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# Prolonged antibiotics for non-cystic fibrosis bronchiectasis in children and adults (Review)

Hnin K, Nguyen C, Carson-Chahhoud KV, Evans DJ, Greenstone M, Smith BJ

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[Intervention Review]

# Prolonged antibiotics for non-cystic fibrosis bronchiectasis in children and adults

Khin Hnin[1], Chau Nguyen[2], Kristin V Carson-Chahhoud[3], David J Evans[4], Michael Greenstone[5], Brian J Smith[6]

[1]Flinders University, Adelaide, Australia. [2]Queen Elizabeth Hospital, Adelaide, Australia. [3]School of Medicine, The University of Adelaide, Adelaide, Australia. [4]Thoracic Medicine, Hemel Hempstead Hospital, Hemel Hempstead, UK. [5]Castle Hill Hospital, Cottingham, UK. [6]Respiratory Medicine Unit, The Queen Elizabeth Hospital, Central Adelaide Local Health Network, Adelaide, Australia

**Contact:** Kristin V Carson-Chahhoud, School of Medicine, The University of Adelaide, Adelaide, Australia.
kristin.carson@adelaide.edu.au.

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## ABSTRACT

### Background

The vicious cycle hypothesis for bronchiectasis predicts that bacterial colonisation of the respiratory tract perpetuates inflammatory change. This damages the mucociliary escalator, preventing bacterial clearance and allowing persistence of pro-inflammatory mediators. Conventional treatment with physiotherapy and intermittent antibiotics is believed to improve the condition of people with bronchiectasis, although no conclusive data show that these interventions influence the natural history of the condition. Various strategies have been tried to interrupt this cycle of infection and inflammation, including prolonging antibiotic treatment with the goal of allowing the airway mucosa to heal.

### Objectives

To determine the benefits of prolonged antibiotic therapy in the treatment of patients with bronchiectasis.

### Search methods

We searched the Cochrane Airways Group Trials Register and reference lists of identified articles. Searches were current as of February 2014.

### Selection criteria

Randomised trials examining the use of prolonged antibiotic therapy (for four or more weeks) in the treatment of bronchiectasis compared with placebo or usual care.

### Data collection and analysis

Two review authors independently assessed trial quality and extracted data. We contacted study authors to ask for missing information.

### Main results

Eighteen trials met the inclusion criteria, randomly assigning a total of 1157 participants. Antibiotics were given for between four weeks and 83 weeks. Limited meta-analysis was possible because of the diversity of outcomes reported in these trials. Based on the number of participants with at least one exacerbation, the meta-analysis showed significant effects in favour of the intervention (odds ratio (OR) 0.31, 95% confidence interval (CI) 0.19 to 0.52; P value < 0.00001), with events occurring in 271 per 1000 people in the intervention arm (95% CI 126 to 385) and in 546 per 1000 in the control population, based on evidence of moderate quality. A non-statistically significant reduction in hospitalisation favoured the use of prolonged antibiotics with a moderate quality grade of supporting evidence (37 per 1000

in the intervention arm (95% CI 13 to 96) and 87 per 1000 in control (OR 0.40, 95% CI 0.14 to 1.11; P value = 0.08). Drug resistance developed in 36 of 220 participants taking antibiotics compared with 10 of 211 participants given placebo or standard therapy (OR 3.48, 95% CI 1.20 to 10.07; P value = 0.02), translating to natural frequencies of 155 per 1000 in the intervention arm (95% CI 59 to 346) and 50 per 1000 in the control arm. The intervention was well tolerated with no overall significant difference in withdrawal between treatment and placebo groups (OR 0.91, 95% CI 0.56 to 1.49). Diarrhoea was commonly reported as an adverse event, particularly with an oral intervention.

**Authors' conclusions**

Available evidence shows benefit associated with use of prolonged antibiotics in the treatment of patients with bronchiectasis, at least halving the odds of exacerbation (with 275 fewer exacerbations per every 1000 people treated in the antibiotic arm compared with the control arm) and hospitalisation (50 fewer hospitalisations per 1000 people in the antibiotic arm compared with the control arm). However, the risk of emerging drug resistance is increased more than threefold. This review is limited by diversity of trials and by evidence of moderate to low quality. Further randomised controlled trials with adequate power and standardised end points are required.

## PLAIN LANGUAGE SUMMARY

**Prolonged antibiotics for purulent bronchiectasis in children and adults**

**Does prolonged antibiotic therapy provide benefit in treatment of patients with purulent bronchiectasis?**

**Why is this question important?**

Non-cystic fibrosis (CF) bronchiectasis is a chronic respiratory condition characterised by abnormal dilatation of the airways. Although its global prevalence is largely unknown, available data from Australia, New Zealand, the United States and England show that bronchiectasis is now diagnosed with increasing frequency. The lungs of patients with bronchiectasis have excessive secretions, which tend to consist of different types of micro-organisms. Long-term antibiotic therapy was proposed to halt persistent and ongoing damage to the lung due to insult from micro-organisms. Therefore, we seek to assess the effects of prolonged antibiotic therapy on patients with bronchiectasis.

**How did we answer the question?**

We looked for all studies comparing prolonged antibiotic therapy versus usual care and/or a dummy medication (placebo).

**What did we find?**

We found 18 studies including 1157 people with non-cystic fibrosis bronchiectasis; most were adults. Twelve studies used a tablet form of antibiotics (e.g. azithromycin, erythromycin, roxithromycin, amoxycillin, clarithromycin, penicillin, oxytetracycline, ciprofloxacin). The remaining six studies reported use of inhaled medications. Antibiotics were given for between four weeks and 83 weeks. In seven studies, similar disease severity at baseline was supported by the similar history of previous hospitalisation and severe attacks.

Overall quality of evidence was rated as moderate. When an outcome is rated as high quality, further research is very unlikely to change our confidence in the estimate of effect, but moderate ratings reflect some uncertainty in the findings.

**Conclusion**

Prolonged antibiotic therapy in bronchiectasis provides benefit, especially in reducing the risk of future exacerbations and hospitalisations. Antibiotics are well tolerated by participants without significant differences in overall adverse effects (e.g. intolerance, chest symptoms, fatigue, fever, palpitations).

However, antibiotic resistance is a matter of concern, particularly for patients with drug allergies, which further limit their future treatment.

## SUMMARY OF FINDINGS

### Summary of findings for the main comparison. Prolonged antibiotics for purulent bronchiectasis in children and adults

**Prolonged antibiotics for purulent bronchiectasis in children and adults**

**Patient or population:** adults and children with purulent bronchiectasis
**Settings:**
**Intervention:** prolonged antibiotics

| Outcomes | Illustrative comparative risks* (95% CI) | | Relative effect (95% CI) | Number of participants (studies) | Quality of evidence (GRADE) | Comments |
|---|---|---|---|---|---|---|
| | Assumed risk | Corresponding risk | | | | |
| | Control | Prolonged antibiotics | | | | |
| **Exacerbations**<br>Number of events<br>Follow-up: 1.5 to 24 months | **546 per 1000** | **271 per 1000**<br>(126 to 385) | **OR 0.31**<br>(0.12 to 0.52) | 654<br>(10 studies) | ⊕⊕⊕⊖<br>**Moderate** [a] | 15 studies reported data on hospitalisations; 10 dichotomous studies are reported here. Generic inverse variance combining dichotomous and continuous data produced statistical significance in favour of antibiotic arm (OR 0.31, 95% CI 0.19 to 0.52; $I^2$ = 51%; P value < 0.00001) |
| **Hospitalisations**<br>Number of events<br>Follow-up: 1.5 to 24 months | **87 per 1000** | **37 per 1000**<br>(13 to 96) | **OR 0.40**<br>(0.14 to 1.11) | 643<br>(7 studies) | ⊕⊕⊕⊖<br>**Moderate** [a] | Cross-over study Drobnic 2005 (n = 30 participants) also reported on hospitalisations with mean (± SD) improvement of 0.15 ± 0.37 observed in antibiotic arm compared with 0.75 ± 1.16 in placebo arm at 13 month follow-up |
| **Emergence of resistance**<br>Number of events<br>Follow-up: 1.5 to 24 months | **47 per 1000** | **148 per 1000**<br>(56 to 334) | **OR 3.48**<br>(1.20 to 10.07) | 431<br>(6 studies) | ⊕⊕⊕⊖<br>**Moderate** [b] | Nine studies reported on emergence of resistance; however, because of variability in reporting of outcome data, only 6 could be meta-analysed. No difference was observed between groups for the remaining 3 studies |
| **St George Respiratory Questionnaire (SGRQ) total**<br>Mean and standard deviation.<br>Scale from 0 to 100 | Mean SGRQ (total) score ranged across control groups from **-6.4 to 4.1 points** | Mean SGRQ (total) score in intervention groups was **2.75 lower**<br>(7.08 lower to 1.57 higher) | | 315<br>(5 studies) | ⊕⊕⊖⊖<br>**Low** [c] | Quality of life was reported in 10 studies, with meta-analysis possible in 5. Substantial heterogeneity was observed between studies. Although sensitivity analysis using a fixed-effect model produced statistically significant results, primary analysis using a random-effects model was not statistically significant |

| | | | | |
|---|---|---|---|---|
| Follow-up: 6 to 16 months | | | | |

*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (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; **OR:** Odds ratio.

GRADE Working Group grades of evidence.
**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.
**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
**Very low quality:** We are very uncertain about the estimate.

[a]Presence of heterogeneity in 30% to 60% range, representing possibility of moderate heterogeneity.
[b]Small number of events producing wide confidence intervals around estimate of effect.
[c]Presence of heterogeneity in 75% to 100% range, representing possibility of considerable heterogeneity.

# BACKGROUND

## Description of the condition

Non-cystic fibrosis (CF) bronchiectasis is a chronic respiratory condition characterised by abnormal dilatation of the bronchial lumen (Loebinger 2009; O'Donnell 2008). Global prevalence of this disorder is largely unknown (Kwak 2010; Maguire 2012), primarily because bronchiectasis may be noted as a secondary diagnosis for other conditions (AIHW 2010). Formal diagnosis requires special investigation and therefore usually occurs only among patients referred to a respiratory specialist (AIHW 2010). However, available data on prevalence show that bronchiectasis is now being diagnosed with increasing frequency (Martínez-García 2011; McShane 2013; O'Donnell 2008). In the United States of America (USA), Seitz 2012 found an increasing yearly prevalence from 2000 to 2007, with an annual percentage change of 8.74%. Prevalence estimates in the USA range from 4.2 per 100,000 persons 18 to 34 years of age to 271.8 per 100,000 among those 75 years of age and older (Weycker 2005). In Finland, the incidence of non-CF bronchiectasis among children younger than 15 years has been estimated at 0.5 per 100,000 per year and at 3.9 per 100,000 for the overall population (Saynajakangas 1998). Higher prevalence estimates have been reported in children living in Northern England with 17.2 per 100,000 per year diagnosed, and in New Zealand with estimates of 3.7 per 100,000 (Twiss 2005). In Australia, however, bronchiectasis among Aboriginal and Torres Strait Islander children is estimated to occur in as many as 14 per 1000 Indigenous youth (Chang 2002), with similar statistics reported when New Zealand children of Pacific and Maōri origin were compared with children of European ancestry (Twiss 2005). Statistics indicate that prevalence increases with age and peaks at around 80 years, and that higher rates have been observed among women (AIHW 2010; Lee 2011; Seitz 2012).

The underlying pathogenesis of non-CF bronchiectasis is not entirely understood (Wilson 2013b). In most patients, the airways become chronically infected with a variety of pathogens involved in the aetiology of this condition (Chalmers 2012; Murray 2011; Tunney 2013), including *Haemophilus influenzae* (which dominates across all ages),*Streptococcus pneumoniae, Moraxella catarrhalis* and *Pseudomonas aeruginosa* (Grimwood 2011). The landmark study by Reid 1950 first refined pathological phenotypes as cylindrical, varicose and saccular, and Cole 1986 further explained the evolution of bronchiectasis through the vicious cycle model. This model continues to be adapted but generally describes development of a vicious cycle of infection and inflammation whereby symptoms persist, with frequent exacerbations causing further airway damage (Cole 1986; King 2009; Murray 2011; O'Donnell 2008). Idiopathic bronchiectasis is the most common diagnosis and tends to be bilateral, cylindrical and lower lobe predominant (Wilson 2013b). Severe infections of any type can damage the bronchial wall sufficiently to induce bronchiectasis localised to the site of infection (Wilson 2013b). The next most common aetiologies are allergic bronchopulmonary aspergillosis, common variable immunodeficiency and primary ciliary dyskinesia (Wilson 2013b).

Bronchiectasis causes significant morbidity and increased risks for mortality. Typically patients will suffer with persistent cough, chronic daily sputum expectoration, recurrent chest infection and poor health-related quality of life (Murray 2011). Mortality was examined in one recent Belgium cohort analysis of 245 participants newly diagnosed between 2006 and 2012; analysis revealed increased risk of death among participants with co-morbid chronic obstructive pulmonary disease (COPD) compared with participants with other bronchiectasis (Goeminne 2014). However, national statistics in Australia show that only a small number of reported deaths are directly attributable to bronchiectasis (AIHW 2010). A long-term survival study that provided 13 years of follow-up among 91 individuals with non-CF bronchiectasis in the United Kingdom found that mortality, as was reported in 29.7% of participants, was associated with a degree of restrictive and obstructive disease, poor gas transfer and chronic *Pseudomonas* infection (Loebinger 2009). Additional risk factors observed to lower the likelihood of survival included increasing age and greater numbers of lobes affected (Goeminne 2014).

## Description of the intervention

Recent evidence has helped improve our understanding of the role of mucus stasis in bacterial colonisation and has led to emphasis on therapies that enhance airway clearance (McShane 2013). Low-dose, long-term macrolide therapy has been shown to decrease exacerbation frequency and airway inflammation (McShane 2013). Long-term use of antibiotics may provide benefit by reducing exacerbations but currently is not recommended as part of routine treatment (Valery 2012; Wu 2014). However, for patients with three or more exacerbations per year requiring antibiotic therapy, or for those with fewer exacerbations causing significant morbidity, prolonged antibiotic therapy should be considered (Pasteur 2010). Long-term use of inhaled antibiotics is believed to be safe and effective in reducing the sputum bacterial load, as these agents deliver a high concentration of drug to the airway along with reduced systemic absorption, thereby reducing the risk of systemic adverse effects (McShane 2013). However, most data supporting the use of tobramycin, gentamycin and colistin compounded or re-constituted into a nebulised form for the management of bronchiectasis have come from studies on the CF population (McShane 2013), thus limiting the generalisability of findings to the non-CF bronchiectasis population.

## How the intervention might work

Various strategies have been developed to interrupt the vicious cycle model of Cole 1986, whereby a repetitious syndrome of cough, sputum production and recurrent exacerbations is said to be the primary cause of bronchiectasis. If bacteria are the primary cause of airway inflammation, then according to this hypothesis, bacterial clearance through the use of short- or long-term antibiotics should reduce airway inflammation (Chalmers 2012; Downey 2007; Ordonez 2003; Sagel 2011). Reducing inflammation would effectively allow time for airway healing and ultimately would modify the long-term course of the disease (Evans 2007; Wu 2014). One study of 49 stable participants with non-CF bronchiectasis reported a link between bacterial load and airway inflammation through bronchoalveolar lavage (Angrill 2001). Another study in patients with COPD that included 43 participants with bronchiectasis also observed the correlation (Hill 2000). A strong evidence base from studies of patients with cystic fibrosis bronchiectasis supports this theory by reporting that antibiotic treatment during both stable and exacerbation periods resulted in reduced markers of inflammation. The disease pathophysiology is different; therefore direct comparison between these conditions is precarious (Chalmers 2012).

### Why it is important to do this review

To date, clinical research trials have described mixed results on the effectiveness of antibiotics for reducing airway inflammation and subsequent bronchiectasis (Chalmers 2012). Some studies have suggested that antibiotic therapy had little or no effect on airway inflammation (Tsang 1999), but others examining long-term use of antibiotics have revealed reduced levels of myeloperoxidase (MPO) and neutrophil elastase activity in sputum (Hill 1988; Lin 1997), indicating reduced airway inflammation (Chalmers 2012). The last Cochrane review update on this topic produced some evidence to suggest a small benefit can be achieved with the use of prolonged antibiotics in the treatment of bronchiectasis (Evans 2007), although recommendations were limited by a paucity of data. Since 2007, several trials using different types of antibiotic therapy have been published. Therefore, an update of the existing Cochrane review undertaken to examine newly published evidence on the role of prolonged antibiotic therapy in the management of non-CF bronchiectasis is required.

## OBJECTIVES

To determine the benefits of prolonged antibiotic therapy in the treatment of patients with bronchiectasis.

## METHODS

### Criteria for considering studies for this review

#### Types of studies

We included randomised controlled parallel and cross-over trials.

#### Types of participants

Adult and paediatric participants diagnosed with bronchiectasis by plain film chest radiograph, bronchography or high-resolution computed tomography who reported daily sputum expectoration for at least three months were included. Studies were excluded if patients had been receiving continuous or high-dose antibiotics immediately before the study, or if they had received a diagnosis of cystic fibrosis (CF), sarcoidosis or allergic bronchopulmonary aspergillosis.

#### Types of interventions

Any dose of prolonged antibiotic therapy of four or more weeks versus placebo or as required treatment.

#### Types of outcome measures

##### *Primary outcomes*

1. Exacerbations.
2. Hospitalisations.

##### *Secondary outcomes*

1. Response rates.
2. Sputum volume and purulence.
3. Measures of lung function (e.g. forced expiratory volume in one second (FEV1)).
4. Systemic markers of infection (e.g. leucocyte count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR)).
5. Adverse events (e.g. cardiac arrhythmias, GI symptoms, hearing impairment).
6. Deaths.
7. Emergence of resistance to antibiotics.
8. Exercise capacity (e.g. Six-Minute Walk Distance (6MWD)).
9. Quality of life (e.g. St George Respiratory Questionnaire (SGRQ)).

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

### Search methods for identification of studies

#### Electronic searches

We identified trials from the Cochrane Airways Group Specialised Register (CAGR), which is maintained by the Trials Search Co-ordinator for the Group. The Register contains trial reports identified through systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, the Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Allied and Complementary Medicine Database (AMED) and PsycINFO, and by handsearching of respiratory journals and meeting abstracts (see Appendix 1 for further details). We searched all records in the CAGR using the search strategy provided in Appendix 2.

We also conducted a search of ClinicalTrials.gov (www.ClinicalTrials.gov) and the World Health Organization (WHO) trials portal (www.who.int/ictrp/en/). We searched all databases from their inception to February 2014, with no restriction on language of publication.

#### Searching other resources

In addition, we checked the reference lists of all available primary studies and review articles to identify potentially relevant citations and made inquiries to the authors of primary studies regarding other published or unpublished trials known to them.

### Data collection and analysis

#### Selection of studies

Two review authors (KH and CN) independently examined the output generated by the literature search. We obtained all potentially relevant articles and selected trials from identified studies on the basis of previously agreed inclusion criteria. Review authors described study characteristics and outcomes.

#### Data extraction and management

Two review authors (KH and CN) independently extracted data and risk of bias data from included trials and resolved conflicts by discussion with a third review author (KVC).

#### Assessment of risk of bias in included studies

Two review authors (KH and CN) assessed each study for risk of bias for random sequence generation, allocation concealment, blinding of participants and outcome assessors, handling of missing data, selective outcome reporting and other threats to validity in the studies, in line with recommendations provided in the*Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We conducted a retrospective risk of bias assessment by applying the above method to all original studies included in the previous version of this review.

### Measures of treatment effect

We extracted and analysed continuous and dichotomous outcome data using standard statistical techniques with a fixed-effect model for all studies deemed similar enough to be pooled. In the presence of significant heterogeneity, we employed a random-effects model.

For continuous outcomes, we calculated mean differences (MDs) with 95% confidence intervals (CIs) and pooled MDs or standardised mean differences (SMDs). For dichotomous outcomes, we calculated risk ratios (RRs) with 95% CIs.

We performed a narrative synthesis for each of the included studies and combined all data using Review Manager software.

### Unit of analysis issues

We included in the review a mixture of cross-over and parallel studies with the potential for unit of analysis issues to occur. We used the generic inverse variance (GIV) method (by entering effect estimates and their standard errors) to adjust for unit of analysis errors when meta-analysing the data, as per Section 7.7.7 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

### Dealing with missing data

We evaluated missing information regarding participants on an available case analysis basis, as described in Chapter 16.2.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). When statistics essential for analysis were missing (e.g. when group means and standard deviations for both groups were not reported) and could not be calculated from other data, we attempted to contact study authors to obtain missing data. Loss of participants that occurred before baseline measurements were obtained was assumed to have no effect on the eventual outcome data of the study. We assessed and discussed losses after baseline measurements were taken by using an intention-to-treat approach.

### Assessment of heterogeneity

We assessed statistical heterogeneity by using a combination of tests including $I^2$ statistic ≥ 50% and visual inspection of data; had 10 or more studies been included, we would have used funnel plots as well. We considered the Der-Simonian and Laird method of analysis presented with a P value less than 0.05 as statistically significant.

In the presence of significant heterogeneity (as per the criteria above), we re-analysed data using both fixed-effect and random-effects models.

### Assessment of reporting biases

We planned to explore potential reporting biases by using a funnel plot if we were able to meta-analyse 10 or more studies. Instead, we extrapolated on this possible risk of bias within the other bias section in the risk of bias tables.

### Data synthesis

We combined data from all trials using Review Manager 5.2 software. We reported studies by using intention-to-treat analysis when all participants who were randomly assigned during the study were assessed, regardless of whether they received the intervention/study treatment to which they were allocated.

### Subgroup analysis and investigation of heterogeneity

Planned subgroups included adults versus children.

### Sensitivity analysis

We planned to conduct a sensitivity based on risk of bias. However, we did not do this as none of the included studies had high risk of bias for sequence generation or allocation concealment.

## RESULTS

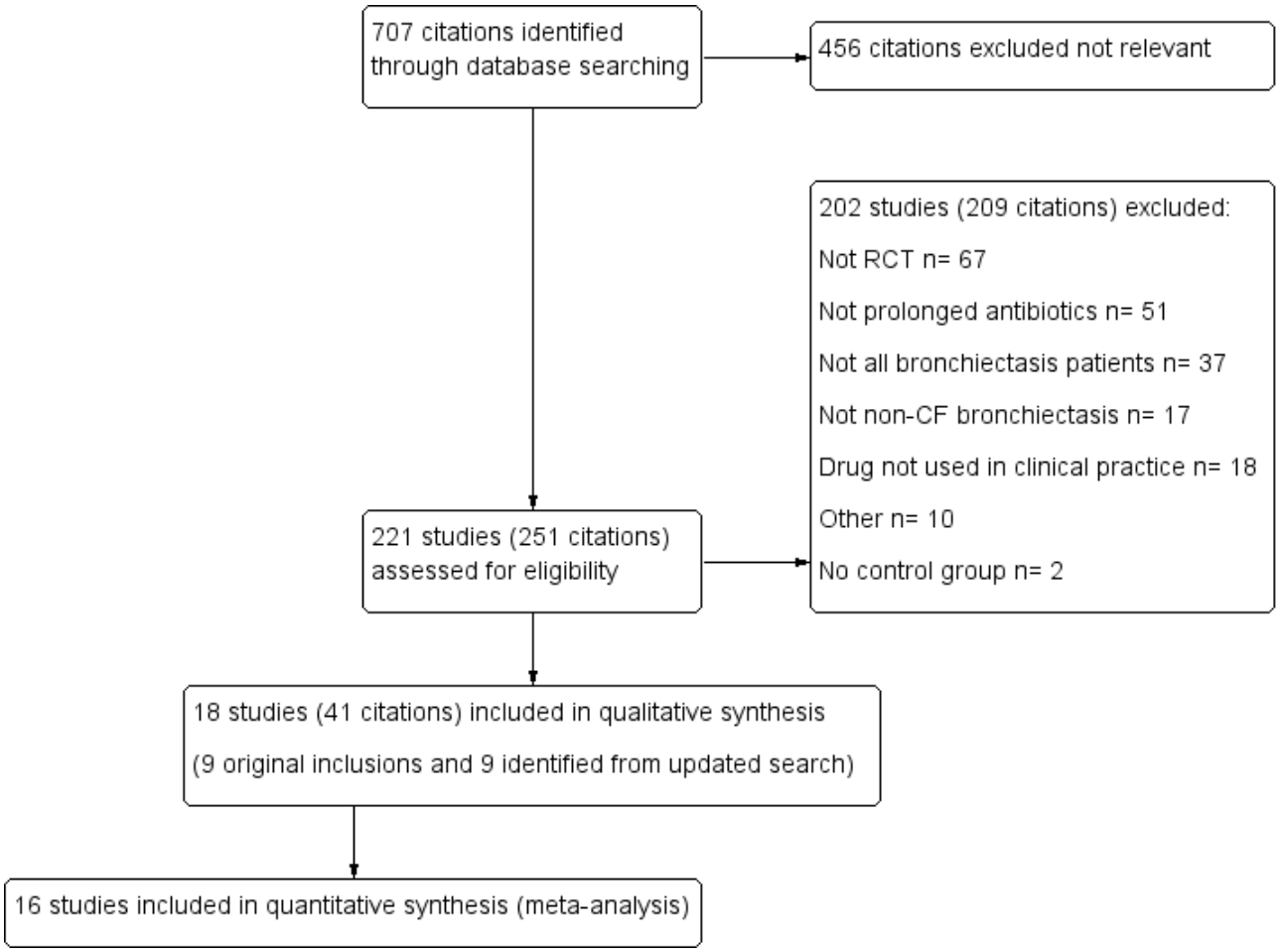
## Description of studies

See Characteristics of included studies, Characteristics of excluded studies and Characteristics of studies awaiting classification for additional details on 18, 202 and four studies, respectively.

