quality from two trials including inpatients shows no beneficial effects of antibiotics on mortality (Peto OR 2.48, 95% CI 0.94 to 6.55). Length of hospital stay (in days) was similar in antibiotic and placebo groups.

The only trial with 93 patients admitted to the ICU showed a large and statistically significant effect on treatment failure (RR 0.19, 95% CI 0.08 to 0.45; moderate-quality evidence; in absolute terms, reduction in treatment failures from 565 to 107 per 1000 treated participants, 95% CI 45 to 254). Results of this trial show a statistically significant effect on mortality (Peto OR 0.21, 95% CI 0.06 to 0.72; moderate-quality evidence) and on length of hospital stay (MD -9.60 days, 95% CI -12.84 to -6.36; low-quality evidence).

Evidence of moderate quality gathered from trials conducted in all settings shows no statistically significant effect on overall incidence of adverse events (Peto OR 1.20, 95% CI 0.89 to 1.63; moderate-quality evidence) nor on diarrhoea (Peto OR 1.68, 95% CI 0.92 to 3.07; moderate-quality evidence).

Authors' conclusions

Researchers have found that antibiotics have some effect on inpatients and outpatients, but these effects are small, and they are inconsistent for some outcomes (treatment failure) and absent for other outcomes (mortality, length of hospital stay). Analyses show a strong beneficial effect of antibiotics among ICU patients. Few data are available on the effects of antibiotics on health-related quality of life or on other patient-reported symptoms, and data show no statistically significant increase in the risk of adverse events with antibiotics compared to placebo. These inconsistent effects call for research into clinical signs and biomarkers that can help identify patients who would benefit from antibiotics, while sparing antibiotics for patients who are unlikely to experience benefit and for whom downsides of antibiotics (side effects, costs, and multi-resistance) should be avoided.

PLAIN LANGUAGE SUMMARY

Are antibiotics beneficial for flare-ups of chronic obstructive pulmonary disease?

Review question

We conducted this systematic review to find out if the benefits of taking antibiotics for flare-ups of COPD outweigh potential harms (e.g. risks of multi-resistant bacteria for this population).

Background

Chronic obstructive pulmonary disease (COPD) is a chronic condition (most often caused by smoking or environmental exposure) that affects the passage of air into and out of the lungs. As a consequence, patients experience shortness of breath and coughing. Flare-ups of COPD are a hallmark of more advanced stages of the disease. Flare-ups are defined as sustained worsening of symptoms from the patient's usual stable state. Commonly reported symptoms include worsening breathlessness, cough, increased sputum production, and change in sputum colour. Clinicians frequently prescribe antibiotics for flare-ups in patients with COPD, although the cause of flare-ups is often difficult to determine (viral, bacterial, environmental).

Study characteristics

Evidence gathered for this review is current to September 2018. We found 19 randomised studies that compared antibiotics versus placebo in a total of 2663 COPD patients with a wide range of flare-up severity.

Key results

Analyses show that currently used antibiotics reduced treatment failures (no improvement in symptoms, despite treatment, within 7 to 28 days, depending on the study) compared with placebo in outpatients with mild to moderate flare-ups, as well as in patients admitted to an intensive care unit for very severe flare-ups with respiratory failure. However, antibiotics did not reduce treatment failures among hospitalised patients with severe flare-ups, although we are less certain about this result because the effect estimate also suggested findings similar to those seen in outpatients, but the confidence interval crossed 1.0. Use of antibiotics led to reduced mortality only in patients admitted to an intensive care unit, but not in patients with mild to moderate (outpatients) or severe (inpatients) flare-ups, although deaths were rare in these latter groups. Antibiotics did not reduce length of hospital stay for hospitalised patients. Patients treated

with antibiotics experienced diarrhoea more often than those given placebo, but the difference was not statistically significant. Reviewers could not compare the severity of underlying COPD across trials because trial authors inconsistently reported lung function and other parameters.

Quality of the evidence

The quality of evidence for review outcomes was low to moderate.

Conclusion

Although trial results show that antibiotics were effective across outcomes for patients with very severe flare-ups and respiratory failure who needed treatment in an intensive care unit, researchers report inconsistent effects in patients with mild to severe flare-ups. Future high-quality studies should examine clinical signs or blood tests at the time of presentation that are useful for identifying patients who can benefit from antibiotic therapy.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Antibiotics compared to placebo for exacerbations of chronic obstructive pulmonary disease: outpatients

Outpatients: antibiotics compared to placebo for exacerbations of chronic obstructive pulmonary disease

Patient or population: exacerbations of COPD
Setting: outpatients
Intervention: antibiotics
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with antibiotics				
Treatment failure within 4 weeks - current drugs only	Study population		RR 0.72 (0.56 to 0.94)	1191 (7 RCTs)	⊕⊕⊖⊖ LOW[a,b]	Antibiotics: amoxicillin-clavulanic acid, trimethoprim-sulphamethoxazole, oxytetracycline, amoxicillin-cotrimoxazole, doxycycline, ciprofloxacin, or amoxicillin
	295 per 1000	212 per 1000 (165 to 277)				
All-cause mortality	Study population		OR 1.27 (0.49 to 3.30)	301 (1 RCT)	⊕⊕⊖⊖ LOW[c,d]	Antibiotics: doxycycline
	53 per 1000	66 per 1000 (27 to 156)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; COPD: chronic obstructive pulmonary disease; OR: odds ratio; RCT: randomised controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgrading for inconsistency: I^2 of 31% is not that high, but results of trials differ and are imprecise.
[b]For one trial (Allegra), not all results are available.
[c]Only one study existing; additional trials likely to change the estimates.
[d]The 95% CIs of the RR 1.27 are very wide (95% CI 0.49 to 3.30).

Summary of findings 2. Antibiotics compared to placebo for exacerbations of chronic obstructive pulmonary disease: inpatients

Inpatients: antibiotics compared to placebo for exacerbations of chronic obstructive pulmonary disease

Patient or population: exacerbations of COPD
Setting: inpatients and ICU
Intervention: antibiotics
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with antibiotics				
Treatment failure within 4 weeks - current drugs only - inpatient	Study population 314 per 1000	204 per 1000 (119 to 352)	RR 0.65 (0.38 to 1.12)	576 (4 RCTs)	⊕⊕⊕⊖ MODERATE[a]	Antibiotics: amoxicillin-clavulanic acid, trimethoprim/sulphamethoxazole, doxycycline, tetracycline hydrochloride, chloramphenicol, penicillin, streptomycin, piperacillin-sulbactam, ceftazidime, or levofloxacin
Treatment failure within 4 weeks - drugs not currently used - ICU	Study population 565 per 1000	107 per 1000 (45 to 254)	RR 0.19 (0.08 to 0.45)	93 (1 RCT)	⊕⊕⊕⊖ MODERATE[b]	Antibiotics: ofloxacin
Duration of hospital stay (days) - inpatients	Range of duration of hospital stay (days) was from 8.1 to 12.3 days	MD 0.09 (-0.79 lower to 0.96 higher)	-	300 (3 RCTs)	⊕⊕⊕⊕ HIGH	Antibiotics: piperacillin-sulbactam, ceftazidime, levofloxacin, amoxicillin-clavulanic acid, trimethoprim/sulphamethoxazole, or cefaclor
Duration of hospital stay (days) - ICU patients	Mean duration of hospital stay (days) was 24.5 days	MD -9.60 (-12.84 lower to -6.36 lower)	-	94 (1 RCT)	⊕⊕⊕⊖ MODERATE[b]	Antibiotics: ofloxacin
All-cause mortality - inpatients	Study population 31 per 1000	41 per 1000 (18 to 90)	OR 2.48 (0.94 to 6.55)	214 (2 RCTs)	⊕⊕⊖⊖ MODERATE[c]	Antibiotics: tetracycline hydrochloride, chloramphenicol, penicillin, streptomycin, chloramphenicol, doxycycline, piperacillin-sulbactam, ceftazidime, or levofloxacin

All-cause mortality - ICU patients	Study population		OR 0.21 (0.06 to 0.72)	93 (1 RCT)	⊕⊕⊕⊖ MODERATE[b]	Antibiotics: ofloxacin
	217 per 1000	45 per 1000 (13 to 152)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; ICU: intensive care unit; COPD: chronic obstructive pulmonary disease; MD: mean difference; OR: odds ratio; RCT: randomised controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgrading for imprecision: the upper limit of the 95% CI overlaps 1.0.
[b]Only one study existing; the effect estimate may be substantially different with additional trials.
[c]Downgrading for imprecision: wide 95% CI of the pooled estimate that precludes any conclusion about the effects of antibiotics on mortality in inpatients.

Summary of findings 3. Antibiotics compared to placebo overall for exacerbations of chronic obstructive pulmonary disease; adverse events

Antibiotics compared to placebo overall for exacerbations of chronic obstructive pulmonary disease

Patient or population: exacerbations of COPD
Setting: outpatients and inpatients
Intervention: antibiotics
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with antibiotics				
Adverse events - diarrhoea	Study population		OR 1.68 (0.92 to 3.07)	1099 (5 RCTs)	⊕⊕⊕⊖ MODERATE[a]	Antibiotics: amoxicillin-clavulanic acid, amoxicillin, ofloxacin, piperacillin-sulbactam, ceftazidime, or levofloxacin-doxycycline
	31 per 1000	52 per 1000 (29 to 90)				
Adverse events - overall (any ad-	Study population		OR 1.20 (0.89 to 1.63)	1544 (6 RCTs)	⊕⊕⊕⊖ MODERATE[a]	Antibiotics: amoxicillin-clavulanic acid, doxycycline, amoxicillin, or ofloxacin

verse events not specified)	129 per 1000	151 per 1000 (116 to 194)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; COPD: chronic obstructive pulmonary disease; OR: odds ratio; RCT: randomised controlled trial; RR: risk ratio.

GRADE Working Group grades of evidence.
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgrading for imprecision: the lower limit of the 95% CI overlaps 1.0.

BACKGROUND

Prescribing antibiotics for treatment of patients with chronic obstructive pulmonary disease (COPD) during acute exacerbations (AECOPDs) has been, and continues to be, controversial (Labaki 2017). This controversy is based largely on data suggesting that only about half of exacerbations are bacterial in origin, and other causes include viral infections and environmental irritants (Patel 2002; Seemungal 2001; Sethi 2004). Bafadhel 2011 suggested that most exacerbations can be categorised as bacteria-predominant, eosinophil-predominant, virus-predominant, or pauci-inflammatory, and thus may be susceptible to antibiotics or corticosteroids or, in the future, to newly developed antiviral drugs.

Antibiotics are widely prescribed (Jones 2008; Pretto 2012). Reasons for using antibiotics include the belief that an AECOPD most likely results from a bacterial infection and that antibiotics should be given to 'be on the safe side' - reflecting the perception that antibiotics can prevent complications of an exacerbation such as pneumonia. Most side effects of antibiotics are relatively minor, thus the potential benefits of antibiotics often appear to outweigh potential harms. The most important arguments against inappropriate use and overuse of antibiotics are the worldwide growing problem of multi-resistance (WHO Factsheet no. 194), polypharmacy, and costs. Current guidelines do not recommend use of antibiotics in general but do recommend antibiotic therapy for moderately or severely ill patients with AECOPDs who have three cardinal symptoms (increase in dyspnoea, sputum volume, and sputum purulence), or who have two of the cardinal symptoms including purulence of sputum, or who require mechanical ventilation (invasive or non-invasive) (GOLD 2018; NICE 2010). The National Institute for Health and Care Excellence (NICE) recommends antibiotic treatment for AECOPDs associated with a history of purulent sputum (NICE 2018). However, no high-quality evidence currently supports these recommendations for symptom- or risk-stratified treatment with antibiotics. In addition, healthcare providers may not always see the sputum, and descriptions provided by the patient may be unreliable.

Description of the condition

Acute exacerbations of COPD are an important cause of morbidity, mortality, hospital admission, impaired health status, reduced physical activity, and increased costs. AECOPD is defined as an acute worsening of respiratory symptoms that results in additional therapy. Definitions of AECOPD may be symptom-based or event-based. Criteria from Anthonisen 1987 are most commonly used to define the severity of an exacerbation based on symptoms (dyspnoea, cough, and (purulent) sputum production). The event-based definition refers to the setting and intensity of treatment as prescribed by the treating physician. Mild AECOPDs are those treated at home by the patient, most often using short-acting bronchodilators. Moderate AECOPDs are those treated on an outpatient basis with oral corticosteroids and/or antibiotics. An AECOPD is severe if the patient requires inpatient treatment with antibiotics and/or oral corticosteroids and/or additional treatments (e.g. breathing support), and very severe if treatment in an intensive care unit (ICU) is required because of acute respiratory failure.

Description of the intervention

Antibiotics are antimicrobial drugs that inhibit the growth of bacteria or kill them, or both. A wide range of antibiotics are available for use against different types and subtypes of bacteria. For treatment of AECOPDs, broad-spectrum antibiotics such as amoxicillin with clavulanic acid or a macrolide are commonly used as first-line treatment, whereas more selective antibiotics are used in cases of treatment failure of broad-spectrum antibiotics, or when cultures guide the use of specific antibiotics (GOLD 2018; NICE 2018).

How the intervention might work

Around half of acute exacerbations of COPD are supposed to be triggered by bacterial infection caused by pathogens that commonly colonise the respiratory tract, such as *Haemophilus influenzae*, *Streptococcus pneumoniae,* and *Moraxella catarrhalis.* The goal of antibiotic treatment is to stop bacterial infection as the likely cause of an AECOPD.

Why it is important to do this review

We conducted this systematic review of the literature to inform patients, healthcare providers, and clinical practice guideline developers in a transparent way (to minimise bias) about the effects of antibiotics on patient-important outcomes. This endeavour is important because antibiotics are likely to be perceived as beneficial in clinical practice by patients and healthcare providers based on the fact that most patients recover within weeks of starting treatment. However, only placebo-controlled trials can determine the cause of such recovery, which might be attributed to natural recovery from exacerbations (i.e. without antibiotics), effects of antibiotics, or effects of other concomitant treatments such as systemic corticosteroids. Knowledge about the effects of antibiotics compared to placebo is important if one is to appreciate the results of the many randomised trials that have compared different antibiotics. Only if antibiotics are effective at all will such head-to-head trials provide useful information (Puhan 2008).

There is growing recognition that COPD is a very heterogeneous disease (Garcia-Aymerich 2011), and that exacerbations are heterogeneous events (Bafadhel 2011). Systematic reviews have been used to guide the development of strong recommendations for clinical practice, and review findings have helped researchers identify areas in which additional research is needed. In the light of uncertainties surrounding the use of antibiotics for COPD exacerbations, it is hoped that the findings presented here will prove useful.

This review is based in part on the protocol of a withdrawn Cochrane Review on the same topic (Ram 2006), and it reflects Cochrane standard methods.

OBJECTIVES

To assess effects of antibiotics on treatment failure as observed between seven days and one month after treatment initiation (primary outcome) for management of acute COPD exacerbations, as well as their effects on other patient-important outcomes (mortality, adverse events, length of hospital stay, time to next exacerbation).

METHODS

Criteria for considering studies for this review

Types of studies

We sought to include randomised controlled trials (RCTs) comparing an antibiotic in the treatment group versus placebo in the control group. We included studies reported as full text, those published as abstract only, and unpublished data.

Types of participants

We planned to include patients with acute exacerbations of COPD (defined as worsening of a previously stable situation with symptoms such as increased dyspnoea, increased cough, increased sputum volume, or change in sputum colour).

We considered studies eligible if more than 90% of participants had received a clinical (physician-based) diagnosis of COPD or, ideally, spirometrically confirmed COPD, and if participants were over 40 years of age. For trials with physician-based diagnosis of COPD (also chronic bronchitis in older studies), we considered for inclusion only those in which more than 90% of participants had a smoking history. We accepted physician-based diagnosis of COPD because spirometry has limited value during an acute exacerbation of COPD, and because restricting the systematic review to patients with spirometrically confirmed COPD would limit inclusion to trials in which detailed medical records, including previous spirometry, were available at the time of enrolment, or in which patients at risk for exacerbation were enrolled in a stable state and were randomised when they developed an exacerbation. We excluded studies of patients with acute bronchitis, pneumonia, asthma, or bronchiectasis.

Types of interventions

We included studies in which researchers administered oral or intravenous antibiotics daily for a minimum of two days. We excluded all studies that used antibiotics for prevention of exacerbations, as this research was conducted to address a different question. Whether oral corticosteroids were used additionally was not an inclusion or exclusion criterion.

Types of outcome measures

Primary outcomes

- Treatment failure as observed between seven days and one month after treatment initiation (no resolution or deterioration of symptoms after trial medication of any duration, or death, when explicitly stated, due to exacerbation or additional course of antibiotics or another medication)

Secondary outcomes

- Treatment failure as observed between seven and 14 days after treatment initiation
- All-cause mortality
- Duration of hospital admission (for inpatients)
- Admission to an ICU
- Re-exacerbations within ≥ two to six weeks from the beginning of the index exacerbation (inpatient or outpatient treatment, rates, or time to event)
- Adverse events
- Dyspnoea
- Hospital admission
- Health-related quality of life or functional status measures
- Time off work
- Time to next exacerbation

Search methods for identification of studies

Electronic searches

We have detailed in Appendix 1 search methods used in the previous version of this review. The previously published version included searches up to September 2012. For this update, we searched the Cochrane Airways Trials Register from September 2012 to 26 September 2018. The Cochrane Airways Trials Register is maintained by the Information Specialist for the Group and contains studies identified from several sources.

- Monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), in the Cochrane Library, via the Cochrane Register of Studies (CRS).
- Weekly searches of MEDLINE Ovid SP.
- Weekly searches of Embase Ovid SP 1974.
- Monthly searches of PsycINFO Ovid SP 1967.
- Monthly searches of the Cumulative Index to Nursing and Allied Health Literature (CINAHL) EBSCO.
- Monthly searches of Allied and Complementary Medicine (AMED) EBSCO.
- Handsearches of the proceedings of major respiratory conferences.

Studies contained in the Trials Register are identified through search strategies based on the scope of Cochrane Airways. We have provided in Appendix 2 details of these strategies, as well as a list of handsearched conference proceedings. See Appendix 3 for search terms used to identify studies for this review.

We searched the following trials registries on 26 September 2018.

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov).
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch).

We applied no restrictions to searches based on date, type, or language of publication.

Searching other resources

We scrutinised bibliographies of all selected RCTs and other systematic reviews for additional potential RCTs. We contacted the authors of identified RCTs and pharmaceutical companies producing antibiotics to ask about other published, unpublished, or ongoing studies.

Data collection and analysis

Selection of studies

Two review authors (DV, RN) independently assessed the titles and abstracts of all identified citations without imposing language restrictions and coded them as "retrieve" (eligible or potentially eligible/unclear) or "do not retrieve". Two review authors (DV, AF) then independently evaluated the full text of articles that

one review author deemed potentially eligible. We resolved disagreements by consensus with close attention to the inclusion/exclusion criteria. We excluded studies that did not fulfil all inclusion criteria and listed their bibliographic details, along with reasons for exclusion.

Data extraction and management

Two review authors (DV, AF) independently abstracted data, which another review author (DV) double-checked and entered into Review Manager 5.3 software (RevMan 2014). Another review author (MP) spot-checked data and study characteristics for accuracy against those provided in the trial report.

Assessment of risk of bias in included studies

Two review authors (DV, AF) assessed risk of bias using the domain-based approach described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Domains included an assessment of how the random sequence was generated, allocation concealment was ensured, and blinding of participants and personnel and outcome assessors was applied, and whether an intention-to-treat analysis was used. We resolved disagreements between review authors by discussion. In addition, we used the GRADE approach to determine the quality of evidence using the standard criteria risk of bias, inconsistency, indirectness, imprecision, and other biases (Guyatt 2011).

We generated a 'Summary of findings table' for the most important outcomes (treatment failure, all-cause mortality, overall adverse events, and diarrhoea) and assessed the quality of evidence using GRADEpro software (GRADEpro GDT), and recommendations provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Measures of treatment effect

We calculated pooled risk ratios (RRs) for binary events, Peto odds ratios (ORs) for rare events, and mean differences (MDs) for continuous outcomes.

For trials that included two groups receiving different antibiotics, we treated treatment groups as one group if effects of the two antibiotics did not differ in a statistically significant or clinically important way.

Unit of analysis issues

The unit of analysis was the participant.

Dealing with missing data

When necessary, we contacted study authors to obtain further information about their trials.

Assessment of heterogeneity

We kept the three groups of outpatients, inpatients, and patients admitted to the ICU separate for most analyses except for adverse events, because we considered these to be clinically too different to be summarised in a single group. We considered outpatients to have a mild to moderate exacerbation, inpatients to have a severe exacerbation, and ICU patients to have a very severe exacerbation (event-based definitions of severity of exacerbations). Within the analysis of outpatients and inpatients, we used the heterogeneity Chi^2 statistic to assess statistical heterogeneity and expressed this by using the I^2 statistic.

Assessment of reporting biases

For trials published after 1990, we tried to find trial registration information and assessed whether researchers had reported all outcomes specified there.

Data synthesis

We used fixed-effect models (or random-effects models if we observed statistical heterogeneity with $I^2 > 30\%$) to calculate MDs for continuous outcomes or inverse-variance weighted pooled RRs. For rare events and trials with treatment groups of similar size, we used Peto's method to pool ORs. We calculated as an absolute measure of effect the number of events avoided or the number of excess events reported per 1000 participants treated with antibiotics compared to participants given placebo.

Subgroup analysis and investigation of heterogeneity

As explained in Assessment of heterogeneity, we kept markers of the severity of exacerbation for outpatients, inpatients, and patients admitted to the ICU separate for all benefit outcomes.

Sensitivity analysis

In performing sensitivity analysis, we restricted analyses to trials that evaluated antibiotics in current use (e.g. amoxicillin-clavulanic acid, trimethoprim/sulphamethoxazole, doxycycline, penicillin, fluoroquinolones), thus excluding antibiotics rarely used for this indication or no longer used because of serious side effects (e.g. oxytetracycline, chloramphenicol).

RESULTS

Description of studies

Results of the search

Searches to 2006

An electronic search of the former non-Cochrane review conducted by this author team yielded 765 references (Puhan 2007). After assessing references on the basis of title and abstract, two review authors independently scanned the full text of 35 studies discovered during the electronic search and an additional 30 studies identified through handsearching. Four studies were ongoing trials (Brusse-Keizer 2009; Fartoukh 2004; NCT00170222; NCT00255983). We included 13 studies (Allegra 1991; Alonso Martinez 1992; Anthonisen 1987; Berry 1960; Elmes 1957; Fear 1962; Jørgensen 1992; Manresa 1987; Nouira 2001; Petersen 1967; Pines 1968; Pines 1972; Sachs 1995).

Searches from 2005 to 2012

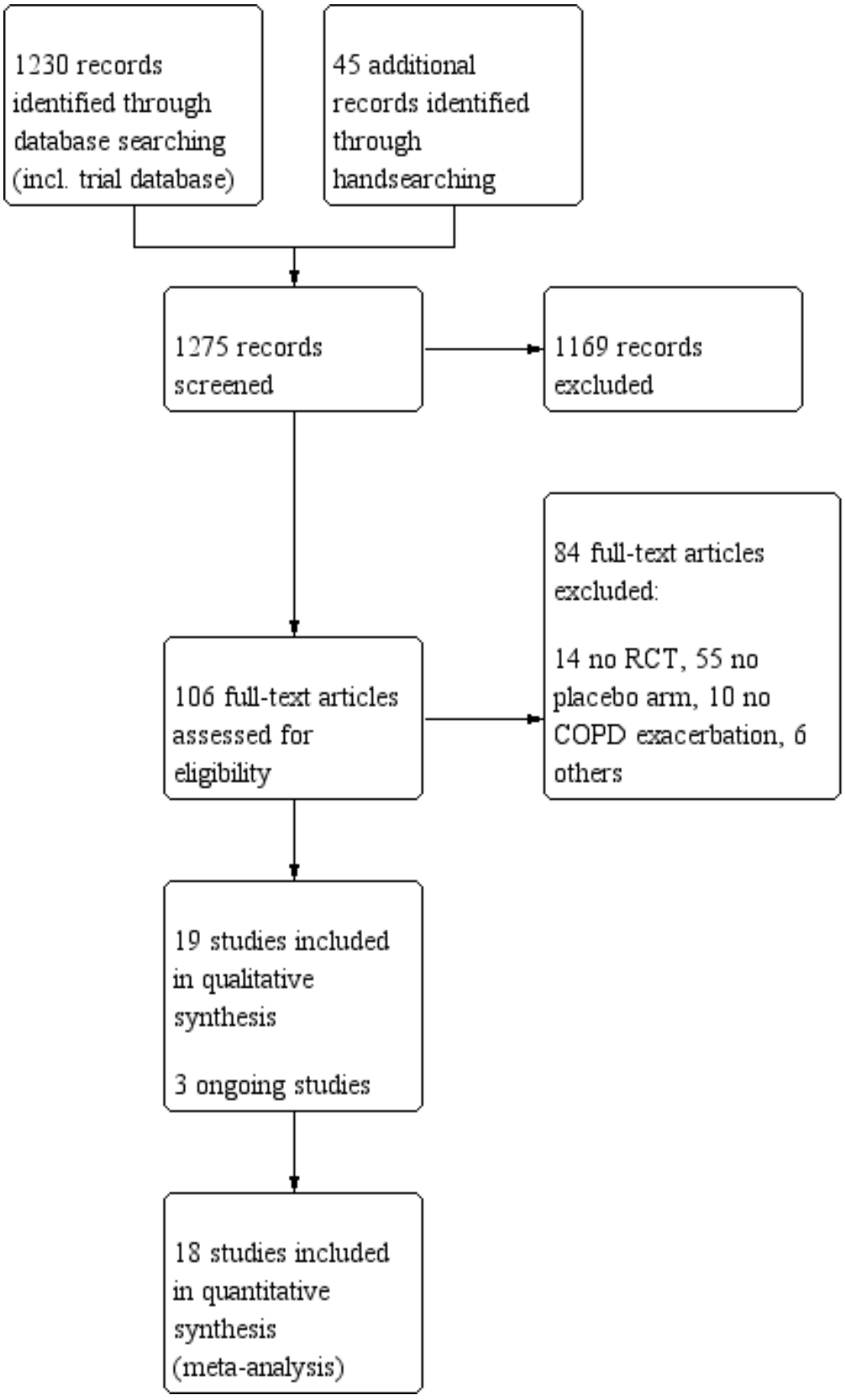
We identified 226 citations via the update search (2005 to 2012) of electronic databases. We retrieved 25 full texts and handsearched nine protocols on www.clinicaltrials.gov. From this search, we identified two eligible trials (Daniels 2010; Llor 2012); we identified one additional trial through handsearching (Brusse-Keizer 2009).

Searches from 2012 to 2018

We identified 244 citations during the updated search (2012 to 2018) of electronic databases. We retrieved seven full texts.

From this search, we identified three eligible trials (Hassan 2015; van Velzen 2017; Wang 2016), as well as three ongoing studies (NCT01091493; NCT01892488; NCT03262142) (see Figure 1).

Figure 1. Study flow diagram.



Included studies

We included 19 studies enrolling 2663 participants. Of these 19 studies, 11 included outpatients (Allegra 1991; Anthonisen 1987; Berry 1960; Brusse-Keizer 2009; Elmes 1957; Fear 1962; Hassan 2015; Jørgensen 1992; Llor 2012; Sachs 1995; van Velzen 2017), seven included patients admitted to a hospital (Alonso Martinez 1992; Daniels 2010; Manresa 1987; Petersen 1967; Pines 1968; Pines 1972; Wang 2016), and one included patients admitted to a medical ICU (Nouira 2001). These studies, on average, were of small sample size with a range from 19 to 310 participants. We could not compare severity of underlying COPD across trials because trial authors inconsistently reported lung function and other parameters.

We identified 15 trials as full reports in English language journals; one trial was published in Spanish (Alonso Martinez 1992), one was published in Italian (Allegra 1991), and one was reported as a clinical letter to a major journal (Manresa 1987). One trial provided only analyses on adverse effects because it reported only on treatment failure within five days of treatment initiation (Allegra 1991). We attempted to retrieve the data on treatment failure within two weeks, which had been assessed but were not reported (personal communication with Dr. Blasi, March 2006), but these data were not made available to us. We have provided further details of included studies in the Characteristics of included studies table, and a summary of interventions across studies in Table 1.

Excluded studies

We excluded 84 trials with reasons (Characteristics of excluded studies). We most often excluded trials because they compared different types of antibiotics against each other and included no placebo arm. We identified three studies as ongoing (NCT01091493; NCT01892488; NCT03262142).

Risk of bias in included studies

Overall we found that studies had low to moderate risk of bias (see Figure 2 and Figure 3). Thirteen of the 19 studies (70%) correctly performed and reported random sequence generation, blinding of participants and personnel, and intention-to-treat analysis. However, information on blinding, completeness of outcome data, and selective reporting was limited.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

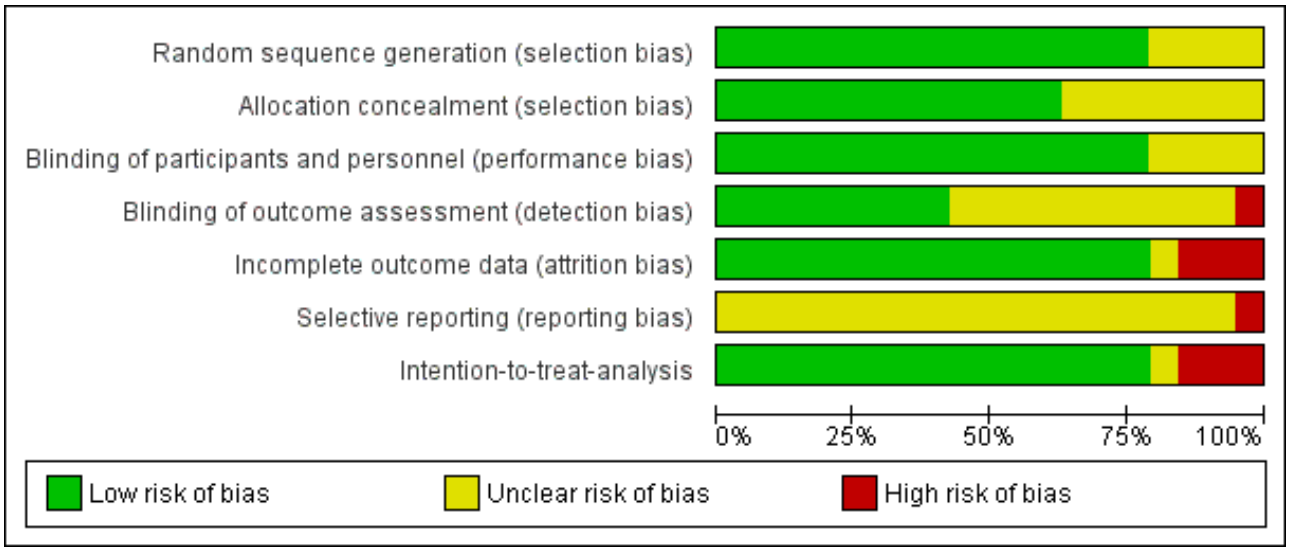
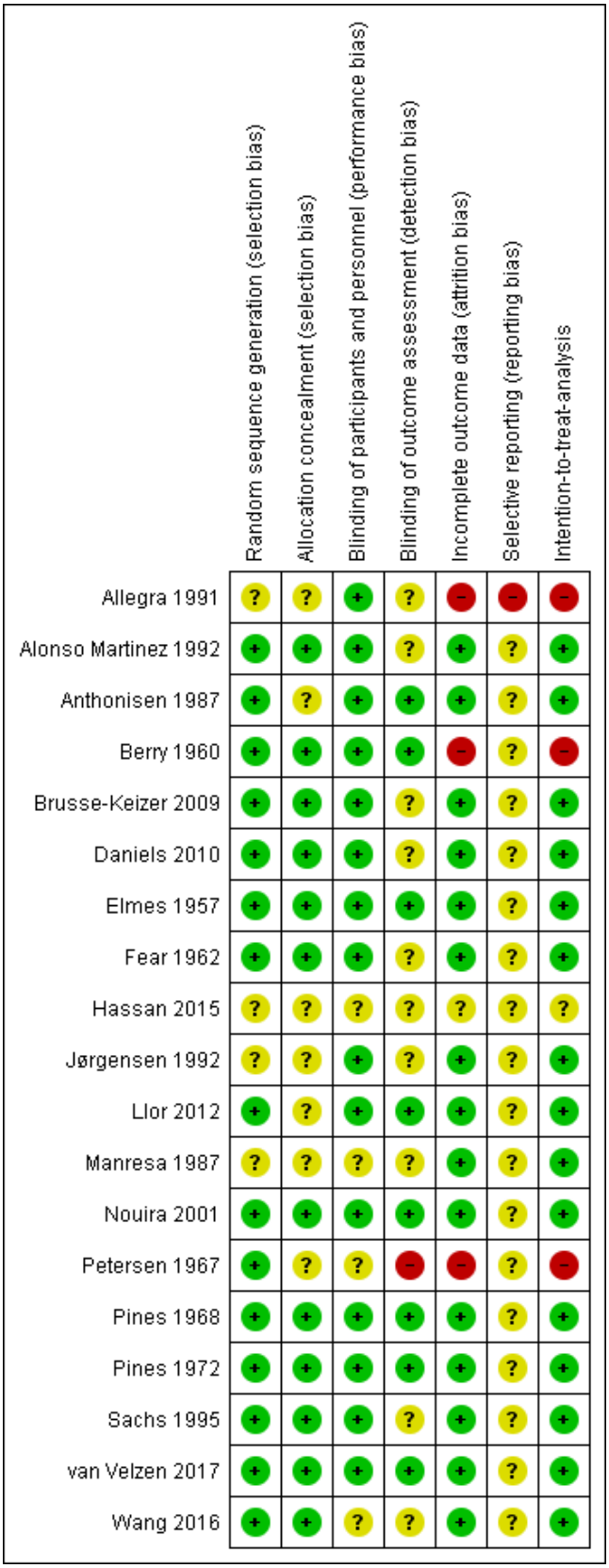


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Fifteen of the 19 trials (80%) correctly performed and reported random sequence generation. Twelve of the 19 studies (60%) correctly performed and reported allocation concealment. We judged the remainder to be at unclear risk.

Blinding

Eight of the 19 studies (55) performed and reported blinding of outcome assessment. We considered one study to be at high risk and the remainder at unclear risk. Fifteen of the 19 studies (80%) correctly performed and reported blinding of participants and personnel.

