Prophylactic antibiotic use in chronic obstructive pulmonary disease (COPD) and the potential anti-inflammatory activities of antibiotics in COPD.

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Literature search strategy

Criteria for Considering Studies for this Review – Do antibiotics have a positive, therapeutic effect in stable COPD?

Trials used in qualitative analysis were randomised control trials, comparing antibiotic to placebo. Non-inferiority trials (which compare two active treatments) were not included, unless they also used a placebo control. Patients with a physician confirmed diagnosis of COPD were included, and other conditions which feature chronic airway limitation e.g. asthma, cystic fibrosis, bronchiectasis were not included. This review looks at the effect of antibiotics on stable COPD, so studies using antibiotics in acute exacerbations were not included. All antibiotics have been included, as an aim of this review was to look at which antibiotics have the most potential as anti-inflammatory agents. Studies which used antibiotics for less than a month were not included in the analysis, as previous research suggests long course, low dose antibiotics have most benefit in stable COPD.

Types of outcomes measured were: i) Primary – Exacerbation-related Outcomes e.g. frequency and duration of exacerbation. ii) Secondary – Adverse Effects; Patient Health Status [measured using an appropriate method e.g. St George's Respiratory Questionnaire, SGRQ (Jones PW et al. Respiratory Medicine 2011;105:57-66), or SF-36 (Mahler DA, Mackowiak JI. Chest 1995;107:1585-1589.)].

The search methods for identification of studies used two main databases: PubMed and Embase (figure S2). The following search was used on PubMed: **(((((((((Randomised Controlled Trial) OR RCT) OR Randomised Control Trial) OR Random) OR Clinical Trial) OR Controlled Clinical Trial)) AND ((((((((((((((Antibiotic) OR antimicrobial) OR macrolide) OR azithromycin) OR clarithromycin) OR erythromycin) OR roxithromycin) OR troleandomycin) OR solithromycin) OR fluoroquinolone) OR moxifloxacin) OR levofloxacin) OR ciprofloxacin) OR nadifloxacin) OR ofloxacin)) AND (((COPD) OR Chronic Obstructive Pulmonary Disease) OR "lung diseases, obstructive"[MeSH Major Topic]) NOT asthma.** This retrieved 1300 publications (see figure S1 for a breakdown of studies per year). Publication titles and abstracts were scanned for relevance. The first 200 abstracts

were scanned (retrospectively, starting with the most recent), until the 2011 RCT 'Azithromycin for Prevention of Exacerbations of COPD' (reference 8 in main article) which was included in the 2013 Cochrane review (reference 7 in the main article), so searching prior to this point was redundant. This yielded 31 studies for full text analysis.

A similar search process was used on Embase: **(antibiotic or antimicrobial or macrolide or azithromycin or clarithromycin or erythromycin or roxithromycin or troleandomycin or solithromycin or fluoroquinolone or moxifloxacin or levofloxacin or ciprofloxacin or nadifloxacin or ofloxacin).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading] AND (COPD or chronic obstructive pulmonary disease).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading] AND (Randomised Controlled Trial or Randomised Control Trial or Random or Clinical Trial or Controlled Clinical Trial).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading].** This retrieved 1162 publications. The first 400 abstracts were scanned, until the 2011 study by Albert et al (reference 8 in the main article) was found. This yielded 35 studies for full text analysis.