### Results of the search

We have provided in Table 1 details of previous searches up to January 2007. Update searches from 2007 to February 2014 retrieved 249 citations. After exclusions based on title and abstract, we assessed 221 full-text papers for eligibility. We determined that nine new studies were eligible for inclusion and hence included a total of 18 studies in this review. See Figure 1 for the study flow diagram.

**Figure 1. Study flow diagram.**




For details on each included study, see Characteristics of included studies and the description of characteristics of included studies provided in Table 2.

### Included studies

#### *Study design*

Sixteen of the included trials were parallel-group studies, and two used a cross-over design (Cymbala 2005; Drobnic 2005). These 18 studies including international multi-centred studies randomly assigned a total of 1157 participants and were published between 1957 and 2013. Two of these studies were conducted in the USA (Barker 2000; Cymbala 2005), three in the United Kingdom (Currie 1990; MRC 1957; Murray 2011), three in Spain (De Diego 2013; Drobnic 2005; Orriols 1999), and one each in one Australia (Serisier 2013a BLESS), China (Liu 2012), Hong Kong (Tsang 1999), the Netherlands (Altenburg 2013), New Zealand (Wong 2012), South Korea (Koh 1997) and Turkey (Yalçin 2006). Three studies were conducted across multiple countries being Serisier 2013b ORBIT (Australia and New Zealand), Valery 2013 (Australia and New Zealand) and the Wilson 2013a study (Australia, Germany, Spain, Sweden, UK and USA).

#### *Participants*

A total of 1157 participants (from n = 1627 eligible participants) were randomly assigned across the 18 studies; most were adults (n = 1009) with a mean age of 59 years. In all, 148 children participated in the three paediatric studies (Koh 1997; Valery 2013; Yalçin 2006). Participants from all of the included studies, except Currie 1990, MRC 1957 and Valery 2013, were diagnosed with non-CF bronchiectasis, confirmed by computed tomography scan. Exclusion criteria were mentioned by all of the included studies and were explicitly described by some.

#### *Baseline lung function*

Fourteen studies reported baseline lung function (Altenburg 2013; Barker 2000; Currie 1990; Cymbala 2005; De Diego 2013; Drobnic 2005; Koh 1997; Murray 2011; Orriols 1999; Serisier 2013a BLESS; Serisier 2013b ORBIT; Tsang 1999; Wilson 2013a; Wong 2012).

#### *Baseline exacerbation rates or episodes*

Seven studies adjusted baseline exacerbation rates or episodes (Altenburg 2013; De Diego 2013; Serisier 2013a BLESS; Serisier 2013b ORBIT; Tsang 1999; Wilson 2013a; Wong 2012). In the Barker 2000 study, the intervention group had more frequent exacerbations (intervention n = 5 vs control n = 1), but the Currie 1990 study reported more frequent exacerbations in the control arm (intervention n = 11 vs control n = 15). Eight studies (Cymbala 2005; Drobnic 2005; Koh 1997; Liu 2012; MRC 1957; Murray 2011; Orriols 1999; Valery 2013) did not report baseline exacerbations.

#### *Pseudomonas aeruginosa isolate*

Altenburg 2013, Barker 2000, Currie 1990, De Diego 2013, Drobnic 2005, Murray 2011, Orriols 1999, Serisier 2013a BLESS, Serisier 2013b ORBIT, Wilson 2013a and Wong 2012 reported *Pseudomonas aeruginosa*. All participants as per trial protocols from Barker 2000, Drobnic 2005, Orriols 1999 and Wilson 2013a had positive *P. aeruginosa* growth at baseline. Currie 1990 cultured 8 of 17 participants taking amoxycillin (intervention) and 7 of 19 given placebo but also reported having 21 participants with *Pseudomnas* at baseline or during treatment. In Serisier 2013a BLESS, 23 of 59 (39%) participants taking erythromycin (intervention) versus 18 of 58 (31%) given placebo had *P. aeruginosa*. Altenburg 2013 reported growth of *P. aeruginosa* in 6 of 43 (14%) participants taking azithromycin(intervention) and in 6 of 40 (15%) given placebo, and De Diego 2013 had *P. aeruginosa* present in 7 of 16 participants taking azithromycin (intervention) and in 5 of 14 given placebo at baseline. Study authors from Wong 2012 reported that 9 of 71(13%) participants taking azithromycin (intervention) and 8 of 70 (11%) given placebo were positive for *P. aeruginosa*. Table 3 provides a summary showing types of interventions and status of *P. aeruginosa*.

#### *Smoking history*

No information on smoking was available in 11 studies (Barker 2000; Currie 1990; De Diego 2013; Drobnic 2005; Koh 1997; Liu 2012; MRC 1957; Orriols 1999; Valery 2013; Wilson 2013a; Yalçin 2006). Smoking was described variably in Tsang 1999 (1 of 11 taking erythromycin and 2 of 10 given placebo were ex-smokers), Cymbala 2005 (8 of 11 participants were past or present smokers), Murray 2011 (8 of 27 taking azithromycin and 8 of 30 given placebo were ex-smokers), Wong 2012 (1% given intervention vs 6% given placebo were smokers), Serisier 2013a BLESS (10 of 59 (16.9%) and 15 of 58 (25.9%) were ex-smokers), Serisier 2013b ORBIT (1 of 20 taking ciprofloxacin was an ex-smoker) and Altenburg 2013 (20 of 43 taking azithromycin and 18 of 40 given placebo were past or present smokers).

#### *Radiological extent of bronchiectasis*

The radiological extent of bronchiectasis was reported in terms of the number of lobes involved by Orriols 1999 (n = 15) and Tsang 1999 (n = 22) (at least three lobes were involved in all participants) and Currie 1990 (12 of 17 taking amoxycillin and 10 of 19 given placebo had three or more lobes).

#### *Interventions*

The length of studies varied with intervention duration and ranged from 4 to 82.8 (mean value from Valery 2013) weeks. Antibiotics (and route of administration) assessed in the studies were tobramycin (Barker 2000; Drobnic 2005; Orriols 1999: nebulised), ceftazidime (Orriols 1999: nebulised), amoxycillin (Currie 1990: oral), roxithromycin (Koh 1997; Liu 2012: oral), penicillin (MRC 1957: oral), oxytetracycline (MRC 1957: oral), erythromycin (Serisier 2013a BLESS; Tsang 1999: oral), clarithromycin (Yalçin 2006: oral) and azithromycin (Altenburg 2013; Cymbala 2005; De Diego 2013; Valery 2013; Wong 2012: oral). All studies were placebo-controlled with the exception of Cymbala 2005, De Diego 2013, Orriols 1999 and Yalçin 2006, in which control groups were given usual medical care.

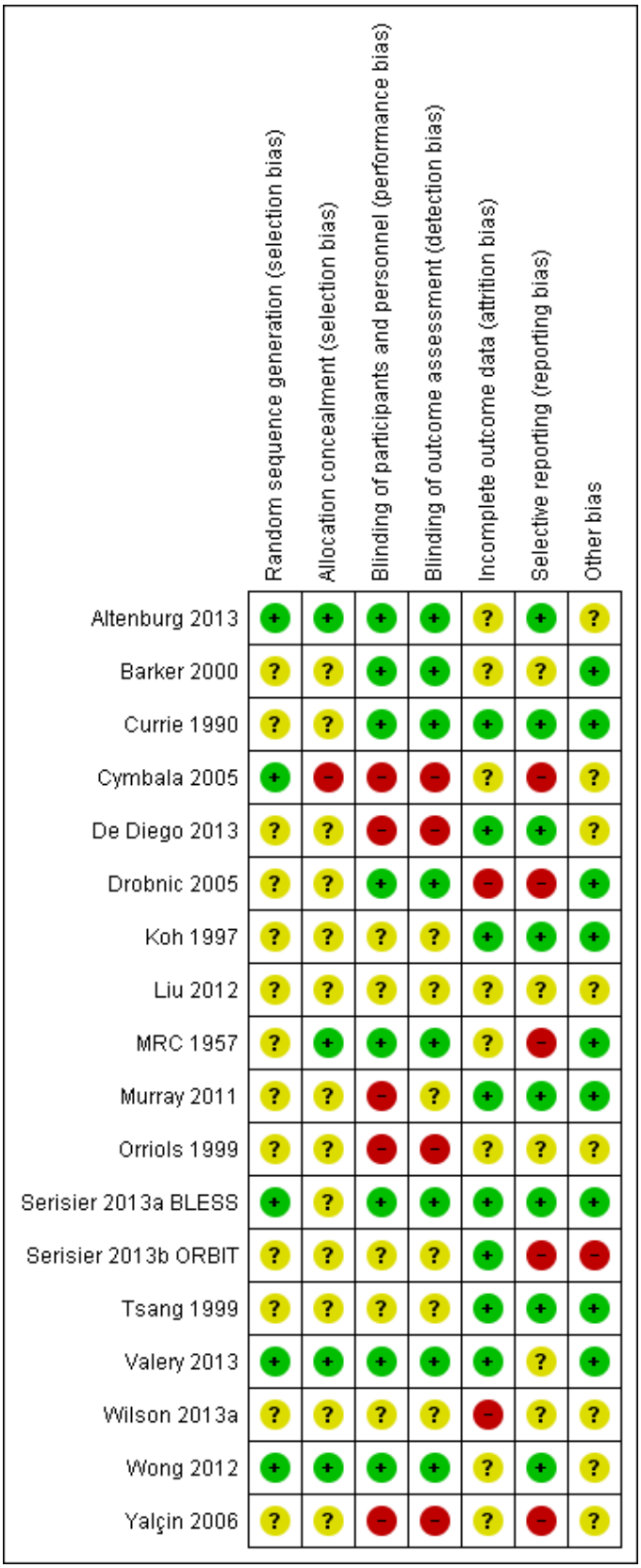
### Excluded studies

We recorded reasons for exclusion of 202 studies in Characteristics of excluded studies. The most common reasons for exclusion in order of prevalence include the following: not a randomised controlled trial (n = 67), no prolonged antibiotics (n = 51), not all bronchiectasis patients (n = 37), full review not possible and drug not used in clinical practice (n = 18), not non-CF bronchiectasis (n = 17), other reasons (n = 10) and no control group (n = 2).

## Risk of bias in included studies

Full details of our risk of bias judgements can be found under the "Risk of bias" section at the end of each Characteristics of included studies table and in Figure 2. Overall, the methodological quality of included studies was good. Two independent review authors (KH and CN) reached agreement when assessing study quality.

**Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.**



### Allocation

Generation of the randomisation sequence was considered adequate in five studies (Altenburg 2013; Cymbala 2005; Serisier 2013a BLESS; Valery 2013; Wong 2012) and unclear in 13 studies (Barker 2000; Currie 1990; De Diego 2013; Drobnic 2005; Koh 1997; Liu 2012; MRC 1957; Murray 2011; Orriols 1999; Serisier 2013b ORBIT; Tsang 1999; Wilson 2013a; Wong 2012).

The method of allocation concealment was determined to be adequate in four studies (Altenburg 2013; MRC 1957; Valery 2013; Wong 2012) and unclear in 13 studies (Barker 2000; Currie 1990; De Diego 2013; Drobnic 2005; Koh 1997; Liu 2012; Murray 2011; Orriols 1999; Serisier 2013a BLESS; Serisier 2013b ORBIT; Tsang 1999; Wilson 2013a; Yalçin 2006). However, Cymbala 2005 was assessed to have high risk of bias for allocation concealment.

### Blinding

Risk associated with participant blinding was deemed to be low when the study provided identical tablets or visually identical liquid and packaging and the same follow-up for participants. Adequate blinding of assessors was reported on the basis of information provided by study authors, such as a clear and well-defined study protocol, central or third party allocation of assessors and treating doctors and the same follow-up, measurements and tests provided for participants from both arms of the study.

Risk of detection bias due to inadequate blinding of outcome assessors has been judged as high in five studies (Cymbala 2005; De Diego 2013; Murray 2011; Orriols 1999; Yalçin 2006) and unclear in five trials (Koh 1997; Liu 2012; Serisier 2013b ORBIT; Tsang 1999; Wilson 2013a), with no specific details provided in the trial reports. Although Murray 2011 was assessed to have high risk of bias for blinding of participants, risk was unclear for blinding of outcome assessors. Altenburg 2013, Barker 2000, Currie 1990, Drobnic 2005, MRC 1957, Serisier 2013a BLESS, Valery 2013 and Wong 2012 were deemed to have low risk of bias.

### Incomplete outcome data

Low risk of bias was assessed in eight studies (Currie 1990; De Diego 2013; Koh 1997; Murray 2011; Serisier 2013a BLESS; Serisier 2013b ORBIT; Tsang 1999; Valery 2013). We report high risk of attrition bias in Wilson 2013a and Drobnic 2005 and unclear risk in eight studies (Altenburg 2013; Barker 2000; Cymbala 2005; Liu 2012; MRC 1957; Orriols 1999; Wong 2012; Yalçin 2006).

### Selective reporting

Selective reporting (reporting bias) was considered to introduce low risk in eight studies (Altenburg 2013; Currie 1990; De Diego 2013; Koh 1997; Murray 2011; Serisier 2013a BLESS; Tsang 1999; Wong 2012); however it was determined to bring high risk in five studies (Cymbala 2005; Drobnic 2005; MRC 1957; Serisier 2013b ORBIT; Yalçin 2006). The remaining five studies (Barker 2000; Liu 2012; Orriols 1999; Valery 2013; Wilson 2013a) were identified to have unclear risk for reporting bias.

### Other potential sources of bias

Other potential sources of bias were not identified in nine studies (Barker 2000; Currie 1990; Drobnic 2005; Koh 1997; MRC 1957; Murray 2011; Serisier 2013a BLESS; Tsang 1999; Valery 2013), but this could not be adequately assessed in eight studies (Altenburg 2013; Cymbala 2005; De Diego 2013; Liu 2012; Orriols 1999; Wilson 2013a; Wong 2012; Yalçin 2006). High risk of the other potential sources of bias was identified in Serisier 2013b ORBIT.

## Effects of interventions

See: **Summary of findings for the main comparison** Prolonged antibiotics for purulent bronchiectasis in children and adults

### Primary outcomes

#### *1. Exacerbations*

Fifteen of 18 included studies with 956 participants reported data on exacerbations. A total of 13 studies (with 884 participants) could be pooled in a meta-analysis using generic inverse variance, with 10 reporting dichotomous data (Barker 2000; Currie 1990; Koh 1997; Liu 2012; Murray 2011; Serisier 2013b ORBIT; Tsang 1999; Valery 2013; Wilson 2013a; Wong 2012) and three continuous data (Altenburg 2013; De Diego 2013; Serisier 2013a BLESS), producing statistically significant benefits in favour of the antibiotic arm (odds ratio (OR) 0.31; 95% confidence interval (CI) 0.19 to 0.52; $I^2$ = 51%; P value < 0.00001; Figure 3) and reporting similar results for the sensitivity analysis using a fixed-effect model (P value < 0.0001; Analysis 2.1). Data from two cross-over studies (Cymbala 2005; Drobnic 2005) involving 12 and 60 participants, respectively, were limited to individual studies. Drobnic 2005 did not detect a significant difference between treatments in terms of mean exacerbations per participant (mean difference (MD) -0.4, P value = 0.32) but found a significant difference in the mean number of admissions in favour of tobramycin (MD -0.6, P value = 0.03). Cymbala 2005, which included 12 participants, reported fewer exacerbations requiring antibacterial therapy in the azithromycin phase than in the control phase (5 events vs 16, P value = 0.019). Exacerbation was not reported by three trials (MRC 1957; Orriols 1999; Yalçin 2006). For absolute treatment differences, 55 of 100 people in the control group had one or more exacerbations over 1.5 to 24 months compared with 32 (95% CI 25 to 41) of 100 given prolonged antibiotics (Figure 4).

**Figure 3. Forest plot of comparison: 1 Continuous antibiotics versus standard treatment with or without added placebo (parallel groups), outcome: 1.1 Exacerbations.**

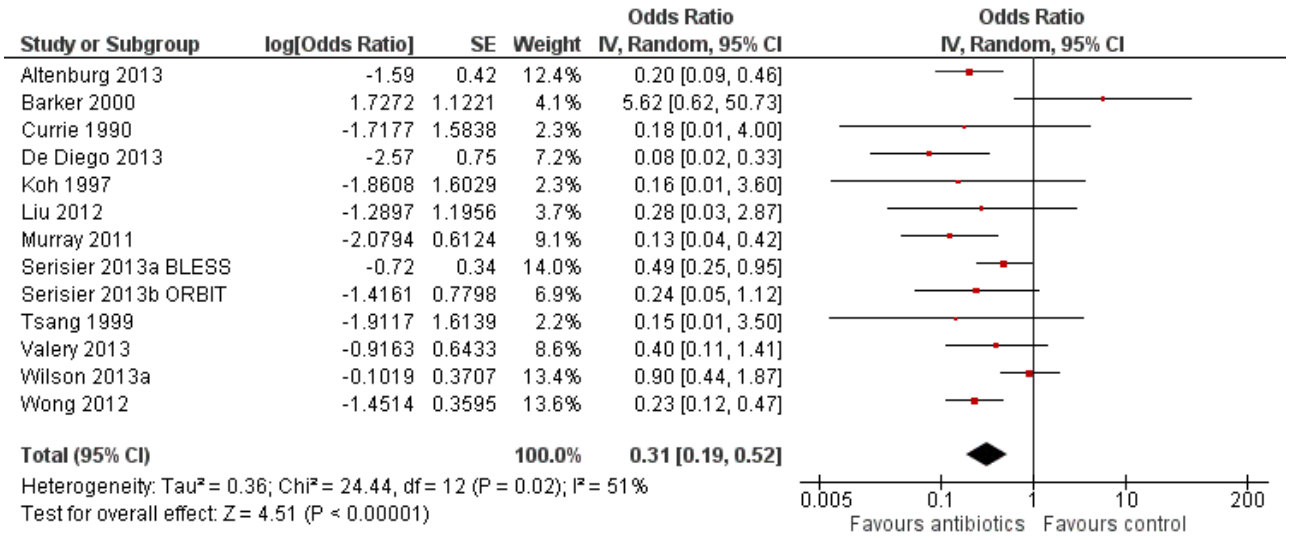



**Figure 4. Absolute treatment differences for exacerbations with events occurring in 546 per 1000 in the control arm and in 271 per 1000 (95% CI 126 to 385) people on the intervention.**

**Number of courses of antibiotics**

Supplemental antibiotic use for pulmonary or non-pulmonary exacerbations was reported in 14 studies including 1021 participants (Altenburg 2013; Barker 2000; Currie 1990; Cymbala 2005; Drobnic 2005; MRC 1957; Murray 2011; Orriols 1999; Serisier 2013a BLESS; Serisier 2013b ORBIT; Tsang 1999; Valery 2013; Wilson 2013a; Wong 2012). Three of the 18 studies analysed did not report on supplementary antibiotic courses during the study treatment phase (Koh 1997; Liu 2012; Yalçin 2006).

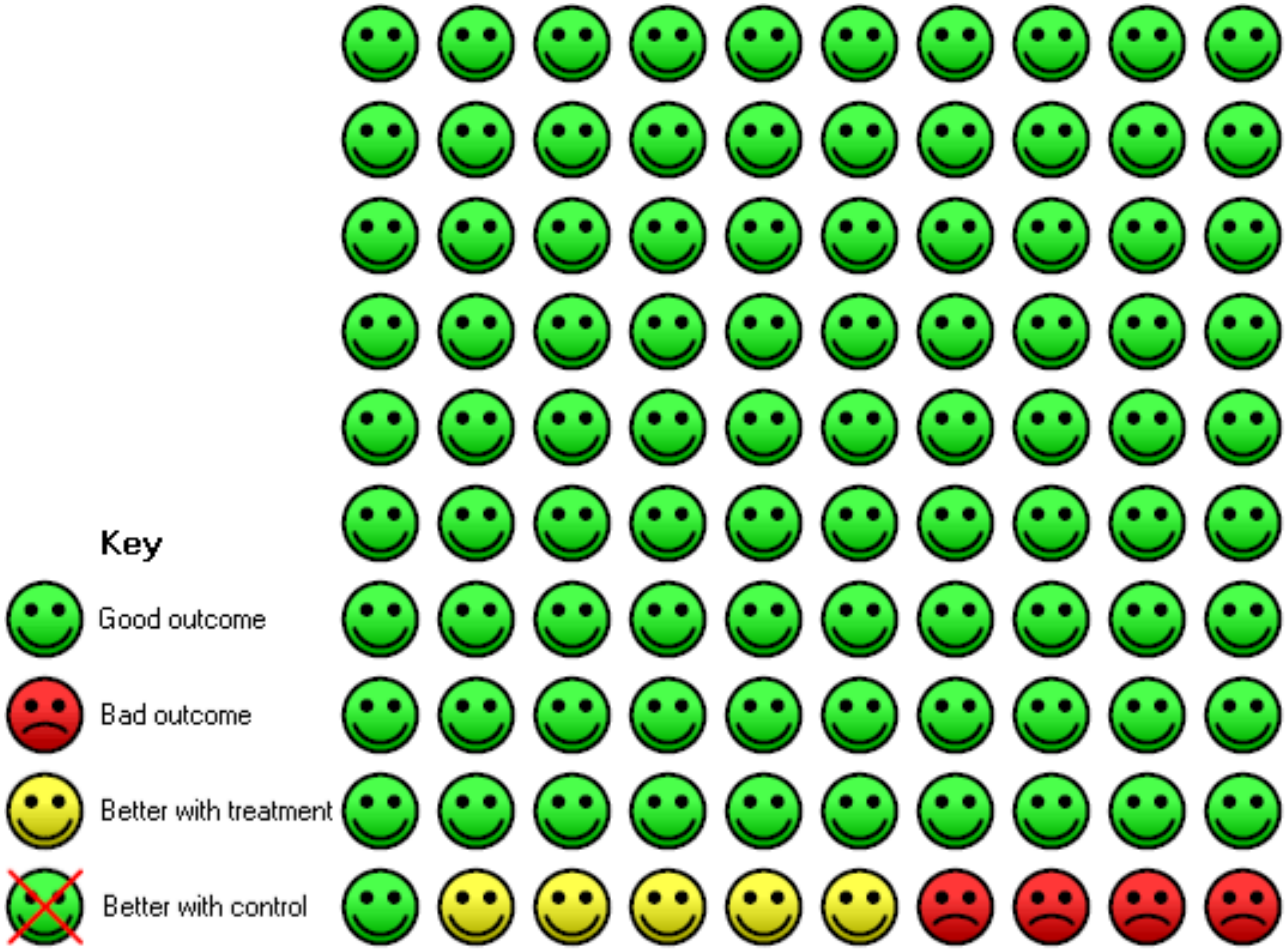
Supplemental antibiotic prescription and use correlated with identified exacerbations; however all but two studies failed to indicate duration or number of courses (Altenburg 2013; Barker 2000; Currie 1990; Cymbala 2005; Drobnic 2005; MRC 1957; Murray 2011; Orriols 1999; Serisier 2013a BLESS; Serisier 2013b ORBIT; Wilson 2013a; Wong 2012). Tsang 1999 recorded that two participants required treatment with sparfloxacin (200 mg daily for 10 days), and Valery 2013 mentioned use of supplemental non-macrolide antibiotics for two weeks following pulmonary exacerbations.

The two cross-over trials (Cymbala 2005; Drobnic 2005) showed that use of supplemental antibiotics correlated with infective pulmonary exacerbations, with less use reported in the treatment arm than in the placebo arm. These trials did not report the number or duration of courses. The number of supplementary antibiotic courses taken during the study treatment phase of the Currie 1990 study was reported to be related to the number of courses taken during the previous year rather than to the allocated treatment regimen.

***2. Hospitalisations***

Seven parallel studies (Altenburg 2013; Barker 2000; Orriols 1999; Serisier 2013a BLESS; Valery 2013; Wilson 2013a; Wong 2012) with 13 of 322 intervention participants and 28 of 321 placebo participants reported hospitalisations, with a non-statistically significant result in favour of the intervention (OR 0.40, 95% CI 0.14 to 1.11; P value = 0.08; $I^2$ = 36%; Analysis 1.2). The sensitivity analysis using the fixed-effect model did however produce statistical significance (P value = 0.02; Analysis 2.2). Drobnic 2005, a cross-over trial with 30 participants, reported improvement in the number of admissions per participant using mean ± SD (0.15 ± 0.37 taking intervention vs 0.75 ± 1.16 given placebo). In terms of absolute treatment differences, 9 of 100 people in the control group had one or more hospitalisations over 1.5 to 24 months compared with 4 (95% CI 2 to 8) of 100 given prolonged antibiotics (Figure 5).

**Figure 5. Absolute treatment differences for hospitalisations with events occurring in 87 per 1000 in the control arm and in 37 per 1000 (95% CI 13 to 96) on the intervention.**



**Secondary outcomes**

***1. Response rates***

A significant treatment effect was noted following meta-analysis for clinical response rates in two studies (OR 3.37, 95% CI 1.60 to 7.09; n = 110; P value = 0.001; Analysis 1.3). In spite of slightly differing definitions of response between studies (Currie 1990 reported physician assessment of diary cards; Barker 2000 reported physician assessment of overall medical condition), no heterogeneity was observed. Currie 1990 reported no significant differences in disease progression (3/17 vs 4/19 participants in the antibiotic and control groups, respectively). Participant-reported symptoms were measured by the Lower Respiratory Tract Infection Visual Analogue Scale (LRTI VAS) in the Altenburg 2013 study, which showed a larger decrease in total score (indicating fewer symptoms) among participants receiving the intervention compared with control participants at the end of the treatment period (six months; P value = 0.047).

