Does antibiotic treatment duration affect the outcomes of exacerbations of asthma and COPD? A systematic review

Marie Stolbrink¹, Jack Amiry² and John D Blakey³,⁴

Abstract
Asthma and chronic obstructive pulmonary disease (COPD) cause significant morbidity and mortality worldwide, primarily through exacerbations. Exacerbations are often treated with antibiotics but their optimal course duration is uncertain. Reducing antibiotic duration may influence antimicrobial resistance but risks treatment failure. The objective of this article is to review published literature to investigate whether shorter antibiotic therapy duration affects clinical outcomes in the treatment of asthma and COPD exacerbations. We systematically searched electronic databases (MEDLINE, EMBASE, CINAHL, World Health Organisation International Clinical Trial Registry Platform, the Cochrane library, and ISRCTN) with no language, location, or time restrictions. We retrieved observational and controlled trials comparing different durations of the same oral antibiotic therapy in the treatment of acute exacerbations of asthma or COPD in adults. We found no applicable studies for asthma exacerbations. We included 10 randomized, placebo-controlled trials for COPD patients, all from high-income countries. The commonest studied antibiotic class was fluoroquinolones. Antibiotic courses shorter than 6 days were associated with significantly fewer overall adverse events (risk ratio (RR): 0.84, 95% confidence interval (CI): 0.75–0.93, \(p=0.001\)) when compared with those of 7 or more days. There was no statistically significant difference for clinical success or bacteriological eradication in sputum (RR: 1.00, 95% CI: 0.88–1.13 and RR: 1.06, 95% CI: 0.79–1.44, respectively). Shorter durations of antibiotics for COPD exacerbations do not seem to confer a higher risk of treatment failure but are associated with fewer adverse events. This is in keeping with previous studies in community acquired pneumonia, but studies were heterogeneous and differed from usual clinical practice. Further observational and prospective work is needed to explore the significance of antibiotic duration in the treatment of asthma and COPD exacerbations.

Keywords
Asthma, COPD, exacerbation, antibiotics, duration, antimicrobial resistance

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Introduction
Background
Asthma and chronic obstructive pulmonary disease (COPD) are common and are becoming more prevalent globally.¹⁻⁴ Exacerbations are a major driver of the morbidity, mortality, and cost associated with these chronic airways diseases.⁵,⁶ The majority of exacerbations are nonbacterial in origin.⁷⁻⁹ They are, however, frequently treated with antibiotics hence...
causing a significant antibiotic burden.\textsuperscript{10,11} For example, over 11 years, 22\% of 16.1 million asthma presentations to US hospitals received antibiotics, largely against current guidelines.\textsuperscript{12}

Antimicrobial resistance is one of the most important public health crises facing the world today. Reduced susceptibility to penicillin or penicillin-resistance in \textit{Streptococcus pneumoniae} exceeds more than 50\% in many countries.\textsuperscript{13} The World Health Organisation (WHO) issued a global action plan on antimicrobial resistance in 2015 which called for optimization of antibiotic prescribing.\textsuperscript{14} Use of shorter antibiotic courses may be beneficial to reduce resistance, improve concordance, costs, and side effects. However, shorter courses risk treatment failure. Patients in middle and lower income countries are more susceptible to failure due to a number of factors: reduced susceptibility to penicillins; limited access to follow-up; malnutrition; and higher risk of abnormal lung architecture caused by air pollution, smoking, and industrial exposures.\textsuperscript{15–17}

The ideal duration of antibiotic treatment for asthma and COPD exacerbations is uncertain and a prescribing consensus is a priority for providers. The last systematic review on antibiotic duration in COPD exacerbations was published in 2008\textsuperscript{18} and none have been published in asthma exacerbations. We therefore undertook an up-to-date review and meta-analysis to investigate whether shorter courses of oral antibiotic treatment for asthma and COPD exacerbations are associated with different outcomes when compared with longer courses.