The most common reason studies were not included for qualitative analysis include: not randomised, controlled trials; non-inferiority trials; used patients currently experiencing an acute exacerbation; did not report relevant outcomes; not relevant to COPD. On this basis five studies were selected from the 66 found from database searching. In addition to those found through databases, the seven studies used in the 2013 review were also examined. Therefore, a total of 12 studies were analysed.
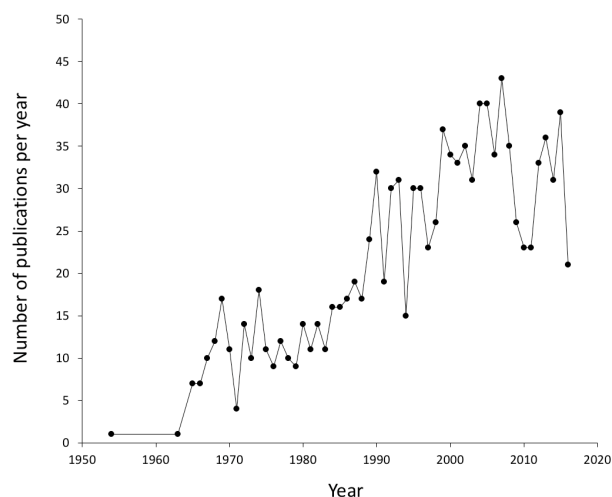

Figure S1. The number of publications per year in the PubMed database for the primary search.

Identification

Records identified through database searching
(n = 600)

Additional records identified through other sources
(n = 7)

Records after duplicates removed
(n = 607)

Screening

Records screened
(n =607)

Records excluded
(n = 541)

Eligibility

Full-text articles assessed for eligibility
(n = 66)

Full-text articles excluded
(n = 54)

Included

Studies included in qualitative synthesis
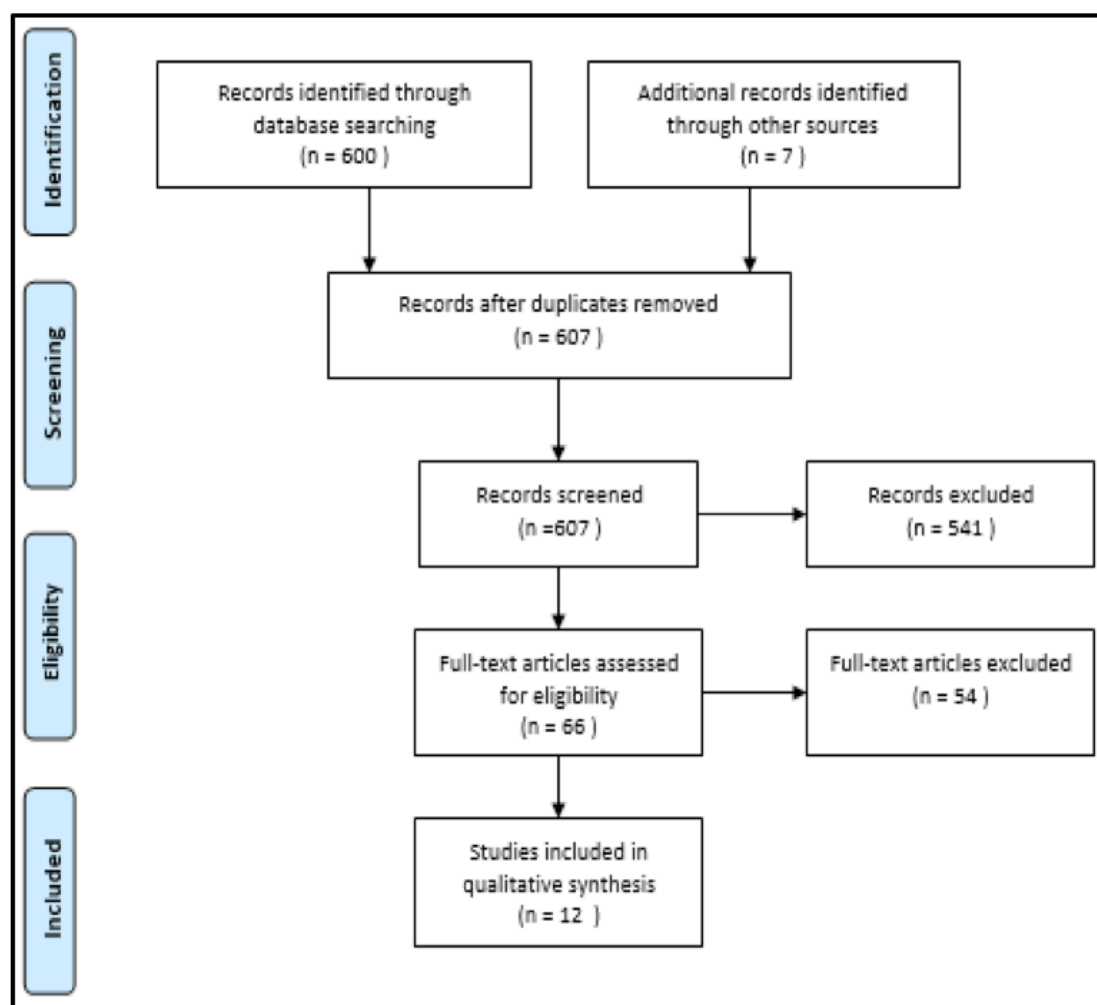(n = 12)