***2. Sputum volume and purulence***

Sputum volume and purulence were reported in 15 studies including 975 participants, one of which was a cross-over study (Currie 1990; Barker 2000; Cymbala 2005; Drobnic 2005; De Diego 2013; Koh 1997; MRC 1957; Murray 2011; Serisier 2013a BLESS; Serisier 2013b ORBIT; Tsang 1999; Valery 2013; Wilson 2013a; Wong 2012; Yalçin 2006). As these results were variably reported, a meta-analysis was not performed. Of these studies, nine recorded data for both sputum volume and purulence (MRC 1957; Currie 1990; Tsang 1999; Yalçin 2006; Murray 2011; Wong 2012; De Diego 2013; Serisier 2013a BLESS; Wilson 2013a). Four of the 15 studies reported on sputum purulence alone (Koh 1997; Barker 2000; Drobnic 2005; Serisier 2013b ORBIT) and one study reported solely on sputum volume (Cymbala 2005).

Of studies reviewing populations of children, Valery 2013 reported on sputum purulence via a sputum colour chart (Bronkotest). However, sputum characteristics were reported as a definition of an exacerbation rather than as a distinct secondary outcome in itself, and no follow-up results were mentioned thereafter. Yalçin 2006 on the other hand reported a significant difference in sputum volume with improvement in the treatment arm of the study. Sputum purulence was measured via total cell number and neutrophil ratios in bronchoalveolar lavage, and also showed a significant improvement in the treatment arm of the study.Both parallel and cross-over trials showed a greater reduction in sputum volume and purulence in the long-term antibiotic group than in the placebo group.

Sputum diary cards were used in one study on 38 participants (Currie 1990). Independent assessment of diary cards in the Currie 1990 study revealed improvement in sputum colour and/or reduction in reported sputum volume, which persisted throughout the post-treatment phase in three intervention participants. Symptomatically, the prolonged antibiotic course was considered successful, as judged by independent assessment of diary card data and in the opinion of participants (Currie 1990).

Koh 1997 reported significantly lower sputum purulence scores in the antibiotic group compared with the placebo group (1.39 ± 0.6 vs 2.17 ± 0.72; P value < 0.01). Yalçin 2006 reported that sputum production was significantly less in the antibiotic group (P value = 0.0001). Cymbala 2005 reported no significant differences in median sputum volume production between treatments (25 mL vs 24 mL). A greater reduction in 24-hour purulent sputum volume was noted in the Currie 1990 study between exacerbations during the study treatment phase in the amoxycillin group (median 20% of pre-treatment volume) compared with the placebo phase (88% of pre-treatment volume; P value = 0.008), although concentrations of *Haemophilus* spp. in sputum between exacerbations were similar in the two groups. However, no differences between groups were observed in the post-treatment phase. The reduction in 24-hour total sputum volume between acute exacerbations during the study treatment phase was also significantly greater in the amoxycillin group (42% of pre-treatment values) than in the placebo group (81%; P value = 0.04), although in the post-treatment phase no differences were observed between groups. Tsang 1999 reported that participants in the erythromycin group (n = 11) but not in the placebo group (n = 10) had significantly improved 24-hour sputum volume after eight weeks (P value < 0.05).

***3. Measures of lung function***

Lung function was reported in 16 studies with a total number of 990 randomly assigned participants (Altenburg 2013; Barker 2000; Currie 1990; Cymbala 2005; De Diego 2013; Drobnic 2005; Koh 1997; Murray 2011; Orriols 1999; Serisier 2013a BLESS; Serisier 2013b ORBIT; Tsang 1999; Valery 2013; Wilson 2013a; Wong 2012; Yalçin 2006). Most studies reported a combination of forced expiratory volume in one second (FEV1) and forced vital capacity (FVC); however some studies reported FEV1 alone. As lung function was variably reported, only limited data were available for meta-analysis. The only available pooled effect estimates showed no evidence of any effect for FEV1% predicted (standardised mean difference (SMD) -0.12, 95% CI -0.34 to 0.10), change in FEV1 (SMD -0.07, 95% CI -0.84 to 0.70) and absolute FEV1 (SMD -0.36, 95% CI -1.03 to 0.30; Analysis 1.4). A sensitivity analysis based on the fixed-effect model also found no evidence of any effect (Analysis 2.3).

Among the adult population, 10 parallel studies showed no evidence of any effect on lung function measurements in intervention and placebo groups at the end of the trial (Barker 2000; Currie 1990; De Diego 2013; Koh 1997; Murray 2011; Orriols 1999; Serisier 2013b ORBIT; Tsang 1999; Wilson 2013a; Wong 2012). Altenburg 2013 showed statistically significant improvement in FEV1 and FVC at the end of the trial period in the intervention group versus the placebo group (P value = 0.047 and P value = 0.02, respectively). However, these results were not maintained over the six months after cessation of the intervention. Serisier 2013a BLESS showed a significant arrest in the decline of FEV1 among participants receiving erythromycin during the treatment period (P value = 0.04).

Two cross-over trials including 72 participants (Cymbala 2005; Drobnic 2005) reported no evidence of any effect on lung function between intervention and placebo groups at the end of the treatment period. Long-term azithromycin administration during Cymbala 2005 demonstrated no significant changes in FEV1 (1.28 ± 0.55 L vs 1.20 ± 0.46 L (azithromycin) vs 1.18 ± 0.51 L (control); P value = 0.153) or FVC (2.25 ± 0.72 L vs 2.22 ± 0.60 L (azithromycin) vs 2.12 ± 0.62 L (control); P value = 0.440). Non-significant changes (%) in these measures between treatment groups (tobramycin vs placebo) were also noted in Drobnic 2005 (FEV1 −3.50, 95% CI −5.95 to −1.02 vs −1.20, 95% CI −4.38 to −1.98; P value = 0.240; FVC −5.45, 95% CI −8.03 to −2.87 vs −1.30, 95% CI −4.88 to −2.28; P value = 0.056).

The two studies involving children (Valery 2013; Yalçin 2006) reported no evidence of any effect on lung function between antibiotic and placebo groups at the end of the trials (total n = 126). Yalçin 2006 showed no evidence of an effect in FEV1% between treatment groups (clarithromycin vs placebo); however, investigators did report improvement in forced expiratory flow at 25% to 75% (FEF25-75%) in the clarithromycin group at the beginning of the study and at month three (P value = 0.015). Similarly, Valery 2013 showed no evidence of any effect on mean predicted FEV1% between antibiotic and placebo groups (84.7 (12.9) vs 81.0 (18.3); P value = 0.38). However, FEV1 data were incomplete, as spirometry was conducted only in participants older than six years.

#### *4. Systemic markers of infection*

##### Leucocyte count

A total of 402 participants - 201 participants taking intervention versus 201 given placebo - were measured for leucocyte counts in six studies (Altenburg 2013; Currie 1990; Drobnic 2005; Koh 1997; Murray 2011; Wong 2012). Koh 1997 (n = 13 taking roxithromycin, n = 12 given placebo), Currie 1990 (n = 17 taking amoxycillin, n = 19 given placebo), Drobnic 2005 (n = 30 on both arms, cross-over trial), Murray 2011 (n = 27 taking intervention, n = 30 given placebo) and Altenburg 2013 (n = 43 taking azithromycin, n = 40 given placebo) reported no changes in both arms. However, Wong 2012 with 141 participants (n = 71 taking azithromycin, n = 70 given placebo) favoured the intervention (P value = 0.013). A meta-analysis of three studies with 165 participants was possible but produced no evidence of any effect for the primary random-effect analysis (MD -0.39, 95% CI -0.87 to 0.09; Analysis 1.5) and the sensitivity analysis (Analysis 2.4).

##### C-reactive protein (CRP)

Six studies (Altenburg 2013; De Diego 2013; Murray 2011; Serisier 2013a BLESS; Wilson 2013a; Wong 2012) with 552 participants (276 in the intervention arm vs 276 in the placebo arm) reported on CRP. As variable reporting methods were used, we were unable to perform a meta-analysis of all data. Altenburg 2013 measured the change in serum CRP levels and leucocyte counts seen in 83 participants (43 taking azithromycin vs 40 given placebo) and showed no significant differences between treatment groups (intervention median 5.0, interquartile range (IQR) 2 to 11.3 mg/dL; control median 4.5, IQR 2 to 15.3 mg/dL). Murray 2011 favoured intervention with 57 participants (27 given intervention and 30 placebo). Wong 2012 reported on 141 participants (71 taking azithromycin and 70 given placebo) and favoured intervention (P value = 0.006). De Diego 2013 reported improvement in the change from baseline for 20 participants (16 taking azithromycin and 14 given placebo). In the Wilson 2013a study, 124 participants (60 given intervention and 64 placebo) showed benefit in favour of the intervention, but this finding was not statistically significant (P value = 0.173). Serisier 2013a BLESS reported no effect on CRP among 54 participants taking erythromycin and 50 given placebo.

##### Erythrocyte sedimentation rate (ESR)

Three studies with 128 participants (Currie 1990; De Diego 2013; Drobnic 2005) reported using ESR as a marker for infection. Two of these studies could be pooled in a meta-analysis, producing no evidence of any effect in the primary analysis (MD -2.47, 95% CI -9.76 to 4.82; Analysis 1.6) or in the sensitivity analysis (Analysis 2.5). Drobnic 2005, a cross-over trial, found no differences between intervention and control groups (n = 30), and the De Diego 2013 study, with 16 participants given intervention and 14 acting as controls, reported a change from baseline (intervention -14 (4) vs control -9 (12)). The ESR in the amoxycillin group of the Currie 1990 study (n = 13 to 17) decreased slightly during treatment but did not fall in the placebo group (n = 11 to 18; P value < 0.05).

#### *5. Adverse events*

Adverse events were reported variably in 15 studies with 683 participants (Altenburg 2013; Barker 2000; Currie 1990; Cymbala 2005; De Diego 2013; Drobnic 2005; MRC 1957; Murray 2011; Orriols 1999; Serisier 2013a BLESS; Serisier 2013b ORBIT; Tsang 1999; Valery 2013; Wilson 2013a; Yalçin 2006), and when possible, meta-analysis was performed for each of the reported adverse events (Analysis 1.7). Eleven studies (Altenburg 2013; Barker 2000; Currie 1990; MRC 1957; Murray 2011; Orriols 1999; Serisier 2013a BLESS; Serisier 2013b ORBIT; Tsang 1999; Wilson 2013a; Yalçin 2006) reported that 39 of 358 participants in the intervention arm and 43 of 325 participants in the placebo arm withdrew from the trials because of intolerable or severe adverse effects. No significant difference was observed when these events were pooled (OR 0.91, 95% CI 0.56 to 1.49; N = 683; Analysis 1.7).

Four studies (Altenburg 2013; Currie 1990; Cymbala 2005; MRC 1957) reported on diarrhoea. Three parallel studies reported that the intervention increased risk of diarrhoea in 24 of 136 participants given antibiotic versus 6 of 95 given placebo (n = 231) (OR 3.33, 95% CI 1.50 to 7.37; P value = 0.003; Analysis 1.7).

Bronchospasm was reported in three studies (Drobnic 2005; Murray 2011; Wilson 2013a) and wheeze in two studies (Barker 2000; Drobnic 2005). Drobnic 2005 had 3 of 30 participants reporting bronchospasm whilst nebulised with tobramycin. Murray 2011 and Wilson 2013a reported that 10 of 92 participants given intervention and 5 of 97 given placebo had bronchospasm (OR 2.19, 95% CI 0.76 to 6.33; P value = 0.15, $I^2$ = 21%; Analysis 1.7). Barker 2000 reported that 6 of 37 participants taking tobramycin and 0 of 37 given placebo had wheeze (OR 8.56, 95% CI 1.63 to 44.93; P value = 0.01), and 12 of 37 participants taking tobramycin and 3 of 37 given placebo had worsening of dyspnoea. However, De Diego 2013 reported statistically significant improvement in dyspnoea with 16 participants taking azithromycin and 14 given placebo (P value < 0.05).

Chest pains/palpitations were reported by Altenburg 2013 using oral azithromycin, Barker 2000 using nebulised tobramycin and Serisier 2013a BLESS using oral erythromycin (8 of 139 participants given intervention vs 1 of 135 given placebo; OR 5.21, 95% CI 1.35 to 20.14; P value = 0.02). Four studies (Altenburg 2013 using oral azithromycin, Currie 1990 using oral amoxycillin, Serisier 2013b ORBIT using inhaled ciprofloxacin, Serisier 2013a BLESS using oral erythromycin) with 15 of 138 participants given intervention and 13 of 137 placebo reported nausea (OR 1.20, 95% CI 0.54 to 2.67; P value = 0.66, $I^2$ = 37%).

No significant differences between treatments were reported for fatigue (Altenburg 2013; Barker 2000), haemoptysis (Barker 2000; MRC 1957; Wilson 2013a), fever (Barker 2000) or increased sputum (Barker 2000). In addition to diarrhoea, which was the most common adverse event reported in the MRC 1957 study, anorexia, nausea, vomiting, flatulence and epigastric discomfort were also reported in order of frequency. Other recorded adverse events

in this study included swelling of the foot accompanied by a rash that lasted a week, which developed eight weeks after the start of treatment with penicillin; paraesthesiae of both hands lasting a few weeks, which occurred 16 weeks after the start of oxytetracycline; and joint pain, which was reported to occur the day after administration of lactose capsules (MRC 1957). No participants withdrew from the Yalçin 2006 study. Valery 2013 reported that the most common adverse events in this trial were non-pulmonary infections (71 of 112 events in the azithromycin group vs 132 of 209 in the placebo group) and bronchiectasis-related events (episodes or investigations; 22 of 112 events in the azithromycin group *vs* 48 of 209 in the placebo group). However, study drugs were well tolerated and no serious adverse events were attributed to the intervention. Authors of the Tsang 1999 study reported that none of the participants given erythromycin experienced haemoptysis during the study period.

Diarrhoea was the most common treatment-related adverse event reported in the Cymbala 2005 cross-over study, with 3 of 12 participants (25%) reporting it during the intervention period. Study authors did not mention any episodes of diarrhoea occurring during the usual care period. One participant's dose of azithromycin was changed to the alternative thrice-weekly regimen, which was reported to improve diarrhoea. The single participant who dropped out of the study had reported diarrhoea during a previous visit. No other serious or severe treatment-related adverse events were reported (Cymbala 2005).

#### *6. Deaths*

No significant difference in mortality (OR 1.48, 95% CI 0.28 to 7.85; n = 595) was noted amongst the seven studies that reported on this outcome (Altenburg 2013; MRC 1957; Murray 2011; Orriols 1999; Serisier 2013a BLESS; Valery 2013; Wilson 2013a); n = 595; Analysis 1.8). The two deaths reported in the intervention arm from Murray 2011 were unexpected and were due to previously undiagnosed metastatic colorectal cancer and myocardial infarction. In Drobnic 2005, a cross-over trial, 5 of 30 participants died from respiratory failure during study periods. Investigators did not report the phase of the study in which these deaths occurred.

#### *7. Emergence of resistance to antibiotics*

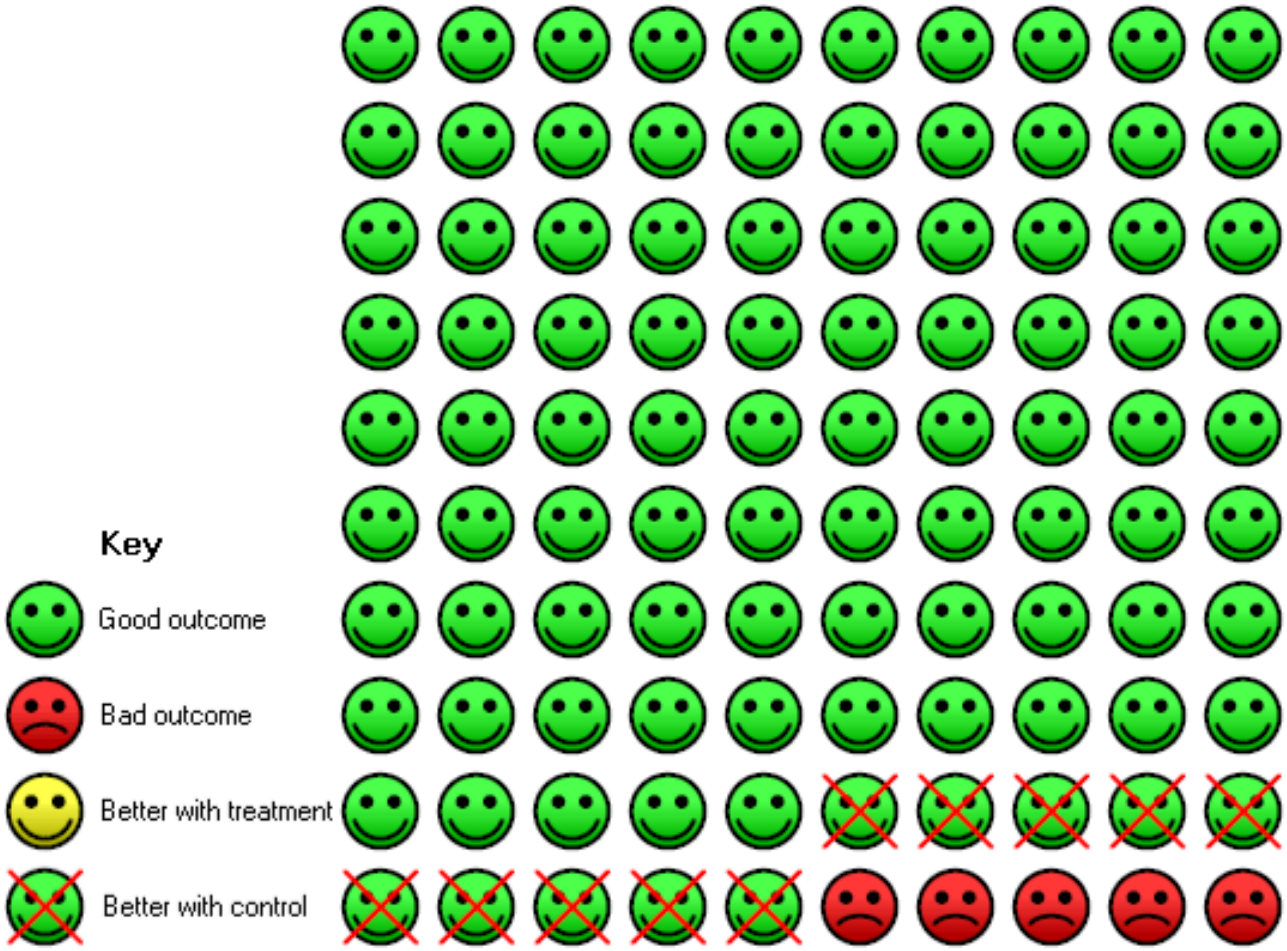
Nine studies (Altenburg 2013; Barker 2000; Drobnic 2005; Murray 2011; Orriols 1999; Serisier 2013a BLESS; Valery 2013; Wilson 2013a; Wong 2012) with a total of 571 participants reported this outcome. As a result of the different types of results presented, data from only six studies (Barker 2000; Drobnic 2005; Orriols 1999; Valery 2013; Wilson 2013a; Wong 2012) with 431 participants were used for the meta-analysis. Drug resistance in 36 of 220 participants taking antibiotic and in 10 of 211 participants given placebo or standard therapy favoured the placebo or standard therapy group (OR 3.48, 95% CI 1.20 to 10.07; P value = 0.02; Analysis 1.9) with modest heterogeneity ($I^2$ = 29%); similar but more significant results were obtained with the sensitivity analysis (P value = 0.006; Analysis 2.6). Murray 2011 detected no resistance at the end of the study.

Resistance patterns were comparable between groups at baseline for the Altenburg 2013 study (35% macrolide resistance in eight participants in the azithromycin group vs 27.5% in nine participants in the placebo group). During treatment, 53 of 60 pathogens (88%) tested for sensitivity in 20 participants in the azithromycin group became macrolide resistant, compared with 29 of 112 pathogens (26%) in 22 participants in the placebo group (P value = 0.001). Macrolide-resistant commensal oropharyngeal streptococci were reported to be significantly increased in the Serisier 2013a BLESS study with erythromycin therapy (median change 27.7%, IQR 0.04% to 41.1%) compared with placebo (median change 0.04%, IQR -1.6% to 1.5%; difference 25.5%, IQR 15.0% to 33.7%; P value < 0.001). In the Barker 2000 study, tobramycin-resistant *P. aeruginosa* strains developed resistance in 11% of intervention participants compared with 3% of placebo participants, although this difference was not significant. Two participants developed resistance during the tobramycin period of the Drobnic 2005 study. Bacteria persisted in both participants until months two and three of the placebo period, and two additional participants had *P. aeruginosa* strains isolated during the second period of placebo treatment. The frequency and emergence of resistance did not differ significantly during the second period of placebo treatment. Other organisms were also monitored, with *Alcaligenes xylosoxidans* and *Streptococcus pneumoniae* identified in sputum cultures of two participants during the intervention treatment period, and with *Acinetobacter* spp and *Stenotrophomona maltophila* identified in two participants during the treatment period (Drobnic 2005).

The Currie 1990 study also reported on emergence of resistance to gentamicin, which occurred with similar frequency in the two study arms (three amoxycillin and two placebo participants). No significant increase in resistance of *P. aeruginosa* isolates to ciprofloxacin was observed in the Serisier 2013b ORBIT study, and likewise in the Liu 2012 study, with no differences between groups observed.

In terms of absolute treatment differences, 5 of 100 people in the control group had emergent antibiotic resistance over 1.5 to 24 months, compared with 15 (95% CI 8 to 27) of 100 in the prolonged antibiotics arm (Figure 6).

**Figure 6. Absolute treatment differences for emergence of antibiotic resistance with events occurring in 47 per 1000 in the control arm and in 148 per 1000 (95% CI 56 to 334) on the intervention.**




**Bacterial colonisation**

A total of 15 studies with 809 participants (403 given intervention and 406 placebo) reported on this outcome (Altenburg 2013; Barker 2000; Currie 1990; Cymbala 2005; De Diego 2013; Drobnic 2005; Murray 2011; Orriols 1999; Serisier 2013a BLESS; Serisier 2013b ORBIT; Tsang 1999; Valery 2013; Wilson 2013a; Wong 2012; Yalçin 2006). Given the expected nature of a trial including participants with multiple organisms from recurrence/regrowth/colonisation/active infection, a meta-analysis was not performed. In the Altenburg 2013 study, the microbiological profile did not differ significantly between groups at baseline or after 52 weeks of treatment. A total of 437 sputum samples were cultured for microbiology; this yielded one or more pathogens on 339 occasions. *Haemophilus influenzae, Streptococcus pneumoniae, Staphylococcus aureus, Moraxella catarrhalis* and *Haemophilus parainfluenzae* were most frequently encountered, together accounting for 87% of the total number of pathogens. All participants with *Haemophilus influenzae*, *Pseudomonas aeruginosa* and *Aspergillus* at baseline from the De Diego 2013 study became culture negative after taking azithromycin for three months; however, study authors did not report the change in bacterial isolates in the placebo arm. Serisier 2013a BLESS reported no differences between the two groups for emergence of new sputum pathogens at any time after the start of erythromycin; however, eradication of sputum pathogens occurred in more erythromycin-treated participants (n = 17 (30.4%) vs n = 6 placebo participants (10.9%); OR 3.6, 95% CI 1.3 to 10.6; P value = 0.01). Serisier 2013b ORBIT also reported on new pathogens isolated from 12 participants given placebo and 9 taking ciprofloxacin. Wong 2012 reported that 6 of 46 participants taking azithromycin cultured new organisms, along with 10 of 45 participants given placebo. Disappearance of *P. aeruginosa* in sputum was observed in four participants taking tobramycin and in four participants given placebo in Drobnic 2005;however, this cross-over study was transient and *P. aeruginosa* re-grew after a mean time of three months. Examination of individual microbiological responses among participants in the Barker 2000 study showed that one-third (13 of 37) of tobramycin-treated individuals had *P. aeruginosa* eradicated from their sputum. Twelve of these 13 participants were assessed as having an improved medical condition at week 6, and an additional third (12 of 37) showed a reduction of at least 2 log10 in *P. aeruginosa* density at week 4. Nine of these 12 participants were assessed as improved. The last third (12 of 37) of tobramycin-treated participants had no microbiological response, and 10 of these individuals were not improved. In contrast, 33 of 35 (94%) participants given placebo had no microbiological response, and only 2 of 35 (6%) had a greater than 2 log10 decrease in *P. aeruginosa* density. Orriols 1999 reported that five of seven individuals taking ceftazidime and

tobramycin and six of eight given placebo cultured *P. aeruginosa*. In the Tsang 1999 study, *Pseudomonas aeruginosa* and *Haemophilus influenzae* were isolated from the sputum in 10 participants and 1 participant taking erythromycin, respectively, and *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Klebsiella pneumoniae* and *Escherichia coli* were isolated in the sputum of six, two, one and one participants given placebo, respectively. Currie 1990 with 38 participants reported *Haemophilus influenzae*, *P. aeruginosa* and *Staphylococcus aureus* at baseline and subsequently several gram-negative bacilli but concluded that no important changes in bacterial flora were observed in either group.

#### *8. Exercise capacity*

Exercise capacity was reported in four studies (Murray 2011; Serisier 2013a BLESS; Serisier 2013b ORBIT; Wong 2012) and was objectively assessed in 365 participants using the six-minute walk test (6MWT). Three of these studies (Serisier 2013a BLESS; Serisier 2013b ORBIT; Wong 2012) reported no statistically significant differences in the 6MWT between intervention and placebo groups at the end of the intervention period. Murray 2011 reported no statistically significant differences in either group until month 12 of the trial, when improvement in exercise capacity was noted (mean 510 m, 95% CI 350 to 690 vs mean 415 m, 95% CI 267.5 to 530; P value = 0.03). These effects were not sustained at follow-up. A meta-analysis of two studies produced no evidence of any effect during primary analysis (SMD 0.18, 95% CI -0.22 to 0.58; Analysis 1.10) or sensitivity analysis (Analysis 2.7).