\textbf{Methods}

\textbf{Data sources and search strategy.} We conducted systematic searches of bibliographic databases including MEDLINE, EMBASE, and CINAHL through National Health Service library services. We also ran a search of the WHO International Clinical Trial Registry Platform, the Cochrane library, and ISRCTN and used search engines on their own websites. All databases were searched from inception until February 29, 2016. There was no restriction of publication language. We removed duplicate references using reference management software (EndNote X7; Thomson Reuters, USA). The search strategy is described below. The reference lists of earlier reviews on the same topic and abstracts of the European Respiratory Society and American Thoracic Society conferences from the previous year (2015) were hand-searched and titles included if the inclusion criteria were fulfilled.

\textbf{Study selection.} We included observational and controlled trials of adults (≥ 18 years) with a clinical diagnosis of asthma or COPD exacerbation. We only included original studies with explicitly different durations of the same oral antibiotic therapy. We excluded the studies of pneumonia treatment and prophylactic antibiotics.

We reviewed the list of titles to exclude publications which were clearly not contributory on this basis and duplicate titles. Two investigators screened the eligible abstracts independently. We obtained full text articles of selected papers via University of Liverpool library, NHS library, and interlibrary loans. Two investigators reviewed the full texts for eligibility independently. Any disagreement was resolved by a third investigator.

\textbf{Data extraction.} Two authors extracted data using a preset data extraction form which included details of the study’s publication, authorship, and funding; study characteristics (design and location); participants (sample size, method of recruitment, selection, and demographics); outcome measures; interventions; data analysis and reporting; confounding adjustments; and the main findings. Disagreements were resolved by discussion. We used RevMan 5.3 (Cochrane Collaboration) and EndNote X7 software in the collection and management of data from abstracts and papers.

\textbf{Quality and risk of bias assessment.} We assessed the studies’ accuracy and risk of bias using the Cochrane Handbook for Systematic Reviews of Interventions criteria.\textsuperscript{19} Controlled trials were additionally analyzed using the Cochrane Collaboration’s tool for assessing risk of bias.

\textbf{Analysis.} We combined intention to treat population data from comparable studies in quantitative analyses. We pooled data using fixed effect model in RevMan 5.3.\textsuperscript{20} We used the Mantel–Haenszel method, presenting data as risk ratio (RR) with 95\% confidence intervals (CIs). We used statistical significance of $p < 0.05$ and assessed the degree of heterogeneity using the $I^2$ statistic.

\textbf{Results}

\textbf{Asthma}

We identified 1604 individual titles through database searches (Figure 1). No additional studies were identified by hand-searching. The commonest reason for noninclusion into abstract screening was a lack of an
We reviewed 29 abstracts. The commonest reason for not progression to full text review was missing explicit antibiotic duration (eight studies), with other reasons demonstrated in Figure 1. The one full text analyzed assessed antibiotics for one duration only and was hence excluded.

COPD

We identified 1762 individual titles in COPD from database searches, 32 from hand-searching of recent reviews and 2 from conference abstracts (Figure 2). The commonest reason for noninclusion in abstract screening was lack of COPD diagnosis (951 studies) and not assessing oral antibiotic treatment (603 studies). We screened 160 abstracts. The commonest reasons for exclusion at this stage were not assessing one antibiotic with two different durations (67 studies) or not comparing specific antibiotic durations (26 studies). Thirty-three full texts were eligible for analysis and 10 full texts were included in the final meta-analysis. One text in Polish was translated but was not applicable.

Characteristics and definitions of COPD studies

Design, participants, and setting. All 10 studies included in the meta-analysis were randomized, placebo-controlled trials (Table 1). Nine studies considered “chronic bronchitis” but included individuals with airflow limitation and a smoking history: their design would have predated the global use of the term “COPD.” Eight studies reported smoking status. The youngest enrolled participant was 18 years old. Four studies recruited from outpatients, three from hospital admissions, one from primary care, and two from primary care and outpatients. Two multicenter studies included patients in the developing world (Latin America, Pakistan, Philippines), and the rest were based in Europe or North America. Where documented, all exacerbations were diagnosed

Figure 1. PRISMA flow diagram of systematic search for asthma studies.

asthma diagnosis for all participants (1304 records).
clinically, one study used microscopically confirmed purulent sputum.\textsuperscript{26} There was a range of exacerbation severities from “mild” in outpatients to inpatients not needing critical care or ventilation.\textsuperscript{26,30} Eight studies characterized the severity of the underlying lung disease.