Incomplete outcome data

We detected incomplete outcome data in three (< 20%) studies. None of the included studies described completeness of outcome data.

Selective reporting

For all studies, except one, it is not clear whether study authors reported all outcomes. We know that Allegra 1991 did not report all measured outcomes.

Other potential sources of bias

We did not identify any other potential sources of bias in the included studies.

Effects of interventions

See: **Summary of findings for the main comparison** Antibiotics compared to placebo for exacerbations of chronic obstructive pulmonary disease: outpatients; **Summary of findings 2** Antibiotics compared to placebo for exacerbations of chronic obstructive pulmonary disease: inpatients; **Summary of findings 3** Antibiotics compared to placebo overall for exacerbations of chronic obstructive pulmonary disease; adverse events

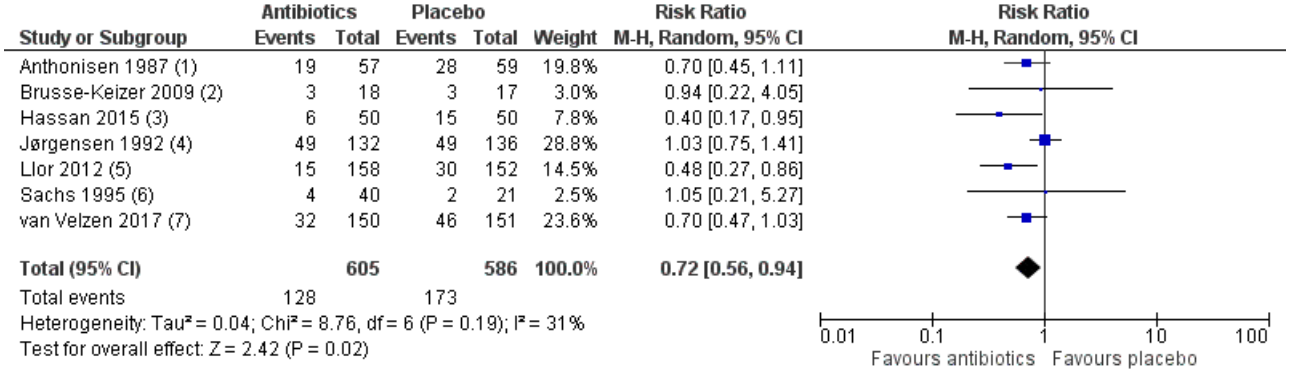
Primary outcome: treatment failure between seven days and one month after treatment initiation

The follow-up period for these studies to assess treatment failure ranged from eight to 28 days. In some studies, treatment failure outcomes were patient reported (Anthonisen 1987; Berry 1960; Brusse-Keizer 2009; Daniels 2010; Elmes 1957; Jørgensen 1992; Sachs 1995; van Velzen 2017; Wang 2016), and in two trials, treatment failure outcomes were provider reported (Llor 2012; Pines 1968), as defined by an additional course of antibiotics (Alonso Martinez 1992; Pines 1972; van Velzen 2017), or by a combined endpoint of additional antibiotics and death (Nouira 2001).

Outpatients

For outpatients (nine trials; 1332 participants), antibiotics statistically significantly reduced the risk for treatment failure (risk ratio (RR) 0.69, 95% confidence interval (CI) 0.53 to 0.90; I^2 = 31%; Analysis 1.1). When we restricted analysis to the seven trials administering currently used drugs (amoxicillin-clavulanic acid, trimethoprim/sulphamethoxazole, doxycycline, penicillin), evidence of low quality suggested a similar effect (RR 0.72, 95% CI 0.56 to 0.94; I^2 = 31%; Analysis 1.2; Figure 4), with 83 treatment failures avoided per 1000 treated participants (95% CI 18 to 130). See Summary of findings for the main comparison.

Figure 4. Forest plot of comparison: 1 Antibiotics versus placebo. Outpatients, outcome: 1.2 Treatment failure within 4 weeks - current drugs only.



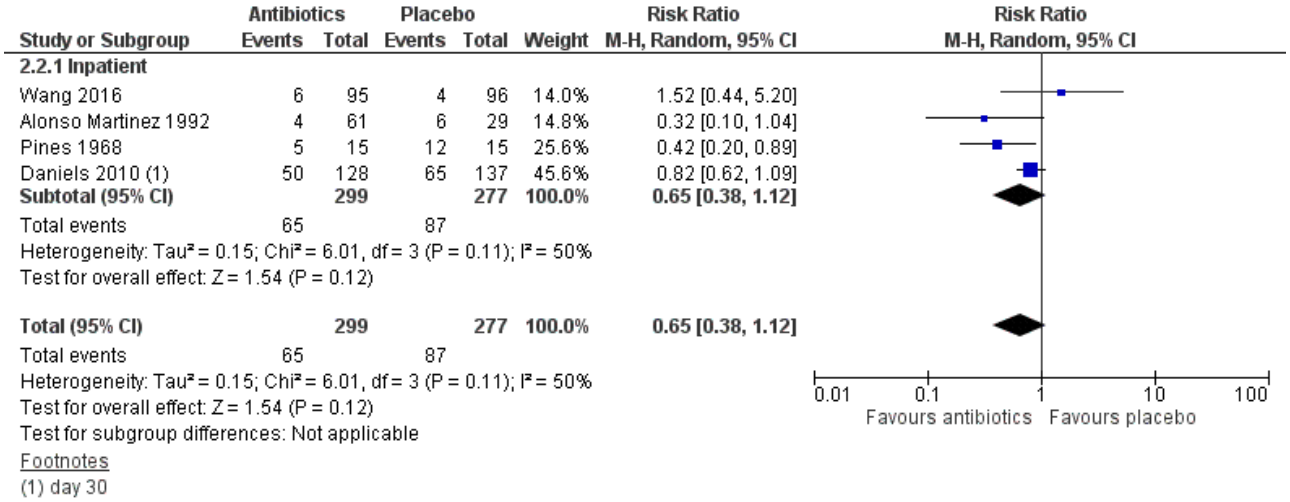
Footnotes
(1) within 21 days
(2) 28 days
(3) day 21
(4) day 8
(5) 20 days
(6) failure between 4-24 days
(7) day 21

Inpatients

For inpatients (five trials; 803 participants), antibiotics had a statistically significant effect (RR 0.76, 95% CI 0.58 to 1.00; I^2 = 39%; Analysis 2.1). When we restricted analysis to the four studies that assessed currently used drugs (amoxicillin-clavulanic acid, trimethoprim/sulphamethoxazole, doxycycline, penicillin),

we noted that evidence of moderate quality showed a similar effect size with an effect that was not statistically significant (RR 0.65, 95% CI 0.38 to 1.12; I^2 = 50%; Analysis 2.2; Figure 5). For ICU patients, one trial with 93 participants given antibiotics showed a statistically significant effect (RR 0.19, 95% CI 0.08 to 0.45; moderate-quality evidence; Analysis 2.1), with 458 treatment failures avoided per 1000 treated participants (95% CI 311 to 520). See Summary of findings 2.

Figure 5. Forest plot of comparison: 2 Antibiotics versus placebo. Inpatients, outcome: 2.2 Treatment failure within 4 weeks - current drugs only.



Secondary outcomes

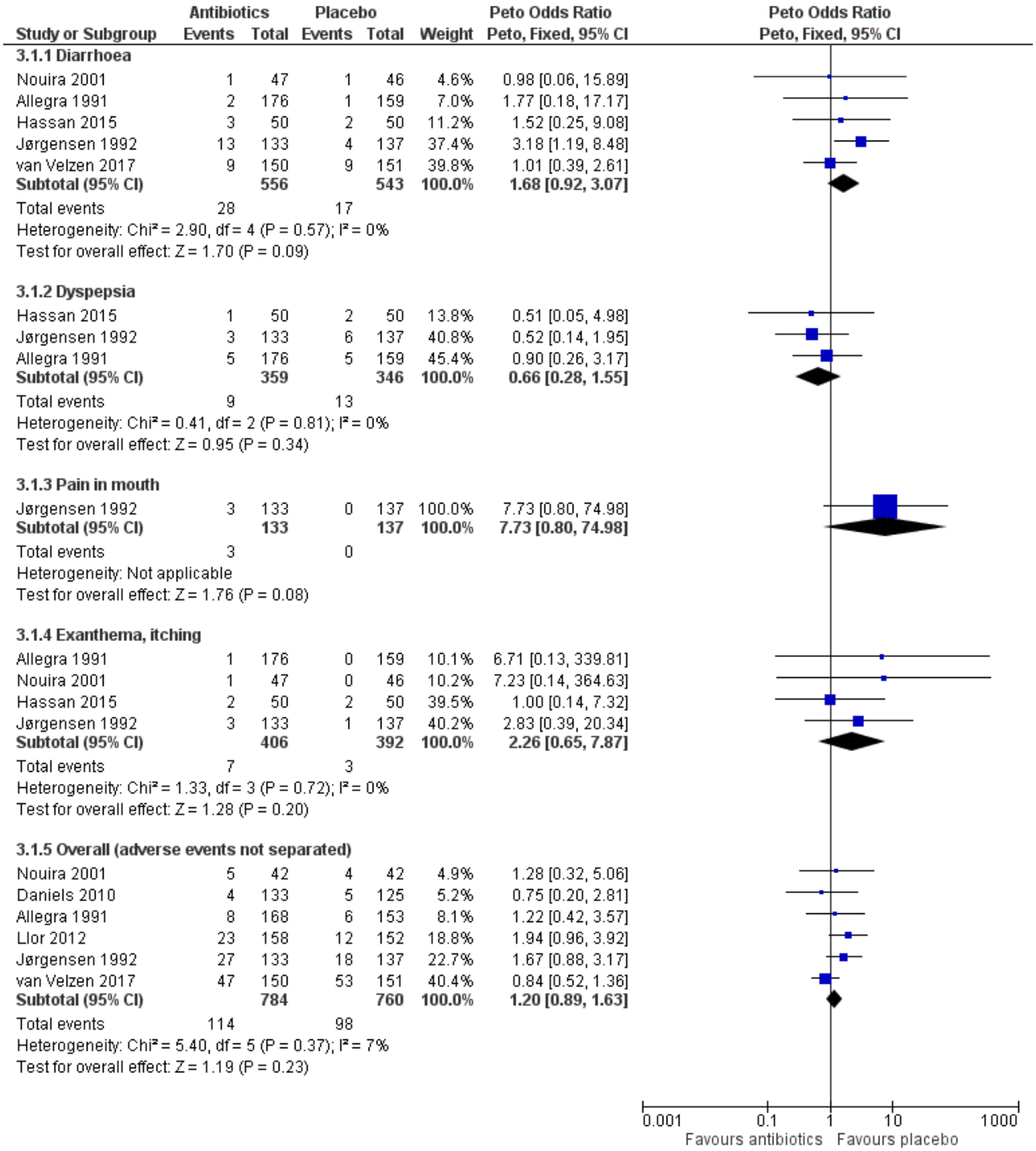
Treatment failure as observed between seven and 14 days after treatment initiation

Included trials did not report this outcome.

All-cause mortality (current drugs only)

Four trials - two inpatient trials (Daniels 2010; Wang 2016), one ICU trial (Nouira 2001), and one outpatient trial (van Velzen 2017) - reported mortality. Researchers reported no statistically significant effects of antibiotics on mortality for inpatients (Peto OR 2.48, 95% CI 0.94 to 6.55; moderate-quality evidence; Analysis 2.3; Figure 6), nor for outpatients (Peto OR 1.27, 95% CI 0.49 to 3.30; low-quality evidence; Analysis 1.3; Summary of findings for the main comparison), but they showed a statistically significant effect among ICU patients favouring antibiotics (Peto OR 0.21, 95% CI 0.06 to 0.72; moderate-quality evidence; Analysis 2.3), with 171 deaths avoided per 1000 treated participants (95% CI 61 to 204; Summary of findings 2).

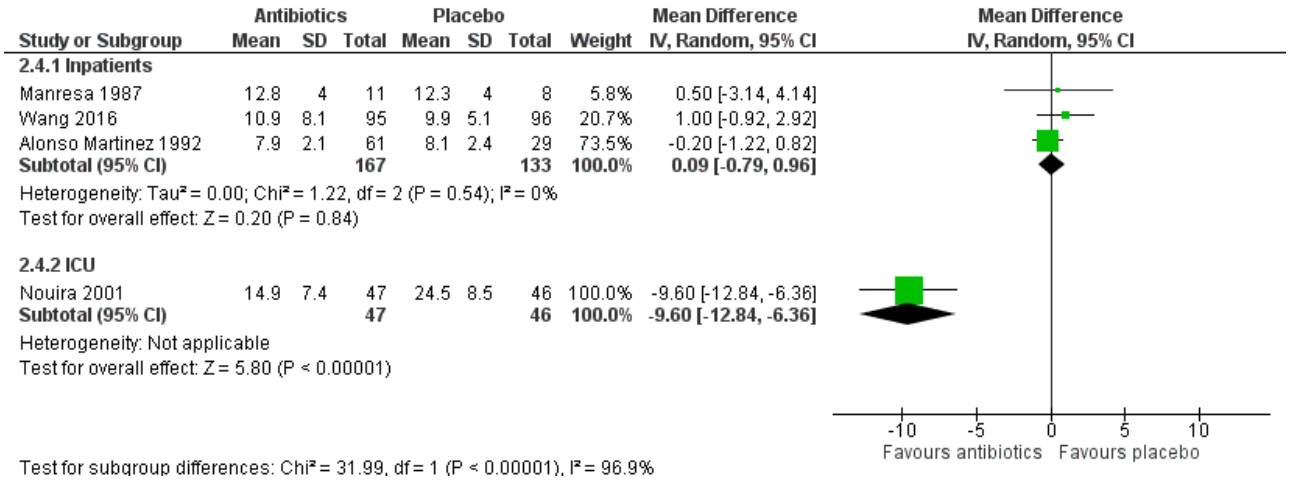
Figure 6. Forest plot of comparison: 3 Antibiotics vs placebo overall, outcome: 3.1 Adverse events.



Duration of hospital admission (for inpatients)

Four trials including 393 participants reported length of hospital stay (measured in days). Pooled results show no clear differences between antibiotics and placebo (mean difference (MD) -1.91, 95% CI -5.48 to 1.66; Analysis 2.4; Figure 7). Considered separately, the three inpatient trials favoured neither antibiotics nor placebo (Alonso Martinez 1992; Manresa 1987; Wang 2016), whereas the fourth trial, an ICU trial, clearly favoured antibiotics (Nouira 2001).

Figure 7. Forest plot of comparison: 2 Antibiotics versus placebo. Inpatients, outcome: 2.4 Duration of hospital stay (days).



Admission to an intensive care unit (ICU)

Included studies did not report this outcome.

Re-exacerbations within ≥ two to six weeks from beginning of index exacerbation (inpatient or outpatient treatment, rates, or time to event)

One outpatient trial with 35 participants reported the number of participants with re-exacerbations within two to six weeks (Brusse-Keizer 2009). Data show two re-exacerbations in the antibiotics group versus one in the placebo group (RR 1.89, 95% CI 0.19 to 18.97; Analysis 1.4).

One inpatient trial with 194 participants reported the number of participants with re-exacerbations (Wang 2016). Trial authors reported 17 re-exacerbations in the antibiotics group versus 11 in the placebo group (RR 1.56, 95% CI 0.77 to 3.16; Analysis 2.5).

Adverse events

Pooled analysis included only trials that evaluated currently used antibiotics in both inpatients and outpatients. Five studies with 1099 participants provided data on the numbers of participants experiencing diarrhoea (Allegra 1991; Hassan 2015; Jørgensen 1992; Nouira 2001; van Velzen 2017). Evidence of moderate quality shows that participants treated with antibiotics had diarrhoea more frequently than those given placebo, but the difference did not reach statistical significance (Peto OR 1.68, 95% CI 0.92 to 3.07; I^2 = 0%; moderate-quality evidence; Analysis 3.1; Figure 6). See Summary of findings 3.

Six studies with 1544 participants provided data on the overall incidence of adverse events in study groups (Allegra 1991; Daniels 2010; Jørgensen 1992; Llor 2012; Nouira 2001; van Velzen 2017). Participants treated with antibiotics had more frequent adverse events, but differences did not reach statistical significance (Peto OR 1.20, 95% CI 0.89 to 1.63; I^2 = 7%; moderate-quality evidence). We have shown results for other adverse events in Figure 6.

Dyspnoea

Two studies with 300 participants reported dyspnoea at the end of the study period (Brusse-Keizer 2009; Daniels 2010). Trial results show no significant differences in dyspnoea between antibiotics and placebo in either trial (outpatients: MD 0.00, 95% CI -0.97 to 0.97; Analysis 1.5; inpatients: MD -0.60, 95% CI -1.27 to 0.07; Analysis 2.6).

Hospital admission

Included studies did not report this outcome.

Health-related quality of life or functional status measures

One outpatient trial with 35 participants reported health-related quality of life and showed no statistically significant differences between treatment and control groups (MD 0.00, 95% CI -1.79 to 1.79; Analysis 1.6) (Brusse-Keizer 2009).

Time off work

Elmes 1957, the oldest trial, reported days off work for outpatients. The antibiotics group had statistically significantly fewer days off work compared with the placebo group (MD -5.18, 95% CI -6.08 to -4.28; Analysis 1.7).