Figure S2. PRYSMA 2009 diagram, search methods for identification of studies for 'Do antibiotics have a positive, therapeutic effect in stable COPD?'

Criteria for Considering Studies for this Review – If antibiotics do have a positive, therapeutic effect in COPD, is this potentially anti-inflammatory in nature?

All experimental study types in humans and animals were included that linked the findings to potential significance for COPD. A variety of samples were investigated in the studies included: broncho-alveolar lavage (BAL), sputum, venous blood sample. All types of antibiotics were included. Outcome measures in the studies included inflammatory cell counts, transcription factor expression and cytokine/chemokine levels.

The search method again employed PubMed and Embase (figure S3). The following search was used on PubMed: **(((((((COPD) OR chronic bronchitis) OR emphysema)) AND (((inflammatory) OR immunomodulatory) OR anti-inflammatory)) AND ((((ex-vivo) OR ex vivo) OR in vitro) OR in vivo))) AND antibiotic**. It yielded 39 publications which were

scanned and 11 studies were picked for full text analysis, six of which are to be used in the review. The following search was used on Embase: **antibiotic.mp. AND (COPD or chronic obstructive pulmonary disease or emphysema or chronic bronchitis).mp. AND (vitro or vivo).mp. AND (inflammatory or immunomodulatory or anti-inflammatory).mp.** It yielded 56 publications which were scanned and 8 studies were picked for full text analysis, three of which are to be used in the review. The most common reason studies were not included for qualitative analysis include: results not linked to COPD; did not report relevant outcomes. One publication was found as it was referenced by another relevant study. Eight studies from the literature search outlined in the section above also reported outcomes relevant to this section.
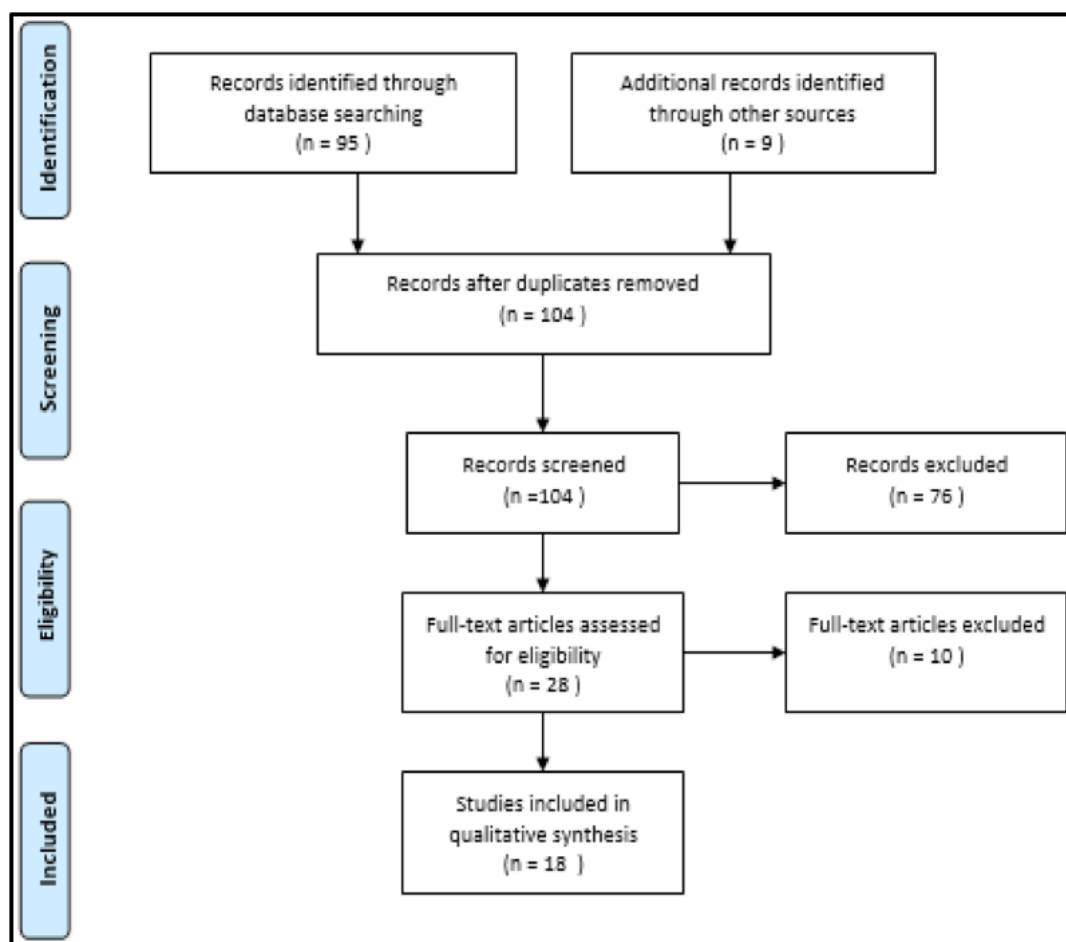