**Interventions and outcomes.** Fluoroquinolones were the most commonly examined antimicrobial class (five studies). Two studies assessed grepafloxacin and two assessed co-amoxiclav. The shortest antibiotic treatment was 3 days, the longest 10 days. One study included the potential administration of intravenous antibiotic in the first 3 days of treatment.\textsuperscript{30} Follow-up duration varied from 0 days to one year to 3 days after final treatment for 1 year. All studies reported clinical responses (based on sputum production and appearance) and adverse effects. Nine studies assessed changes in sputum microbiology. Spirometry and inflammatory markers were assessed by a smaller number of studies. No studies compared outcomes in high versus low or middle income countries.

**Risk of bias.** One study had low risk of bias across all domains (Table 2).\textsuperscript{26} One study had a high risk of bias due to not considering smoking as a confounding factor.\textsuperscript{27} Two studies did not recruit enough patients for the primary end point based on their power calculations.\textsuperscript{20,22}

Those with unclear risk of bias lacked information on blinding of participants, personnel, and outcome assessments (8 of 10 studies). All studies were commercially funded, one additionally received noncommercial funding.\textsuperscript{30} We did not detect publication bias.

**Analysis**

Combining the populations of the 10 included studies, 1990 patients received short antibiotic courses (fewer than 6 days) and 1989 patients received long courses (7 or more days).

**Clinical response.** Nine studies used the resolution of clinical signs or symptoms of acute exacerbations as their primary outcome. Bennett et al.\textsuperscript{22} used the