Time to next exacerbation

Two outpatient trials assessed effects of antibiotics over the long term, measured as time to next exacerbation within one year (Llor 2012; n = 310) and within two years (van Velzen 2017; n = 301). Llor 2012 found that the median time to the next exacerbation was significantly longer in the antibiotics group (233 days; interquartile ratio (IQR) 110 to 365 days) than in the control group (160 days; IQR 66 to 365 days; Kaplan-Meier survival analysis, P = 0.015). In contrast, median time to the next exacerbation did not differ between groups in van Velzen 2017, with 148 days (IQR 95 to 200) reported for the treatment group versus 161 days (IQR 118 to 211) for the control group.

DISCUSSION

Summary of main results

Meta-analyses show that antibiotics for acute exacerbations of chronic obstructive pulmonary disease (AECOPDs) reduced treatment failure in a statistically significant way for patients with mild to moderate AECOPDs (outpatients) and for those with

very severe AECOPDs (admitted to the intensive care unit (ICU); only one trial). Trial results show a similar magnitude of effect in patients with severe AECOPDs (inpatients), but these findings were more uncertain and the confidence interval revealed no differences between antibiotics and placebo. Researchers reported a statistically significant reduction in the risk of mortality among ICU patients with the use of antibiotics (only one trial available), but not for inpatients and not for outpatients. Trial reports show that hospital stay was not significantly reduced by antibiotics, except for ICU patients (only one available trial). Review authors found few data on the effects of antibiotics on health-related quality of life or on other patient-reported symptoms such as dyspnoea, and noted no statistically significant increase in the risk of adverse events with antibiotics compared to placebo.

Overall completeness and applicability of evidence

Review authors could not study the clinical severity of underlying chronic obstructive pulmonary disease (COPD) as a potential source of heterogeneity. Trials with information on COPD severity are rare, as lung function tests are difficult to perform during exacerbations, and lung function results from the pre-exacerbation period are not always available. Also, definitions and classifications of COPD have changed over the years, so we could extract from the included studies no uniform classifications of COPD. Nevertheless, the results of this review appear to be applicable to patients with moderate to severe COPD, who typically experience exacerbations.

Trials used no common definitions for severity of exacerbation. Review authors noted uncertainty about the thresholds of admitting patients to hospital, and about whether this concern was comparable among trials. Stratification according to the setting in which patients were treated represents only an approximation of the severity of AECOPD, although COPD researchers commonly use such an event-based definition (Rodriguez-Roisin 2000). Our finding for beneficial effects of antibiotics for patients with very severe AECOPD is to some extent consistent with that described in the Anthonisen 1987 trial, which reported benefit for patients with the most severe exacerbations but not for those with mild to moderate exacerbations. Results of meta-analyses for treatment failure in outpatients and inpatients (non-ICU patients) were somewhat inconsistent and may indicate that our rather conservative approach of keeping outpatients and inpatients separate was not necessary, and that there are other determinants of hospital admission besides the severity of an exacerbation.

Only two small trials presented patient-important outcomes such as health-related quality of life and days off work, which are heavily influenced by exacerbations and are among the main targets of COPD treatments. Given the rather small and statistically non-significant increase in side effects, it could be argued that treating outpatients with antibiotics is not problematic, in that some patients may still benefit. However, this disregards the consistent and growing problem of resistance against antibiotics and the need to decrease utilisation of unnecessary antibiotics (WHO Factsheet no. 194).

Overall, antibiotics provide a strong beneficial effect for ICU patients. They provide some effects for inpatients and for outpatients, but these effects are small and inconsistent for some outcomes (treatment failure) and absent for other outcomes (mortality, length of hospital stay). It should be noted that the study including ICU patients was conducted approximately 20 years ago, and advances in the care of people admitted to the ICU have been made since that time. Therefore, these results should be interpreted and applied with caution.

Quality of the evidence

We restricted our systematic review to randomised controlled trials (RCTs) and identified 19 placebo-controlled RCTs with 2663 participants. The two most common reasons for downgrading the quality of the evidence were heterogeneity and imprecision. Statistical heterogeneity within outcomes is consistent with the inconsistent results reported across outcomes for outpatients and inpatients. Overall, we rated the quality of evidence as high for hospital stay for inpatients; for six outcomes, we rated quality as moderate (treatment failures in inpatients and ICU patients, mortality in ICU patients and inpatients, diarrhoea, and any adverse events), and for three outcomes, we rated the quality of evidence as low (treatment failure in outpatients, mortality in outpatients and inpatients).

Potential biases in the review process

Although meta-analyses commonly include treatment failure, it is a limitation of this review that definitions of treatment failure differed across trials. It is difficult to standardise the definition of treatment failure because it may include patient-reported symptoms and clinical signs as well as results from laboratory testing or imaging. However, we do not have reason to believe that different definitions of treatment failure caused heterogeneity in our meta-analyses. Also, we could not assess the influence of factors such as season, severity of underlying COPD, comorbidities, or concurrent use of medications such as systemic corticosteroids or bronchodilators, as researchers reported these details inconsistently and to a limited extent. Although these factors should not affect the validity of trial results (balanced between groups), it would be interesting to analyse whether the chance to find an effect of antibiotics depends on concurrent medications that are known to improve patients' health status during an AECOPD (e.g. systemic corticosteroids).

A limitation of the present systematic review is publication bias, which is a potential threat to any systematic review. Studies demonstrating a positive effect for antibiotics may be more likely to be published than those showing a negative effect. To minimise effects of missing studies, we used extensive trial search criteria with no language restrictions and made every effort to detect unpublished and ongoing studies, and we contacted the authors of our included trials, some of whom provided additional information about their data.

Agreements and disagreements with other studies or reviews

Our systematic review is still largely in agreement with former versions of this review (Puhan 2007; Vollenweider 2012), and our findings have not changed substantially with the addition of three new trials (Hassan 2015; van Velzen 2017; Wang 2016). Evidence still favours the use of antibiotics in patients with very severe exacerbations admitted to the ICU and remains inconclusive for hospitalised patients with severe exacerbations and outpatients with mild to moderately severe exacerbations. Also, the evidence concerning patient-important outcomes such as health-related quality of life has not become stronger.

Results presented in this review are substantially less clear than those described in the former and withdrawn Cochrane Review on this topic (Ram 2006); this is due to the availability of more trials and some differences in how the reviews were conducted. The former Cochrane Review used several different outcomes - such as peak flow, lung function, sputum purulence, and blood gases - that we believe are not patient-important outcomes to estimate the value of antibiotics for management of AECOPD. Also, the former review included Elmes 1965 - a study that was not an RCT - and excluded Berry 1960 - a study that actually was an RCT. In addition, we were able to obtain COPD-specific data from one RCT (Sachs 1995), which reported results for both asthma patients and COPD patients. Our results for mortality among inpatients differ from those of the former Cochrane Review because that review included the Elmes trial and did not keep ICU patients and inpatients separate (Elmes 1965).

One systematic review - Saint 1995 - combined results from different outcomes in a meta-analysis. Nevertheless, review authors concluded that an overall combined standardised mean effect size estimate of 0.22 (95% confidence interval (CI) 0.1 to 0.34) indicated a small but statistically significant effect favouring antibiotics over placebo. We suggest that combining different outcomes and using standardised effect sizes is an inappropriate way to pool results.

Several systematic reviews and (network) meta-analyses have examined the topic of antibiotics and AECOPD, but they did not focus on the comparison of antibiotics versus placebo for treatment of AECOPD, nor did they focus on comparisons of different antibiotics (Zhang 2017), use of prophylactic antibiotics to minimise the risk of AECOPD (Donath 2013; Herath 2013), or use of biomarkers such as procalcitonin to guide treatment with antibiotics (Lin 2018).

AUTHORS' CONCLUSIONS

Implications for practice

With the exception of patients with very severe AECOPD, who require treatment on an ICU and derive benefit from antibiotics, uncertainty continues as to whether antibiotics reduce the risk of treatment failure, mortality, and re-exacerbations, or improve health-related quality of life, among COPD patients with AECOPD who can be treated on an outpatient basis or an inpatient basis. Current data are not conclusive enough to show whether antibiotics should generally be used, because results among outpatients and inpatients are heterogeneous and are associated with some risk of bias, and because evidence on patient-important outcomes such as health-related quality of life is not available. This Cochrane Review provides guideline developers with an evidence base, but we stress that additional factors such as patient preferences, resistance of bacteria to antibiotics, and cost are important to consider when recommendations or treatment decisions are made.

Implications for research

For the large majority of COPD patients who are treated on an outpatient or inpatient basis because of mild to moderate exacerbations, additional placebo-controlled trials could determine the effectiveness of antibiotics for short- and long-term outcomes and for patient-important outcomes such as health-related quality of life. It is challenging to recruit outpatients for placebo-controlled trials because of widespread beliefs about the positive effects of antibiotics. But as our review suggests, the evidence for benefit in an outpatient or inpatient setting is not conclusive, meaning that placebo-controlled RCTs may still be justified.

Conflicting evidence stimulates discussion about (bio-)markers that could predict a bacterial infection and assist in selection of patients who might benefit from antibiotic treatment and identification of those who are unlikely to benefit. Sputum purulence is one of the most frequently discussed indicators that can be used to guide antibiotic therapy. It is noteworthy that no adequately powered RCTs have assessed effect modification by the presence or absence of purulent sputum. Indirect evidence on effect modification is available from the trials included in this systematic review. Four trials included patients with purulent sputum only or positive gram stain (Brusse-Keizer 2009; Elmes 1957; Pines 1968; Pines 1972), but trial authors provided few details on how purulent sputum was defined and measured. Of these four trials, only one showed a statistically significant effect on treatment failure (Pines 1968), and only the most recent trial reported no effects on any reported outcomes (Brusse-Keizer 2009). Also, the trials included in this review have provided no indication that their results differ from those reported by trials that did not restrict the study population to patients with purulent sputum. Biomarkers may also be promising as a guide to antibiotic treatment for COPD exacerbations. C-reactive protein (CRP) or B-type natriuretic peptide may be useful because both are relatively cheap and are easily available in inpatient and outpatient settings (Daniels 2010b; Llor 2012). Trials exploring additional candidates for guiding antibiotic treatment have shown an antibiotic-sparing effect when the decision to use antibiotics is guided by procalcitonin (Mathioudakis 2017).

Different types of studies can be done to determine the utility of clinical signs and biomarkers in guiding antibiotic therapy for COPD exacerbations. Additional placebo-controlled trials could assess whether the effects of antibiotics (vs placebo) are different in patients with (or without) purulent sputum, or with different levels of a biomarker. Such trials would require relatively large sample sizes to formally assess subgroup effects (effect modification). Alternatively, researchers could undertake more pragmatic trials, in which physicians are randomised to using or not using a clinical sign or biomarker to guide the prescription of antibiotics. Such trials typically would be non-inferiority trials, which aim to show that clinical benefit is not worse when a clinical sign or biomarker is used but that adverse effects, cost, and bacterial resistance could be limited by diminished use of antibiotics. One Cochrane Review showed that procalcitonin guidance was not associated with increased mortality nor treatment failure in patients with acute respiratory infection but significantly reduced overall antibiotic use (Schuetz 2012). In addition, new developments in subgroup analyses based on advanced statistical methods may help to generate hypotheses by which patients may benefit from antibiotics (Seibold 2016). Finally, observational studies may be undertaken to look into the potential of clinical signs or biomarkers for predicting outcomes of patients with COPD exacerbations. Such studies could assess the independent predictive properties of clinical signs or biomarkers, or could compare outcomes with antibiotic treatment versus outcomes with no antibiotic treatment in patients with or without a clinical sign or certain biomarker levels, while adequately adjusting for selection

mechanisms and confounding. Such observational studies appear more feasible than additional placebo-controlled RCTs, but they often are more likely to be hypothesis-generating than to provide high-quality evidence as a basis for treatment recommendations.

It would be important to gather additional high-quality evidence on the long-term effects (re-exacerbations, health-related quality of life, and mortality) of antibiotics for COPD patients with mild to moderate exacerbations. Head-to-head antibiotic trials continue to be important for COPD patients treated for exacerbations in inpatient and ICU settings because the susceptibility of strains is dynamic and may differ over time and from setting to setting. Finally, outcomes used in the studies included in this review are very heterogeneous. To make studies more comparable and to interpret them more easily in the context of other studies, a harmonised approach to outcome measurement is needed. For example, treatment failure and re-exacerbations can be defined more uniformly and adjudicated centrally. Time horizons could be harmonised (e.g. for treatment failure and re-exacerbations), and standard outcomes of COPD research such as those reported on St. George's Respiratory Questionnaire or the Chronic Respiratory Questionnaire could be used.

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Han Ni was the Editor for this review and commented critically on the review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Allegra 1991

Methods	RCT
Participants	Participants: patients recruited from pulmonary departments received antibiotic or placebo on an out-patient basis in case of self-reported worsening of respiratory symptoms Inclusion criteria: aged > 40 years; chronic bronchitis (defined as continuous cough and expectoration, present for at least 3 months of the year, in more than 2 consecutive years); FEV_1 < 80% predicted Exclusion criteria: reversible obstruction, cancer, liver insufficiency, renal insufficiency, heart failure, pneumonia Baseline demographics: 335 patients included; mean age 63 years; 73% male; mean FEV_1 1.37 L/s Spirometrically confirmed COPD: yes
Interventions	Mean follow-up: 5 days Treatment group: amoxicillin-clavulanic acid 2 g/d (oral) for 5 days Control group: placebo for 5 days
Outcomes	Treatment success/failure (patient-reported symptoms and clinical signs) at 5 days (not analysed in this systematic review) Dyspnoea (not analysed in this systematic review because data were not in a format that we could use) Adverse events
Notes	According to an author of the study (personal communication with Dr. Blasi, March 2006), data after 14 days of follow-up were obtained but were not published and were not made available for this review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported

Allegra 1991 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Only participants with complete follow-up were analysed
Selective reporting (reporting bias)	High risk	Data on treatment failure within 2 weeks were assessed but were not reported
Intention-to-treat-analysis	High risk	Only participants with complete follow-up were analysed

Alonso Martinez 1992

Methods	Randomised double-blinded placebo-controlled trial
Participants	Participants: patients admitted to hospital with exacerbation (increasing symptoms such as dyspnoea, sputum volume, or cough) of COPD Inclusion criteria: clinical diagnosis of COPD at the time of hospital admission Exclusion criteria: antibiotic treatment during the previous 2 weeks, left ventricular failure, stroke, pneumonia, pneumothorax, non-cutaneous cancer, coma, temperature > 38°C, psychological disorders related to COPD Baseline demographics: 90 patients included; mean age 68 years, 84% male, mean FEV_1 % predicted (SD) 29.98% (11.07) Spirometrically confirmed COPD: yes
Interventions	Mean follow-up: 7.2 days Treatment group: trimethoprim-sulphamethoxazole 1.9 g/d or amoxicillin/clavulanic acid 1.9 g/d orally for 8 days Control group: placebo for 8 days
Outcomes	Length of hospital stay Treatment success (use of additional antibiotics) Re-exacerbations (in 3 months - not analysed in this systematic review)
Notes	All participants were treated with theophylline, inhaled bronchodilators, and oxygen. If the numerical score was high or FEV_1 < 40%, they received 6-methylprednisolone 0.75 mg/kg/d

Risk of bias

Bias	Authors' judgement	Support for judgement

Alonso Martinez 1992 *(Continued)*

Random sequence generation (selection bias)	Low risk	Arithmetic combination
Allocation concealment (selection bias)	Low risk	Randomisation was performed through the hospital pharmacy from which investigators received group allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear if outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome data were analysed
Selective reporting (reporting bias)	Unclear risk	Unclear if all outcome data were reported
Intention-to-treat-analysis	Low risk	Analysed as intention to treat

Anthonisen 1987

Methods	Randomised double-blinded placebo-controlled trial
Participants	Participants: 173 patients with stable COPD were recruited from the community; 116 developed exacerbations (increased dyspnoea, sputum volume, or sputum purulence) and each time were randomly assigned to receive antibiotics or placebo Inclusion criteria: aged > 35 years; clinical diagnosis of COPD, not asthma; FEV_1 and FVC < 70% predicted; TLC > 80% Exclusion criteria: FEV_1 increased to 80% of predicted post-bronchodilator use; other disease serious enough to influence quality of life or clinical course (e.g. cancer, left ventricular failure, stroke); other disease likely to require antibiotics (e.g. recurrent sinusitis, UTI) Baseline demographics: 116 participants included; mean age 67 years, 80% male, mean FEV_1 % predicted (SD) 33.9% (13.7) Spirometrically confirmed COPD: yes
Interventions	Follow-up: 21 days Treatment group: trimethoprim/sulphamethoxazole 1.9 g/d or amoxicillin 1 g/d or doxycycline 0.1 to 0.2 g/d orally for 10 days Control group: placebo for 10 days
Outcomes	Treatment failure (patient-reported symptoms) Side effects (% of exacerbations with side effects)
Notes	Analysis was based on number of participants with first exacerbations (only first exacerbation). Side effects were not analysed as they were expressed as % of all exacerbations

Anthonisen 1987 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random schedule
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Neither patients nor medical staff knew which medication was active"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Medical staff" was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome data were analysed
Selective reporting (reporting bias)	Unclear risk	Unclear if all outcome data were reported
Intention-to-treat-analysis	Low risk	Analysed as intention to treat