#### *9. Quality of life*

Quality of life measure as measured on the St George Respiratory Questionnaire (SGRQ) was reported in 10 studies involving 667 participants (Altenburg 2013; Cymbala 2005; De Diego 2013; Drobnic 2005; Liu 2012; Murray 2011; Serisier 2013a BLESS; Serisier 2013b ORBIT; Wilson 2013a; Wong 2012). Six of these studies (Altenburg 2013; Cymbala 2005; De Diego 2013; Liu 2012; Murray 2011; Wilson 2013a) demonstrated significant improvement in quality of life among participants with bronchiectasis who were given long-term antibiotic treatment when compared with those given placebo. De Diego 2013 reported clinically and statistically significant changes in quality of life in the antibiotic group (-7.9 ± 3.1 vs 4.1 ± 3.8; P value < 0.05) but no difference in SGRQ scores at six months. A meta-analysis on total SGRQ scores from five parallel trials with 161 participants given intervention and 154 controls found a non-statistically significant benefit favouring the intervention (MD -2.75, 95% CI -7.08 to -1.57; $I^2$ = 67%). On sensitivity analysis and re-evaluation based on a fixed-effect model, results remained non-statistically significant (P value = 0.06; Analysis 2.8). Following re-analysis based on the random-effects model, results were no longer statistically significant (MD -3.71, 95% CI -9.84 to 2.41; $I^2$ = 90%; Analysis 1.11).

Among the cross-over studies, Cymbala 2005 reported that 82% of participants receiving long-term antibiotics had improved quality of life; however, formal objective measures were not employed. On the other hand, Drobnic 2005 showed no significant differences in quality of life (via SGRQ) between treatment and placebo arms at the end of the trial (mean –0.90 ± 3.93 vs –0.83 ± 6.89).

## DISCUSSION

### Summary of main results

The primary aim of this review was to assess the effects of prolonged antibiotic therapy in adults and children with non-cystic fibrosis bronchiectasis. We reviewed the evidence from 18 trials (1162 participants) between 1957 and 2013. Our primary outcome, exacerbation, was reported differently by 15 studies involving 925 participants and was significantly reduced by the intervention. However, the baseline exacerbation rate was adjusted (by individual study authors) in 7 (Altenburg 2013; De Diego 2013; Serisier 2013a BLESS; Serisier 2013b ORBIT; Tsang 1999; Wilson 2013a; Wong 2012) out of 18 trials. Other influential factors such as *Pseudomonas* colonisation, smoking history and lobar involvement were variably reported and adjusted. All participants from five studies (Barker 2000; Drobnic 2005; Orriols 1999; Serisier 2013b ORBIT; Wilson 2013a) had *Pseudomonas aeruginosa* at baseline. The effect of prolonged antibiotic therapy on hospitalisation was favourable across six of seven studies with 643 participants (Altenburg 2013; Serisier 2013a BLESS; Valery 2013; Wilson 2013a; Wong 2012; Orriols 1999) (Analysis 1.2), although results were not statistically significant. The baseline rate of hospitalisation for these studies was not described adequately, limiting the reliability of change scores from baseline. Participants included in this review were drawn from diverse populations. It does not necessarily follow that patients with differing anatomical distribution or aetiologically distinct underlying diseases or baseline characteristics will respond in a homogenous way to the same intervention. No significant effect on mortality, exercise capacity, lung function or quality of life was reported. However, follow-up plans of the included studies ranging from 4 to 96 weeks suggest that the effect on mortality may not be conclusive.

### Overall completeness and applicability of evidence

Despite an extensive literature search and relatively high burden of disease in the community, only 18 studies met the inclusion criteria of this review. The primary aim of this review was to address the possible benefit of prolonged antibiotic therapy for individuals with non-cystic fibrosis bronchiectasis.

The trials were of differing duration. We arbitrarily chose a cutoff of four weeks of treatment for eligibility because this duration was longer than the standard 7 to 10 day course of treatment traditionally provided for uncomplicated exacerbations. Furthermore, long-term use of antibiotics was defined as use of this treatment with a prophylactic intent in patients at a chronic stable phase (i.e. not for exacerbations). The studies reported by Wilson 2013a (four weeks), Barker 2000 (four weeks), De Diego 2013 (12 weeks), Koh 1997 (12 weeks) and Tsang 1999 (eight weeks) were probably too brief to allow firm conclusions about disease-modifying effects.

Inclusion of six trials using inhaled antibiotics (Barker 2000; Drobnic 2005; Murray 2011; Orriols 1999; Serisier 2013b ORBIT; Wilson 2013a) is also worthy of consideration. The mechanism of action of inhaled antibiotics may differ from that of antibiotics given by the oral route; however, increased withdrawals due to severe adverse events or intolerable effects were noted in both study arms when compared with oral interventions.

In conclusion, 15 trials in this review demonstrate a trend supporting use of prolonged antibiotics in the management of bronchiectasis with significant risk of emergence of drug resistance. Therefore, appropriate patient selection is essential. The intervention was safe and tolerated by study participants, particularly when the oral route was used. Trials exhibited significant shortcomings, particularly in terms of study duration, baseline exacerbation, hospitalisation and bacterial colonisation/isolation, hence further research is required. These new studies should incorporate methods allowing separate study of specific issues such as *Pseudomonas aeruginosa* colonisation and drug resistance at individual and community levels.

### Quality of the evidence

The overall quality of studies included in this review was moderate. Most included studies reported that they blinded assessors and participants from allocation; however not enough information was provided for this assessment. In addition, information was insufficient to assess attrition bias, especially with reporting bias (Cymbala 2005; Drobnic 2005; MRC 1957; Serisier 2013b ORBIT; Yalçin 2006). Small sample sizes further limited the ability of study authors to draw reliable conclusions regarding efficacy, tolerability and safety.

Attempts to outline a mechanism for clinical effects (other than sputum volume, purulence, cultures and resistance patterns) were limited to the studies reported by Tsang 1999 and Orriols 1999. In the former investigation, no change was seen in sputum cytokines or leukotrienes despite improvements in lung function and sputum volume. Orriols 1999 showed a reduction in airway responsiveness and suggested that this might have occurred through indirect effects on airway inflammation.

In general, the trials suggest that long-term antibiotics in bronchiectasis are an effective intervention for reducing sputum volume and purulence, but they have a very limited impact on the natural history of the condition. However, several important issues related to this review weaken the power of review authors to draw final conclusions; these will be addressed in turn.

### Potential biases in the review process

No significant biases were anticipated or were found to occur during the review process. Criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* were strictly followed to limit the potential for bias during screening, data extraction and analyses of included studies. Risk of bias was assessed independently by two review authors (KH and CN), who resolved conflicts by discussion with a third review author (KVC). We contacted the corresponding author of two included studies (Altenburg 2013; Serisier 2013a BLESS; Serisier 2013b ORBIT) and the authors of the three initially unclassified citations to ask for raw data and clarification of methodological techniques. The review authors of this meta-analysis have reported no conflicts of interest.

### Agreements and disagreements with other studies or reviews

Emergence of drug resistance was reported by Barker 2000 and was repeatedly reproduced by newer studies with follow-up longer than six months (Analysis 1.9). Widespread use of antibiotics poses a high likelihood of inducing substantial population-level antibiotic resistance in a range of micro-organisms (Serisier 2014). In particular, the long-acting agent azithromycin rapidly induces sustained macrolide resistance, and its introduction in the USA in 1992 was temporally associated with a substantial increase in rates of macrolide resistance in pneumococcal isolates (Serisier 2013). This review was limited to emergence of drug resistance among participants; however, available evidence from this review supports the imperative importance of patient selection for intervention, especially with long-acting antibiotics. The process of patient selection can be assisted by the bronchiectasis severity index (BSI), which is based on prior hospital admission(s), Medical Research Council dyspnoea score greater than or equal to 4, forced expiratory volume in one second (FEV1) < 30% predicted, *Pseudomonas aeruginosa* colonisation, colonisation with other pathogenic organisms and three or more lobes involved as seen on high-resolution computed tomography (Chalmers 2013), which was validated across five cohorts (1310 participants) with four-year follow-up. Similar clinical domains were based on another score called "FACED" (F for forced expiratory volume in one second; A for Age; C for *Pseudomonas* colonisation; E for extent of bronchiectasis counting lobar involvement on CT scan; and D for dyspnoea, using the Medical Research Council dyspnoea score proposed by Martinez-Garcia et al, with an intent to predict five-year mortality in mild, moderate and severe disease (defined as scores of 0 to 2, 3 to 4 and 5 to 7, respectively) of 4%, 25% and 56%, respectively (Martinez-Garcia 2014; Saleh 2014). Moreover, the development of multi-drug-resistant organisms among patients with drug allergy will add extra burden. Therefore, in clinical practice, conscientious selection of an appropriate intervention for each patient is of utmost importance.

Another recent review of long-term macrolides for non-cystic fibrosis bronchiectasis found that macrolides were a reliable treatment option for individuals with stable bronchiectasis, as revealed by available data (Wu 2014). However, similar to our review, for outcomes such as macrolide resistance, meta-analysis of all included studies was not possible because outcome data were incompletely reported. Authors of the Wu 2014 review conclude that their results justify further investigation of macrolides in combination with usual treatment regimens for bronchiectasis.

## AUTHORS' CONCLUSIONS

### Implications for practice

This review has demonstrated a positive effect for prolonged antibiotics in bronchiectasis at the cost of emergence of resistance. Available data support the use of prolonged courses of antibiotics in selected patients.

### Implications for research

Further trials are required to examine this question in relation to issues surrounding the management of *Pseudomonas aeruginosa* colonisation, which should be addressed separately, as should the question of route of administration. A non-antibacterial effect of macrolide antibiotics should also be sought. Possible adverse effects intervention based on route of administration of the intervention, particularly patient tolerance, should be monitored in future studies. These new trials should be appropriately powered and of adequate duration. They should have standardised endpoints and should report baseline characteristics of participants, particularly extent of disease (lung function, radiological extent/lobes involved), disease burden

(baseline exacerbation, hospitalisation, sputum volume and purulence), smoking status and co-morbidities.

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The Background and Methods sections of this review are based on a standard template used by the Cochrane Airways Group.

# REFERENCES

## References to studies included in this review

**Altenburg 2013** *{published and unpublished data}*

* Altenburg J. Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis. *JAMA* 2013;**209**(12):1251-9.

Altenburg J, de Graaff C, van der Werf T, Boersma W. Long-term azithromycin treatment: a randomised placebo-controlled trial in non-CF bronchiectasis; results from the BAT trial. European Respiratory Society 21st Annual Congress; 2011 Sep 24-28; Amsterdam. 2011; Vol. 38.

Boersma WG, Altenburg J, Werf TS. Evaluation of symptoms score and QOL in azithromycin maintenance treatment: results of a RCT trial in patients with bronchiectasis. *American Journal of Respiratory and Critical Care Medicine* 2012;**185**:A3658.

**Barker 2000** *{published data only}*

* Barker AF, Couch L, Fiel SB, Gotfried MH, Ilowite J. Tobramycin solution for inhalation reduces sputum *Pseudomonas aeruginosa* density in bronchiectasis. *American Journal of Respiratory and Critical Care Medicine* 2000;**162**(2 Pt 1):481-5.

Couch LA. Treatment with tobramycin solution for inhalation in bronchiectasis patients with *Pseudomonas aeruginosa*. *Chest* 2001;**120**(3):114S-17S.

Fiel SB. The relationship between antimicrobial efficacy and improved medical condition in tobramycin solution for inhalation therapy in bronchiectasis. *European Respiratoy Journal* 2000;**16**(Suppl 31):494s.

O'Donnell A, Tully H, Kylstra JW, Wells C, Schaeffler B, Barker AF. Tobramycin solution for inhalation (TOBI) as maintenance treatment for bronchiectasis patients with Pseudomonas aeruginosa. *Thorax* 1999;**54**(Suppl 3):A68.

**Currie 1990** *{published data only}*

Currie DC, Garbett ND, Chan KL, Higgs E, Todd H, Nunn AJ, et al. Double blind randomised placebo controlled study of long term high dose antibiotic in patients with bronchiectasis. *Clinical Research* 1987;**72**(Suppl 16):79P.

* Currie DC, Garbett ND, Cole PJ. Double-blind randomized study of prolonged higher-dose oral amoxycillin in purulent bronchiectasis. *Quarterly Journal of Medicine* 1990;**76**(280):799-816.

**Cymbala 2005** *{published data only}*

Cymbala AA, Edmonds LC, Bauer MA, Jederlinic PJ, May JJ, Victory JM, et al. The disease-modifying effects of twice-weekly oral azithromycin in patients with bronchiectasis. *Treatments in Respiratory Medicine* 2005;**4**(2):117-22.

**De Diego 2013** *{published and unpublished data}*

De Diego A, Milara J, Martinez-Moragon E, Palop M, Leon M, Cortijo J. Effects of long-term azithromycin therapy on airway oxidative. *Respirology (Carlton, Vic.)* 2013;**18**(7):1056-62.

**Drobnic 2005** *{published data only}*

Drobnic ME, Sune P, Montoro JB, Ferrer A, Orriols R. Inhaled tobramycin in non-cystic fibrosis patients with bronchiectasis and chronic bronchial infection with *Pseudomonas aeruginosa*. *Annals of Pharmacotherapy* 2005;**39**(1):39-44.

**Koh 1997** *{published data only}*

Koh YY, Lee MH, Sun YH, Sung KW, Chae JH. Effect of roxithromycin on airway responsiveness in children with bronchiectasis: a double-blind, placebo-controlled study. *European Respiratory Journal* 1997;**10**(5):994-9.

**Liu 2012** *{published data only}*

Liu JF, Zhong XN, He ZY, Zhong DJ, Bai J, Zhang JQ, et al. [Impact of treatment with low dose roxithromycin on stable bronchiectasis]. *Zhonghua Jie He He Hu Xi Za Zhi [Chinese Journal of Tuberculosis and Respiratory Diseases]* 2012;**35**(11):824-7.

* Wu Q, Shen W, Cheng H, Zhou X. Long-term macrolides for non-cystic fibrosis bronchiectasis: a systematic review and meta-analysis. *Respirology* 2014;**19**(3):321-9.

**MRC 1957** *{published data only}*

Medical Research Council. Prolonged antibiotic treatment of severe bronchiectasis: a report by a subcommittee of the Antibiotics Clinical Trials (Non-Tuberculous) Committee of the Medical Research Council. *British Medical Journal* 1957;**2**:255-9.

**Murray 2011** *{published data only}*

Antoniu SA, Trofor AC. Inhaled gentamicin in non-cystic fibrosis bronchiectasis: effects of long-term therapy. *Expert Opinion on Pharmacotherapy* 2011;**12**(7):1191-4.

* Murray M, Govan J, Doherty C, Simpson A, Wilkinson T, Chalmers J, et al. A randomized controlled trial of nebulized gentamicin in non–cystic fibrosis bronchiectasis. *American Journal of Respiratory and Critical Care Medicine* 2011;**183**:491-9.

**Orriols 1999** *{published data only}*

Orriols R, Roig J, Ferrer J, Sampol G, Rosell A, Ferrer A, et al. Inhaled antibiotic therapy in non-cystic fibrosis patients with bronchiectasis and chronic bronchial infection by *Pseudomonas aeruginosa*. *Respiratory Medicine* 1999;**93**(7):476-80.

**Serisier 2013a BLESS** *{published and unpublished data}*

Chen AC-H, Martin MM, Burr L, Hasnain SZ, Lourie R, Bowler SD, et al. Clinical benefits of long-term, low-dose erythromycin in bronchiectasis are not due to anti-inflammatory effects. American Thoracic Society International Conference; 2013 May 17-22; Philadelphia. 2013.

* Serisier D, Martin M, McGuckin M, Lourie R, Chen A, Brain B, et al. Effect of long-term, low-dose erythromycin on pulmonary exacerbations among patients with non-cystic fibrosis bronchiectasis. *JAMA* 2013;**309**(12):1260-6.

Serisier DJ, Bowler SD, McGuckin M, Chen A, Lourie R, Martin ML. The Bronchiectasis and Low-dose Erythromycin Study (BLESS).

*American Journal of Respiratory and Critical Care Medicine* 2012;**185**:A6862.

Serisier DJ, Martin M. Long-term, low-dose erythromycin in bronchiectasis subjects with frequent infective exacerbations. *Respirology* 2011;**105(6)**:946-9.

**Serisier 2013b ORBIT** *{published and unpublished data}*

Bruinenberg P, Serisier D, Blanchard J, Cipolla D, Gonda I. Effects and modulation of release rate of inhaled ciprofloxacin with liposomal formulations in healthy subjects and patients with bronchiectasis. European Respiratory Society 20th Annual Congress; 2010 Sep 18-22; Barcelona. 2010.

Cipolla DC, Gonda I, Serisier D, Bruinenberg P. Dual release ciprofloxacin for inhalation (DRCFI) improves time to first exacerbation in bronchiectasis. Journal of Aerosol Medicine and Pulmonary Drug Delivery. 2011; Vol. 24, issue 3:A27.

Serisier D, Kolbe J, Greville H, Gonda I, Bruinenberg P. Inhaled liposomal ciprofloxacin significantly reduces sputum *Pseudomonas aeruginosa* density and increases time to first exacerbation in a 168 day placebo controlled study in non-cystic fibrosis bronchiectasis. American Thoracic Society International Conference; 2011 May 13-18; Denver. Denver, Colorado, 2011; Vol. 183:A4866.

* Serisier DJ, Bilton D, De Soyza A, Thompson PJ, Kolbe J, Greville HW, et al. Inhaled, dual release liposomal ciprofloxacin in non-cystic fibrosis bronchiectasis (ORBIT-2): a randomised, double-blind, placebo-controlled trial. *Thorax* 2013;**68**:812-7.

Serisier DJ, Thompson PJ, Greville H, Kolbe J, Bruinenberg PR. Dual release ciprofloxacin for inhalation (DRCFI) reduces sputum *Pseudomonas aeruginosa* (Pa) density and delays time to infective pulmonary exacerbation in non-cystic fibrosis (CF) bronchiectasis (BE). American Thoracic Society International Conference; 2011 May 13-18; Denver. 2011; Vol. 28:334s [1928].

**Tsang 1999** *{published data only}*

* Tsang KW, Ho PI, Chan KN, Ip MS, Lam WK, Ho CS, et al. A pilot study of low-dose erythromycin in bronchiectasis. *European Respiratory Journal* 1999;**13**(2):361-4.

Tsang KW, Ho PL, Ho CS, Chan KN, Ip M, Lam WK, et al. Erythromycin reduces sputum volume and improves lung functions in bronchiectasis. *American Journal of Respiratory and Critical Care Medicine* 1998;**157**(Suppl 3):A174.

**Valery 2013** *{published data only}*

Mobberley C, Kake S, Faasalele H, Paterson J, Byrnes CA. Improving enrolment and retention of Maori and Pacifica families in respiratory research. *Respirology* 2011;**16**(Suppl):TP-135.

* Valery P, Morris PS, Byrnes CA, Grimwood K, Torzilla PJ, Bauert PA, et al. Long-term azithromycin for indigenous children with non-cystic fibrosis bronchiectasis or chronic suppuratives lung disease (Bronchiectasis Intervention Study): a multicentre, double-blind, randomised controlled trial. *Lancet Respiratory Medicine* 2013;**1**:610-20.

Valery PC, Morris PS, Grimwood K, Torzillo PJ, Byrnes CA, Masters BI, et al. Azithromycin for Indigenous children with bronchiectasis: study protocol for a multi-centre randomised controlled trial. *BMC Pediatrics* 2012;**12**:122-31.

**Wilson 2013a** *{published and unpublished data}*

Alder J, Wilson R, Welte T, Polverino E, De Soyza A, Greville H. Antimicrobial efficacy of ciprofloxacin dry powder for inhalation in patients with non-cystic fibrosis bronchiectasis. European Respiratory Society 21st Annual Congress; 2011 Sep 24-28; Amsterdam. 2011.

Antoniu S, Azoicai D. Ciprofloxacin DPI in non-cystic fibrosis bronchiectasis: a Phase II randomized study. *Expert Opinion on Investigational Drugs* 2013;**22**(5):671-3.

* Wilson R, Welte T, Polverino E, De Soyza A, Greville H, O'Donnell A, et al. Ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis: a phase II randomised study. *European Respiratory Journal* 2013;**41**(5):1107-15.

Wilson R, Welte T, Poverino E, Di Soyza A, Greville H, O'Donnell A. Randomized, placebo-controlled, double-blind, multi-center study to evaluate the safety and efficacy of ciprofloxacin dry powder for inhalation (ciprofloxacin DPI) compared with placebo In patients with non-cystic fibrosis bronchiectasis. *American Journal of Respiratory and Critical Care Medicine* 2011;**183**:A6407.

**Wong 2012** *{published data only}*

Jayaran L, Wong CA, Karalus N, Eaton T, Tong C, Hockey H. Azithromycin decreases exacerbations in non-cystic fibrosis bronchiectasis. *Respirology* 2012;**17**:35.

* Wong C, Jayaram L, Karalus N, Eaton T, Tong C, Hockey H, et al. Azithromycin for prevention of exacerbation in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial. *Lancet* 2012;**380**:660-7.

Wong CA, Jayaram L, Karalus N, Eaton T, Tong C, Hockey H. Azithromycin decreases exacerbations in non-cystic fibrosis bronchiectasis. *American Journal of Respiratory and Critical Care Medicine* 2012;**185**:A3657.

**Yalçin 2006** *{published data only}*

Yalcin E, Kiper N, Ozcelik U, Dogru D, Firat P, Sahin A, et al. Effects of clarithromycin on inflammatory parameters and clinical conditions in children with bronchiectasis. *Journal of Clinical Pharmacy and Therapeutics* 2006;**31**(1):49-55.

## References to studies excluded from this review

**Adachi 1988** *{published data only}*

Adachi F, Yamamoto K, Suzuki K, Yamamoto T. Preclinical and clinical studies on TE-031(A-56268) in elderly subjects. *Chemotherapy* 1988;**36**:660-6.

Takeda H, Oshitani H, Yondea Y, Kobayashi H. Basic and clinical studies on TE-031 (A-56268). [Japanese]. *Chemotherapy* 1988;**36**(Suppl 3):569-75.

**Alberto 1968** *{published data only}*

* Alberto S, Colongo PG, Brusasco L, Frigerio G. [Studies of the clinical and respiratory functional effects of a mucolytic-antibiotic preparation in chronic bronchopulmonary diseases. Controlled double-blind single code studies]. [Italian]. *Minerva Medica* 1968;**59**(53):2995-3002.

**Alekseenko 1978** *{published data only}*

Alekseenko AV, Sokolov SB, Kobrin LI, Opalinskii VN, Lavrent'ev IuA. [Direct current in the overall treatment of inflammatory suppurative diseases of the lungs]. [Article in Russian]. *Voprosy Kurortologii, Fizioterapii, i Lechebonoi Fizicheskoi Kultury* 1978;**2**:44-6.

**Allen 1988** *{published data only}*

* Allen MB, Fitzpatrick R. Amoxycillin with and without probenecid in the management of patients with bronchiectasis. *Clinical Science* 1988;**74(Suppl 18)**:56P.

**Allen 1990** *{published data only}*

Allen MB, Fitzpatrick RW, Barratt A, Cole RB. The use of probenecid to increase the serum amoxycillin levels in patients with bronchiectasis. *Respiratory Medicine* 1990;**84**(2):143-6.

**Al Mobeireek 1998** *{published data only}*

Al Mobeireek A, Kambal AM, Al Balla SR, Al Sawwaf H, Saleemi S. *Pseudomonas aeruginosa* in hospitalized patients with infective exacerbations of bronchiectasis: clinical and research implications. *Annals of Saudi Medicine* 1998;**18**(5):469-71.

**Alora 1978** *{published data only}*

Alora BD, Lloren PR. A comparative study between papase with tetracycline and tetracycline plain in the treatment of respiratory tract infections. *Philippine Journal of Microbiology and Infectious Diseases* 1978;**7**(1):7-16.

**Anwar 2008** *{published data only}*

Anwar GA, Bourke SC, Afolabi G, Middleton P, Ward C, Rutherford RM. Effects of long-term low-dose azithromycin inpatients with non-CF bronchiectasis. *Respiratory Medicine* 2008;**102**:1494-6.

**Barach 1952** *{published data only}*

Barach AL, Bickerman HA, Beck GJ. Antibiotic therapy in infections of the respiratory tract. *Archives of Internal Medicine* 1952;**90**(6):808-49.

**Begg 2000** *{published data only}*

Begg EJ, Robson RA, Saunders DA, Graham CG, Buttimore RC, Neill AM, et al. The pharmacokinetics of oral fleroxacin and ciprofloxacin in plasma and sputum during acute and chronic dosing. *British Journal of Clinical Pharmacology* 2000;**49**(1):32-8.

**Bergogne 1982** *{published data only}*

Bergogne Berezin E, Berthelot G, Kafe H. Study of the diffusion of cefotiam in the bronchial secretions. *Chemotherapy* 1982;**28**(5):327-33.

**Bergogne 1985** *{published data only}*

Bergogne Berezin E, Berthelot G, Kafé HP, Dournovo P. Influence of a fluidifying agent (bromhexine) on the penetration of antibiotics into respiratory secretions. *International Journal of Clinical Pharmacology Research* 1985;**5**(5):341-4.