Figure S3. PRYSMA 2009 diagram, search methods for identification of studies for 'If antibiotics do have a positive, therapeutic effect in COPD, is this potentially anti-inflammatory in nature?'

Supplemental Table 1. Characteristics of Included Studies – Do antibiotics have a positive, therapeutic effect in stable COPD?

Albert et al. 2011 (ref. 8)	
Methods	Prospective, randomised, placebo controlled clinical trial. Double blinded. Intention to treat analysis.
Participants	n = 1142. Mean age 66y in azithromycin group and 65y in placebo group Mean FEV_1 1.10±0.50 in azithromycin group versus 1.12±0.52 in placebo group Females 41% in both groups Exclusions: asthma, FEV_1 > 80%, history of hearing impairment, resting tachycardia, risk of prolonged QT interval, exacerbation in past four weeks
Interventions	Prophylaxis: 1. Azithromycin 250mg daily for 12 months 2. Placebo
Outcomes	Primary • Time to First Exacerbation of COPD Secondary • Health Status, using SGRQ • Nasopharyngeal Colonisation with Select Respiratory Pathogens • Adverse Events
Notes	Funding: Grant from National Institutes of Health

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Banerjee et al. 2004 (ref. 14)	
Methods	Prospective, randomised, placebo controlled clinical trial. Double blinded. Intention to treat analysis.

Participants	n = 67.
	Mean age 65y in clarithromycin group and 68y in placebo group
	Mean FEV$_1$ 1.12±0.07 in clarithromycin group versus 1.13±0.07 in placebo group
	Females 31% in both groups
	Exclusions: asthma, FEV$_1$ > 60%, history of bronchiectasis, lung cancer, uncontrolled ischaemic heart disease or diabetes mellitus, exacerbation in past six weeks
Interventions	Prophylaxis: 1. Clarithromycin 500mg daily for three months 2. Placebo
Outcomes	Primary • Health Status, using SQRQ and SF-36 Secondary • Sputum Bacterial Load • Infective Exacerbation Rate • Shuttle Walk Test • C-reactive Protein Levels • Adverse Events
Notes	Funding: Grant from Abbott Pharmaceuticals

Berkhof et al. 2013 (ref. 9)