Berry 1960

Methods	RCT
Participants	Participants: patients at general practitioner visit for new or aggravated respiratory symptoms Inclusion criteria: chronic bronchitis (persistent or recurrent cough with diffuse physical signs in the chest, for which X-ray had excluded other disease) with exacerbation (worsening characterised by 1 or more of the following: increased cough, increased volume of sputum, increased purulence of sputum, increased breathlessness or fever) Exclusion criteria: none Baseline demographics: 58 patients included; mean age 59 years, 53% male, FEV_1 not reported Spirometrically confirmed COPD: no
Interventions	Mean follow-up: 14 days Treatment group: oxytetracycline 1 g/d (oral) for 5 days Control group: placebo for 5 days
Outcomes	Treatment success/failure (patient reported)
Notes	Patients with severe exacerbations were not included because antibiotics were deemed indispensable
Risk of bias	

Berry 1960 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Low risk	Identical bottles; key to numbers was kept by another person
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical bottles and capsules
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Practitioners doing outcome assessments were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Patients with possible toxic effects from drugs were excluded
Selective reporting (reporting bias)	Unclear risk	Unclear if all outcome data were reported
Intention-to-treat-analysis	High risk	Patients with possible toxic effects from drugs were excluded

Brusse-Keizer 2009

Methods	RCT
Participants	Participants: outpatients seen by chest physicians received antibiotic or placebo for moderately severe exacerbations Inclusion criteria: clinical diagnosis of COPD (GOLD criteria); current smoker or ex-smoker; aged 40 to 80 years; presenting as an outpatient with signs and symptoms of an exacerbation (change in dyspnoea, sputum volume and colour, and cough); able to produce sputum sample; 1 or 2 of the following: positive sputum Gram's stain, clinically relevant decrease in lung function, or ≥ 2 exacerbations in the previous year Exclusion criteria: pneumonia, exacerbation or use of antibiotics or prednisolone 4 weeks before enrolment (except ≤ 5 mg prednisolone), other disease influencing lung function, maintenance antibiotics, hypersensitivity to amoxicillin-clavulanic acid, serious medical or psychiatric comorbidity, uncontrolled diabetes mellitus, home oxygen therapy Baseline demographics: 35 patients included; mean age 67 years, 60% male, mean FEV_1/FVC 40% Spirometrically confirmed COPD: yes
Interventions	Follow-up: 28 days for primary outcome; 4 months for new exacerbations Treatment group: amoxicillin-clavulanic acid 1.5 g/d for 7 days and oral prednisolone 30 mg for 7 days Control group: placebo for 7 days and oral prednisolone 30 mg for 7 days
Outcomes	Resolution of exacerbation (patient-reported symptom diary) Relapse of exacerbation within 28 days

Brusse-Keizer 2009 *(Continued)*

	Chronic respiratory questionnaire Clinical COPD questionnaire
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation list
Allocation concealment (selection bias)	Low risk	Based on the randomisation list, the hospital pharmacy sequentially numbered containers with both amoxicillin/clavulanic acid and placebo. This list was kept in a safe at the hospital pharmacy throughout the course of the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information on blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome data were analysed
Selective reporting (reporting bias)	Unclear risk	Unclear if all outcome data were reported
Intention-to-treat-analysis	Low risk	All participants were analysed in the groups to which they were randomised

Daniels 2010

Methods	RCT
Participants	Participants: hospitalised patients with acute exacerbations of COPD Inclusion criteria: aged > 45 years, diagnosis of COPD (GOLD criteria), acute exacerbation (Anthonisen 1 and 2) Exclusion criteria: inability to take oral medication, fever (> 38.5°C), antibiotic treatment for > 24 hours, extensive treatment with corticosteroids (> 30 mg > 4 days), history of severe exacerbation requiring mechanical ventilation, lung malignancy, other infectious disease requiring antibiotic therapy, heart failure (NYHA III-IV), apparent immunodeficiency, impaired renal function (creatinine clearance < 20 mL/min) Baseline demographics: 223 patients included; 265 exacerbations, mean age 72 years, 59.6% male, mean FEV_1 (SD) doxycycline group 43.9% (17.2%), placebo group 46.9% (18.5%) Spirometrically confirmed COPD: yes
Interventions	Mean follow-up: 30 days Treatment group: 7-day course of oral doxycycline, IV prednisolone taper

Daniels 2010 *(Continued)*

	Control group: 7-day course of placebo, IV prednisolone taper
Outcomes	Primary outcome Clinical response on day 30 (success/failure) Secondary outcomes Clinical success on day 10, dyspnoea score, adverse events, mortality
Notes	Analysis based on numbers of exacerbations and participants (mortality)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated
Allocation concealment (selection bias)	Low risk	"Allocation sequence was kept in a safe at the hospital pharmacy"; "study medication was delivered in pre-numbered containers"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described (only "double-blind")
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome data were analysed
Selective reporting (reporting bias)	Unclear risk	Unclear if all outcome data were reported
Intention-to-treat-analysis	Low risk	Analysed as intention to treat and per protocol (we used only intention to treat)

Elmes 1957

Methods	RCT
Participants	Participants: patients were instructed to take antibiotic or placebo without a doctor visit as soon as new or aggravated respiratory symptoms were present Inclusion criteria: aged < 65 years; regular employment; productive winter cough for > 3 years, during which time they had at least 2 illnesses with purulent sputum, causing loss of time from work Exclusion criteria: other disabling disease Baseline demographics: 88 patients included; mean 54 age years, 84% male, FEV_1 not stated Spirometrically confirmed COPD: no
Interventions	Mean follow-up: 17 days

Elmes 1957 *(Continued)*

	Treatment group: oxytetracycline 1 g/d orally for 5 to 7 days Control group: placebo for 5 to 7 days
Outcomes	Treatment success/failure (need for further antibiotics) Time off work Side effects
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Fisher and Yates' table of random numbers
Allocation concealment (selection bias)	Low risk	"Key list was held by the hospital's pharmacist"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Dummy tablets... neither doctors nor patients knowing which was which"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Dummy tablets... neither doctors nor patients knowing which was which"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome data were analysed
Selective reporting (reporting bias)	Unclear risk	Unclear if all outcome data were reported
Intention-to-treat-analysis	Low risk	Analysed as intention to treat

Fear 1962

Methods	RCT
Participants	Participants: patients recruited from bronchitis and asthma clinics received antibiotic or placebo as an outpatient based on case of self-reported worsening of respiratory symptoms Inclusion criteria: aged 20 to 65 years; winter cough and sputum for at least 3 years, with shortness of breath on effort without evidence of other cause; some degree of disability from the bronchitis (e.g. limitation of normal activity, loss of time at work) Exclusion criteria: none Baseline demographics: 62 patients included; mean age, % male, and FEV_1 not stated Spirometrically confirmed COPD: no
Interventions	Mean follow-up: 14 days

Fear 1962 *(Continued)*

	Treatment group: oxytetracycline 1 g/d (oral) for 7 days Control group: placebo for 7 days
Outcomes	Improvement in symptoms (not analysed in this systematic review) Days of illness (not analysed in this systematic review)
Notes	Second trial of the article

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	List of random numbers
Allocation concealment (selection bias)	Low risk	"Similar to that used by Elmes 1957"; "identical appearance"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Double-blind"; "identical appearance"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear if outcome assessment was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome data were analysed
Selective reporting (reporting bias)	Unclear risk	Unclear if all outcome data were reported
Intention-to-treat-analysis	Low risk	Analysed as intention to treat

Hassan 2015

Methods	RCT
Participants	Participants: patients referred to outpatient clinics for treatment of COPD exacerbations Inclusion criteria: type 1 exacerbation of COPD (defined as increase in dyspnoea, sputum purulence, sputum volume) Exclusion criteria: antibiotic treatment during last 2 weeks; other disease such as left ventricular failure, stroke, pneumonia, pneumothorax, cancer, coma, allergy to quinolone derivatives, concomitant infection requiring systemic antibacterial therapy Baseline demographics: 100 patients included; mean age 62 years, 83% male, mean FEV_1 % predicted (SD) 54.5 (17.6) control group, 56.7 (14.0) intervention group Spirometrically confirmed COPD: no
Interventions	Follow-up 21 days

Hassan 2015 *(Continued)*

	Treatment group: 10-day course ciprofloxacin 500 mg twice daily or amoxicillin 500 mg/8 h Control group: placebo for 10 days
Outcomes	FEV_1, FVC, FEV_1/FVC, and peak expiratory flow rate at beginning and end of study period Failure rate (no resolution or deterioration of symptoms after trial of medication and at day 21, or death) Success rate (reduction in sputum volume and purulence measured at day 21) Additional course of antibiotics Improvement in dyspnoea measured at day 21 (not analysed in this review) Change in vital signs measured at day 21 Side effects
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not stated
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not stated in Methods section, only in Discussion section ("double blind")
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information on dropouts not reported
Selective reporting (reporting bias)	Unclear risk	Unclear if all outcome data were reported
Intention-to-treat-analysis	Unclear risk	Analysed as intention to treat, but information on dropouts, etc., not reported

Jørgensen 1992

Methods	Randomised double-blind placebo-controlled trial
Participants	Participants: patients at general practitioner visits for new or aggravated symptoms Inclusion criteria: aged > 18 years with acute exacerbation (subjective worsening due to change in sputum (increased volume, change in viscosity or colour) possibly accompanied by cough or dyspnoea, lasting longer than 3 days, or chronic bronchitis (defined as continuous cough and expectoration), present for at least 3 months of the year, in more than 2 consecutive years) Exclusion criteria: pneumonia (on auscultation or X-ray), temperature > 38.5°C, heart rate > 100 beats/min, antibiotics within previous 7 days, pregnancy, allergy to penicillin, uncompensated heart disease, treatment with oral corticosteroids or immunosuppressants

Jørgensen 1992 *(Continued)*

	Baseline demographics: 270 patients included; mean age 60 years, 43% male, FEV_1 not stated Spirometrically confirmed COPD: no
Interventions	Mean follow-up: 8 days Treatment group: amoxicillin 1.5 g (oral) for 7 days Control group: placebo for 7 days
Outcomes	Treatment failure (patient-reported symptoms) Adverse events
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Patients were randomised to treatment or placebo", with no other details
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not enough information
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome data were analysed
Selective reporting (reporting bias)	Unclear risk	Unclear if all outcome data were reported
Intention-to-treat-analysis	Low risk	Analysed as intention to treat

Llor 2012

Methods	Randomised double-blind placebo-controlled trial
Participants	Participants recruited from 13 primary care centres Inclusion criteria: aged > 40 years, diagnosis of mild to moderate COPD (smoking history > 10 pack-years, ratio of post-bronchodilator FEV_1:FVC < 70%, post-bronchodilator FEV_1 > 50% of predicted value), presence of an exacerbation (at least 1 of the following: increase in dyspnoea, increase in sputum volume, sputum purulence, or a combination) Exclusion criteria: antibiotic use in previous 2 weeks, bronchial asthma, cystic fibrosis, bronchiectasis of origin other than COPD, active neoplasm, tracheotomy, need for hospital admission, immunosuppression, hypersensitivity to beta-lactams, clavulanate or lactose, institutionalisation, unable to provide informed consent

Llor 2012 *(Continued)*

	Baseline demographics: 310 patients included; mean age 68 years, 81% male, mean FEV_1/FVC 62%
	Spirometrically confirmed COPD: yes
Interventions	Mean follow-up: 20 days
	Treatment group: amoxicillin/clavulanate 500/125 mg 3 times daily (oral) for 8 days
	Control group: placebo for 8 days
Outcomes	Primary outcome
	Clinical cure/improvement or failure at end of therapy visit (days 9 to 11; physician assessed)
	Secondary outcomes
	Clinical cure/improvement or failure at follow-up visit at day 20
	Re-exacerbations
	Adverse events
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random numbers table
Allocation concealment (selection bias)	Unclear risk	Not adequately described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients, investigators, and data assessors were blinded to treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Patients, investigators, and data assessors were blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome data were analysed
Selective reporting (reporting bias)	Unclear risk	Unclear if all outcome data were reported
Intention-to-treat-analysis	Low risk	Analysed as intention to treat

Manresa 1987

Methods	Randomised double-blind placebo-controlled trial
Participants	Participants: patients admitted to hospital with exacerbations of COPD

Manresa 1987 *(Continued)*

	Inclusion criteria: at the time of a hospital admission: increase in symptoms (cough, dyspnoea, and volume and purulence of sputum) Exclusion criteria: evidence of parenchymal consolidation on chest X-ray or of other pulmonary or cardiac disease Baseline demographics: 19 patients included; mean age 67 years, % male and FEV_1 not stated Spirometrically confirmed COPD: no
Interventions	Mean follow-up: 13 days Treatment group: cefaclor 1.5 g/d (oral) for 8 days Control group: placebo for 8 days
Outcomes	Length of hospital stay
Notes	Research letter to the editor

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not reported
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as "double-blind" in the abstract (exists only in the abstract)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described ("double-blind")
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome data were analysed
Selective reporting (reporting bias)	Unclear risk	Unclear if all outcome data were reported
Intention-to-treat-analysis	Low risk	Analysed as intention to treat

Nouira 2001

Methods	Randomised double-blind placebo-controlled trial
Participants	Participants: patients admitted to medical ICU with exacerbations of COPD and need for mechanical ventilation Inclusion criteria: aged > 40 years; COPD diagnosed on the basis of clinical history, physical examination, and chest radiograph; acute respiratory failure requiring mechanical ventilation within first 24 hours of admission

Nouira 2001 *(Continued)*

	Exclusion criteria: antimicrobial treatment in previous 10 days, alveolar infiltrates on chest X-rays, previously enrolled in the study, known history of asthma or bronchiectasis, allergy to quinolone derivatives, pregnancy or breastfeeding, terminally ill or immunocompromised, hepatic disease or severe renal impairment, gastrointestinal disease that could affect drug absorption, concomitant infection requiring systemic antibacterial therapy Baseline demographics: 93 patients included; mean age 66 years, 90% male, mean FEV_1 0.77 L/s Spirometrically confirmed COPD: no
Interventions	Mean follow-up: 10 days All participants were monitored until discharge from hospital Treatment group: ofloxacin 400 mg/d (oral) for 10 days Control group: placebo for 10 days
Outcomes	Mortality Treatment failure (need for additional antibiotics and death combined) Length of hospital stay Adverse events
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned to treatment or placebo via random numbers
Allocation concealment (selection bias)	Low risk	All drugs and placebo packages were prepared and numbered by the hospital pharmacy and were used consecutively. Assignments of patients were placed in closed envelopes with identification numbers that were stored in the ICU
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical appearance of the medication
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All study investigators and hospital staff were masked to treatment status until data completion
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome data were analysed
Selective reporting (reporting bias)	Unclear risk	Unclear if all outcome data were reported
Intention-to-treat-analysis	Low risk	Analysed as intention to treat

Petersen 1967

Methods	Randomised double-blind controlled trial

Petersen 1967 *(Continued)*

Participants	Participants: patients admitted to hospital with exacerbations (not defined) of COPD Inclusion criteria: aged 45 to 75 years, chronic bronchitis (history of cough and expectoration on most days during at least 3 consecutive months in each of 2 or more successive years) Exclusion criteria: severe deformities of the spine or chest, localised or generalised specific lung disease, signs of cardiac insufficiency Baseline demographics: 19 patients included; mean age 62 years, 53% male Spirometrically confirmed COPD: no
Interventions	Mean follow-up: 10 days Treatment group: chloramphenicol 2 g/d for 10 days Control group: placebo for 10 days
Outcomes	Mortality Patient-reported well-being
Notes	-

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants: yes; personnel: no
Blinding of outcome assessment (detection bias) All outcomes	High risk	Control group underwent clinical examination on day 0
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropouts were not analysed
Selective reporting (reporting bias)	Unclear risk	Unclear if all outcome data were reported
Intention-to-treat-analysis	High risk	Dropouts were not analysed (only per protocol reported)

Pines 1968

Methods	Randomised double-blind placebo-controlled trial
Participants	Participants: patients admitted to hospital with exacerbation of symptoms of chronic bronchitis

Pines 1968 *(Continued)*

	Inclusion criteria: > 50 years old, history of chronic bronchitis > 5 years and history during past 6 weeks of an exacerbation, male, moderate to severe illness on admission (as judged by the receiving SHO), persistent purulent sputum and PEFR < 200 L/min (unless too ill to do so) Exclusion criteria: allergy to penicillin, asthma, extensive bronchiectasis, active tuberculosis, lung cancer, sputum eosinophilia (> 10%) or blood urea > 60 mg/100 mL Baseline demographics: 30 participants; mean age 68 years, 100% males, FEV_1 not reported Spirometrically confirmed COPD: no
Interventions	Mean follow-up: 14 days Treatment group: penicillin 6 million units/d for 14 days and streptomycin 1 g/d parenterally for 7 days Control group: placebo for 14 days
Outcomes	Treatment failure (physician reported) Mortality
Notes	Pilot trial of the paper

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Fisher and Yates' tables
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Placebo injection"; "double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"blind assessors"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome data were analysed
Selective reporting (reporting bias)	Unclear risk	Unclear if all outcome data were reported
Intention-to-treat-analysis	Low risk	Analysed as intention to treat

Pines 1972

Methods	Randomised double-blind controlled trial
Participants	Participants: patients admitted to hospital with exacerbations of COPD Inclusion criteria: aged > 60 years, history of chronic bronchitis > 5 years and definite history during previous 6 weeks of an exacerbation, male, failure of at least 1 previous treatment with antibiotics, mod-