**Bevilacqua 1973** *{published data only}*

* Bevilacqua M, Gironi G, Marinai E, Ulivieri P, Frigerio G. [Comparative study of the clinical activity of tetracycline and a combination of tetracycline and thiamphenicol in respiratory tract infections. Controlled study of a cooperative type]. [Italian]. *Minerva Medica* 1973;**64**(10):466-80.

**Bilton 2006** *{published data only}*

Bilton D, Henig N, Morrissey B, Gotfried M. Addition of inhaled tobramycin to ciprofloxacin for acute exacerbations of *Pseudomonas aeruginosa* infection in adult bronchiectasis. *Chest* 2006;**130**(5):1503-10.

**Bilton 2013** *{published data only}*

Bilton D, Daviskas E, Anderson SD, Kolbe J, King G, Stirling RG, et al. Phase 3 randomized study of the efficacy and safety of inhaled dry powder mannitol for the symptomatic treatment of non-cystic fibrosis bronchiectasis. *Chest* 2013;**144**(1):215-25.

**Bradley 2011** *{published data only}*

Bradley JM, Treacy K, O'Neill B, McCourt F, Green L, Gardner E, et al. A randomised double blind 13 week crossover trial of hypertonic saline(HTS) (6%) vs isotonic saline (ITS) (0.9%) in patients with bronchiectasis. *Thorax* 2011;**66**:A49 [S106].

**Brambilla 1992** *{published data only}*

Brambilla C, Kastanakis S, Knight S, Cunningham K. Cefuroxime and cefuroxime axetil versus amoxicillin plus clavulanic acid in the treatment of lower respiratory tract infections. *European Journal of Clinical Microbiology and Infectious Diseases* 1992;**11**(2):118-24.

**Bruninx 1973** *{published data only}*

Bruninx M, De Koster JP, Golard P, Libert P, Minette A, Mottard L, et al. Prophylactic administration of Bactrim in chronic bronchitis: a double blind clinical and biological study. *Acta Tuberculosea et Pneumologica Belgica* 1973;**64**:483-501.

Brunix M, De Koster JP, Golard P, Libert P, Minette A, Mottard L, et al. Prophylactic administration of Bactrim in chronic bronchitis. A double blind clinical and biological study (author's transl). *Acta Tuberculosea et Pneumologica Belgica* 1974;**64**:483-501.

**Chan 1996** *{published data only}*

Chan TH, Ho SS, Lai CKW, Cheung SW, Chan RCY, Cheng AFB, et al. Comparison of oral ciprofloxacin and amoxycillin in treating infective exacerbations of bronchiectasis in Hong Kong. *Chemotherapy* 1996;**42**(2):150-6.

**Chang 2010** *{published data only}*

Chang KC, Leung CC, Yew WW, Lau TY, Leung WM, Tam CM, et al. Newer fluoroquinolones for treating respiratory infection: do they mask tuberculosis?. *European Respiratory Journal* 2010;**35**(3):606-13.

**Chang 2012** *{published data only}*

Chang AB, Grimwood K, Robertson CF, Wilson AC, van Asperen P, O'Grady KF, et al. Antibiotics for bronchiectasis exacerbations in children: rationale and study protocol for a randomised placebo controlled trial. *Trials* 2012;**13**:156.

**Cherniack 1959** *{published data only}*

* Cherniack NS, Vosti KL, Dowling HF, Lepper MH, Jackson GG. Long-term treatment of bronchiectasis and chronic bronchitis. *AMA Archives of Internal Medicine* 1959;**103**:345-53.

**Cherniack 1966** *{published data only}*

Cherniack NS, Carton RW. Factors associated with respiratory insufficiency in bronchiectasis. *American Journal of Medicine* 1966;**41**(4):562-71.

**Choi 1996** *{published data only}*

Choi YS, Kim YW, Yun SJ, Cho HK, Kim KH. A study about IgG subclass concentration of chronic cough patient and changes of immunoglobulin levels after RU 41.740 administration. *Korean Journal of Pediatrics* 1996;**39**:1385-94.

**Chonabayashi 1988** *{published data only}*

Chonabayashi N, Yoshimura K, Nakatani T, Nakamori Y, Nakata K, Tanimoto H, et al. Clinical study of TE-031 (A-56268) in the treatment of 17 patients with respiratory infections [Japanese]. *Chemotherapy* 1988;**36**(Suppl 3):586-93.

**Chonabayashi 1988a** *{published data only}*

Chonabayashi N, Yoshimura K, Nakatani T, Nakamori Y, Nakata K, Tanimoto H, et al. Clinical studies of T-3262 in respiratory tract infection [Japanese]. *Chemotherapy* 1988;**36**(Suppl 9):694-8.

**Chuchalin 1997** *{published data only}*

Chuchalin AG, Novikovlu K, Avdeev SN, Belevski AS. [Effectiveness of ciprofloxacin in the treatment of hospital infections of the lower respiratory tract]. *Antibiotiki i Khimioterapiia [Antibiotics and Chemotherapy]* 1997;**42**(6):34-8.

**Clarke 1981** *{published data only}*

Clarke CS, Rawal BD. Co-trimoxazole-ascorbic acid in the treatment of chronic *Pseudomonas aeruginosa* infection of the lower respiratory tract. *Journal of Antimicrobial Chemotherapy* 1981;**7**(3):311-2.

**Crowther 1999** *{published data only}*

Crowther Labiris NR1, Holbrook AM, Chrystyn H, Macleod SM, Newhouse MT. Dry powder versus intravenous and nebulized gentamicin in cystic fibrosis and bronchiectasis. A pilot study. *American Journal of Respiratory and Critical Care Medicine* 1999;**160**(5 Pt 1):1711-6.

**Cseri 1975** *{published data only}*

Cseri T, Kelemen S. Treatment with Sumetrolim in chronic non-specific respiratory tract infections. *Therapia Hungarica* 1975;**23**(3):115-7.

**Currie 1987** *{published data only}*

* Currie DC, Gargett ND, Cole PJ. Penetration of antibiotics into the respiratory tract. *British Medical Journal* 1987;**295**(6590):119.

**Czako 1968** *{published data only}*

Czako K, Schnitzler J, Nagy M. Surgical results in primary bronchiectasis. *Zeitschrift fur Tuberkulose und Erkrankungen der Thoraxorgane* 1968;**129**(3):153-6.

**Danesi 1985** *{published data only}*

* Danesi R, Del Tacca M. Clinical study on the efficacy of clofoctol in the treatment of infectious respiratory diseases. *International Journal of Clinical Pharmacology Research* 1985;**5**(3):175-9.

**Davies 1983** *{published data only}*

Davies BI, Maesen FP, van Noord JA. Treatment of chronic and recurrent respiratory infections with intramuscular ceftazidime. *Journal of Antimicrobial Chemotherapy* 1983;**12(Suppl A)**:1-8.

**Dobrev1990** *{published data only}*

Dobrev P, Maksimov Vl, Tafradzhiiska M, Nikolova P, Popov B. Giramid in lung diseases. *Pnevmologiya i Ftiziatriya* 1990;**27**(4):27-30.

**Douglas 1957** *{published data only}*

Douglas AC, Somner AR, Marks BL, Grant IWB. Effect of antibiotics on purulent sputum in chronic bronchitis and bronchiectasis. *Lancet* 1957;**273**(6988):214-8.

**Doutsu 1988** *{published data only}*

Doutsu Y, Inoue Y, Masaki M, Masuyama Y, Yamashita K, Mashimoto H, et al. Laboratory and clinical studies on NY-198 [Japanese]. *Chemotherapy* 1988;**36**(Suppl 2):II.

**Finelgold 1981** *{published data only}*

* Finegold SM, Gentry LO, Mogabgab W, Campbell SC, Skatrud J. Controlled comparative trial of bacampicillin and amoxicillin in therapy of bacterial infections of the lower respiratory tract. *Reviews of Infectious Diseases* 1981;**3**(1):150-3.

**Foweraker 1993** *{published data only}*

* Foweraker JE, Cooke NH, Hawkey PM. Ecology of *Haemophilus influenzae* and *Haemophilus parainfluenzae* in sputum and saliva and effects of antibiotics on their distribution in patients with lower respiratory tract infections. *Antimicrobial Agents and Chemotherapy* 1993;**37**(4):804-9.

**Franklin 1953** *{published data only}*

Franklin AW, Garrod LP. Chloramphenicol treatment of bronchiectasis in children. *British Medical Journal* 1953;**2**:1067-9.

**Garcia 1984** *{published data only}*

Garcia Rodriquez JA, Gomez Garcia AC. A comparison of cefotaxime and cefoperazone in respiratory tract infections. *Journal of Antimicrobial Chemotherapy* 1984;**14**(Suppl B):301-6.

**Grau 1992** *{published data only}*

Grau S, Saballs P, Drobnic L, Del Villar A, Salas E, Monterde J, et al. Substitution of cefamandol by cefonicid. A prospective study of use according to protocol. *Revista Espanola de Quimioterapia* 1992;**5**(4):337-42.

**Haidl 2013** *{published data only}*

Haidl P, Bargon J, Gessler T, Pfeifer M, Randerath W, Voshaar T, et al. Effect of inhalation of tobramycin for 12 months on reduction of hospitalisation rate in severe COPD. *Pneumologie* 2013;**67**(9):514-9.

**Hara 1997** *{published data only}*

* Hara K, Kohno S, Kadota JI, Kazunori T, Yoichi H, Shigefumi M, et al. Clinical investigation of ciprofloxacin IV in severe and/or refractory infections in the internal medicine field. *Japanese Journal of Chemotherapy* 1997;**45**(11):923-35.

**Harada 1988** *{published data only}*

Harada S, Harada Y, Kitahara Y, Takamoto M, Ishibashi T, Shinoda A. Ampicillin in lower respiratory tract infections [Japanese]. *Chemotherapy* 1988;**36**(Suppl 8):237-43.

**Hayashi 1989** *{published data only}*

Hayashi T, Yamada H, Tasuoka A, Sasayama K, Doutsu Y, Kohno S, et al. Basic and clinical studies on cefdinir [Japanese]. *Chemotherapy* 1989;**37**(Suppl 2):565-78.

**Helm 1956** *{published data only}*

Helm WH, May JR, Livingstone JL. Long-term oxytetracycline (terramycin) therapy in advanced chronic respiratory infections. *Lancet* 1956;**1**:775-7.

**Hernandez 2002** *{published data only}*

Hernandez C, Abreu J, Jimenez A, Fernandez R, Martin C. Pulmonary function and quality of life in relation to bronchial colonization in adults with bronchiectasis not caused by cystic fibrosis. *Medicina Clinica* 2002;**118**(4):130-4.

**Hill 1986** *{published data only}*

* Hill SL, Burnett D, Hewetson KA, Stockley RA. Short term response of patients with bronchiectasis to treatment with amoxycillin given in standard or high doses orally or by inhalation. *Thorax* 1986;**41**(7):559-65.

**Hill 1988** *{published data only}*

* Hill SL, Morrison HM, Burnett D, Stockley RA. The response of patients with purulent bronchiectasis to antibiotics for four months. *Quarterly Journal of Medicine* 1988;**66**(250):163-73.

**Hill 1992** *{published data only}*

Hill SL, Bilton D, Johnson MM, Pye A, Mitchell JL, Stockley RA. Sputum and serum pharmacokinetics of loracarbef (a new carbacephem antibiotic) in patients with bronchiectasis [Abstract]. *European Respiratory Journal* 1992;**5**(Suppl 15):142s.

**Hill 1994** *{published data only}*

Hill SL, Bilton D, Johnson MM, Pye A, Mitchell JL, Stockley RA. Sputum and serum pharmacokinetics of loracarbef (LY163892) in patients with chronic bronchial sepsis. *Journal of Antimicrobial Chemotherapy* 1994;**33**(1):129-36.

**Hossain 2010** *{published data only}*

Hossain A, Ahamed M, Sharkar ZH. Change in clinical outcome of exacerbation of bronchiectasis on addition of nebulised gentamicin to systemic antibiotics. Congress of the Asian Pacific Society of Respirology; 2010; 22-25 Nov; Manila. 2010.

**Howie 1976** *{published data only}*

Howie JG. Antibiotics and purulent sputum. *British Medical Journal* 1976;**2**(6040):882.

**Hughes 1973** *{published data only}*

Hughes DT. Use of combinations of trimethoprim and sulphamethoxazole in the treatment of chest infections. *Medical Journal of Australia* 1973;**1**(2 Suppl):58-61.

**Hughes 1973a** *{published data only}*

Hughes DT. Use of combinations of trimethoprim and sulfamethoxazole in the treatment of chest infections. *Journal of Infectious Diseases* 1973;**128**(Nov Suppl):701-5.

**Ida 1988** *{published data only}*

Ida S, Shindoh Y, Takishima T. Antimicrobial activity and clinical evaluation of NY-198. [Japanese]. *Chemotherapy* 1988;**36**(Suppl 2):II.

**Iino 1993** *{published data only}*

* Iino Y, Sugita K, Toriyama M, Kudo K. Erythromycin therapy for otitis media with effusion in sinobronchial syndrome. *Archives of Otolaryngology* 1993;**119**(6):648-51.

**Inoue 1989** *{published data only}*

Inoue Y, Masuyama Y, Dotsu Y, Kaku M, Suyama N, Hayashi T, et al. Basic and clinical studies on 7432-S. [Japanese]. *Chemotherapy* 1989;**37**(Suppl 1):285-97.

**Ip 1993** *{published data only}*

* Ip M, Shum D, Lauder I, Lam WK, So SY. Effect of antibiotics on sputum inflammatory contents in acute exacerbations of bronchiectasis. *Respiratory Medicine* 1993;**87**(6):449-54.

**Ip 1998** *{published data only}*

Ip M, Tsang K, Chan WM, Ho PL, Lam B, Lam WK. Randomised controlled study of levofloxacin versus ceftazidime in acute exacerbations of bronchiectasis. *American Journal of Respiratory and Critical Care Medicine* 1998;**157**(3 Suppl):A173.

**Irabu 1989** *{published data only}*

Irabu Y, Tamaki K, Fukuhara H, Nakamura H, Kaneshima H, Shimoij K, et al. Laboratory and clinical studies on cefdinir. [Japanese]. *Chemotherapy* 1989;**37**(Suppl 2):603-11.

**Irabu 1992** *{published data only}*

Irabu Y, Fukuhara H, Nakamura H, Kaneshima H, Simoji K, Kitsukawa K, et al. Laboratory and clinical studies of ME1207. [Japanese]. *Chemotherapy* 1992;**40**(Suppl 2):452-8.

**Izumi 1994** *{published data only}*

* Izumi S. Clinical studies of tazobactam/piperacillin in respiratory tract infection. *Chemotherapy* 1994;**42**(Suppl 2):716-8.

**Izumikawa 1988** *{published data only}*

Izumikawa K, Koteda T, Sakamoto Y, Sawatari K. Basic and clinical studies on TE-031 (A-56268) in treatment of respiratory tract infections [Japanese]. *Chemotherapy* 1988;**36**(Suppl 3):729-36.

**Jia 2010** *{published data only}*

Jia B, Lu P, Huang W, Li C, Huang A, Zhou X, et al. A multicenter, randomized controlled clinical study on biapenem and imipenem/cilastatin injection in the treatment of respiratory and urinary tract infections. *Chemotherapy* 2010;**56**(4):285-90.

**Kaji 1988** *{published data only}*

Kaji M, Saito A, Shimada J, Ohmori M, Shiba K, Yamaji T, et al. Clinical studies on NY-198. [Japanese]. *Chemotherapy* 1988;**36**(Suppl 2):II.

**Kanaij, 1963** *{published data only}*

Kanai J, Tanaka S, Matsumoto T, Noda S. Clinical trial use of phenoxypropyl penicillin. *Journal of Antibiotics* 1963;**16**:25-6.

**Karachalios 1985** *{published data only}*

* Karachalios GN. Treatment of respiratory tract infections with a combination of amoxycillin and clavulanic acid. *International Journal of Clinical Pharmacology, Therapy, and Toxicology* 1985;**23**(12):647-9.

**Kawai 1988** *{published data only}*

Kawai S, Kawahira M, Oshitani H, Kobayashi H. NY-198 in the treatment of respiratory infections. [Japanese]. *Chemotherapy* 1988;**36**(Suppl 2):II.

Nakatani T, Noguchi M, Yoshimura K, Nakamori Y, Chonabayashi N, Nakata K, et al. Clinical trial with NY-198 against respiratory tract infections. [Japanese]. *Chemotherapy* 1988;**36**(Suppl 2):II.

**Kawai 1996** *{published data only}*

Kawai S, Sakayori S, Kobayashi H. Clincial study on NM441 in respiratory tract infections. [Japanese]. *Japanese Journal of Chemotherapy* 1996;**44**:594-6.

**Kawano 1974** *{published data only}*

Kawano M, Irimajiri K, Higuchi J, Uchiyama T, Tsubura E. Studies on amikacin (BB-K8), a new aminoglycoside antibiotic (author's transl). *Japanese Journal of Antibiotics* 1974;**27**(4):446-50.

**Kawashima 1989** *{published data only}*

Kawashima K, Yamamoto H, Kadoya M, Kato M, Nata T, Iida E, et al. Clinical role of *Branhamella catarrhalis* infection in pulmonary disorders. [Japanese]. *Saishin Igaku [Modern Medicine]* 1989;**44**(6):1268-72.

**Kellett 2011** *{published data only}*

Kellett F, Robert NM. Nebulised 7% hypertonic saline improves lung function and quality of life in bronchiectasis. *Respiratory Medicine* 2011;**105**:1831-5.

**Kikuchi 1991** *{published data only}*

* Kikuchi N1, Kawashima T, Yamagishi F, Suzuki K, Yasuda J, Niijima Y, et al. Clinical evaluation of ciprofloxacin in pulmonary infections in the patients with chronic respiratory diseases. *Japanese Journal of Antibiotics* 1991;**44**(8):839-45.

**Knox 1955** *{published data only}*

Knox K, Elmes PC, Fletcher CM. Chronic bronchitis: an attempt to control chronic infection by Haemophilus Influenzae by aerosol therapy. *Lancet* 1955;**268**(6855):120-2.

**Kobayashi 1984** *{published data only}*

Kobayashi H, Takamura K, Kono K, Onodera S, Sasaki N, Nagahama F, et al. Comparison of DL-8280 and amoxicillin in the treatment of respiratory tract infections. *Journal of the Japanese Association for Infectious Diseases* 1984;**58**(6):525-55.

**Kobayashi 1995** *{published data only}*

* Kobayashi H, Takeda H, Watanabe H, Ohtami H, Sakayori S. Clinical evaluation of grepafloxacin in the treatment of various infectious diseases in the field of internal medicine. *Japanese Journal of Chemotherapy* 1995;**43**(Suppl 1):333-51.

**Koh 2000** *{published data only}*

Koh YY, Park Y, Jeong JH, Kim CK, Min YG, Chi JG. The effect of regular salbutamol on lung function and bronchial responsiveness in patients with primary ciliary dyskinesia. *Chest* 2000;**117**(2):427-33.

**Koyama 1992** *{published data only}*

Koyama M. ME1207: a clinical study. [Japanese]. *Chemotherapy* 1992;**40**(Suppl 2):692-5.

**Krawczyk 1981** *{published data only}*

Krawczyk Z, Gornicka Wilczynska M, Pilarska Machowicz A, Pruszynska S. Comparative evaluation of certain antibiotics and Biceptol preparation in the treatment of chronic bronchial disease exacerbations. [Polish]. *Polski Tygodnik Lekarski* 1981;**36**(25):927-30.

**Krofton 1971** *{published data only}*

Krofton DV. [Chemotherapy of respiratory diseases]. [Russian]. *Antibiotiki* 1971;**16**(8):743-9.

**Kudo 1988** *{published data only}*

Kudo K, Komase Y, Kowada A, Kabe J. Preclinical and clinical studies on TE-031 (A-56268) in treatment of bacterial respiratory tract infections. [Japanese]. *Chemotherapy* 1988;**36**(Suppl 3):617-22.

**Kudo 1992** *{published data only}*

Kudo K, Ishii A, Kabe J. ME1207 in respiratory infections. [Japanese]. *Chemotherapy* 1992;**40**(Suppl 2):696-9.

**Kulpati 1990** *{published data only}*

Kulpati DDS, Sahai S. Anaerobes in pleuropulmonary infections. *Journal International Medical Sciences Academy* 1990;**3**(1):13-9.

**Kurasawa 1988** *{published data only}*

Kurasawa T, Kuze F, Kato M, Yamamoto K, Ikeda N, Matsubara T, et al. NY-198 in the treatment of respiratory infections. [Japanese]. *Chemotherapy* 1988;**36**(Suppl 2):II.

**Kurishima 1992** *{published data only}*

Kurishima S, Hirose H, Fukui T, Katsu M. Basic and clinical studies on cefclidin. [Japanese]. *Chemotherapy* 1992;**40**(Suppl 4):273-9.

**Kuze 1988** *{published data only}*

Kuze F, Kurasawa T, Kato M, Kagioka A, Inaba N, Kuroda N, et al. Cefodizime (THR-221) in respiratory tract infections. [Japanese]. *Chemotherapy* 1988;**36**(Suppl 5):467-72.

**Lam 1986a** *{published data only}*

Lam WK, Chau PY, So SY, Leung YK, Chan JC, Sham MK, et al. A double-blind randomized study comparing ofloxacin and amoxicillin in treating infective episodes in bronchiectasis. *Infection* 1986;**14(Suppl 4)**:S290-2.

**Lam 1989** *{published data only}*

* Lam WK1, Chau PY, So SY, Leung YK, Chan JC, Ip M, Sham MK. Ofloxacin compared with amoxycillin in treating infective exacerbations in bronchiectasis. *Respiratory Medicine* 1989;**83**(4):299-303.

**Lam 2006** *{published data only}*

Lam PK, Griffith DE, Aksamit TR, Ruoss SJ, Garay SM, Daley CL, et al. Factors related to response to intermittent treatment of *Mycobacterium avium* complex lung disease. *American Journal of Respiratory and Critical Care Medicine* 2006;**173**(11):1283-9.

**Lamotte 1981** *{published data only}*

Lamotte A. Bronchiectasis. [French]. *Ouest-Medical* 1981;**34**(14):969-72.

**Ledson 2000** *{published data only}*

Ledson MJ, Cowperthwaite C, Walshaw MJ, Gallagher MJ, Williets T, Hart CA. Nebulised taurolidine and *B cepacia* bronchiectasis. *Thorax* 2000;**55**(1):91-2.

**Lin 1996** *{published data only}*

Lin HC, Wang CH, Liu CY, Yu CT, Kuo HP. Amoxicillin down-regulates the release of neutrophil derived pro-inflammatory cytokines and C5a in patients with bronchiectasis. *European Respiratory Journal* 1996;**9**(23):400s.

Lin HC, Wang CH, Liu CY, Yu CT, Kuo HP. Erithromycin upregulates β2-Integrins (CD11B/CD118) expression and intracellular oxidant capacity in airway neurophils of patients with bronchiectasis. *European Respiratory Journal* 1996;**23**(Suppl 9):400s.

**Lin 1997** *{published data only}*

* Lin HC, Cheng HF, Wang CH, Liu CY, Yu CT, Kuo HP. Inhaled gentamicin reduces airway neutrophil activity and mucus secretion in bronchiectasis. *American Journal of Respiratory and Critical Care Medicine* 1997;**155**(6):2024-9.

**Lin 2006** *{published data only}*

Lin JT, Yu XZ, Cui DJ, Chen XY, Zhu JH, Wang YZ, et al. A multicenter randomized controlled study of the efficacy and safety of oseltamivir in the treatment of influenza in a high risk population. [Chinese].. *Chinese Journal of Tuberculosis and Respiratory Diseases* 2004;**27**(7):455-9.

Lin JT, Yu XZ, Cui DJ, Chen XY, Zhu JH, Wang YZ, et al. A multicentre, randomized, controlled trial of oseltamivir in the treatment of influenza in a high-risk Chinese population. *Current Medical Research and Opinion* 2006;**22**(1):75-82.

**Lioberes 1990** *{published data only}*

Lioberes P, Barber E, Montserrat JM, Picado C. Intermittent antibiotic treatment in patients with stable bronchiectasis: a comparative study between amoxycillin and cefonicid [abstract]. *European Respiratory Journal Supplement* 1990;**3(Suppl 10)**:88S.

**Lunacharskaia 1968** *{published data only}*

Lunacharskaia TV, Kopeiko IP. Intratracheal use of morphocycline. [Russian]. *Antibiotiki* 1968;**13**(12):1123-6.

**Maekawa 1967** *{published data only}*

Maekawa N, Tsukuma S, Nakanishi M, Yamashita M, Kanda M. Clinical results of the use of cephaloridine in lung diseases, especially pulmonary tuberculosis. [Japanese]. *Journal of Antibiotics [B]* 1967;**20**(2):140-4.

**Mahashur 1993** *{published data only}*

* Mahashur AA, Chaudhuri RA, Bowalekar SK, Raghu CN. Pefloxacin in the treatment of nosocomial respiratory tract infections. *Current Therapeutic Research, Clinical and Experimental* 1993;**54**(4):437-42.

**Mahashur 2002** *{published data only}*

Mahashur AA, Pal M, Parikh HS, Karkera SG, Kukreja A. Study of the efficacy of immunomodulator imunocin, as an add-on therapy in the management of patients with chronic obstructive pulmonary disorder and bronchiectasis. *Indian Practitioner* 2002;**55**(6):393-9.

**Masekela 2013** *{published data only}*

Masekela R, Anderson R, Gongxeka H, Steel HC, Becker PJ, Green RJ. Lack of efficacy of an immunomodulatory macrolide in childhood. *Journal of Antivirals & Antiretrovirals* 2013;**5**(2):044-9.