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**Figure 2.** PRISMA flow diagram of systematic search for COPD studies. COPD: chronic obstructive pulmonary disease.
| Study design | Study name | Location | Sample selection and setting | Sample size | Antibiotic and durations | Year | Recruitment | Outcome measures |
|--------------|------------|----------|-----------------------------|-------------|--------------------------|------|-------------|------------------|
| RCT          | Bennett et al.²² | United Kingdom (1 center) | Disease: chronic bronchitis Diagnosis made: "as defined by Medical Research Council (1965)" Exacerbation diagnosis: not specified—likely clinical Exacerbation severity: not specified Randomization: unclear LTFU: 5% Smokers; age: “all past or current smokers”; youngest patient 40 years | 41 | Amoxicillin 3 g twice daily for 3 days versus 500 mg three times daily for 7 days | January 1984–March 1985 | Admissions to one hospital | Duration of hospital admission Reduction in sputum volume, pus or mucous Change in forced expiratory volume in 1 second (FEV1) Treatment failure Time to first exacerbation Mean number of exacerbations Number of deaths over 1 year Number of deaths during admission Clinical response Sputum microbiology Adverse effects |
| RCT          | Chodosh et al.²³ | USA (56 centers) | Disease: chronic bronchitis and COPD Diagnosis made: clinically for chronic bronchitis; unspecified for COPD Exacerbation diagnosis: clinical Exacerbation severity: mild-moderate (I–III American Thoracic Society and Anthonisen category) Randomization: Simple random allocation LTFU: 9% Smokers; age: “yes” (86% short course, 83% long course); youngest patient 19 years | 614 | Moxifloxacin 400 mg once daily for 5 days versus 7 days | November 1996–April 1998 | Outpatients | (continued) |
| Study design | Study name | Location | Sample selection and setting | Sample size | Antibiotic and durations | Year | Recruitment | Outcome measures |
|--------------|------------|----------|-----------------------------|-------------|--------------------------|------|-------------|------------------|
| RCT          | Graham et al.\textsuperscript{24} | USA (29 centers) | Disease: chronic bronchitis Diagnosis made: clinically Exacerbation diagnosis: clinical Exacerbation severity: not specified Randomization: simple random allocation LTFU: 22% Smokers; age: not specified; youngest patient 19.4 years | 389 | Grepafloxacin 400 mg once daily for 5 days versus 7 days | Not given | Outpatients | Clinical response Sputum microbiology Adverse effects |
| RCT          | Johnston et al.\textsuperscript{25} | USA (35 sites) | Disease: chronic bronchitis Diagnosis made: clinically Exacerbation diagnosis: clinically Exacerbation severity: nonhospitalized patients only; Anthonisen I–III Randomization: stratified random allocation LTFU: 13% Smokers; age: 68% short course, 63% long course current smokers; youngest patient 18 years | 349 | Gatifloxacin 400 mg once daily for 5 days versus 7 days (secondary outcome) | November 1998–July 1999 | Primary care | Clinical response Adverse effects (nausea and diarrhoea only) Sputum microbiology |
| RCT          | Gotfried et al.\textsuperscript{26} | North America (96 sites) | Disease: chronic bronchitis and COPD Diagnosis made: clinically for chronic bronchitis; radiography and spirometry for COPD Exacerbation diagnosis: clinically and microscopically confirmed purulent sputum Exacerbation severity: mild (Anthonisen I and II criteria) Randomization: simple random allocation at each site LTFU: 12% Smokers; age: 89% short course, 88% long course current or previous smoker; youngest patient 18 years | 444 | Clarithromycin extended-release 1 g once daily for 5 days versus immediate-release 500 mg twice daily for 7 days | December 2002–April 2004 | “Ambulatory patients”—presumed outpatients | Clinical cure Sputum microbiology Adverse events Recurrence or superinfection |
| Study design | Study name          | Location                                                                 | Sample selection and setting                                                                                                                                                                                                                   | Sample size | Antibiotic and durations | Year   | Recruitment        | Outcome measures                                                                 |
|-------------|---------------------|---------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|--------------------------|--------|--------------------|--------------------------------------------------------------------------------|
| RCT         | Langan et al. 27    | Belgium, Canada, Czech Republic, France, Germany, Poland, Portugal, Spain, United Kingdom (78 centers) | Diagnosis: chronic bronchitis Diagnosis made: presumed clinical Exacerbation diagnosis: clinically Exacerbation severity: nonhospitalized patients only Randomization: not specified—"randomised" LTFU: 27% Smokers; age: not specified; youngest patient 19 years | 541         | Grepafloxacin 400 mg once daily for 5 days versus 10 days | Not given | Outpatients         | Clinical response Sputum microbiology Adverse effects                          |
| RCT         | Lorenz et al. 28     | Germany ("multicenter")                                                  | Diagnosis: chronic bronchitis Diagnosis made: not specified Exacerbation diagnosis: clinically Exacerbation severity: "highest grade of Anthonisen exacerbation" (type I) Randomization: not specified—"randomised" LTFU: 23% Smokers; age: 25% short course, 24% long course current smoker; youngest patient not specified | 217         | Cefixime 400 mg once daily for 5 days versus 10 days | Not given | Not documented—presumed hospital | Clinical response Sputum microbiology Change in spirometry and FEV1 Inflammatory markers Adverse effects |
| RCT         | Masterton and Burley 29 | 10 countries (seven in Europe, three in Latin America; 48 centers)      | Diagnosis: chronic bronchitis Diagnosis made: clinically Exacerbation diagnosis: clinically Exacerbation severity: clinically, mild-severe Randomization: unclear—"random" LTFU: 9% Smokers; age: 63% short course, 64% long course current or ex-smokers; youngest patient 18 years   | 530         | Levofloxacin 500 mg once daily for 5 days versus 7 days | Not given | Primary care or outpatients | Clinical response Sputum microbiology Adverse effects                          |
| Study design | Study name | Location | Sample selection and setting | Sample size | Antibiotic and durations | Year | Recruitment | Outcome measures |
|--------------|------------|----------|-----------------------------|-------------|---------------------------|------|-------------|------------------|
| RCT          | Roede et al.\(^{30}\) | Netherlands (6 centers) | Diagnosis: COPD  
Diagnosis made: clinically  
Exacerbation diagnosis: clinically  
Exacerbation severity: all not needing ventilation or critical care  
Randomization: Cluster random sample selection  
LTFU: 19% at day 21  
44% at 3 months  
Smokers; age: 48% short course, 60% long course smokers; youngest patient not specified | 48 | Co-amoxiclav 625 mg for 3 days versus 10 days (NB: first 3 days could have been intravenous antibiotics) | November 2000–December 2003 | “Hospital”—not specified | Clinical response  
Sputum microbiology  
Adverse effects  
Repeat antibiotic prescription  
Symptom scores  
Oxygen use  
Use of concomitant medications |
| RCT          | Sethi et al.\(^{31}\) | 85 centers in Belgium, Canada, Czech Republic, France, Germany, Hong Kong, Pakistan, Philippines, Poland, Romania, Singapore, Switzerland, Taiwan, and USA | Diagnosis: chronic bronchitis  
Diagnosis made: clinically, GOLD criteria for severity  
Exacerbation diagnosis: clinically  
Exacerbation severity: not specified  
Randomization: unclear—“randomised”  
LTFU: 8%  
Smokers; age: 76.7% short course, 76.7% long course ever smoker; youngest patient 32 years | 893 | Co-amoxiclav 2000/125 mg twice daily for 5 days versus co-amoxiclav 875/125 mg twice daily for 7 days | November 2001–May 2002 | “Community” and “hospital”—not specified | Clinical success  
Sputum microbiology  
Adverse events |