Pines 1972 *(Continued)*

	erately severely illness on admission (as judged by the receiving SHO), persistent purulent sputum and PEFR < 200 L/min Exclusion criteria: asthma, bronchiectasis, other pulmonary disease, sputum eosinophilia (> 10%) Baseline demographics: 259 participants included; mean age 71 years, 100% male, FEV_1 not reported Spirometrically confirmed COPD: no
Interventions	Mean follow-up: 12 days Exacerbations were followed at beginning and end of trial and 1 and 4 weeks later Treatment groups 1 and 2: tetracycline hydrochloride 2 g/d or chloramphenicol 2 g/d orally for 12 days Control group: placebo for 12 days
Outcomes	Treatment failure (physician reported) day 12 Treatment failure (additional antibiotics) days 7 to 28 Mortality Adverse events
Notes	Patients with very severe exacerbations were not included for ethical reasons

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Fisher & Yates' tables
Allocation concealment (selection bias)	Low risk	Total course of capsules for each participant was put into a sealed bottle by an independent pharmacist
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical capsules
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Assessments were made by independent trained observers
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome data were analysed
Selective reporting (reporting bias)	Unclear risk	Unclear if all outcome data were reported
Intention-to-treat-analysis	Low risk	No withdrawals

Sachs 1995

Methods	RCT

Sachs 1995 *(Continued)*

Participants	Participants: patients at general practitioner visit for new or aggravated respiratory (increase in dyspnoea with or without sputum production) symptoms Inclusion criteria: aged > 18 years, positive diagnosis of asthma or COPD made by a pulmonary physician during previous 10 years Exclusion criteria: daily use of oral corticosteroids or antimicrobial drugs, diabetes mellitus, alcoholism, history of pulmonary surgery or tuberculosis, severe bronchiectasis, a psychiatric history Baseline demographics: 61 participants included; mean age ˜ 52 years, % male and mean FEV_1 not stated Spirometrically confirmed COPD: unclear
Interventions	Mean follow-up: 35 days Treatment group: amoxicillin 1.5 g or co-trimoxazole 1.9 g/d orally for 7 days Control group: placebo for 7 days
Outcomes	Treatment success/failure (patient-reported symptoms)
Notes	We included only the subgroup with COPD

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	List of random numbers
Allocation concealment (selection bias)	Low risk	Hospital pharmacist had the code of allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"double-blind"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome data were analysed
Selective reporting (reporting bias)	Unclear risk	Unclear if all outcome data were reported
Intention-to-treat-analysis	Low risk	Analysed as intention to treat

van Velzen 2017

Methods	RCT
Participants	Participants: patients with exacerbations at outpatient clinics or primary care centres

van Velzen 2017 *(Continued)*

	Inclusion criteria: ≥ 45 years; smoking history ≥ 10 pack-years; diagnosis of mild to severe COPD, defined as post-bronchodilator FEV_1/FVC of 0.7 or lower and post-bronchodilator FEV_1 of at least 30%, according to GOLD stages 1 to 3; at least 1 exacerbation during past 3 years (not in last 4 weeks) Exclusion criteria: poor mastery of language, poor cognitive functioning, known allergy to doxycycline, pregnancy, life expectancy shorter than 1 month, fever (> 38.5°C), hospital admission, current use of antibiotics, use of antibiotics for respiratory tract infection in previous 3 weeks Baseline demographics: 301 patients included; mean age 66 years, 60% male, mean FEV_1 % predicted (SD) 60.6 (17.8) Spirometrically confirmed COPD: yes
Interventions	Follow-up: 2 years Treatment group: oral doxycycline 100 mg daily (200 mg on first day) for 7 days Control group: placebo for 7 days
Outcomes	Primary outcome Time between first exacerbation and next exacerbation Secondary outcomes Treatment failure at day 21 and day 84 (late follow-up) Mortality Number of exacerbations COPD-specific health status (SGRQ) Decline in lung volume (post-bronchodilator FEV_1 and FVC) at end of follow-up Total antibiotic use Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Automated and centralised randomisation service
Allocation concealment (selection bias)	Low risk	Automated and centralised randomisation service
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and investigators were masked to treatment assignment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Those assessing outcomes were masked to treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome data were analysed

van Velzen 2017 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Unclear if all outcome data were reported
Intention-to-treat-analysis	Low risk	Analysed as intention to treat

Wang 2016

Methods	RCT
Participants	Participants: hospitalised patients with acute exacerbations of COPD and low procalcitonin Inclusion criteria: aged > 40 years, sound understanding and language abilities, PCT level < 0.1 ng/mL Exclusion criteria: fever (≥ 38°C), tracheal intubation within 24 hours after hospital admission, PCT level ≥ 0.1 ng/mL, pneumonia, chronic renal failure, history of malignant disease, immunosuppressive therapy, refusal to participate Baseline demographics: 194 patients included; mean age 73 years, 71% male, mean FEV_1 % predicted (SD) antibiotics group 36.7 (15.8), placebo group 38.4 (16.5) Spirometrically confirmed COPD: yes
Interventions	Mean follow-up: 30 days Treatment group: piperacillin-sulbactam; ceftazidine or levofloxacin in case of allergy (duration determined by physician) Control group: placebo for 7 days
Outcomes	Primary outcome Treatment success rate on day 10 after admission Secondary outcomes Symptoms assessed by VAS (at hospital admission, 3 days after hospitalisation, on the day of hospital discharge) Length of hospital stay Intubation rate Mortality during hospitalisation and in the 30-day follow-up period Rate of antibiotic use Re-admission due to AECOPD within 30-day follow-up
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer digital table method
Allocation concealment (selection bias)	Low risk	Stated that it was concealed

Wang 2016 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not exactly stated
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not stated
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete outcome data were analysed
Selective reporting (reporting bias)	Unclear risk	Unclear if all outcome data were reported
Intention-to-treat-analysis	Low risk	Analysed as intention to treat

AECOPD: acute exacerbation of COPD; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; ICU: intensive care unit; IV: intravenous; NYHA: New York Heart Association; PCT: procalcitonin testing; PEFR: peak expiratory flow rate; RCT: randomised controlled trial; SD: standard deviation; SGRQ: St. George's Respiratory Questionnaire; SHO: senior house officer; TLC: total lung capacity; UTI: urinary tract infection; VAS: visual analogue scale

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

Study	Reason for exclusion
Aitchison 1968	No placebo group
Alix 1979	No placebo group
Allan 1966	No placebo group
Allegra 1996	No placebo group
Alvarez-Sala 2006	No placebo group
Andrijevic 2011	No comparison group
Anon 1969	No placebo group
Anon 1972	No placebo group
Banerjee 2001	No COPD exacerbations
Bekçi 2009	Participants did not have an exacerbation of COPD (stable patients)
Bennion-Pedley 1969	No placebo group
Braendli 1982	No placebo group
Burgi 1975	No placebo group
Burrow 1975	No placebo group

Study	Reason for exclusion
Chatterjee 2011	No placebo group
Chen 2000	No placebo group
Christiansen 1963	No placebo group
Citron 1969	Not an RCT
Dong 2005	No placebo group
Douglas 1957	Not randomised and study had no placebo group
Egede 1993	No placebo group
Elmes 1965	Not randomised. Matched pairs
Fartoukh 2004	Protocol. Trial not initiated due to recruitment problems
Filipovic 2000	No placebo group
Francis 1960	Use of long-term prophylactic antibiotics
Francis 1964	No placebo group
Fruensgaard 1972	No placebo group
Gaillat 2007	No placebo group
Gocke 1964	No placebo group
Goddard 2003	Not an RCT
Gomez 2000	Prophylactic antibiotic use. Participants were treated with azithromycin 500 mg/d for 3 days every 21 days during the winter months, and a control group was given no treatment
Gotfried 2007	No placebo group
Guerin 1987	No placebo group
Haanaes 1980	No placebo group
Hansen 1986	Not an RCT
Hansen 1990	No clinical outcomes
Hauke 2002	No placebo group
Hopkins 1962	No placebo group
Jacobsen 2002	Not an RCT, but a retrospective chart review
Jia 2010	No placebo group
Johnston 1961	Study assessed outcomes of long-term antibiotic use in stable patients (no exacerbation)

Study	Reason for exclusion
Kaul 1967	No placebo group
King 1996	Study not in patients with COPD, but in patients with acute bronchitis
Leophonte 1998	Study not in patients with COPD, but in patients with acute bronchitis
Lirsac 2000	No placebo group. In addition, the antibiotic treatment group received fenspiride (from day 0 to day 30) and the control group received a placebo
Maesen 1976	No placebo group
Maesen 1980	No placebo group
Malone 1968	No placebo group
May 1964	No placebo group
Miravitlles 2009	Study compared participants with stable disease (no exacerbation)
NCT00255983	This study terminated early (financial reasons) and results were never published
Nicotra 1982	No clinical outcomes
Nonikov 2001	No placebo group
Parnham 2005	Study looked at participants with stable disease (no exacerbation)
Peng 2003	Not an RCT, but a retrospective cohort study
Pham 1964	Not an RCT
Pines 1967	No placebo group
Pines 1969	No placebo group
Pines 1972a	No placebo group
Pines 1973	No placebo group
Pines 1973a	No placebo group
Pines 1974	Not an RCT
PRITZL 1959	Not an RCT
Puchelle 1975	No placebo group
Pugh 1964	No placebo group
Rethly 1961	Not an RCT
Roede 2007	Placebo group began after 3 days of antibiotics in both groups
Romanovskikh 2007	No placebo group

Study	Reason for exclusion
Ross 1973	No placebo group
Sethi 2007	No placebo group
Sethi 2010	Study looked at participants with stable disease (no exacerbation)
Smyllie 1972	No placebo group
Sohy 2002	Not an RCT, but a narrative review
Soler 2003	No placebo group
Soltaninejad 2016	Nebulised antibiotics
Stolz 2007	No placebo group
Suzuki 2001	Prophylactic antibiotic use
Tremolieres 2000	No placebo group
Williams 1981	No placebo group
Wilson 2004	No placebo group in the trial. Moxifloxacin was compared to standard antibiotic therapy
Wilson 2011	No placebo group
Wilson 2012	Head-to-head trial of 2 different antibiotic regimens
Zapulla 1988	No placebo group
Zervos 2005	No placebo group

COPD: chronic obstructive pulmonary disease; RCT: randomised controlled trial.

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

NCT01091493

Trial name or title	Utility of antibiotic treatment in non-purulent exacerbations of chronic obstructive pulmonary disease: a double-blinded, randomized, placebo-controlled trial of security and efficacy (AEPOC-ATB)
Methods	RCT
Participants	Inclusion criteria: aged 40 to 90 years; COPD diagnosis according to GOLD guidelines; hospitalisation for any acute exacerbation of COPD; failure of outpatient treatment, increasing dyspnoea in previous days; comorbidity that caused detriment to respiratory function Exclusion criteria: life expectancy < 6 months; mechanical ventilation; cardiovascular condition that causes exacerbation; immunosuppression; pulmonary infiltrates that suggest pneumonia; antibiotic treatment in the last month; pregnancy; ECG with a large QT segment; hypokalaemia; hepatic failure or renal failure
Interventions	Drug: moxifloxacin 400 mg administered once a day for 5 days Control: no intervention

NCT01091493 *(Continued)*

Outcomes	Primary outcome measures: efficacy of treatment WITHOUT antibiotics in non-purulent exacerbations of COPD (time frame: 6 months) Secondary outcome measures: efficacy/safety in treatment on re-hospitalisation at 6 months (time frame: 6 months); in-hospital stay (days) (time frame: 6 months); all-cause mortality (time frame: 1 and 6 months); determination of procalcitonin (time frame: hospitalisation day 1, 1 month, and 6 months); quality of life measured by St. George's Respiratory Questionnaire (time frame: hospitalisation day 1 and 6 months); measure of CRP (time frame: hospitalisation day 1, 1 month, and 6 months); measure of cytokines (IL-1, IL-6, IL-8, IL-10) (time frame: hospitalisation day 1, 1 month, and 6 months); measure of TNF-α (time frame: hospitalisation day 1, 1 month, and 6 months)
Starting date	July 2010
Contact information	Nestor Soler, MD, PhD; email:nsoler@clinic.ub.es
Notes	-

NCT01892488

Trial name or title	Randomized double-blind placebo-controlled study to demonstrate that antibiotics are not needed in moderate acute exacerbations of COPD - the ABACOPD Study
Methods	RCT
Participants	Inclusion criteria: • Adults, either sex, 40 years of age and older • For female patients, the following conditions are to be met: has been postmenopausal for at least 1 year, or is surgically incapable of bearing children, or is of childbearing potential, and the following conditions are met: has a negative pregnancy test (urine- or serum-based) immediately before study entry (i.e. before the start of treatment or any other study procedure that could potentially harm the foetus), and 1 or more of following criteria: must agree to abstinence or use an accepted method of contraception. The patient must agree to continue with the same method throughout the study, having only female sexual partners or sexual relationships with sterile male partners only • Patients with diagnosis of COPD stages I to IV as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) and • Doctor's diagnosis of acute (onset < 7 days) moderate exacerbation of COPD defined by sustained worsening of the patient's condition (including at least 2 of the following symptoms: increased dyspnoea, increased sputum production, sputum purulence, and increased cough), from the stable state and beyond normal day-to-day variations, necessitating a change in regular medication in patients with underlying COPD needing additional medical assistance • Absence of community-acquired pneumonia or lower respiratory tract infection with a clear indication for antibiotic treatment as determined by procalcitonin level < 0.25 ng/mL and/or absence of pulmonary infiltrates on routine chest X-ray • Smoking history of 10 or more pack-years • Must be able to complete diaries and quality of life questionnaires • Must sign and date an informed consent before beginning any study procedures
Interventions	Placebo vs sultamicillin
Outcomes	Antibiotic therapy added to study medication during treatment period or until the test of cure visit (at day 30) Relapse rate

NCT01892488 *(Continued)*

	Time to relapse Clinical cure rate at the "end of therapy visit" (at day 6) Clinical cure rate at the "test of cure visit" (at day 30) Changes in CAT Changes in Exacerbations of Chronic Pulmonary Disease Tool-Patient Reported Outcome (EXACT-PRO) Additional antibiotic therapy Time to next exacerbation Number of exacerbations during follow-up Per-participant relapse rate at LFU (late follow-up) visits in the subset of participants who were clinically cured at the TOC visit Changes in length of stay in hospital for hospitalised participants All-cause mortality
Starting date	June 2013
Contact information	Grit Barten: grit.barten@capnetz.de Waldemar Kroener: waldemar.kroener@capnetz.de
Notes	

NCT03262142

Trial name or title	Targeted antibiotics for chronic obstructive pulmonary disease (Target-ABC)
Methods	RCT
Participants	Inclusion criteria: • Adults of either sex 40 years of age and older • 1 positive sputum sample for *P aeruginosa* • COPD (verified by pulmonologist based on clinical and spirometric criteria) • Minimum 1 previous AECOPD requiring hospitalisation/emergency department visit and administration of systemic prednisolone ± antibiotic treatment within the last 12 months • Completed and signed informed consent Exclusion criteria: • Immune-modulating therapy (except ≤ 5 mg prednisolone/d) • Men < 40 years • Women < 55 years • Non-menopausal women > 55 years • Life expectancy < 90 days • Severe mental illness • Severe language difficulties or inability to provide informed consent • Known drug allergy to (1) fluoroquinolones or (2) piperacillin/tazobactam, cephalosporins, and carbapenems

NCT03262142 *(Continued)*	• Attempted eradication of *P aeruginosa* × 2 within the last 12 months, or completed eradication therapy within the last 14 days • Investigator 's opinion is that the participant requires antibiotic treatment. This exclusion criterion must be discussed with the co-ordinating investigator before the final decision on exclusion is made • Has had menstruation within the last 12 months • Treatment with same antibiotics as used in the trial
Interventions	Intravenous piperacillin/tazobactam + oral ciprofloxacin for 14 days vs no antibiotic treatment
Outcomes	Primary: time to systemic corticosteroid and/or antibiotic requiring AECOPD (in both primary and secondary sectors) or death Secondary: alive and without AECOPD; death; microbiological cure; clinical cure; number of re-admissions with AECOPD; number of days with non-invasive ventilation (NIV) or respiratory therapy; change in FEV_1; fall in $FEV_1 \geq 200$ mL/y; change in COPD assessment test (CAT); changes in body mass index (BMI)
Starting date	January 2018
Contact information	Josefin Eklof; josefin.viktoria.ekloef@regionh.dk
Notes	

AECOPD: acute exacerbation of COPD; BMI: body mass index; CAT: COPD Assessment Test; COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; ECG: electrocardiogram; EXACT-PRO: Exacerbations of Chronic Pulmonary Disease Tool-Patient Reported Outcome; FEV_1: forced expiratory volume in one second; GOLD: Global Initiative for Chronic Obstructive Lung Disease; IL: interleukin; LFU: late follow-up; NIV: non-invasive ventilation; *P aeruginosa: Pseudomonas aeruginosa*; RCT: randomised controlled trial; TNF-α: tumour necrosis factor-alpha; TOC: Test of Cure.