**Masuno 1992** *{published data only}*

Masuno T, Ikeda T, Kishimoto S, Morimoto Y, Tsujimoto T, Igarashi T, et al. A clinical study of cefclidin [Japanese]. *Chemotherapy* 1992;**40**(Suppl 4):331-40.

**Matsumoto 1983** *{published data only}*

* Matsumoto K, Harada T, Shishido H. Laboratory and clinical evaluation on ceftazidime with the special reference to respiratory infections caused by *Pseudomonas aeruginosa*. *Chemotherapy* 1983;**31**(Suppl 3):434-47.

**Matsumoto 1984** *{published data only}*

* Matsumoto K, Chung HY, Hsieh WC. Asian multicenter trial of cefoperazone in respiratory tract infection. *Clinical Therapeutics* 1984;**6**(6):824-38.

**Matsumoto 1984a** *{published data only}*

Matsumoto K, Nagatake T, Shishido H. Laboratory and clinical evaluation of lenampicillin (KBT-1585) in respiratory infection. [Japanese]. *Chemotherapy* 1984;**32**(Suppl 8):397-411.

**Matsumoto 1986** *{published data only}*

Matsumoto K, Takahashi A, Yamamoto M. A study on the evaluation of the efficacy of chemotherapy for chronic respiratory tract infections. [Japanese]. *Chemotherapy* 1986;**34**(4):316-30.

**Matsumoto 1992** *{published data only}*

Matsumoto M, Koga Y, Ando M, Araki S. Clinical studies on ME1207 in the treatment of respiratory tract infections. [Japanese]. *Chemotherapy* 1992;**40**(Suppl 2):740-3.

**Matsushima 1988** *{published data only}*

Matsushima T, Ikeda H, Adachi M, Tomisawa S, Kawanishi M, Tanabe J, Tano Y. Clinical study of NY-198 in pulmonary infections. [Japanese]. *Chemotherapy* 1988;**36**(Suppl 2):II.

**Matsuura 1993** *{published data only}*

Matsuura T, Suzuki K, Yamamoto T. Clinical studies of S-1108 in elderly patients. *Chemotherapy* 1993;**41**(Suppl 1):795-9.

**Matzeu 1981** *{published data only}*

Matzeu M, Mancini PA, Parola D. The use of sisomicin in chronic bronchopulmonary disorders. *Drugs Under Experimental and Clinical Research* 1981;**7**(4):503-6.

**May 1972** *{published data only}*

May JR, Ingold A. Amoxycillin in the treatment of chronic non-tuberculous bronchial infections. *British Journal of Diseases of the Chest* 1972;**66**(3):185-91.

**May 1974** *{published data only}*

May JR, Ingold A. Amoxicillin in the treatment of infections of the lower respiratory tract. *Journal of Infectious Diseases* 1974;**129**(Suppl):S189-93.

May JR, Ingold H. Amoxicillin in the treatment of lower respiratory infections. *Advances in Clinical Pharmacology* 1974;**7**:85-90.

**Mazzei 1993** *{published data only}*

Mazzei JA, Vujacich P, Fernandez A, Tanco J. Ciprofloxacin in the treatment of lower respiratory tract infections. *Drugs* 1993;**46**(Suppl 3):407-9.

**McVay 1953** *{published data only}*

McVay LV Jr, Sprunt DH. Antibiotic prophylaxis in chronic respiratory diseases. *Archives of Internal Medicine* 1953;**92**(6):833-46.

**Mehta 1991** *{published data only}*

Mehta AP, Phutane L, Patel MH, Rupwate RU, Kamat SR. Comparative study of amoxycillin and amoxycillin/clavulanic acid in lower respiratory infections. *Journal of the Association of Physicians of India* 1991;**39**(3):251-3.

**Messens 1973** *{published data only}*

Messens Y, Oger A, Cornette M, Calay G. [Double-blind study of the sulfamethoxazole-trimethoprim association in the treatment of pulmonary infections]. *Acta Clinica Belgica* 1973;**28**(2):92-9.

**Mijuskovic 1972** *{published data only}*

Mijuskovic B, Macanovic J. Bisolvomycin and Bisolvon in the treatment of chronic bronchitis, bronchial asthma and bronchiectasis. *Plucne Bolesti i Tuberkuloza* 1972;**24**(3):229-33.

**Milcev 1985** *{published data only}*

Milcev M, Ovcarova H, Ivanov S. Antibacterial treatment of anaerobic lung infections. [Bulgarian]. *Pnevmologiya i Ftiziatriya* 1985;**22**(3):20-4.

**Min 1988** *{published data only}*

Min KY. Clinical evaluation of TE-031 in the chronic respiratory infections. [Japanese]. *Japanese Pharmacology and Therapeutics* 1988;**16**(7):335-47.

**Minami 1996** *{published data only}*

* Minami H, Sakai S, Shimokata K. Combination regimen of low dose erythromycin and ofloxacin against chronic airway infections. *Japanese Journal of Chest Diseases* 1996;**55**(10):845-50.

**Ming 2005** *{published data only}*

Ming O, Yong L, Zhang W. Efficacy of macrolide and theophylline in the management of bronchiectasis [Abstract]. *Respirology (Carlton, Vic)* 2005;**10**(Suppl 3):A168.

**Miyamoto 1984** *{published data only}*

Miyamoto Y, Horiuchi T, Wantanabe T. Experience with AT-2266. [Japanese]. *Chemotherapy* 1984;**32**(Suppl 3):441-7.

**Molodtsova 1980** *{published data only}*

Molodtsova VP, Fedoseev GB, Gerasin VA. [Cleansing of the bronchial tree in treating chronic inflammatory lung disease]. [Russian]. *Sovetskaia Meditsina* 1980;**11**:90-2.

**Morrone 1989** *{published data only}*

Morrone N, Saito M, Brito VC, Hayashi F. Pulmonary infections in adults: two therapeutics regimens of ofloxacin. *A Folha MÃ©dica* 1989;**98**(4):253-8.

**Murayama 1992** *{published data only}*

Murayama T, Kuze F, Oida K, Nanbu Y, Iwata T, Ikeda N, et al. A clinical study of the effects of ME1207 on respiratory infections. [Japanese]. *Chemotherapy* 1992;**40**(Suppl 2):724-7.

**Music 1989** *{published data only}*

Music E, Kumelj M, Prlja D, Paulin A, Potokar T. Comparison of amoxicillin and amoxiclav in the therapy of respiratory infections. *Plucne Bolesti: Casopis Udruzenja Pneumoftiziologa Jugoslavije [Journal of Yugoslav Association of Physiology and Pneumology]* 1989;**41**(3-4):187-92.

**Nagy 1968** *{published data only}*

Nagy M, Meszaros G. [Late results of the conservative treatment of bronchiectasis in adults]. [German]. *Zeitschrift fur Tuberkulose und Erkrankungen der Thoraxorgane* 1968;**127**(5):283-90.

**Nakagawa 1993** *{published data only}*

Nakagawa M, Tsubura E. Clinical study of S-1108 in respiratory infections. *Chemotherapy* 1993;**41**(Suppl 1):803-6.

**Nakagawa 1995** *{published data only}*

Nakagawa Y, Niki Y, Hino J, Kishimoto T, Kawane H, Soejima R. Clinical effect of balofloxacin in respiratory tract infections. [Japanese]. *Japanese Journal of Chemotherapy* 1995;**43**(Suppl 5):547-9.

**Nakamori 1992** *{published data only}*

Nakamori Y, Tsuboi E, Narui K, Nakatani T, Sugi H. Sputum penetration of levofloxacin and its clinical efficacy in patients with chronic lower respiratory tract infections. [Japanese]. *Japanese Journal of Antibiotics* 1992;**45**(5):539-47.

**Nakamura 2007** *{published data only}*

Nakamura M, Hasegawa N, Miyao N, Nakajima T, Terashima T, Sakamaki F, et al. [Comparison of 5 day short-course therapies for secondary infection in patients with chronic respiratory disease using gatifloxacin and levofloxacin]. *Japanese Journal of Chemotherapy* 2007;**55**(6):451-62.

**Nakatani 1993** *{published data only}*

* Nakatani T, Tsuboi E, Narui K, Nakamori Y, Nakata K, Sugi H. Clinical efficacy of temafloxacin in respiratory infections and its pharmacokinetics in sputum. *Chemotherapy* 1993;**41**(Suppl 5):361-8.

**Nasu 1988** *{published data only}*

Nasu M, Yamazaki T, Yamazaki H, Kuroda Y, Goto J, Tashiro T, et al. T-3262 in respiratory tract infections. [Japanese]. *Chemotherapy* 1988;**36**(Suppl 9):699-709.

**Neumayr 1963** *{published data only}*

Neumayr A, Stoeffler G. Clinical trials of the new antibiotic, rifamycin sv: preliminary report. *Chemotherapy* 1963;**12**:437-8.

**Nobuoka 1985** *{published data only}*

Nobuoka T, Kobayashi Y, Fujimori I. Clinical study on BAY o 9867 in the field of internal medicine. [Japanese]. *Chemotherapy* 1985;**33**(Suppl 7):373-9.

**O'Donovan, 1987** *{published data only}*

O'Donovan C, Rudd R, O'Neill S, Fitzgerald MX, McNicholas W, Flavell-Matts SG, et al. Augmentin (intravenous then oral) compared with cefuroxime followed by cephalexin for chest infections in hospitalised patients. *British Journal of Clinical Practice* 1987;**41**(12):1044-52.

**Oishi 1994** *{published data only}*

* Oishi K, Sonoda F, Kobayashi S, Iwagaki A. Role of interleukin-8 (IL-8) and an inhibitory effect of erythromycin on IL-8 release in the airways of patients with chronic airway diseases. *Infection and Immunity* 1994;**62**(10):4145-52.

**Oizumi 1978** *{published data only}*

Oizumi K, Wantanabe A, Konno K, Hayashi I, Kawamorida K, Nagai K, et al. [Therapeutic effect of amikacin for infections with gram-negative bacilli, especially for stubborn respiratory infections (author's transl)]. [Japanese]. *Japanese Journal of Antibiotics* 1978;**31**(1):15-23.

**Oki 1993** *{published data only}*

* Oki Y, Morishita M, Miyachi A. An evaluation of low dose long term erythromycin chemotherapy in bronchiectasis. *Japanese Journal of Chest Diseases* 1993;**52**(1):54-8.

**Ovcharenko 1991** *{published data only}*

Ovcharenko SI, Loginov LE, Zavodnov Ya V. Antibiotic therapy of bronchial pyoinflammation using endobronchial low-frequency ultrasound. [Russian]. *Klinicheskaia Meditsina* 1991;**69**(9):29-31.

**Patterson 2005** *{published data only}*

Patterson JE, Bradley JM, Hewit O, Bradbury I, Elborn JS. Airway clearance during oral antibiotic therapy in bronchiectasis, a randomized trial of acapella versus usual airway clearance [Abstract]. American Thoracic Society 2005 International Conference; May 20-25; San Diego, California. 2005:B25; Poster: 917.

**Patterson 2007** *{published data only}*

Patterson JE, Hewitt O, Kent L, Bradbury I, Elborn JS, Bradley JM. Acapella versus 'usual airway clearance' during acute exacerbation in bronchiectasis: a randomized crossover trial. *Chronic Respiratory Disease* 2007;**4**(2):67-74.

**Pezza 1983** *{published data only}*

Pezza A, Giacomelli P, Montella R, Casino G. [Clinical study of a new cephalosporin: ceftriaxone (RO 13-9904) in resurgent acute and chronic bronchopneumopathies]. [Italian]. *Archivio Monaldi per la Tisiologia e le Malattie dell'Apparato Respiratorio* 1983;**38**(1-2):17-24.

**Pines 1967** *{published data only}*

* Pines A, Raafat H, Khorasani M, Mullinger BM. Cephaloridine compared with penicillin and streptomycin in chronic purulent bronchitis. Controlled trials of increasing dosage of cephaloridine. *British Journal of Diseases of the Chest* 1967;**61**(2):101-10.

**Pines 1979** *{published data only}*

Pines A, Raafat H. Cefuroxime in severe respiratory infections: a double-blind comparison of two doses. *British Journal of Diseases of the Chest* 1979;**73**(4):395-8.

**Pines 1981** *{published data only}*

* Pines A, Raafat H, Plucinski K, Greenfield JS, Linsell WD. Cefuroxime and ampicillin compared in a double-blind study in the treatment of lower respiratory tract infections. *Chemotherapy* 1981;**27**(6):459-65.

**Piovano 1997** *{published data only}*

Piovano CF, Palombini BC, Dagrosa EE, Mendoza F, Facco EB. Cefodizime once daily in the treatment of lower respiratory tract infections. *Arzneimittel-Forschung* 1997;**47**(5):674-7.

**Popov 1988** *{published data only}*

Popov B, Kalfin EM. Peflacin - clinical study in patients with pulmonary diseases. [Bulgarian]. *Pnevmologiya i Ftiziatriya* 1988;**25**(3):30-5.

**Prigogine 1988** *{published data only}*

Prigogine T, Glupczynski Y, Carpiaux JP, Blogie M, Yourassowsky E, Schmerber JS. Enoxacin in acute exacerbations of chronic bronchitis: a comparison with amoxycillin. *Journal of Antimicrobial Chemotherapy* 1988;**21(Suppl B)**:131-6.

**Ramer 1981** *{published data only}*

Ramer P, Medici TC, Hatt RR, Unger S, Ronner B. [Trimethoprim-sulfamethoxazole versus amoxycillin in the therapy of acute bacterial exacerbations in chronic non-specific respiratory tract diseases: a controlled study]. *Schweizerische Medizinische Wochenschrift* 1981;**111**(48):1823-9.

**Rayner 1994** *{published data only}*

* Rayner CFJ, Tillotson G, Cole PJ, Wilson R. Efficacy and safety of long-term ciprofloxacin in the management of severe bronchiectasis. *Journal of Antimicrobial Chemotherapy* 1994;**34**(1):149-56.

**Rimoldi 1987** *{published data only}*

Rimoldi R, Fioretti M, Bandera M. Use of miocamycin in respiratory infection. *Annali dell'Istituto Superiore di Sanita* 1987;**23**(4):891-4.

**Saito 1993** *{published data only}*

Saito A, Kusano N, Fukuhara H, Soejima R, Nakahama C, Niki Y, et al. A study of the clinical effects of clindamycin on respiratory infections - Focusing on inhibition of beta-lactamase production. [Japanese]. *Chemotherapy* 1993;**41**(11):1232-45.

**Saito 1999** *{published data only}*

Saito A, Ohmichi M, Arakawa M, Wada K, Tsukada H, Iwata F, et al. Dose-finding study of gatifloxacin, a new oral, quinolone, in chronic respiratory tract infection. [Japanese]. *Japanese Journal of Chemotherapy* 1999;**47**(Suppl 2):419-37.

**Saito 2002** *{published data only}*

Saito A. Clinical studies of gatifloxacin for infections in internal medicine. *Japanese Journal of Chemotherapy* 2002;**50**(10):646-73.

**Santiveri 1995** *{published data only}*

Santiveri C, Orriols R, Roig J, Balcells E, Bellver P, Ferrer A, et al. Effectiveness of inhaled antibiotic treatment for *Pseudomonas aeruginosa* in outpatients with colonized bronchiectasis without mucoviscidosis [Abstract]. *Archivos de Bronconeumologia* 1995;**31**(Suppl):42.

**Sawae 1991** *{published data only}*

* Sawae Y, Kashiwagi S, Kumagai Y, Ishimaru T, Takii M, Shigeoka H, et al. Clinical studies on the utility of ofloxacin for lower respiratory infections. *Japanese Journal of Antibiotics* 1991;**44**(1):48-57.

**Sawae 1995** *{published data only}*

Sawae Y, Ninomiya K, Takaki K, Shimono N, Misumi H, Okada K. A comparative study of ofloxacin twice and three times daily in the treatment of respiratory tract infections. *Drugs* 1995;**49**(Suppl 2):430-2.

**Sawaki 1986** *{published data only}*

Sawaki M, Mikami R, Mikasa K, Kunimatsu M, Ito S, Narita N. The long term chemotherapy with erythromycin in chronic lower respiratory tract infections: first report - comparing with amoxicillin. *Japanese Association of Infectious Disease* 1986;**60**(1):37-44.

**Schulz 1972** *{published data only}*

Schulz G. [Comparative studies on the toxicity of tetracyclines and chloramphenicol in the treatment of nonspecific bronchopulmonary infections]. [German]. *Zeitschrift fur Erkrankungen der Atmungsorgane mit Folia Bronchologica* 1972;**136**(2):185-96.

**Serisier 2011a** *{published data only}*

Serisier DJ, Martin ML. Long-term, low-dose erythromycin in bronchiectasis subjects with frequent infective exacerbations. *Respiratory Medicine* 2011;**105**(6):946-9.

**Serisier 2011b** *{published data only}*

Serisier DJ, Martin M, Bowler SD. Research bronchoscopic biopsy in adult bronchiectasis subjects is associated with significant bleeding risk. *Respirology* 2011;**16**(Suppl):62 [TP-100].

**Shewsbury 2004** *{published data only}*

Shrewsbury SB, Bilton D, Gotfried M, Jones SA. [The TABLE study (TOBI in acute bronchiectasis: additional treatment for exacerbations): rationale and methology]. American Thoracic Society 100th International conference; 2004 May 21-26; Orlando. Orlando, 2004:A42 Poster A53.

**Shigeno 1984** *{published data only}*

Shigeno Y, Masaki M, Nakazato H. Laboratory and clinical studies on lenampicillin (KBT-1585) a new penicillin antibiotic. [Japanese]. *Chemotherapy* 1984;**32**(Suppl 8):382-96.

**Shimada 1996** *{published data only}*

Shimada K, Oka S, Saito A, Tomizawa M, Hiraga Y, Ohmichi M, et al. A dose-finding study on pazufloxacin in chronic respiratory tract infections. *Japanese Journal of Chemotherapy* 1996;**44**(4):231-47.

**Shimada K 1988** *{published data only}*

Shimada K, Inamatsu T, Fukayama M, Kato A, Adachi K, Sasaki M, et al. Antimicrobial activity and clinial evaluation of NY-198. *Chemotherapy* 1988;**36**(Suppl 2):701-12.

**Shimokata 1990** *{published data only}*

* Shimokata K, Kawazu H, Nishiwaki K, Yamamoto M, Sakai S, Senda Y. Evaluation of imipenem/cilastatin sodium in the treatment of respiratory tract infections. *Japanese Journal of Antibiotics* 1990;**43**(1):14-22.

**Shimokata 1992** *{published data only}*

Shimokata K, Sakai S, Senda Y, Nishiwaki K, Yamaoto M, Murate T, et al. Evaluation of cefclidin on respiratory tract infections. *Chemotherapy* 1992;**40**(Suppl 4):748-52.

**Shirai 1995** *{published data only}*

Shirai T, Sato A, Chida K. Effect of 14-membered ring macrolide therapy on chronic respiratory tract infections and polymorphonuclear leukocyte activity. *Internal Medicine* 1995;**34**(6):469-74.

**Shishido 1988** *{published data only}*

Shishido H, Takasugi M, Uzuka Y, Takahashi A, Akiyama M, Hirose H, et al. Sultbactam.ampicillin (1:2) in respiratory tract infections with special reference to beta-lactamase-producing organisms. *Chemotherapy* 1988;**36**(Suppl 8):257-72.

**Shishido 1995** *{published data only}*

Shishido H, Furukawa K, Nagai H, Kawakami K, Kono H. Oral levofloxacin 600mg and 300mg daily doses in difficult-to-treat respiratory infections. *Drugs* 1995;**49**(Suppl 2):433-5.

**Singleton 2007** *{published data only}*

IInternational Collaboration of Bronchiectasis Network, Singleton R, Morris P, Leach A, Roseby R, White A, et al. Multicentre bronchiectasis study; a collaboration and international study of bronchiectasis in indigenous children [Abstract]. *Respirology (Carlton, Vic)* 2007;**12**(Suppl 4):A192.

**Singleton 2008** *{published data only}*

Singleton R, Morris P, Leach A, Roseby R, White A, Valery P, et al. Multicentre bronchiectasis study: an international observational and interventional study of bronchiectasis in indigenous children [Abstract]. *Respirology (Carlton, Vic)* 2008;**13**(Suppl 2):A19.

**Soejima 1988** *{published data only}*

Soejima R, Niki Y, Hino J, Nakagawa Y, Sumi M, Kishimoto T, Matsumoto A. Clinical studies on TE-031 (A-56268). *Chemotherapy* 1988;**36**(Suppl 3):673-8.

**Stass 2013** *{published data only}*

Stass H, Nagelschmitz J, Kappeler D, Weimann B. Lung deposition of ciprofloxacin dry powder for inhalation in healthy subjects and patients suffering from chronic obstructive pulmonary disease or non-cystic fibrosis bronchiectasis. *American Journal of Respiratory and Critical Care Medicine* 2013;**187**(Meeting Abstracts):A1507.

**Stockley 1984** *{published data only}*

* Stockley RA, Hill SL, Burnett D. Effect of antibiotic treatment on sputum elastase in bronchiectatic outpatients in a stable clinical state. *Thorax* 1984;**39**(6):414-9.

**Stockley 1985** *{published data only}*

* Stockley RA, Hill SL, Morrison HM. Nebulized amoxicillin in chronic purulent bronchiectasis. *Clinical Therapeutics* 1985;**7**(5):593-9.

**Suga 1988** *{published data only}*

Suga M, Ando M, Tanaka F, Ito K, Aakata T, Sugimoto M, Araki S. Clinical studies of T-3262 in respiratory tract infection. [Japanese]. *Chemotherapy* 1988;**36**(Suppl 9):694-8.

**Suyama 1988** *{published data only}*

Suyama N, Inoue Y, Masaki M, Mashimoto H, Masuyama Y, Dohtsu Y, et al. Laboratory and clinical studies on cefodizime (THR-221). *Chemotherapy* 1988;**36**(Suppl 5):529-44.

**Tagaya 2002** *{published data only}*

Tagaya E, Tamaoki A, Kondo M, Nakada J, Nagai A. [Effect and action mechanism of short-term administration of calrithromycin for airway hypersecretion]. [Japanese]. *Japanese Journal of Antibiotics* 2001;**54**(Suppl A):33-5.

Tagaya E, Tamaoki J, Kondo M, Nagai A. Effect of a short course of clarithromycin therapy on sputum production in patients with chronic airway hypersecretion. *Chest* 2002;**122**(1):213-8.

**Tageldin 1994** *{published data only}*

* El-Din MA, Palmer LB, El-Tayeb MN, Khalil I, Gabr MS. Nebulizer therapy with antibiotics in chronic suppurative lung disease. *Journal of Aerosol Medicine* 1994;**7**(4):345-50.

**Takamoto 1994** *{published data only}*

* Takamoto M, Ishibashi T, Toyoshima H, Tanaka H, Tamaru N, Watanabe K, et al. Imipenem/cilastatin sodium alone or combined with amikacin sulfate in respiratory infections. *Japanese Journal of Antibiotics* 1994;**47**(9):1131-44.

**Tamura 1992** *{published data only}*

Tamura S, Tokita K, Tsutsumi Z, Ohkawa T, Fujioka H, Kurabori J, et al. Clinical studies on cefclidin [Japanese]. *Chemotherapy* 1992;**40**(Suppl 4):737-7.

**Tanimoto 1992** *{published data only}*

Tanimoto H, Obara K, Komatuzaki K, Tanabe O, Okamura T. A clinical study on ME1207 in respiratory infections. *Chemotherapy* 1992;**40**(Suppl 2):683-5.

**Tanimoto 1993** *{published data only}*

Tanimoto H, Obara K, Tateishi O, Okamura T. Clinical studies on S-1108 in respiratory infections. *Chemotherapy* 1993;**41**(Suppl 1):751-4.

**Taskar 1992** *{published data only}*

Taskar VS, Sharma RR, Goswami R, John PJ, Mahashur AA. Effect of bromhexeine on sputum amoxycillin levels in lower respiratory infections. *Respiratory Medicine* 1992;**86**(2):157-60.

**Tsang 1993** *{published data only}*

Tsang KT, Roberts P, Read R, Coles SJ, Wilson R, Cole PJ. The concentration of clarithromycin and its active 14-hydroxy metabolite in sputum of patients with bronchiectasis following single dose oral administration. *British Journal of Clinical Pharmacology* 1993;**35**:84P.

**Tsang 1994** *{published data only}*

Tsang KWT, Roberts P, Read RC, Kees R, Wilson R, Cole PJ. The concentrations of clarithromycin and its 14-hydroxy metabolite in sputum of patients with bronchiectasis following single dose oral administration. *Journal of Antimicrobial Chemotherapy* 1994;**33**(2):289-97.

**Tsang 1999a** *{published data only}*

Tsang KW, Chan WM, Ho PL, Chan K, Lam WK, Ip MS. A comparative study on the efficacy of levofloxacin and ceftazidime in acute exacerbation of bronchiectasis. *European Respiratory Journal* 1999;**14**(5):1206-9.

**Unoura 1988** *{published data only}*

Unoura T, Masuda M, Takeuchi K, Itoh T, Tamura M, Ykui T, et al. Clinical study on TE-031 (A56268) against respiratory infections. *Chemotherapy* 1988;**36**(Suppl 3):544-8.

**Vergnon 1985** *{published data only}*

Vergnon JM, Vincent M, Ros A, Brun Y, Brune J. Comparative clinical trial of cefoperazone vs ampicillin + tobramycin in severe bronchopulmonary and pleural infectious pathology. *Revue di Pneumologie Clinique* 1985;**41**(3):205-11.

**Watanabe 1982** *{published data only}*

Watanabe K, Hibino J, Ikemoto H. Clinical trials of netilmicin against respiratory tract infection. *Japanese Journal of Antibiotics* 1982;**35**(8):1907-10.