RCT: randomized controlled trial; COPD: chronic obstructive pulmonary disease; LTFU: lost to follow-up.
### Table 2. Table of risk of bias and study analysis methods.

| Study               | Blinding/analysis method                        | Adjustment/confounders | Multiple testing | Risk of bias | Cochrane Collaboration’s tool for assessing risk of bias |
|---------------------|------------------------------------------------|------------------------|------------------|--------------|----------------------------------------------------------|
| Bennett et al. 22   | Blinding: unclear—“double blind” but all examined by the same physician | Poorly addressed but “all smoking or ex-smoker” | Few analyses | Funding Commercial | Random sequence generation Allocation concealment Blinding of participants and personnel Reporting bias Other |
|                     | Analysis per risk factor                        |                        |                  | Selection Unclear | Unclear for personnel, low for participants |
|                     |                                                  |                        |                  | Response Low | Low |
|                     |                                                  |                        |                  | Follow-up Unclear | Low |
|                     |                                                  |                        |                  | Reporting Attrition bias | Low |
|                     |                                                  |                        |                  | Allocation Reporting bias | Low |
|                     |                                                  |                        |                  | Other High: under-powered study | Low |
| Chodosh et al. 23   | Blinding: unclear—“adherence to pre-defined criteria by assessor” | Adequately addressed | Few analyses | Funding Commercial | Random sequence generation Allocation concealment Blinding of participants and personnel Reporting bias Other |
|                     | Analysis per risk factor                        |                        |                  | Selection Low | Low |
|                     |                                                  |                        |                  | Response Low | Unclear for personnel, low for participants |
|                     |                                                  |                        |                  | Follow-up Low | Low |
|                     |                                                  |                        |                  | Reporting Attrition bias | Low |
|                     |                                                  |                        |                  | Allocation Reporting bias | Low |
|                     |                                                  |                        |                  | Other | Low |
| Graham et al. 24    | Blinding: unclear for personnel/statistician | Poorly addressed | Few analyses | Funding Commercial | Random sequence generation Allocation concealment Blinding of participants and personnel Reporting bias Other |
|                     | Analysis per risk factor                        |                        |                  | Selection Low | Low |
|                     |                                                  |                        |                  | Response Low | Unclear |
|                     |                                                  |                        |                  | Follow-up Low | Unclear |
|                     |                                                  |                        |                  | Reporting Attrition bias | Low |
|                     |                                                  |                        |                  | Allocation Reporting bias | Low |
|                     |                                                  |                        |                  | (continued) | |