Methods	Prospective, randomised, placebo controlled clinical trial. Double blinded. Intention to treat analysis.
Participants	n = 84.
	Mean age 67y in azithromycin group and 68y in placebo group
	Mean FEV$_1$ 1.41±0.52 in azithromycin group versus 1.32±0.42 in placebo group
	Females 26% in azithromycin group and 24% in placebo group

Exclusions: asthma, use of antibiotics or corticosteroids for an exacerbation three weeks before inclusion, other relevant lung pathology (Clinician's discretion), pregnancy, use of macrolides six weeks prior to inclusion, intolerance to macrolides

Interventions	Prophylaxis: 1. Azithromycin 250mg three times weekly for three months 2. Placebo
Outcomes	Primary • Health Status, using LCQ Secondary • Health Status, using SGRQ and SF-36 • Time to First Exacerbation • Exacerbation Rate • Hospitalisation Rate • Adverse Events
Notes	n/a

Brill et al. 2015 (ref. 10)	
Methods	Prospective, randomised, placebo controlled clinical trial. Single blinded. Intention to treat analysis.
Participants	n = 99. Mean age 68y in azithromycin group, 71y in moxifloxacin group, 70y in doxycycline group, and 69y in placebo group Mean FEV$_1$ 1.2±0.5 in azithromycin group, 1.4±0.5 in moxifloxacin group, 1.5±0.5 in doxycycline group, and 1.5±0.6 Females 36% in azithromycin group, 32% in moxifloxacin group, 28% in doxycycline group, and 25% in placebo group Exclusions: exacerbation in past 4 weeks
Interventions	Prophylaxis:

	1. Azithromycin 250mg three times per week for 13 weeks 2. Pulsed Moxifloxacin 400mg daily for five days every four weeks for 13 weeks 3. Doxycycline 100mg daily for 13 weeks 4. Placebo
Outcomes	Primary • Sputum Bacterial Load Secondary • Changes in resistance • Health Status, using SGRQ • Adverse Events
Notes	Funding: Independent Research Grant from National Institute for Health Research.

He et al. 2010 (ref. 15)

Methods	Prospective, randomised, placebo controlled clinical trial. Double blinded. Intention to treat analysis.
Participants	n = 36. Mean age 69y in erythromycin group and 69y in placebo group Mean FEV_1 1.02±0.41 in erythromycin group versus 1.12±0.47 in placebo group Females 11% in erythromycin group and 17% in placebo group Exclusions: exacerbation in last four weeks, history of unstable cardiovascular disorders, macrolide hypersensitivity
Interventions	Prophylaxis: 1. Erythromycin 125mg three times daily for six months 2. Placebo
Outcomes	Primary • Number of Exacerbations • Sputum Neutrophil Numbers Secondary • Health Status, using SGRQ and SF-36

	• Adverse Events
Notes	Funding: National Nature Science Foundation of China

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Mygind 2010 (ref. 12)

Methods	Prospective, randomised, placebo controlled clinical trial. Double blinded. Intention to Treat Analysis.
Participants	n = 575. All participants >50y Mean FEV_1 0.9 in both groups Exclusions: history of asthma, bronchiectasis or other significant respiratory pathology, current usage of antibiotics
Interventions	Prophylaxis: 1. Azithromycin 200-400mg daily for 12 months 2. Placebo
Outcomes	Primary • Lung Function Secondary • Frequency of Exacerbation • Duration of Exacerbation • Number of Days in Hospital • Health Status, using SGRQ • Adverse Events • Mortality
Notes	n/a

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Seemungal et al. 2008 (ref. 16)

Methods	Prospective, randomised, placebo controlled clinical trial. Double blinded. Intention to treat analysis.
Participants	n = 109.