**Watanabe 1989** *{published data only}*

Watanabe A, Oizumi K, Aonuma S, Ono R, Honda Y, Tokue Y, et al. In vitro antimicrobial activity of 7432-S and its therapeutic efficacy in chronic respiratory tract infections. *Chemotherapy* 1989;**37**(Suppl 1):148-57.

**Watanabe 1991** *{published data only}*

Watanabe A. Once daily versus every two week multidose ofloxacin in patients with acute exacerbations of chronic respiratory disease. *Infection* 1991;**19(Suppl 7)**:S384-7.

**Watanabe 1994** *{published data only}*

* Watanabe A, Motomiya M, Nukiwa T, Nakai Y, Honda Y, Konno K, et al. A well-controlled comparative clinical study of the combination regimen of ciprofloxacin plus erythromycin for the treatment of repeated acute exacerbations of chronic respiratory tract infections. [Japanese]. *Chemotherapy* 1994;**42**(10):1194-201.

**Watanabe 1995** *{published data only}*

Watanabe A, Oizumi K, Motomiya M, Nukiwa T. Daily single-dose regimen and alternate-two-week triple-dose/day regimen of oral ofloxacin for the prophylaxis and control of exacerbations of chronic respiratory tract infections. *Tohoku Journal of Experimental Medicine* 1995;**176**(1):25-33.

**Watanabe 2001** *{published data only}*

Watanabe A, Kohno S, Niki Y, Saito A. Comparison of chest X-ray findings and other parameters in acute exacerbation of chronic bronchitis in Japan and the West. *Journal of Infection and Chemotherapy* 2001;**7**(1):37-44.

**Yamada 1993** *{published data only}*

Yamada H, Katoh O, Aoki Y, Nakata H, Yamaguchi M. Clinical study on S-1108 in respiratory tract infections. *Chemotherapy* 1993;**41**(Suppl 1):816-9.

**Yamaki 1988** *{published data only}*

Yamaki K, Takagi K, Suzki R, Sumita T, Gonda H, Satake T, et al. T-3262 in respiratory tract infection and effect on blood theophylline concentration. *Chemotherapy* 1988;**36**(Suppl 9):567-74.

**Young Whan 1993** *{published data only}*

Young WK, Yeon MO, Man PJ, Chul GY, Sung KH, Young SS, et al. The effect of low-dose longterm erythromycin on bronchiectasis. *Tuberculosis and Respiratory Diseases* 1993;**40**(4):390-4.

**Zhang 2003** *{published data only}*

Zhang JJ. Observations on the effect of sodium fosfomycin on the lower respiratory tract infection. *Chinese Journal of Antibiotics* 2003;**28**(6):361-3.

## References to studies awaiting assessment

**Aksamit 2017** *{published data only}*

Aksamit T, Bandel TJ, Criollo M, De Soyza A, Elborn JS, Operschall E, et al. The RESPIRE trials: two phase III, randomized, multicentre, placebo-controlled trials of Ciprofloxacin Dry Powder for Inhalation (Ciprofloxacin DPI) in non-cystic fibrosis bronchiectasis. Contemporary clinical trials. United States, 2017; Vol. 58:78-85.

**Alder 2012** *{published data only}*

Alder J, Hampel B, Reimnitz P, Wilson R. Correlation of bacterial species and density at baseline to exacerbations requiring antibiotic treatment in a phase 2 trial of ciprofloxacin dry powder for inhalation (ciprofloxacin DPI) compared with placebo in patients with non-cystic fibrosis bronchiectasis. American journal of respiratory and critical care medicine. American Thoracic Society, 2012; Vol. 185.

**Altenburg 2016** *{published data only}*

Altenburg J, Wilms E, Boersma W. The relationship between serum-and sputum levels of azithromycin and clinical endpoints in bronchiectasis patients in bronchiectasis patients using maintenance treatment. Pneumologie (stuttgart, germany). Georg Thieme Verlag, 2016; Vol. 70, issue 10.

**Altenburg 2016a** *{published data only}*

Altenburg J, Wolf R, Go S, van Rijn P, Boersma W, van der Werf T. Changes of computed tomography features of bronchiectasis during one year of azithromycin treatment. European respiratory journal 2016; Vol. 48, issue Suppl 60:OA278.

**Altenburg 2016b** *{published data only}*

Altenburg J, Wolf R, Go S, Van Rijn P, Boersma W, Van Der Werf T. Changes of computed tomography features of bronchiectasis during one year of azithromycin treatment. European respiratory journal. Conference: european respiratory society annual congress 2016. United kingdom. European Respiratory Society, 2016; Vol. 48, issue no pagination.

**Barker 2014** *{published data only}*

Barker AF, O'Donnell AE, Flume P, Thompson PJ, Ruzi JD, de Gracia J, et al. Aztreonam for inhalation solution in patients

with non-cystic fibrosis bronchiectasis (AIR-BX1 and AIR-BX2): two randomised double-blind, placebo-controlled phase 3 trials. The Lancet. Respiratory medicine. England: Lancet Publishing Group, 2014; Vol. 2, issue 9:738-49.

**Burr 2015** *{published data only}*

Burr L, Rogers G, Taylor S, Mcguckin M, Serisier D. Sub inhibitory erythromycin reduces the expression of key p. aeruginosa virulence determinants in non-CF bronchiectasis subjects. Respirology (Carlton, Vic.). Blackwell Publishing, 2015; Vol. 20, issue Suppl 2:29 [TO 043].

**Burr 2016** *{published data only}*

Burr LD, Rogers GB, Chen AC, Hamilton BR, Pool GF, Taylor SL, et al. Macrolide Treatment Inhibits Pseudomonas aeruginosa Quorum Sensing in Non-CF Bronchiectasis: an Analysis from the BLESS Trial. Annals of the american thoracic society 2016; Vol. 13, issue 10:1697-703.

**Chalmers 2012** *{published data only}*

Chalmers JD, Smith MP, McHugh BJ, Doherty C, Govan JR, Hill AT. Short- and long-term antibiotic treatment reduces airway and systemic inflammation in non-cystic fibrosis bronchiectasis. American journal of respiratory and critical care medicine 2012; Vol. 186, issue 7:657-65.

**Chang 2013** *{published data only}*

Chang AB, Grimwood K, Wilson AC, van Asperen PP, Byrnes CA, O'Grady KF, et al. Bronchiectasis exacerbation study on azithromycin and amoxycillin-clavulanate for respiratory exacerbations in children (BEST-2): study protocol for a randomized controlled trial. *BioMed Central* 2013;**14**:53-63.

**Chen 2014** *{published data only}*

Chen A, Martin M, Lourie R, Burr L, Hasnain S, Bowler S, et al. Clinical benefits of long-term, low-dose erythromycin in bronchiectasis are not due to modulation of sputum mucin content [Abstract]. Respirology (Carlton, Vic.). Blackwell Publishing, 2014; Vol. Conference: 2014 Annual Scientific Meetings of the Thoracic Society of Australia and New Zealand and the Australian and New Zealand Society of Respiratory Science Adelaide, SA Australia. Conference Start: 20140404 Conference End: 20140409. Conference Publication:, issue var.pagings:88 [TP 093].

**De Soyza 2016** *{published data only}*

De Soyza A, Aksamit TR, Bandel T-J, Criollo M, Elborn J S, Krahn U, et al. RESPIRE 1: ciprofloxacin DPI 32.5mg b.d. administered 14 day on/off or 28 day on/off vs placebo for 48 weeks in subjects with non-cystic fibrosis bronchiectasis (NCFB). European respiratory journal 2016; Vol. 48, issue Suppl 60:OA272.

**Dimakou 2014** *{published data only}*

Dimakou K, Triantafillidou C, Tsikritsaki K, Gousiou A, Dervas A, Toumbis M. Non CF bronchiectasis: The effect of inhaled antibiotics (tobramycin and colistin) in patients with pseudomonas aeruginosa [Abstract]. European respiratory journal 2014; Vol. 44, issue Suppl 58:P244.

**Hare 2015** *{published data only}*

Hare KM, Grimwood K, Chang AB, Chatfield MD, Valery PC, Leach AJ, et al. Nasopharyngeal carriage and macrolide resistance in Indigenous children with bronchiectasis randomized to long-term azithromycin or placebo. European journal of clinical microbiology & infectious diseases. Germany: Springer Verlag, 2015; Vol. 34, issue 11:2275-85.

**Haworth 2013** *{published data only}*

Haworth C, Bilton D, Kenyon R. Nebulised colistimethate sodium improves quality of life in patients with bronchiectasis colonised by *Pseudomonas aeruginosa* [Abstract]. European Respiratory Society 23rd Annual Congress; 2013 Sep 7-11; Barcelona. 2013; Vol. 42:577s [P2732].

**Haworth 2013a** *{published data only}*

Haworth C, Bilton D, Kenyon R. Nebulised colistimethate sodium improves quality of life in patients with bronchiectasis colonised by pseudomonas aeruginosa [Abstract]. 2013; Vol. 42:577s [P2732].

**Haworth 2014** *{published data only}*

Haworth CS, Foweraker JE, Wilkinson P, Kenyon RF, Bilton D. Inhaled colistin in patients with bronchiectasis and chronic Pseudomonas aeruginosa infection. American journal of respiratory and critical care medicine. United States: American Thoracic Society, 2014; Vol. 189, issue 8:975-82.

**Juthong 2011** *{published and unpublished data}*

Juthong S, Eiamsa-ard S. The effects of roxithromycin as anti-inflammatory agent on clinical outcomes in patient with bronchiectasis: a double blinded randomized controlled study. European Respiratory Society 21st Annual Congress; 2011 Sep 24-28; Amsterdam. 2011; Vol. 38:819s [4496].

**Kobbernagel 2016** *{published data only}*

Kobbernagel HE, Buchvald FF, Haarman EG, Casaulta C, Collins SA, Hogg C, et al. Study protocol, rationale and recruitment in a European multi-centre randomized controlled trial to determine the efficacy and safety of azithromycin maintenance therapy for 6 months in primary ciliary dyskinesia. BMC pulmonary medicine. England: BioMed Central Ltd., 2016; Vol. 16, issue 1) (no pagination:104.

**Liu 2012a** *{published data only}*

Liu JF, Zhong XN, He ZY, Zhong DJ, Bai J, Zhang JQ, et al. Impact of treatment with low dose roxithromycin on stable. *Zhonghua jie he he hu xi za zhi [Chinese journal of tuberculosis and respiratory diseases]* 2012;**35**(11):824-7.

**Liu 2014** *{published data only}*

Liu J, Zhong X, He Z, Wei L, Zheng X, Zhang J, et al. Effect of low-dose, long-term roxithromycin on airway inflammation and remodeling of stable noncystic fibrosis bronchiectasis. Mediators of inflammation. United States, 2014; Vol. 2014:708608.

**Lourdesamy 2014** *{published data only}*

Lourdesamy Anthony AI, Muthukumaru U. Efficacy of azithromycin in the treatment of bronchiectasis. Respirology

(Carlton, Vic.). Australia: Blackwell Publishing, 2014; Vol. 19, issue 8:1178-82.

**New Study** *{published data only}*

Corrections to The effect of long-term macrolide treatment on respiratory microbiota composition in non-cystic fi brosis bronchiectasis: an analysis from the randomised, double-blind, placebo-controlled BLESS trial. Lancet respiratory medicine. United Kingdom: Lancet Publishing Group, 2015; Vol. 3, issue 4:e15.

**O'Donnell 2016** *{published data only}*

O'Donnell AE, Bilton D, Serisier D, Wanner A, Froehlich J, Bruinenberg P, et al. ORBIT-3 and ORBIT-4: design of a Phase 3 Program to Investigate Safety and Efficacy of Pulmaquin in Non-Cystic Fibrosis Bronchiectasis (NCFBE) Patients Chronically Colonized with Pseudomonas Aeruginosa (PA). American journal of respiratory and critical care medicine 2016; Vol. 193, issue Meeting Abstracts:A1775.

**O'Donnell 2016a** *{published data only}*

O'Donnell A, Bilton D, Serisier D, Wanner A, Froehlich J, Bruinenberg P, et al. A phase 3 study design of Pulmaquin in non-cystic fibrosis bronchiectasis (NCFBE) patients chronically colonized with pseudomonas aeruginosa (PA). Pneumologie. Conference: 1st world bronchiectasis conference. Germany. Conference start: 20160707. Conference end: 20160709. Georg Thieme Verlag, 2016; Vol. 70, issue 10) (no pagination.

**Orriols 2015** *{published data only}*

Orriols R, Hernando R, Ferrer A, Terradas S, Montoro B. Eradication therapy against pseudomonas aeruginosa in non-cystic fibrosis bronchiectasis. Respiration; international review of thoracic diseases. Switzerland: S. Karger AG, 2015; Vol. 90, issue 4:299-305.

**Rogers 2014** *{published data only}*

Rogers GB, Bruce KD, Martin ML, Burr LD, Serisier DJ. The effect of long-term macrolide treatment on respiratory microbiota composition in non-cystic fibrosis bronchiectasis: an analysis from the randomised, double-blind, placebo-controlled BLESS trial.[Erratum appears in Lancet Respir Med. 2015 Apr;3(4): e15; PMID: 25890660]. The Lancet. Respiratory medicine. England: Lancet Publishing Group, 2014; Vol. 2, issue 12:988-96.

**Tabernero 2014** *{published data only}*

Tabernero E, Gil P, Alkiza R, Garros J, Hernandez A, Artola JL. Inhaled colistin in elderly patients with non-cystic fibrosis. *Chest* 2014;**145**(3 Suppl):431A.

**Tabernero 2015** *{published data only}*

Tabernero Huguet E, Gil Alana P, Alkiza Basanez R, Hernandez Gil A, Garros Garay J, Artola Igarza JL. Inhaled colistin in elderly patients with non-cystic fibrosis bronchiectasis and chronic Pseudomonas aeruginosa bronchial infection]. [Spanish. *Revista espanola de geriatria y gerontologia* 2015;**50**(3):111-5.

**Terpstra 2016** *{published data only}*

Terpstra L, Altenburg J, Boersma W. Effects of long term tobramycin inhalation solution (TIS) once daiLy on exacerbation rate in patients with non-cystic fibrosis bronchiectasis. A doubleblind, randomized, placebo controlled trial. The BATTLE study. Pneumologie. Conference: 1st world bronchiectasis conference. Germany. Conference start: 20160707. Conference end: 20160709. Georg Thieme Verlag, 2016; Vol. 70, issue 10) (no pagination.

**Twiss 2008** *{published data only}*

Twiss J, Byrnes C. Nebulized antibiotics reduce symptoms, bacterial density and oral antibiotic usage in children with non-cystic fibrosis bronchiectasis. 2009 Thoracic Society of Australia & New Zealand (TSANZ) and Australian & New Zealand Society of Respiratory Science (ANZSRS) Annual Scientific Meeting; 2009 3-8 April; Darwin. Darwin, Australia, 2009; Vol. 14:A76.

Twiss J, Byrnes CA. Nebulized antibiotics reduce symptoms, bacterial density and oral antibiotic usage in children with non-cystic fibrosis bronchiectasis. American Thoracic Society International Conference; 2008 May 16-21; Toronto. Toronto, 2008:A681 [#C40].

**Yalcin 2006** *{published data only}*

Yalcin E, Kiper N, Ozcelik U, Dogru D, Firat P, Sahin A, et al. Effects of claritromycin on inflammatory parameters and clinical conditions in children with bronchiectasis. *Journal of clinical pharmacy and therapeutics* 2006;**31**(1):49-55.

## Additional references

**AIHW 2010**

Australian Institute of Health and Welfare. Asthma, chronic obstructive pulmonary disease and other respiratory diseases in Australia. http://www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=6442453795 (accessed 13 November 2014). [URL: http://www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=6442453795 [date accessed 18/07/2014]]

**Angrill 2001**

Angrill J, Agusti C, De Celis R, Filella X, Rano A, Elena M, et al. Bronchial inflammation and colonization in patients with clinically stable bronchiectasis. *American Journal of Respiratory and Critical Care Medicine* 2001;**164**:1628-32.

**Chalmers 2012**

Chalmers JD, Smith MP, McHugh BJ, Doherty C, Govan JR, Hill AT. Short- and long-term antibiotic treatment reduces airway and systemic inflammation in non–cystic fibrosis bronchiectasis. *American Journal of Respiratory and Critical Care Medicine* 2012;**186**(7):657-65.

**Chalmers 2013**

Chalmers JD, Goeminne P, Aliberti S, McDonnel M, Lonni S, Davidson J, et al. The Bronchiectasis Severity Index. An international derivation and validation study. *American Journal of Respiratory and Critical Care Medicine* 2013;**189**:576-85.

**Chang 2002**

Chang A, Grimwood K, Mulholland E, Torzillo P. Bronchiectasis in indigenous children in remote Australian communities. *Medical Journal of Australia* 2002;**177**:200-4.

**Cole 1986**

Cole PJ. Inflammation: a two-edged sword—the model of bronchiectasis. *European Journal of Respiratory Diseases Supplement* 1986;**147**:6-15.

**Downey 2007**

Downey DG, Brockbank S, Martin SL, Ennis M, Elborn JS. The effect of treatment of cystic fibrosis pulmonary exacerbations on airways and systemic inflammation. *Pediatric Pulmonology* 2007;**42**(8):729-35.

**Goeminne 2014**

Goeminne PC, Nawrot TS, Ruttens D, Seys S, Dupont LJ. Mortality in non-cystic fibrosis bronchiectasis: a prospective cohort analysis. *Respiratory Medicine* 2014;**108**(2):287-96.

**Grimwood 2011**

Grimwood K. Airway microbiology and host defences in paediatric non-CF bronchiectasis. *Paediatric Respiratory Reviews* 2011;**12**:111-8.

**Higgins 2011**

Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;**343**:d5928.

**Hill 2000**

Hill AT, Campbell EJ, Hill SL, Bayley D, Stockley RA. Association between airway bacterial load and markers of airway inflammation in patients with stable chronic bronchitis. *American Journal of Medicine* 2000;**109**:288-95.

**King 2009**

King PT. The pathophysiology of bronchiectasis. *International Journal of Chronic Obstructive Pulmonary Disease* 2009;**4**:411-9.

**Kwak 2010**

Kwak HJ. High prevalence of bronchiectasis in adults: analysis of CT findings in a health screening program. *The Tohoku Journal of Experimental Medicine* 2010;**222**:237-42.

**Lee 2011**

Lee YM. The clinical characteristics of patients with non-CF bronchiectasis. *Chest* 2011;**140**:459A.

**Loebinger 2009**

Loebinger M. Mortality in bronchiectasis: a long-term study assessing the factors influencing survival. *European Respiratory Journal* 2009;**34**(4):843-9.

**Maguire 2012**

Maguire G. Bronchiectasis: a guide for primary care. *Australian Family Physician* 2012;**41**:842-50.

**Martinez-Garcia 2014**

Martinez-Garcia MA, de Gracia J, Vendrell RM. Multidimensional approach to non-cystic fibrosis bronchiectasis: the FACED score. *European Respiratory Journal* 2014;**43**:1357-67.

**Martínez-García 2011**

Martínez García M, Máiz Carro L, Catalán Serra P. Treatment of non-cystic fibrosis bronchiectasis. *Archivos de Bronconeumologia* 2011;**47**:599-609.

**McShane 2013**

McShane PJ, Naureckas ET, Tino G, Strek ME. Non-cystic fibrosis bronchiectasis. *American Journal of Respiratory and Critical Care Medicine* 2013;**188**:647-56.

**O'Donnell 2008**

O'Donnell AE. Bronchiectasis. *Chest* 2008;**134**(4):815-23.

**Ordonez 2003**

Ordonez CL, Henig NR, Mayer-Hamblett N, Accurso FJ, Burns JL, Chmiel JF, et al. Inflammatory and microbiologic markers in induced sputum after intravenous antibiotics in cystic fibrosis. *American Journal of Respiratory and Critical Care Medicine* 2003;**168**(12):1471-5.

**Pasteur 2010**

Pasteur MC, Bilton D, Hill AT, British Thoracic Society Bronchiectasis non-CF Guideline Group. British Thoracic Society guideline for non-CF bronchiectasis. *Thorax* 2010;**65**:i1-i58.

**Reid 1950**

Reid LM. Reduction in bronchial subdivision in bronchiectasis. *Thorax* 1950;**5**:233-47.

**Sagel 2011**

Sagel SD, Kapsner R, Osberg I, Sontag MK, Accurso FJ. Airway inflammation in children with cystic fibrosis and healthy children assessed by sputum induction. *American Journal of Respiratory and Critical Care Medicine* 2011;**164**:1425-31.

**Saleh 2014**

Saleh A, Hurst J. How to assess the severity of bronchiectasis. *European Respiratory Journal* 2014;**45**:1217-9.

**Saynajakangas 1998**

Saynajakangas O, Keistinen T, Tuuponen T, Kivela SL. Evaluation of the incidence and age distribution of bronchiectasis from the Finnish hospital discharge register. *Central European Journal of Public Health* 1998;**6**:235-7.

**Seitz 2012**

Seitz AE, Olivier KN, Adjemian J, Holland SM, Prevots R. Trends in bronchiectasis among Medicare beneficiaries in the United States, 2000 to 2007. *Chest* 2012;**142**:432-9.

**Serisier 2013**

Serisier DJ. Risks of population antimicrobial resistance associated with chronic macrolide use for inflammatory airway diseases. *Lancet Respiratory Medicine* 2013;**1**:262-74.

**Serisier 2014**

Serisier DJ. The evidence base for non-CF bronchiectasis is finally evolving. *Respirology* 2014;**19**(3):295-7.

**Tunney 2013**

Tunney M. Lung microbiota and bacterial abundance in patients with bronchiectasis when clinically stable and during exacerbation. *American Journal of Respiratory and Critical Care Medicine* 2013;**187**(10):1118-26.

**Twiss 2005**

Twiss J, Metcalfe R, Edwards E, Byrnes C. New Zealand national incidence of bronchiectasis "too high" for a developed country. *Archives of Disease in Childhood* 2005;**90**:737-40.

**Valery 2012**

Valery P, Morris P, Grimwood K, Torzillo P, Byrnes C, Masters IB, et al. Azithromycin for Indigenous children with bronchiectasis: study protocol for a multi-centre randomized controlled trial. *BMC Paediatrics* 2012;**12**:122.

**Weycker 2005**

Weycker D, Edelsberg J, Oster G, Tino G. Prevalence and economic burden of bronchiectasis. *Clinical Pulmonary Medicine* 2005;**12**:205-9.

**Wilson 2013b**

Wilson R, Hansell DM, Loebinger MR. Definition and aetiology of non-CF bronchiectasis. In: Blasi F, Miravitlles M editor(s). The Spectrum of Bronchial Infection. Sheffield: European Respiratory Society, 2013:107-19. [ISBN: 978-1-84984-034-7 ]

**Wu 2014**

Wu Q, Shen W, Cheng H, Zhou X. Long-term macrolides for non-cystic fibrosis bronchiectasis: a systematic review and meta-analysis. *Respirology* 2014;**19**(3):321-9.