(continued)
| Study                  | Blinding/analysis method | Adjustment/confounders | Multiple testing | Risk of bias          | Cochrane Collaboration’s tool for assessing risk of bias |
|-----------------------|--------------------------|------------------------|------------------|-----------------------|--------------------------------------------------------|
| Gotfried et al.25      | Blinding: unclear for statisticians Analysis per risk factor | Poorly addressed       | Few analyses     | Funding Commercial    | Random sequence generation                                |
|                       |                          |                        |                  | Selection Low         | Allocation concealment Low                              |
|                       |                          |                        |                  | Response Low          | Blinding of participants and personnel Unclear          |
|                       |                          |                        |                  | Follow-up Unclear     | Blinding of outcome assessment Unclear for statisticians |
|                       |                          |                        |                  | Reporting Unclear     | Attrition bias Unclear—not specified how many people were lost during study |
| Johnston et al.26      | Blinding: good Analysis per risk factor Adequately addressed Few analyses | Allocation Low Funding Commercial | Reporting bias Random sequence generation Unclear Low |
|                       |                          |                        |                  | Selection Low         | Allocation concealment Low                              |
|                       |                          |                        |                  | Response Low          | Blinding of participants and personnel Low              |
|                       |                          |                        |                  | Follow-up Low         | Blinding of outcome assessment Low                      |
|                       |                          |                        |                  | Reporting Low         | Attrition bias Low                                      |
| Langan et al.27        | Blinding: unclear for personnel Analysis per risk factor Poorly addressed Few analyses | Allocation Low Funding Commercial | Reporting bias Random sequence generation Unclear Low |
|                       |                          |                        |                  | Selection Unclear: not specified | Allocation concealment Unclear                          |
|                       |                          |                        |                  | Response Low          | Blinding of participants and personnel Unclear          |
|                       |                          |                        |                  | Follow-up Unclear: high LTFU | Blinding of outcome assessment Unclear for personnel |
|                       |                          |                        |                  | Reporting Low         | Attrition bias Unclear for loss to follow-up           |
|                       |                          |                        |                  | Allocation High: confounding factor smoking was not considered | Reporting bias Low                                     |
| Study                  | Blinding/analysis method | Adjustment/confounders | Multiple testing | Risk of bias            | Cochrane Collaboration's tool for assessing risk of bias |
|-----------------------|--------------------------|------------------------|------------------|-------------------------|--------------------------------------------------------|
| Lorenz et al. 28       | Blinding: unclear for assessors and statisticians, Analysis per risk factor | Poorly addressed       | Few analyses     | Funding: Commercial     | Random sequence generation, Allocation concealment, Unclear |
|                       |                          |                        |                  | Selection: Unclear—not specified |                          |
|                       |                          |                        |                  | Response: Low           |                          |
|                       |                          |                        |                  | Follow-up: Unclear: 23% LTFU |                          |
|                       |                          |                        |                  | Reporting: High: per protocol population used for most analyses |                          |
|                       |                          |                        |                  | Allocation: Unclear     |                          |
|                       |                          |                        |                  | Reporting bias: Low     |                          |
| Masterton and Burley 29| Blinding: good Analysis per risk factor | Adequately addressed | Few analyses     | Funding: Commercial     | Random sequence generation, Allocation concealment, Unclear |
|                       |                          |                        |                  | Selection: Low          |                          |
|                       |                          |                        |                  | Response: Low           |                          |
|                       |                          |                        |                  | Follow-up: Low          |                          |
|                       |                          |                        |                  | Reporting: Low          |                          |
|                       |                          |                        |                  | Allocation: Unclear     |                          |
|                       |                          |                        |                  | Reporting bias: Low     |                          |
| Roede et al. 30        | Blinding: good Analysis per risk factor | Adequately addressed | Few analyses     | Funding: Commercial and noncommercial | Random sequence generation, Allocation concealment, Low |
|                       |                          |                        |                  | Selection: Low          |                          |
|                       |                          |                        |                  | Response: Low           |                          |
|                       |                          |                        |                  | Follow-up: Low          |                          |
|                       |                          |                        |                  | Reporting: Low          |                          |
|                       |                          |                        |                  | Allocation: Low         |                          |
|                       |                          |                        |                  | Reporting bias: Low     |                          |
|                       |                          |                        |                  | Other: High risk: unable to recruit enough patients to power study | | (continued)
absence of mucoid sputum in isolation and was hence excluded from meta-analysis for this outcome. Some studies reported outcomes at multiple time points so we presented clinical success as early (within 6 days of treatment completion), middle (7–14 days after treatment completion), or late (more than 20 days after treatment completion). Two studies assessed outcomes at 7–17 days and 17–23 days after treatment completion—they were excluded from this analysis.\textsuperscript{23,28}