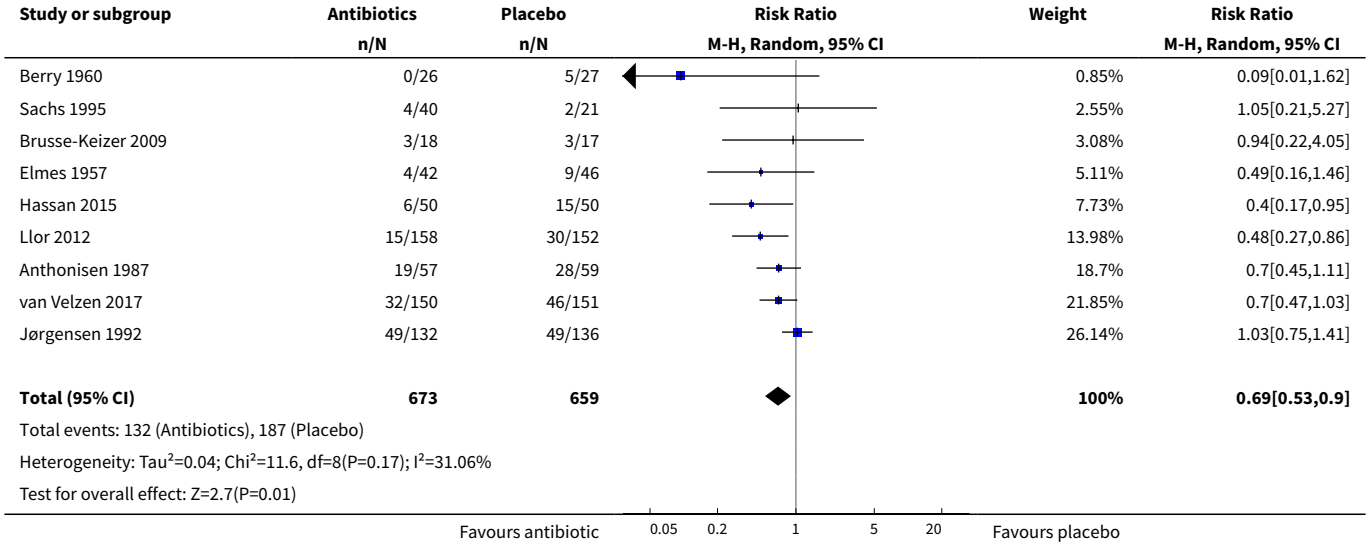
DATA AND ANALYSES

Comparison 1. Antibiotics versus placebo: outpatients

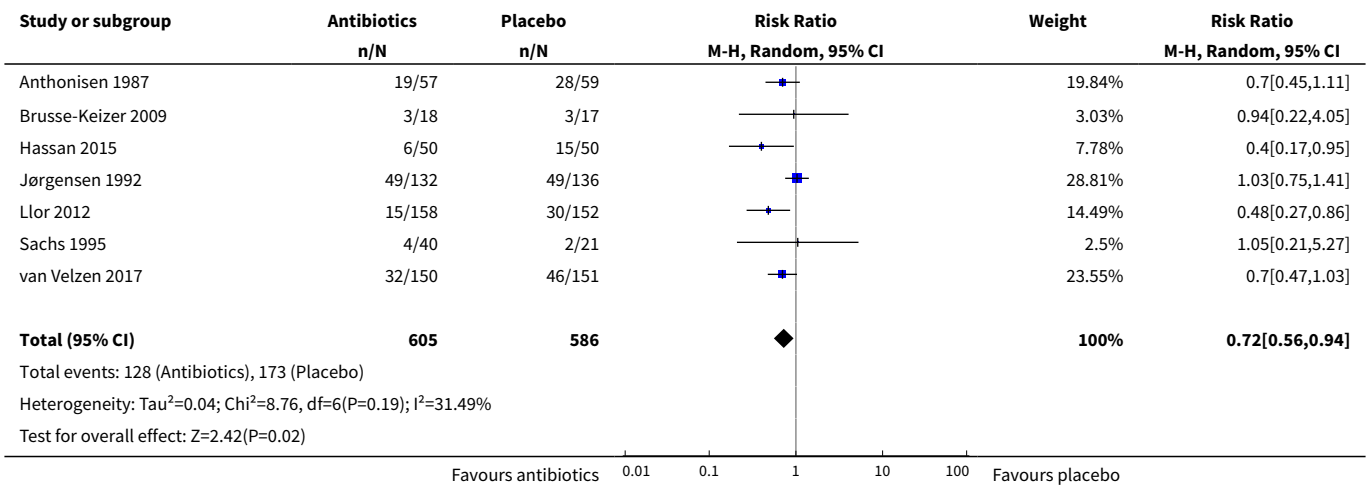
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure up to 4 weeks (no resolution or deterioration after trial medication of any duration or death when explicitly stated due to exacerbation or additional course of antibiotics)	9	1332	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.53, 0.90]
2 Treatment failure within 4 weeks - current drugs only	7	1191	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.56, 0.94]
3 All-cause mortality	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
4 Re-exacerbations within ≥ 2 to 6 weeks since beginning of index exacerbation (rates)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
5 Improvement in dyspnoea measured at the end of the study period	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Health-related quality of life or functional status measures	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7 Days off work	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Antibiotics versus placebo: outpatients, Outcome 1 Treatment failure up to 4 weeks (no resolution or deterioration after trial medication of any duration or death when explicitly stated due to exacerbation or additional course of antibiotics).

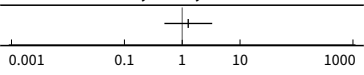


Analysis 1.2. Comparison 1 Antibiotics versus placebo: outpatients, Outcome 2 Treatment failure within 4 weeks - current drugs only.



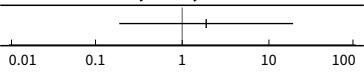
Analysis 1.3. Comparison 1 Antibiotics versus placebo: outpatients, Outcome 3 All-cause mortality.

Study or subgroup	Antibiotics n/N	Placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI
van Velzen 2017	10/150	8/151		1.27[0.49,3.3]



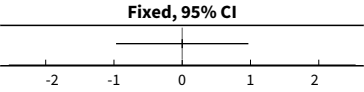
Analysis 1.4. Comparison 1 Antibiotics versus placebo: outpatients, Outcome 4 Re-exacerbations within ≥ 2 to 6 weeks since beginning of index exacerbation (rates).

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Brusse-Keizer 2009	2/18	1/17		1.89[0.19,18.97]



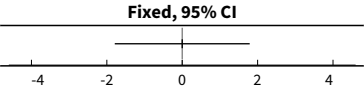
Analysis 1.5. Comparison 1 Antibiotics versus placebo: outpatients, Outcome 5 Improvement in dyspnoea measured at the end of the study period.

Study or subgroup	Antibiotics N	Antibiotics Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Brusse-Keizer 2009	18	0.5 (1.3)	17	0.5 (1.6)		0[-0.97,0.97]



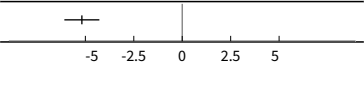
Analysis 1.6. Comparison 1 Antibiotics versus placebo: outpatients, Outcome 6 Health-related quality of life or functional status measures.

Study or subgroup	Antibiotics N	Antibiotics Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Brusse-Keizer 2009	18	-2.3 (2.7)	17	-2.3 (2.7)		0[-1.79,1.79]



Analysis 1.7. Comparison 1 Antibiotics versus placebo: outpatients, Outcome 7 Days off work.

Study or subgroup	Antibiotics N	Antibiotics Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Elmes 1957	42	4.3 (1)	46	9.4 (3)		-5.18[-6.08,-4.28]

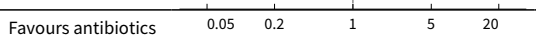


Comparison 2. Antibiotics versus placebo: inpatients

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure up to 4 weeks (no resolution or deterioration after trial medication of any duration or death when explicitly stated due to exacerbation or additional course of antibiotics)	6	896	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.39, 0.91]
1.1 Inpatient	5	803	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.58, 1.00]
1.2 ICU	1	93	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.08, 0.45]
2 Treatment failure within 4 weeks - current drugs only	4	576	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.38, 1.12]
2.1 Inpatient	4	576	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.38, 1.12]
3 All-cause mortality	3	507	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.95 [0.45, 2.02]
3.1 Inpatients	2	414	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.48 [0.94, 6.55]
3.2 ICU patients	1	93	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.21 [0.06, 0.72]
4 Duration of hospital stay (days)	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 Inpatients	3	300	Mean Difference (IV, Random, 95% CI)	0.09 [-0.79, 0.96]
4.2 ICU	1	93	Mean Difference (IV, Random, 95% CI)	-9.6 [-12.84, -6.36]
5 Re-exacerbations within ≥ 2 to 6 weeks since beginning of index exacerbation (rates)	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6 Improvement in dyspnoea measured at the end of the study period	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.1 Inpatients	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Health-related quality of life or functional status measures	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
8 Days off work	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

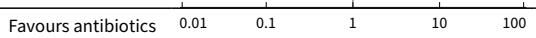
Analysis 2.1. Comparison 2 Antibiotics versus placebo: inpatients, Outcome 1 Treatment failure up to 4 weeks (no resolution or deterioration after trial medication of any duration or death when explicitly stated due to exacerbation or additional course of antibiotics).

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 Inpatient					
Wang 2016	6/95	4/96		8.31%	1.52[0.44,5.2]
Alonso Martinez 1992	4/61	6/29		8.79%	0.32[0.1,1.04]
Pines 1968	5/15	12/15		15.11%	0.42[0.2,0.89]
Daniels 2010	50/128	65/137		26.6%	0.82[0.62,1.09]
Pines 1972	93/160	46/67		28.08%	0.85[0.69,1.04]
Subtotal (95% CI)	**459**	**344**		**86.88%**	**0.76[0.58,1]**
Total events: 158 (Antibiotics), 133 (Placebo)					
Heterogeneity: Tau^2=0.03; Chi^2=6.57, df=4(P=0.16); I^2=39.16%					
Test for overall effect: Z=1.97(P=0.05)					
2.1.2 ICU					
Nouira 2001	5/47	26/46		13.12%	0.19[0.08,0.45]
Subtotal (95% CI)	**47**	**46**		**13.12%**	**0.19[0.08,0.45]**
Total events: 5 (Antibiotics), 26 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=3.78(P=0)					
Total (95% CI)	**506**	**390**		**100%**	**0.6[0.39,0.91]**
Total events: 163 (Antibiotics), 159 (Placebo)					
Heterogeneity: Tau^2=0.15; Chi^2=18.22, df=5(P=0); I^2=72.56%					
Test for overall effect: Z=2.42(P=0.02)					
Test for subgroup differences: Chi^2=9.12, df=1 (P=0), I^2=89.04%					

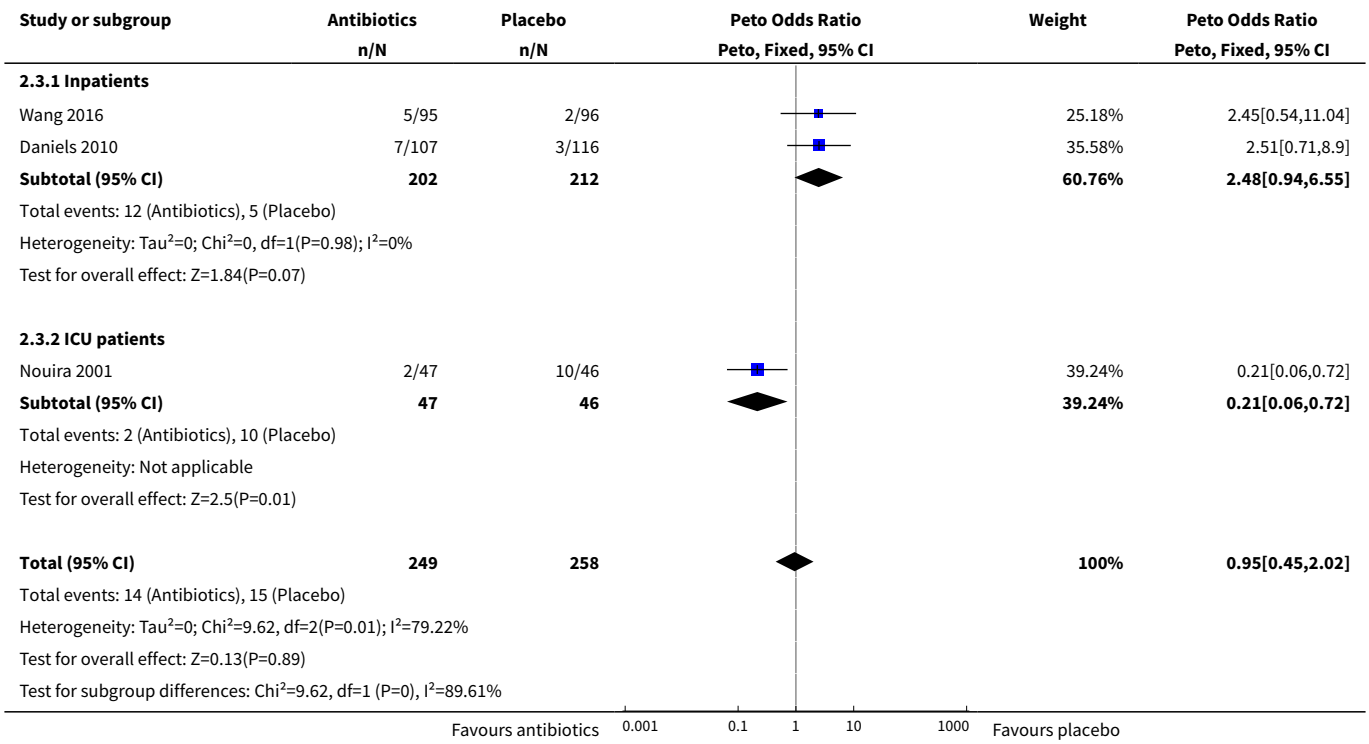


Analysis 2.2. Comparison 2 Antibiotics versus placebo: inpatients, Outcome 2 Treatment failure within 4 weeks - current drugs only.

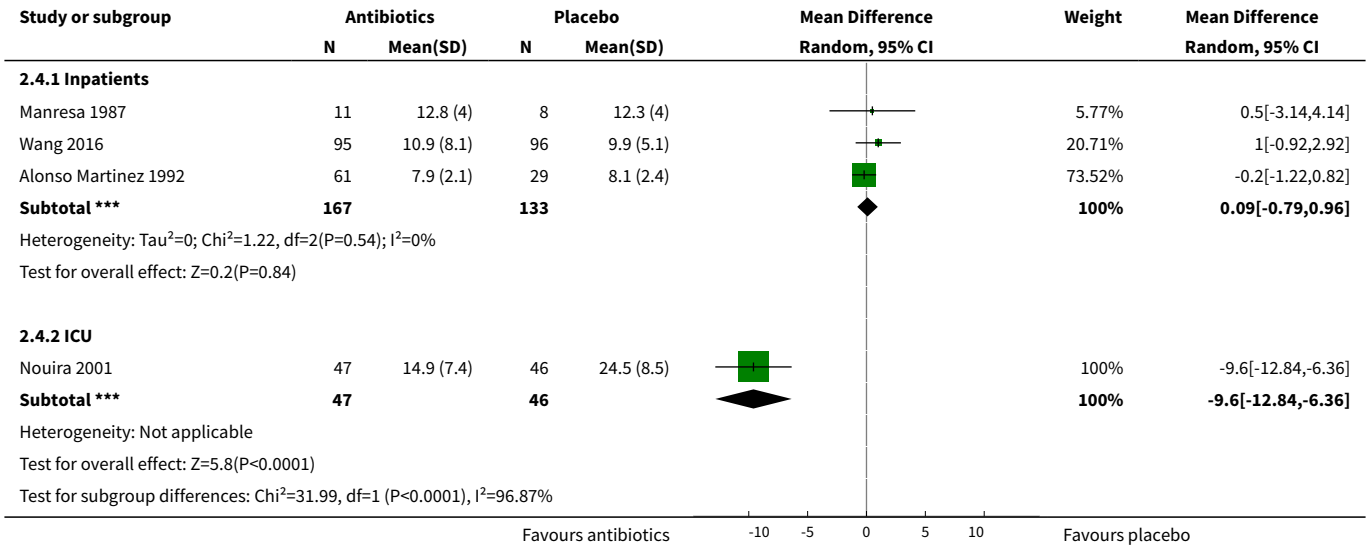
Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 Inpatient					
Wang 2016	6/95	4/96		14%	1.52[0.44,5.2]
Alonso Martinez 1992	4/61	6/29		14.82%	0.32[0.1,1.04]
Pines 1968	5/15	12/15		25.61%	0.42[0.2,0.89]
Daniels 2010	50/128	65/137		45.56%	0.82[0.62,1.09]
Subtotal (95% CI)	**299**	**277**		**100%**	**0.65[0.38,1.12]**
Total events: 65 (Antibiotics), 87 (Placebo)					
Heterogeneity: Tau^2=0.15; Chi^2=6.01, df=3(P=0.11); I^2=50.1%					
Test for overall effect: Z=1.54(P=0.12)					
Total (95% CI)	**299**	**277**		**100%**	**0.65[0.38,1.12]**
Total events: 65 (Antibiotics), 87 (Placebo)					
Heterogeneity: Tau^2=0.15; Chi^2=6.01, df=3(P=0.11); I^2=50.1%					
Test for overall effect: Z=1.54(P=0.12)					



Analysis 2.3. Comparison 2 Antibiotics versus placebo: inpatients, Outcome 3 All-cause mortality.