Mean age 68y in erythromycin group and 67y in placebo group

Mean FEV$_1$ 1.27±0.51 in erythromycin group versus 1.36±0.55 in placebo group

Females 38% in erythromycin group and 36% in placebo group

Exclusions: history of asthma, bronchiectasis, lung neoplasia, unstable cardiac status, history of macrolide allergy, history of hepatic impairment

Interventions	Prophylaxis: 1. Erythromycin 250mg twice daily for 12 months 2. Placebo
Outcomes	Primary • Exacerbation Frequency • Exacerbation Duration Secondary • Sputum Inflammatory Markers • Adverse Events
Notes	n/a

Sethi et al.	**2010 (ref. 19)**
Methods	Prospective, randomised, placebo controlled clinical trial. Double blinded. Intention to Treat Analysis.
Participants	n = 1149. Mean age 66y in moxifloxacin group and 67y in placebo group Mean FEV$_1$ 1.2±0.5 in moxifloxacin group versus 1.2±0.5 in placebo group Females 26% in moxifloxacin group and 26% in placebo group Exclusions: history of significant respiratory disease, prolonged QT value, history of quinolone hypersensitivity, history of hepatic impairment

Interventions	Prophylaxis:
	1. Pulsed moxifloxacin 400mg daily for five days, repeated every eight weeks for a total of six courses 2. Placebo
Outcomes	Primary • Frequency of Exacerbations Secondary • Mortality • Hospitalisation • Health Status, using SGRQ • Adverse Events
Notes	Funding: Grant from Bayer HealthCare

Shafuddin et al. 2015 (ref. 18)

Methods	Prospective, randomised, placebo controlled clinical trial. Double blinded. Intention to Treat Analysis.
Participants	n = 292. Mean age 66y in roxithromycin + doxycycline group, 68y in roxithromycin group, and 67y in placebo group Mean FEV_1 0.85±0.33 in roxithromycin + doxycycline group, 0.97±0.46 in roxithromycin group, 0.99±0.49 in placebo group Females 36% in roxithromycin + doxycycline group, 17% in roxithromycin group, and 33% in placebo group Exclusions: pulmonary disease other than COPD, treatment with antibiotics or exacerbation four weeks before randomisation, sensitivity to macrolides or tetracyclines, impaired hepatic function
Interventions	Prophylaxis: 1. Roxithromycin 300mg + Doxycycline 100mg daily for 12 weeks 2. Roxithromycin 300mg daily for 12 weeks 3. Placebo
Outcomes	Primary

- Frequency of Exacerbations in 48 Week Post Treatment Period

Secondary

- Exacerbations Over 12 Week Treatment Period
- Adverse Events

Notes	Funding: Sanofi-Aventis Australia Pty Ltd

Simpson et al. 2014 (ref. 11)

Methods	Prospective, randomised, placebo controlled clinical trial. Double blinded. Intention to Treat Analysis.
Participants	n = 30. Mean age 72y in azithromycin group and 70y in placebo group Mean FEV_1 as percent of predicted 57% in azithromycin group versus 51% in placebo group Females 33% in azithromycin group and 40% in placebo group Exclusions: exacerbation in past four weeks, unable to produce sputum sample, FEV_1 <0.5L, hypersensitivity to macrolides, prolonged QT interval or liver impairment
Interventions	Prophylaxis: 1. Azithromycin 250mg daily for three months 2. Placebo
Outcomes	Primary • Airway Neutrophil and CXCL8 levels Secondary • Bacterial Load • Severe Exacerbations of COPD • Adverse Events
Notes	n/a

Suzuki et al. 2001 (ref. 17)

Methods	Prospective, randomised, placebo controlled clinical trial. Double Blinded. Type of Analysis Not Mentioned
Participants	n = 109. Mean age 72y in erythromycin group and 69y in placebo group Mean FEV_1 1.47 in erythromycin group versus 1.30 in placebo group Females 13% in erythromycin group and 18% in placebo group Exclusions: history of bronchiectasis or diffuse panbronchiolitis
Interventions	Prophylaxis: 1. Erythromycin 200-400mg daily for 12 months 2. Placebo
Outcomes	Primary - Number of Common Colds Secondary - Acute Exacerbations of COPD - Adverse Events
Notes	n/a

Uzun et al. 2014 (ref. 13)