There was no statistically significant difference between shorter and longer antibiotic courses in early clinical success (RR: 1.00, 95% CI: 0.96–1.03) in the five studies that considered this (Figure 3).

There was no statistically significant difference in medium (RR: 1.08, 95% CI: 0.91–1.27; five studies; Figure 4) or late clinical success (RR: 1.00, 95% CI: 0.99–1.11; six studies; Figure 5).

**Adverse events.** Nine studies reported overall adverse events (1882 and 1877 patients for the shorter and longer duration, respectively). There was a statistically significant lower risk of developing adverse events in the shorter treatment group compared with the longer treatment group (RR: 0.84, 95% CI: 0.75–0.93, \( p = 0.001 \); Figure 6). For nausea, the risk was statistically significantly lower in the shorter treatment group (RR: 0.71, 95% CI: 0.52–0.98, \( p = 0.04 \); eight studies; Online Supplemental Material). No significant difference was found for diarrhea (RR: 1.03, 95% CI: 0.82–1.29; seven studies; see Online Supplemental Material).

**Bacteriological response in sputum.** Eight studies assessed eradication or presumed eradication of pathogens which were present in pretreatment sputum samples. Presumed eradication was defined as improvement in clinical symptoms without sputum that could be cultured at follow-up. All studies used populations that had an identified pretreatment pathogen in sputum. There was no statistically significant difference between shorter and longer antibiotic treatment 0–6 days after treatment completion (RR: 1.08, 95% CI: 0.71–1.65; three studies) and 7–23 days after treatment completion (RR: 1.08, 95% CI: 0.83–1.39; seven studies; both in Online Supplemental Material).

| Study                          | Blinding/analysis method               | Adjustment/confounders | Multiple testing | Risk of bias | Funding      | Random sequence generation | Allocation concealment | Cochrane Collaboration’s tool for assessing risk of bias |
|-------------------------------|--------------------------------------|------------------------|------------------|--------------|--------------|-----------------------------|-----------------------|---------------------------------------------------------|
| Sethi et al.\textsuperscript{31} | Blinding: unclear for personnel Analysis per risk factor | Adequately addressed Few analyses | Funding Commercial | Random sequence generation | Allocation concealment | Unclear | Unclear |
| Response                      | Low                                  | Blinding of participants and personnel | Unclear for personnel | Reporting bias Other | Low | Low | Unclear: patients with previous antibiotic use were not excluded |

LTFU: lost to follow-up.
Figure 3. Forest plot of early clinical success, within 6 days of treatment completion, <6 versus ≥7 days antibiotic duration.

Figure 4. Forest plot of medium clinical success, 7–14 days after treatment completion, <6 versus ≥7 days antibiotic duration.

Figure 5. Forest plot of late clinical success, >20 days after treatment completion, <6 versus ≥7 days antibiotic duration.