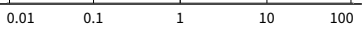


Analysis 2.4. Comparison 2 Antibiotics versus placebo: inpatients, Outcome 4 Duration of hospital stay (days).



Analysis 2.5. Comparison 2 Antibiotics versus placebo: inpatients, Outcome 5 Re-exacerbations within ≥ 2 to 6 weeks since beginning of index exacerbation (rates).

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Brusse-Keizer 2009	2/18	1/17		1.89[0.19,18.97]
Wang 2016	17/95	11/96		1.56[0.77,3.16]

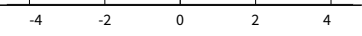


Analysis 2.6. Comparison 2 Antibiotics versus placebo: inpatients, Outcome 6 Improvement in dyspnoea measured at the end of the study period.

Study or subgroup	Antibiotics N	Antibiotics Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
2.6.1 Inpatients						
Daniels 2010	128	-2.4 (2.8)	137	-1.8 (2.8)		-0.6[-1.27,0.07]

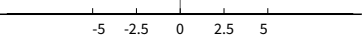
Analysis 2.7. Comparison 2 Antibiotics versus placebo: inpatients, Outcome 7 Health-related quality of life or functional status measures.

Study or subgroup	Antibiotics N	Antibiotics Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Brusse-Keizer 2009	18	-2.3 (2.7)	17	-2.3 (2.7)		0[-1.79,1.79]



Analysis 2.8. Comparison 2 Antibiotics versus placebo: inpatients, Outcome 8 Days off work.

Study or subgroup	Antibiotics N	Antibiotics Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Elmes 1957	42	4.3 (1)	46	9.4 (3)		-5.18[-6.08,-4.28]



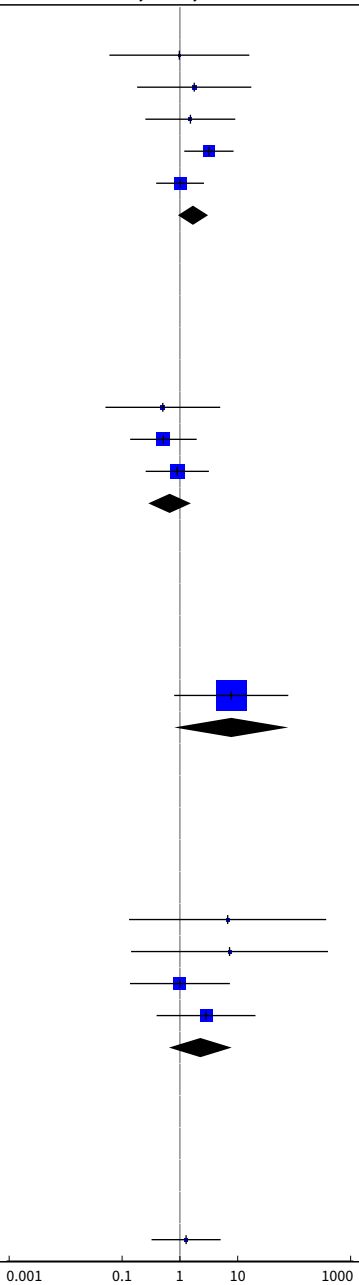
Comparison 3. Antibiotics versus placebo: adverse events

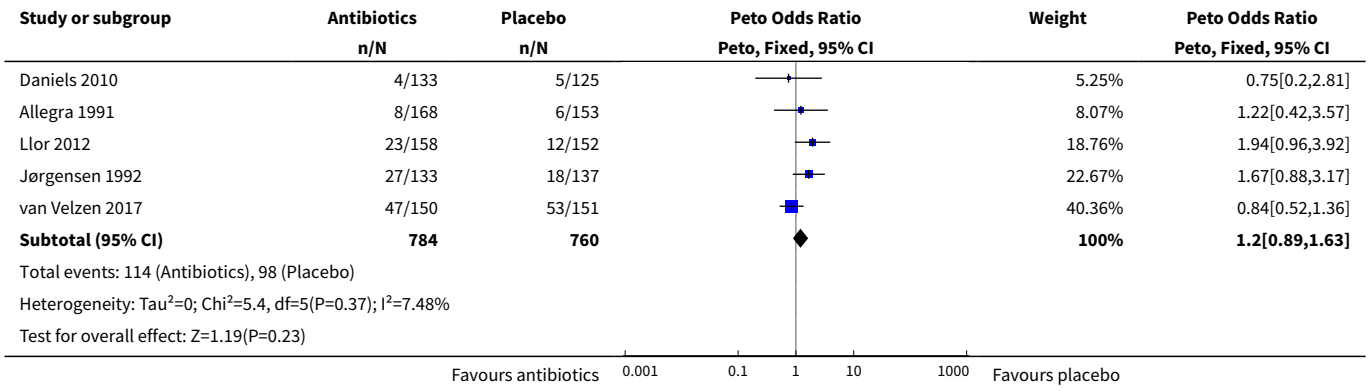
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse events	7		Peto Odds Ratio (Peto, Fixed, 95% CI)	Subtotals only
1.1 Diarrhoea	5	1099	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.68 [0.92, 3.07]
1.2 Dyspepsia	3	705	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.66 [0.28, 1.55]
1.3 Pain in mouth	1	270	Peto Odds Ratio (Peto, Fixed, 95% CI)	7.73 [0.80, 74.98]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.4 Exanthema, itching	4	798	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.26 [0.65, 7.87]
1.5 Overall (adverse events not separated)	6	1544	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.20 [0.89, 1.63]

Analysis 3.1. Comparison 3 Antibiotics versus placebo: adverse events, Outcome 1 Adverse events.

Study or subgroup	Antibiotics n/N	Placebo n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
3.1.1 Diarrhoea					
Nouira 2001	1/47	1/46		4.63%	0.98[0.06,15.89]
Allegra 1991	2/176	1/159		6.96%	1.77[0.18,17.17]
Hassan 2015	3/50	2/50		11.23%	1.52[0.25,9.08]
Jørgensen 1992	13/133	4/137		37.42%	3.18[1.19,8.48]
van Velzen 2017	9/150	9/151		39.75%	1.01[0.39,2.61]
Subtotal (95% CI)	**556**	**543**		**100%**	**1.68[0.92,3.07]**
Total events: 28 (Antibiotics), 17 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.9, df=4(P=0.57); I^2=0%					
Test for overall effect: Z=1.7(P=0.09)					
3.1.2 Dyspepsia					
Hassan 2015	1/50	2/50		13.75%	0.51[0.05,4.98]
Jørgensen 1992	3/133	6/137		40.84%	0.52[0.14,1.95]
Allegra 1991	5/176	5/159		45.41%	0.9[0.26,3.17]
Subtotal (95% CI)	**359**	**346**		**100%**	**0.66[0.28,1.55]**
Total events: 9 (Antibiotics), 13 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.41, df=2(P=0.81); I^2=0%					
Test for overall effect: Z=0.95(P=0.34)					
3.1.3 Pain in mouth					
Jørgensen 1992	3/133	0/137		100%	7.73[0.8,74.98]
Subtotal (95% CI)	**133**	**137**		**100%**	**7.73[0.8,74.98]**
Total events: 3 (Antibiotics), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.76(P=0.08)					
3.1.4 Exanthema, itching					
Allegra 1991	1/176	0/159		10.15%	6.71[0.13,339.81]
Nouira 2001	1/47	0/46		10.17%	7.23[0.14,364.63]
Hassan 2015	2/50	2/50		39.46%	1[0.14,7.32]
Jørgensen 1992	3/133	1/137		40.23%	2.83[0.39,20.34]
Subtotal (95% CI)	**406**	**392**		**100%**	**2.26[0.65,7.87]**
Total events: 7 (Antibiotics), 3 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.33, df=3(P=0.72); I^2=0%					
Test for overall effect: Z=1.28(P=0.2)					
3.1.5 Overall (adverse events not separated)					
Nouira 2001	5/42	4/42		4.9%	1.28[0.32,5.06]





ADDITIONAL TABLES

Table 1. Type and dose of antibiotic used

Study	Antibiotic	Dose (g/d)	Duration (days)	Currently available and used?	Co-interventions	Control	Setting
Allegra 1991	Amoxicillin-clavulanic acid (oral)	2	5	Yes		Placebo	Outpatient
Alonso Martinez 1992	Trimethoprim-sulphamethoxazole or amoxicillin-clavulanic acid	1.9	8	Yes	Prednisone	Placebo and prednisone	Hospital
Anthonisen 1987	Trimethoprim/sulphamethoxazole (oral)	1.9	10	Yes		Placebo	Outpatient
	Amoxicillin (oral)	1					
	Doxycycline (oral)	0.1-0.2					
Berry 1960	Oxytetracycline (oral)	1 g/d	5	No		Placebo	Outpatient
Brusse-Keizer 2009	Amoxicillin-clavulanic acid (oral)	1.5	7	Yes	Oral prednisolone 30 mg for 7 days	Placebo for 7 days and oral prednisolone 30 mg for 7 days	Outpatient
Daniels 2010	Doxycycline (oral)	Not stated	7	Yes	IV prednisolone taper	Placebo plus IV prednisolone taper	Hospital
Elmes 1957	Oxytetracycline (oral)	1	5-7	No		Placebo	Outpatient
Fear 1962	Oxytetracycline (oral)	1	7	No		Placebo	Outpatient
Hassan 2015	Ciprofloxacin (oral)	1	10	Yes	Oral prednisolone 40 mg/d for 3 days followed by 5–10 mg for 12 days if steroid responsive	Placebo	Outpatient
	Amoxicillin (oral)	1.5					
Jørgensen 1992	Amoxicillin (oral)	1.5	7	Yes		Placebo	Outpatient

Table 1. Type and dose of antibiotic used *(Continued)*

Llor 2012	Amoxicillin-clavulanate (oral)	1.5	8	Yes		Placebo	Outpatient
Manresa 1987	Cefaclor (oral)	1.5	8	Yes		Placebo	Hospital
Nouira 2001	Ofloxacin (oral)	0.4	10	Yes		Placebo	Medical ICU
Petersen 1967	Chloramphenicol (oral)	2	10	No		Placebo	Hospital
Pines 1968	Penicillin (parenteral)	1	14	Yes		Placebo	Hospital
Pines 1972	Tetracycline hydrochloride (oral) or chloramphenicol	2	12	No		Placebo	Hospital
Sachs 1995	Amoxicillin (oral)	1.5 or 1.9	7	yes		Placebo	Outpatient
	Co-trimoxazole	1.9					
van Velzen 2017	Doxycycline (oral)	0.1	7	Yes	30 mg oral prednisolone daily for 10 days	Placebo and 30 mg oral prednisolone daily for 10 days	Outpatient
Wang 2016	Piperacillin-sulbactam, ceftazidine, or levofloxacin	Not stated	As needed	Yes	No	Placebo	Hospital

IV: intravenous.

APPENDICES

Appendix 1. Search methods used in the previous version of this review (published 2012)

Electronic searches

We identified trials using the Cochrane Airways Group Specialised Register of trials, which is derived from systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, CINAHL, AMED, and PsycINFO, and handsearching of respiratory journals and meeting abstracts (see appendix for further details). All records in the Specialised Register coded as 'COPD' were searched using the following terms:

- antibiotic* or penicillin* or amoxycillin or ampicillin or cefalosporin* or cefaclor or cefalexine or cephalotin or cefazolin or cefixime or cefotaxime or cefpodoxime or cephradine or ceftizoxime or ceftriaxone or cefuroxime or tetracyclin* or demeclocycline or doxycycline or minocycline or oxytetracycline or *cycline or macrolides or azithromycin or clarithromycin or dirithromycin or erythromycin or roxithromycin or telithromycin or troleandomycin or *thromycin or (*mycin) or fluoroquinoln* or ciprofloxacin or gatifloxacin or gemfloxacin or grepafloxacin or levofloxacin or lomefloxacin or moxifloxacin or ofloxacin or sparfloxacin or trovafloxacin or *floxacin or chloramphenicol or clindamycin or trimethoprim or sulfamethxazole or cotrimoxazole or carbapenem* or meropenem or imipenem.

A search of ClinicalTrials.gov was also conducted. Databases were searched from 2005 (their inception) to April 2012. The search from inception to 2006 is described elsewhere (Puhan 2007). There was no restriction on the language of publication.

Searching other resources

Bibliographies of each selected RCT, as well as other systematic reviews, were scrutinised for additional potential RCTs. Authors of identified RCTs and pharmaceutical companies producing antibiotics were contacted for other published, unpublished, or ongoing studies.

Appendix 2. Sources and search methods for the Cochrane Airways Register of Trials

Electronic searches: core databases

Database	Frequency of search
CENTRAL (the Cochrane Library)	Monthly
MEDLINE (Ovid)	Weekly
Embase (Ovid)	Weekly
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards

(Continued)

British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the CAGR

COPD search

1. Lung Diseases, Obstructive/

2. exp Pulmonary Disease, Chronic Obstructive/

3. emphysema$.mp.

4. (chronic$ adj3 bronchiti$).mp.

5. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.

6. COPD.mp.

7. COAD.mp.

8. COBD.mp.

9. AECB.mp.

10. or/1-9

Filter to identify RCTs

1. exp "clinical trial [publication type]"/

2. (randomised or randomised).ab,ti.

3. placebo.ab,ti.

4. dt.fs.

5. randomly.ab,ti.

6. trial.ab,ti.

7. groups.ab,ti.

8. or/1-7

9. Animals/

10. Humans/

11. 9 not (9 and 10)

12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases

Appendix 3. Search strategy to identify relevant trials from the Cochrane Airways Trials Register

Via the Cochrane Register of Studies (CRS)

#1 MeSH DESCRIPTOR Pulmonary Disease, Chronic Obstructive Explode All

#2 MeSH DESCRIPTOR Bronchitis, Chronic

#3 (obstruct*) near3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)

#4 COPD:MISC1

#5 (COPD OR COAD OR COBD):TI,AB,KW

#6 #1 OR #2 OR #3 OR #4 OR #5

#7 antibiotic*

#8 penicillin*

#9 amoxycillin

#10 amoxicillin

#11 ampicillin

#12 cefalosporin*

#13 cefaclor

#14 cefazolin

#15 cefixime

#16 cefotaxime

#17 cefpodoxime

#18 cephradine

#19 ceftizoxime

#20 ceftriaxone

#21 cefuroxime

#22 tetracyclin*

#23 demeclocycline

#24 doxycycline

#25 minocycline

#26 oxytetracycline

#27 *cycline

#28 macrolides

#29 azithromycin

#30 clarithromycin

#31 dirithromycin

#32 erythromycin

#33 roxithromycin

#34 telithromycin

#35 troleandomycin

#36 *thromycin

#37 *mycin

#38 ciprofloxacin

#39 gatifloxacin

#40 grepafloxacin

#41 levofloxacin

#42 lomefloxacin

#43 moxifloxacin

#44 ofloxacin

#45 sparfloxacin

#46 trovafloxacin

#47 *floxacin

#48 chloramphenicol

#49 clindamycin

#50 trimethoprim

#51 cotrimoxazole

#52 carbapenem*

#53 meropenem

#54 imipenem

#55 cefalexin*

#56 cephalothin

#57 cefalotin

#58 fluoroquinolone*

#59 gemifloxacin

#60 sulfamethoxazole

#61 cephalosporin

#62 #7 or#8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61

#63 #6 and #62

WHAT'S NEW

Date	Event	Description
29 October 2018	Amended	Corrected search date.

HISTORY

Review first published: Issue 12, 2012

Date	Event	Description
30 April 2018	New search has been performed	New literature search run
30 April 2017	New citation required but conclusions have not changed	Three trials added to the review. New outcome added: time to next exacerbation. Review refreshed to reflect up-to-date Cochrane practice, for example, background rewritten under correct headings, summary of findings tables added

CONTRIBUTIONS OF AUTHORS

All review authors conceived the idea for the review and wrote the protocol.
DV, AF, MAP, and CSS contributed towards the following: trial selection, data, and extraction of trial characteristics.

AF and MAP checked the data extraction.

DV, AF, and MAP contributed to trial grading.

DV wrote the first draft and all review authors critically reviewed the draft.

DV and MP are guarantors for this review.

DECLARATIONS OF INTEREST

Claudia Steurer-Stey has lectured for the antibiotic-producing companies AstraZeneca, GlaxoWellcome, Merck Sharp & Dome, Pfizer, and Novartis.

JGA has received consultation and lecture fees from AstraZeneca and lecture fees from Esteve and Chiesi.

The remaining authors (DV, AF, and MAP) have no known conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- The review authors declare that no such funding was received for this systematic review, Other.

External sources

- The review authors declare that no such funding was received for this systematic review, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We added time to next exacerbation as an additional outcome.

Changes made to the protocol for the last published version of the review include the following.

- We had to change our primary outcome from treatment failure within two weeks to four weeks because reporting of the time of the endpoint was too heterogeneous.
- Some outcomes were not reported at all (hospital admissions, admissions to an ICU).

- We did not analyse subgroups on duration of antibiotic intervention or type of antibiotic intervention because the number of studies was too small.

INDEX TERMS

Medical Subject Headings (MeSH)

Ambulatory Care; Anti-Bacterial Agents [adverse effects] [*therapeutic use]; Disease Progression; Hospitalization; Intensive Care Units; Pulmonary Disease, Chronic Obstructive [classification] [*drug therapy] [mortality]; Randomized Controlled Trials as Topic; Treatment Failure

MeSH check words

Humans