Methods	Prospective, randomised, placebo controlled clinical trial. Double blinded. Intention to Treat Analysis.
Participants	n = 92. Mean age 65y in azithromycin group and 65y in placebo group Mean FEV_1 1.1±0.47 in azithromycin group versus 1.1±0.43 in placebo group

Females 53% in azithromycin group and 60% in placebo group

Exclusions: history of clinically significant respiratory disease, maintenance antibiotic therapy, macrolide allergy, pregnancy, liver disease, malignancy, heart failure, contraindicated medication

Interventions	Prophylaxis: 3. Azithromycin 500mg three times weekly for 12 months 4. Placebo
Outcomes	Primary • Exacerbation Rate Secondary • Time to First Exacerbation • Hospital Admission • Change in Proportion of Exacerbations Requiring Hospital Care Vs Outpatient Treatment • FEV_1 • Health Status, using SGRQ and SF-12 • Sputum Bacteriology • Adverse Events
Notes	n/a

Abbreviations: FEV_1 – Forced Expiratory Volume, SGRQ – St George's Respiratory Questionnaire, SF-12 – Short Form 12, SF-36 – Short Form 36

Supplemental Table 2. Characteristics of Included Studies – If antibiotics do have a positive, therapeutic effect in COPD, is this potentially anti-inflammatory in nature?

Study	Type of Trial	Types of Sample
Balloy et al 2014, (ref. 42) azithromycin, CSY0073	• In vitro – testing bacterial growth • In vivo – LPS-challenged mice	In vivo: • BAL fluid • Lung homogenates
Blasi et al 2010, (ref.34) azithromycin	• In vivo – COPD patients, recently undergone tracheostomy • Ex vivo – testing minimum inhibitory concentrations	In vivo: • Venous blood • Exhaled breath condensate
He et al 2010, (ref. 15) erythromycin	• In vivo – COPD patients	In vivo: • Sputum sample
Hodge et al 2006, (ref.32) azithromycin	• In vitro	In vitro: • Alveolar macrophages
Hodge et al 2008, (ref. 33) azithromycin	• In vitro – investigate functional link between azithromycin activities and alveolar macrophage phagocytic ability	In vitro: • Venous blood • Exhaled breath condensate
Kobayashi et al 2013, (ref. 41) solithromycin	• In vitro	In vitro: • Human monocytic cell line, U937 • Peripheral blood mononuclear cells
Li et al 2012, (ref. 39) erythromycin	• In vitro	In vitro: • Human monocytic cell line, U937
Marjanovic et al 2011, (ref. 35) macrolides	• In vitro – cytokine production	In vitro: • Sputum sample
Nakanishi et al 2009, (ref. 38) clarithromycin	• In vivo – testing lung response to clarithromycin • In vitro	In vivo: • BAL fluid In vitro: • Macrophages harvested from peritoneal cavities

Prins et al 2016, (ref. 31) doxycycline	• In vivo	In vivo: • Sputum sample
Schild et al 2011, (ref. 29) moxifloxacin	• Ex vivo – IL-5 expression	Ex vivo: • Venous blood
Seemungal et al 2008, (ref. 16) erythromycin	• In vivo – cytokine production	In vivo: • Serum and sputum sample
Segal et al 2016, (ref. 37) azithromycin	• In vivo – cytokine production	In vivo: • BAL fluid
Simpson et al 2014, (ref. 11) azithromycin	• In vivo – cytokine production	In vivo: • Sputum sample
Stellari et al 2014, (ref. 36) azithromycin	• In vivo – transcription factor activation	In vivo: • BAL
Siva et al 2014, (ref. 30) levofloxacin	• In vivo – cytokine production	In vivo: • Sputum sample
Tan et al 2016, (ref. 40) erythromycin	• In vivo – cytokine production	In vivo: • Venous blood • Sputum sample
Zimmermann et al 2009, (ref. 28) azithromycin, levofloxacin, moxifloxacin	• Ex vivo	Ex vivo: • Human bronchial epithelial cells, from patients undergoing lung surgery (not COPD patients)