Figure 6. Forest plot of overall adverse events, <6 versus ≥7 days antibiotic duration.
Other outcomes. Two studies considered spirometric change—there was no statistically significant change in either study between shorter and longer durations.\textsuperscript{22,28} One study assessed inflammatory markers, showing no difference between the different durations.\textsuperscript{28} One study followed patients up to 1 year, assessing occurrence and time to new exacerbations, demonstrating no statistically significant differences between the groups.\textsuperscript{22} Two studies included patients in the developing world but no subgroup analyses for these were reported.\textsuperscript{29,31}

Discussion

Summary of main findings

The prescription of antibiotics for COPD or asthma exacerbations is a very common clinical activity with serious potential adverse effects. Despite this, we found few studies had investigated optimal antibiotic duration for this indication. There was no difference in clinical success or bacteriological eradication for patients receiving fewer than 6 or more than 7 days of antibiotics for COPD exacerbations. There was, however, a significantly lower risk of side effects overall and specifically nausea in the shorter duration group.

Strengths and limitations

This review was undertaken systematically following best practice guidance from the Cochrane Collaboration. Interpretation of our findings should be made in the context of the analyzed studies having been largely undertaken at a time of significant variation in the diagnosis and treatment of COPD. The populations were therefore heterogeneous in key aspects such as smoking exposure and airflow obstruction (or did not have these clearly recorded) and by description of exacerbation outcomes. It is plausible that some study participants had other diagnoses such as bronchiectasis and chronic asthma. As many studies were undertaken prior to widespread use of standards for the assessment of COPD, it was not possible to stratify results by severity or GOLD criteria.

A sensitivity analysis without the study where the confounding factor smoking caused a high risk of bias showed no difference in our main findings (see Online Supplemental Material). Most of the older studies also had an “unclear” risk of bias by current standards. Fluoroquinolones were the commonest antibiotic class studied, but these are not first line treatment for uncomplicated exacerbations in usual clinical practice. This diminishes the external validity of the findings.\textsuperscript{33}

Setting in existing literature

Antibiotic courses of 5 or fewer days were as successful as longer courses for clinical and bacteriological cure for chronic bronchitis and COPD exacerbations in a meta-analysis in 2006. However, this study compared course length regardless of drug (e.g., 10 days of cefuroxime with 5 days of telithromycin).\textsuperscript{21} Our study adds to the literature by including a search of the last 10 years of medical publications and by restricting analyses to consider only whether shorter courses of the same antibiotic are as effective and well tolerated. This reduces bias created by different mechanisms of action irrespective of duration.

Shorter courses of antibiotics have already been found to be as effective as longer courses in community acquired pneumonia and pharyngitis, and our findings are consistent with this.\textsuperscript{18,21,34–36} Antibiotics are not routinely recommended for the treatment of asthma exacerbations, and three published studies suggest no benefit above placebo.\textsuperscript{7,10,25,37} However, antibiotics continue to be prescribed extensively for asthma exacerbations.\textsuperscript{10,12} This discrepancy between observed antibiotic prescribing and limited available evidence highlights the need for further studies.

Implications for future research

This review supports the use of shorter courses of antibiotics for the treatment of COPD exacerbations. However, further research is required to ascertain if these findings hold true in the context of current COPD care, antibiotic use, and antibiotic resistance patterns. The development of extensive electronic health record databases of routinely collected data could be used to provide initial evidence in this regard and could support the design of targeted interventional studies. Future studies in high-income countries are likely to also include biomarker-guided treatment. However, significant challenges exist in lower and middle income countries where antibiotic resistance is prevalent and only fixed duration regimens are currently feasible.

Conclusions

This systematic review highlights the paucity of research evidence relevant to usual clinical practice
informing selection of antibiotic duration for asthma and COPD exacerbations. It appears that courses of antibiotics of 6 or fewer days are equally as effective as those of 1 week or longer, but associated with fewer side effects. However, due to the limitations of the published studies, new observational and interventional studies are needed to robustly inform guidelines.

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ORCID iD
Marie Stolbrink http://orcid.org/0000-0001-6091-9316

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