## References to other published versions of this review

**Evans 2003**

Evans DJ, Bara AI, Greenstone M. Prolonged antibiotics for purulent bronchiectasis. *Cochrane Database of Systematic Reviews* 2003, Issue 4. [DOI: 10.1002/14651858.CD001392]

**Evans 2007**

Evans DJ, Bara AI, Greenstone M. Prolonged antibiotics for purulent bronchiectasis in children and adults. *Cochrane Database of Systematic Reviews* 2007, Issue 2. [DOI: 10.1002/14651858.CD001392.pub2]

* Indicates the major publication for the study

## CHARACTERISTICS OF STUDIES

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

#### Altenburg 2013

| | |
|---|---|
| Methods | *Country:* the Netherlands<br><br>*Design:* randomised double-blind placebo-controlled trial<br><br>*Objective/aim:* to determine efficacy of macrolide maintenance treatment for adults with non-cystic fibrosis bronchiectasis<br><br>*Study site:* outpatient<br><br>*Methods of analysis:*<br><br>1. Intention-to-treat |
| Participants | *Eligible for study:* 360<br><br>*Randomly assigned:* 89<br><br>*Completed:* intervention 42, control 39<br><br>*Age:* intervention 59.9 ± 12.3, control 64.6 ± 9.1<br><br>*Gender (M/F):* intervention 18/25, control 12/28<br><br>*Bronchiectasis diagnosis criteria:*<br><br>1. 18 years or older and non-CF bronchiectasis diagnosed by plain bronchography or HRCT<br>2. Minimum of 3 lower respiratory tract infections treated with oral or intravenous antibiotics in preceding year with at least 1 sputum culture yielding 1 or more bacterial respiratory pathogens in the year before study entry<br><br>*Recruitment:* outpatient clinics |

**Altenburg 2013** *(Continued)*

| | |
|---|---|
| | *Co-morbidities:* not mentioned<br><br>*Reasons for* participant*exclusion:*<br><br>1. Excluded if patients received prolonged (> 4 weeks) macrolide therapy during previous 3 months, oral or IV course of corticosteroids within 30 days of screening or any antimicrobial treatment for an LRTI in the past 2 weeks<br>2. Known allergy or intolerance to macrolides<br>3. Women with childbearing potential avoiding contraceptives, as well as lactating women<br>4. Patients with liver disease or with elevated transaminase levels<br><br>*Baseline FEV:* intervention 77.7 (24.4% predicted), control 82.7 (27.2% predicted)<br><br>*Baseline exacerbations:* intervention 4 (3-9), control 5.0 (3-12) |
| Interventions | *Setting:* outpatient<br><br>*Duration of intervention:* 52 weeks<br><br>*Type of antibiotic(s):* azithromycin (250 mg daily)<br><br>*Type of control:* placebo |
| Outcomes | *Pre-specified outcomes:*<br><br>Primary:<br><br>1. Number of infectious exacerbations during 12 months of treatment<br><br>Secondary:<br><br>1. Lung function<br>2. Sputum bacteriology<br>3. Inflammatory markers<br>4. Adverse effects<br>5. Symptom scores<br>6. Quality of life<br><br>*Follow-up period:* 90 days after 12 months of treatment |
| Notes | The study was supported by an unrestricted research grant from GlaxoSmithKline. Teva Netherlands supplied the azithromycin tablets used in this study |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Computer-generated allocation sequence was used |
| Allocation concealment (selection bias) | Low risk | Centrally controlled allocation was used |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Identical process for both placebo and intervention. Clearly defined instructions and protocol for participants and personnel |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | 1. Unlikely to have blinding broken<br>2. Clear protocol available to differentiate exacerbation |

**Altenburg 2013** *(Continued)*

| | | |
|---|---|---|
| | | 3. Treating physicians during exacerbation were not investigators and were blinded |
| Incomplete outcome data (attrition bias) All outcomes | Unclear risk | Insufficient information |
| Selective reporting (reporting bias) | Low risk | Reported pre-specified outcomes |
| Other bias | Unclear risk | No other biases identified |

**Barker 2000**

| | |
|---|---|
| Methods | *Country:* United States of America<br><br>*Design:* placebo-controlled double-blind randomised study<br><br>*Objective/aim:* to evaluate microbiological efficacy and safety of inhaled tobramycin for treatment of patients with bronchiectasis and *Pseudomonas aeruginosa*<br><br>*Study site:* homes and clinics<br><br>*Methods of analysis:*<br><br>1. Logistic regression<br>2. Wilcoxon signed rank test (treatment group for assessing airway reactivity) |
| Participants | *Eligible for study:* 78<br><br>*Randomly assigned:* 74<br><br>*Completed:* intervention 31, control 29<br><br>*Age:* intervention 66.6 ± 13, control 63.2 ± 13.5<br><br>*Gender (M/F):* intervention 14/23, placebo 15/22<br><br>*Bronchiectasis diagnosis criteria:* confirmed by high-resolution computer tomography<br><br>*Inclusion criteria:* grossly purulent sputum containing ≥ $10^4$ cfu/g *P. aeruginosa*<br><br>*Recruitment:* 16 sites<br><br>*Co-morbidities:* nil<br><br>*Reasons for participant exclusion:*<br><br>1. Sputum contained fewer than $10^4$ cfu/g *P. aeruginosa*<br>2. Diagnosis of cystic fibrosis, allergic bronchopulmonary aspergillosis, acute pulmonary process requiring medical intervention indicated by new infiltrate on CXR, significant recent haemoptysis or received antibiotics within 2 weeks of screening visit<br><br>*Baseline FEV:* intervention 56.2 (21.2), control 53.3 (22.1)<br><br>*Baseline exacerbations:* intervention 5, control 1 |
| Interventions | *Setting:* hospital clinics<br><br>*Duration of intervention:* 4 weeks |

**Barker 2000** *(Continued)*

| | |
|---|---|
| | *Type of antibiotic(s):* 300 mg nebulised tobramycin<br><br>*Type of control:* matched placebo (1.25 mg quinine sulfate) |
| Outcomes | *Pre-specified outcomes:*<br><br>Primary endpoints:<br><br>1. Change in *P. aeruginosa* density from baseline to 4 weeks<br><br>Secondary endpoints:<br><br>1. Change in *P. aeruginosa* density from baseline value to week 2 and week 6<br>2. Investigators' subjective assessment of change in participant's general medical condition<br>3. Per cent change in FEV1 percent predicted and in FVC per cent predicted from week 0 to week 4<br>4. Safety endpoints including incidence of adverse events, change in serum chemistry and haematological measures and airway reactivity<br><br>*Follow-up:* 6 weeks |
| Notes | However, paper also states that this was an 8-week study that was sponsored by PathoGenesis Corporation, Seattle, WA, USA |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Participants assigned in blocks of 2 parallel groups |
| Allocation concealment (selection bias) | Unclear risk | Insufficient information available to reveal adequacy of allocation concealment |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Both investigators and participants blinded<br><br>Drugs chosen (similar taste, pH)<br><br>Self-administered via same neb |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Both investigators and participants blinded<br><br>Drugs chosen (similar taste, pH)<br><br>Self administered via same neb<br><br>Although double-blinded study with same follow-up protocol, source of serum drug level not mentioned clearly (e.g. from both groups vs from intervention) |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | No information regarding missing data but missing data/withdrawn numbers apparently balanced between the 2 groups |
| Selective reporting (reporting bias) | Unclear risk | Reported pre-specified outcomes but some numerical data not mentioned |
| Other bias | Low risk | No other biases identified |

**Currie 1990**

| | |
|---|---|
| Methods | *Country:* United Kingdom<br><br>*Design:* randomised double-blind placebo-controlled parallel-group study<br><br>*Objective/aim:* to determine the value of prolonged course of higher-dose oral amoxycillin in a double-blind randomised placebo-controlled study<br><br>*Study site:* clinics and homes<br><br>*Methods of analysis:*<br><br>1. Wilcoxon rank sum test, $\chi^2$ test and Kendall's rank correlation<br>2. Group results were expressed as medians (because of the distribution of results) |
| Participants | *Eligible for study:* 69<br><br>*Randomly assigned:* intervention 19, control 19<br><br>*Completed:* intervention 15, control 14<br><br>*Age:* intervention 54 (median), control 51 (median)<br><br>*Gender (M/F):* intervention 9/6, control 10/4<br><br>*Bronchiectasis diagnosis criteria:* daily purulent sputum expectoration for at least 3 months and definitive evidence of bronchiectasis on bronchogram or plain chest radiograph<br><br>*Recruitment:* via hospital admissions and clinics<br><br>*Co-morbidities:* not included<br><br>*Reasons for participant exclusion:* < 16 y/o, pregnant or planning pregnancy, on OCP, on continuous higher-dose oral antibiotics or nebulised antibiotics during previous month, on continuous oral higher-dose amoxycillin (6 g OD) for > 1 month during previous 3 months, major alterations in other therapy in previous 8 weeks, evidence of allergic bronchopulmonary aspergillosis, primary ciliary dyskinesia, CF, sarcoidosis, NIDDM, cardiac failure, low daily sputum volume, haemoptysis, too ill, likely to be poor complier<br><br>*Baseline FEV:* intervention 1.9 (0.9), 54% (median), control 1.6 (0.9), 51% (median)<br><br>*Baseline exacerbations (3 or more in the past year):* intervention 11, control 15 |
| Interventions | *Setting:* outpatient (specialised bronchiectasis clinic in tertiary referral centre)<br><br>*Duration of intervention:* 32 weeks<br><br>*Type of antibiotic(s):* amoxycillin (6 g daily)<br><br>*Type of control:* placebo |
| Outcomes | *Pre-specified outcomes:*<br><br>1. Sputum bacteriology<br>2. Host inflammatory activity<br>3. Extent and severity of lung damage (radiology, pulmonary function tests)<br>4. Screening for adverse effects<br><br>*Follow-up period:* 12 months |
| Notes | Study was supported by the Chest, Heart and Stroke Association |
| ***Risk of bias*** | |

**Currie 1990** *(Continued)*

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Method of randomisation not mentioned |
| Allocation concealment (selection bias) | Unclear risk | Not mentioned |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Double-blinded; packaging of drugs matched and same protocol used for both groups |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Blinding unlikely to be broken<br>Same protocol |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Reported missing/withdrawal data |
| Selective reporting (reporting bias) | Low risk | Reported pre-specified outcomes |
| Other bias | Low risk | No other biases identified |

**Cymbala 2005**

| | |
|---|---|
| Methods | *Country:* United States of America<br>*Design:* open-label, cross-over study<br>*Objective/aim:* to determine whether long-term low-dose azithromycin would decrease the number of exacerbations and improve pulmonary function<br>*Study site:* clinics and homes<br>*Methods of analysis:*<br>1. Mann-Whitney rank sum test to compare number of exacerbations between study phases<br>2. Bonferroni *t*-test<br>3. Paired *t*-test |
| Participants | *Eligible for study:* 12<br>*Randomly assigned:* intervention 9 receiving azithromycin first, then followed by 1 month washout period, then normal treatment regimen<br>Control 3 started with normal treatment regimen first, then received azithromycin<br>*Completed:* intervention 8, control 3<br>*Age:* 70.8 ± 9.7 years<br>*Gender:* M/F 5/6<br>*Bronchiectasis diagnosis criteria:* high-resolution CT scan demonstrating airways larger than accompanying vessels |

**Cymbala 2005** *(Continued)*

| | |
|---|---|
| | *Recruitment:* hospital (teaching, rural), regional health centres<br><br>*Co-morbidities:* not mentioned<br><br>*Reasons for participant exclusion:*<br><br>1. < 18 y/o<br>2. Serious intolerance, allergy or sensitivity to azithromycin and macrolides<br>3. Deemed unable to follow instructions<br><br>*Baseline FEV:* 48.5 ± 18.9<br><br>*Baseline exacerbations:* not mentioned |
| Interventions | *Setting:* homes<br><br>*Duration of intervention:* 6 months<br><br>*Type of antibiotic(s): a*zithromycin (500 mg twice weekly*)*<br><br>*Type of control:* usual treatment regimen |
| Outcomes | *Pre-specified outcomes:* not mentioned<br><br>*Follow-up period:* 13 months for azithromycin group, 12 months for regular regimen group |
| Notes | First year of study was unfunded, although investigators were fortunate enough to receive donations of study medication from local sales representatives. During second year of study, a small unrestricted stipend was received from manufacturer of azithromycin that covered participant incidentals (i.e. travel expenses, extra pulmonary function tests) only |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Study authors reported to use randomisation schedule via random numbers table |
| Allocation concealment (selection bias) | High risk | Cross-over design without blinding |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | No blinding as per study authors (no matching placebo)<br><br>No placebo used<br><br>Phone calls made to increase compliance during intervention |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | No blinding as per study authors<br><br>No matching placebo and not clear regarding control arm and its execution |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Lack of pre-specified outcomes<br><br>Diary cards not reported (e.g. QOL mentioned but no data available) |
| Selective reporting (reporting bias) | High risk | Reported only sputum volume and pulmonary function<br><br>Pre-specified outcomes not mentioned<br><br>Lack of report regarding exacerbation and management of exacerbation |

**Cymbala 2005** *(Continued)*

| | | |
|---|---|---|
| Other bias | Unclear risk | Unclear regarding other biases due to lack of published protocol |

**De Diego 2013**

| | |
|---|---|
| Methods | *Country:* Spain<br><br>*Design:* randomised open-label prospective study<br><br>*Objective/aim:* to explore the effect of long-term therapy with azithromycin with regards to airway oxidative stress markers in exhaled breath condensate (EBC) of adult patients with stable non-cystic fibrosis (CF) bronchiectasis<br><br>*Study site:* homes<br><br>*Methods of analysis:*<br><br>1. Wilcoxon test for quantitative variables<br>2. Chi$^2$ test for qualitative variables |
| Participants | *Eligible for study:* 40<br><br>*Randomly assigned:* 36<br><br>*Completed:* intervention 16, control 14<br><br>*Age:* intervention 57 ± 11, control 61 ± 12<br><br>*Gender (M/F):* intervention 7/9, control 7/7<br><br>*Bronchiectasis diagnosis criteria:* clinical data and high-resolution computed tomography lung scan<br><br>*Recruitment:* outpatient clinics<br><br>*Co-morbidities:* not mentioned<br><br>*Reasons for participant exclusion:*<br><br>1. Patients with bronchiectasis secondary to CF<br>2. Pulmonary surgical processes<br>3. Immunodeficiency secondary to human immunodeficiency virus, malignancy, common variable immunodeficiency<br>4. Emphysema<br>5. Allergic bronchopulmonary aspergillosis or diffuse interstitial pulmonary disease<br>6. Known intolerance to macrolides or severe liver disease<br><br>*Baseline FEV:* intervention 1.48 (0.8), 56% (6), control 1.63 (0.7), 68% (7)<br><br>*Baseline exacerbations:* intervention 3.5 (1.8)/last year, control 3.1 (1.3)/last year |
| Interventions | *Setting:* outpatient setting<br><br>*Duration of intervention:* 3 months<br><br>*Type of antibiotic(s):* azithromycin (oral 250 mg 3 times a week)<br><br>*Type of control:* not mentioned |
| Outcomes | *Pre-specified outcomes:*<br><br>Primary outcomes: |

**De Diego 2013** *(Continued)*

| | |
|---|---|
| | 1. Changes in nitric oxide, 8-isoprostane, pH, nitrites and nitrates in exhaled breath condensate<br><br>Secondary outcomes:<br><br>1. Changes in exacerbation rates, dyspnoea (Borg scale), sputum volume (mL), sputum colour (15-point scale), bacterial infection, health-related quality of life (St George Respiratory Questionnaire), lung function and radiological extension<br><br>*Follow-up period:* not mentioned |
| Notes | This work was supported by a grant from Fundacion Valenciana de Neumologia |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Method of randomisation not mentioned |
| Allocation concealment (selection bias) | Unclear risk | No further information available |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Open label without a placebo, no further information available |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | Open label intervention and no information on the blinding of an outcome assessment |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | |
| Selective reporting (reporting bias) | Low risk | Reported pre-specified outcomes |
| Other bias | Unclear risk | No other biases identified |

**Drobnic 2005**

| | |
|---|---|
| Methods | *Country:* Spain<br><br>*Design:* double-blind placebo-controlled cross-over trial<br><br>*Objective/aim:* to determine whether direct aerosol delivery of tobramycin to lower airways may control infection and produce only low systemic toxicity<br><br>*Study site:* homes and clinics<br><br>*Methods of analysis:*<br><br>1. Student's *t*-test<br>2. Mann-Whitney U test<br>3. $\chi^2$test<br>4. Fisher's exact test |

**Drobnic 2005** *(Continued)*

| | |
|---|---|
| Participants | *Eligible for study:* 60<br><br>*Randomly assigned:* intervention 30, control 30<br><br>*Completed:* intervention 20, control 20<br><br>*Age:* intervention 64.5 (38-75), control 64.5 (38-75)<br><br>*Gender:* not mentioned<br><br>*Bronchiectasis diagnosis criteria:* diagnosed with bronchiectasis confirmed by HRCT at a tertiary referral centre<br><br>*Recruitment:* via clinics, hospital admissions<br><br>*Co-morbidities:* not mentioned<br><br>*Reasons for participant exclusion:*<br><br>1. Tobramycin hypersensitivity<br>2. *Pseudomonas aeruginosa* in sputum resistant to tobramycin<br>3. Auditory threshold in either ear > 20 dB at frequencies between 500 and 8000 Hz<br>4. Serum creatinine ≥ 1.5 mg/dL<br>5. Cystic fibrosis<br><br>*Baseline* FEV1 (predicted): 51.78 ± 16.45<br><br>*Baseline exacerbation:* not mentioned but defined exacerbation |
| Interventions | *Setting:* outpatient<br><br>*Duration of intervention:* 6 months<br><br>*Type of antibiotic(s):* tobramycin (nebulised) 100 mg/2 mL was diluted in NaCl 0.9% to make 8 mL<br><br>*Type of control:* nebulised 8 mL of 0.9% NaCl |
| Outcomes | *Pre-specified outcomes:* nil mentioned<br><br>*Follow-up period:* 12 months for those who commenced with placebo; 13 months for those who commenced with tobramycin (allowing 1 month washout period) |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Method of randomisation not mentioned |
| Allocation concealment (selection bias) | Unclear risk | Insufficient information available to determine adequacy of allocation concealment |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Double-blind placebo-controlled cross-over study; although trial was double-blinded, apparent that participants receiving placebo used only 1 type of agent (NaCl). However, 2 agents mixed for participants given intervention (i.e. drug + NaCl) |
| Blinding of outcome assessment (detection bias) | Low risk | Double-blind placebo-controlled cross-over study |

**Drobnic 2005** *(Continued)*
All outcomes

| | | |
|---|---|---|
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Withdrawal and attrition described according to protocol<br>3 participants with adverse effects excluded from analysis<br>1. Unclear whether 10 with missing/incomplete data affected results/analysis<br>(10 missing/incomplete vs final 20 participants) |
| Selective reporting (reporting bias) | High risk | 1. No data on PA density except for a figure (PA density one of the key areas of interest for the trial)<br>2. Report on toxicity, which is one of the key areas, not clear<br>3. 3 participants with adverse effects excluded from the analysis<br>4. Supplementary use of oral antibiotics not reported |
| Other bias | Low risk | No other biases identified |

**Koh 1997**

| | |
|---|---|
| Methods | *Country:* Korea<br>*Design:* randomised double-blind parallel placebo-controlled study<br>*Objective/aim:* to see whether roxithromycin could reduce the degree of airway responsiveness in bronchiectasis<br>*Study site:* clinics<br>*Methods of analysis:*<br>1. Paired *t*-test<br>2. Wilcoxon signed rank test<br>3. ANOVA to analyse variance |
| Participants | *Eligible for study:* 27<br>*Randomly assigned:* 25<br>*Completed:* intervention 13, control 12<br>*Age:* intervention 13.3 ± 2.5, control 12.9 ± 2.6<br>*Gender(M/F):* intervention 7/6, control 7/5<br>*Bronchiectasis diagnosis criteria:* based on clinical features and confirmed by CT with bronchography when necessary<br>*Recruitment:* outpatient clinics<br>*Co-morbidities:* atopy, asthma (treated with prn beta-agonists)<br>*Reasons for participant exclusion:*<br>1. Could not perform PFT<br>2. PC20 < 25 mg/mL<br>3. Clinically unstable bronchiectasis<br>4. Antibioic use within 1 month of study<br>5. Upper respiratory tract infection within 4 weeks before study |

**Koh 1997** *(Continued)*

| | |
|---|---|
| | 6. Failed to attain maximal response plateau both before and after treatment<br>7. Normal or reduced airway responsiveness<br>8. Cystic fibrosis, humoral immune deficiency, bronchopulmonary aspergillosis<br><br>*Baseline FEV:*<br><br>1. Intervention FEV1 max: 42.2 ± 8.3, FEV %: 83 ± 6<br>2. Control FEV1 max 39.6 ± 9.3, FEV %: 84 ± 7<br><br>*Baseline exacerbations:* not mentioned |
| Interventions | *Setting:* outpatient<br><br>*Duration of intervention:* 12 weeks<br><br>*Type of antibiotic(s):* roxithromycin (4 mg/kg BD)<br><br>*Type of control:* placebo (BD) |
| Outcomes | *Pre-specified outcomes:*<br><br>1. Changes in FEV1<br>2. Sputum purulence<br>3. Sputum leucocyte scores<br><br>*Follow-up period:* 12 weeks |
| Notes | Study was supported by grant No. 2- 94-112 from the Seoul National University Hospital Research Fund |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | No further information available |
| Allocation concealment (selection bias) | Unclear risk | No further information available although stated to be double-blinded |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | No further information available |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Assessors not involved in dividing participants into 2 separate groups |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | 2 patients had exacerbations and given antibiotics. Graphs show reduced number of participants at 12 week assessment. |
| Selective reporting (reporting bias) | Low risk | Reported pre-specified outcomes |
| Other bias | Low risk | No other biases identified |

**Liu 2012**

| | |
|---|---|
| Methods | *Country:* China<br>*Design:* randomised controlled trial<br>*Objective/aim:*<br>to investigate impact of treatment with low-dose roxithromycin on clinical symptoms and CT scores in patients with stable bronchiectasis<br>*Study site:* not mentioned<br>*Methods of analysis:* not mentioned |
| Participants | *Eligible for study:* 50<br>*Randomly assigned:* not mentioned<br>*Completed:* intervention 24, control 22<br>*Age:* not mentioned<br>*Gender (M/F):* not mentioned<br>*Bronchiectasis diagnosis criteria:* not mentioned<br>*Recruitment:* not mentioned<br>*Co-morbidities:* not mentioned<br>*Reasons for* participant*exclusion:* not mentioned<br>*Baseline FEV:* not mentioned<br>*Baseline exacerbations:* not mentioned |
| Interventions | *Setting:* not mentioned<br>*Duration of intervention:* 6 months<br>*Type of antibiotic(s):* oral roxithromycin 150 mg daily<br>*Type of control:* ambroxol hydrochloride tablet 90 mg 3 times a day |
| Outcomes | *Pre-specified outcomes:*<br>1. Quality of life (SGRQ)<br>2. Degree of dyspnoea (British MRC scale)<br>3. Score for CT evaluation of thorax<br>*Follow-up period:* not mentioned |
| Notes | Abstract and data from Wu 2014 (long-term macrolides for non-cystic fibrosis bronchiectasis: a systematic review and meta-analysis) |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Based on the abstract only, no specific details available |

**Liu 2012** *(Continued)*

| | | |
|---|---|---|
| Allocation concealment (selection bias) | Unclear risk | Based on the abstract, no specific details available |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Based on the abstract, no specific details available |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Based on the abstract, no specific details available |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Based on the abstract, no specific details available |
| Selective reporting (reporting bias) | Unclear risk | Based on the abstract, no specific details available |
| Other bias | Unclear risk | Based on the abstract, no specific details available |

**MRC 1957**

| | |
|---|---|
| Methods | *Country:* United Kingdom<br>*Design:* randomised double-blind placebo-controlled parallel-group study (with 3 arms)<br>*Objective/aim:* not mentioned<br>*Study site:* not mentioned<br>*Methods of analysis:* not mentioned |
| Participants | *Eligible for study:* 122<br>*Randomised:* 36 (penicillin), 44 (oxytetracycline), 40 (lactose)<br>*Completed:* 36 (penicillin), 40 (oxytetracycline), 36 (lactose)<br>*Age:* penicillin 34.3, oxytetracycline 32.3, control 32.6.<br>*Gender (M/F):* 76/56<br>*Bronchiectasis diagnosis criteria:* symptoms for 3 months, frank bronchiectasis affecting at least 2 lung segments on bronchogram<br>*Recruitment:* outpatient clinics<br>*Co-morbidities:* adjusted but no detail mentioned<br>*Reasons for participant exclusion:* tuberculosis, patients receiving antibiotics or sulphonamides in preceding 4 weeks<br>*Baseline FEV:* not mentioned<br>*Baseline exacerbations:* not mentioned |
| Interventions | *Setting:* outpatient<br>*Duration of intervention:* 52 weeks |

**MRC 1957** *(Continued)*

| | |
|---|---|
| | *Type of antibiotic(s):* oral penicillin or oral oxytetracycline (4 g/wk)<br><br>*Type of control:* oral lactose |
| Outcomes | *Pre-specified outcomes:*<br><br>1. 24-Hour specimen of sputum<br>2. Observation on severity of cough, dyspnoea, haemoptysis, disability<br>3. Final assessment: clubbing, weight, general assessment of progress, participant's own assessment of response to treatment<br><br>*Follow-up period:* 52 weeks |
| Notes | Report by a subcommittee of antibiotics clinical trials (non-tuberculosis), committee of Medical Research Council |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Method not mentioned |
| Allocation concealment (selection bias) | Low risk | Allocated randomly according to centrally held list |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Same capsules (packaging) used and issued in bottles to participants |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Centrally controlled list of cohort; same protocol for assessments, visits and measurements |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Missing data not explained/addressed |
| Selective reporting (reporting bias) | High risk | The primary and secondary outcomes to the trial were not clearly defined and reported |
| Other bias | Low risk | No other biases identified |

**Murray 2011**

| | |
|---|---|
| Methods | *Country:* Scotland<br><br>*Design:* randomised controlled trial<br><br>*Objective/aim:*<br><br>To assess the efficacy of continuous nebulised gentamicin over 1 year in non-cystic fibrosis bronchiectasis<br><br>To assess whether treatment effects are sustained over a 3 month treatment-free period<br><br>*Study site:* bronchiectasis clinic |

**Murray 2011** *(Continued)*

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|---|---|
| | *Methods of analysis:*<br><br>1. Mann-Whitney U test for unpaired numerical data<br>2. Wilcoxon for paired numerical data<br>3. Fisher's exact test to compare categorical variables |
| Participants | *Eligible for study:* 65<br><br>*Randomly assigned:* intervention 32, control 33<br><br>*Completed:* intervention 27, control 30<br><br>*Age:* intervention 58 (53-67), control 64 (55.7-69)<br><br>*Gender (M/F):* intervention 9/18, control 15/15<br><br>*Bronchiectasis diagnosis criteria:* clinically significant and radiologically proved bronchiectasis (HRCT)<br><br>*Recruitment:* regional bronchiectasis services<br><br>*Co-morbidities:* not mentioned<br><br>*Reasons for participant exclusion:*<br><br>Current smokers, cystic fibrosis, active pulmonary mycobacteria, active sarcoidosis; active allergic bronchopulmonary aspergillosis; chronic obstructive pulmonary disease; poorly controlled asthma (> 20% diurnal variation in peak expiratory flows despite treatment); creatinine clearance < 30 mL/min; vestibular instability; previously documented intolerance to aminoglycosides (ototoxicity or nephrotoxicity)<br><br>*Baseline FEV:* intervention 1.8 (1.34-2.31), control 1.61 (1.22-3.41)<br><br>*Baseline exacerbations:* not mentioned |
| Interventions | *Setting:* bronchiectasis clinics<br><br>*Duration of intervention:* 12 months<br><br>*Type of antibiotic(s):* nebulised gentamicin 80 mg BD<br><br>*Type of control:* nebulised saline BD |
| Outcomes | *Pre-specified outcomes:*<br><br>Primary:<br><br>1. ≥ 1 log unit reduction in sputum bacterial density<br><br>Secondary:<br><br>1. Qualitative sputum bacteriology<br>2. Emergence of gentamicin-resistant *Pseudomonas* strains<br>3. Sputum myeloperoxidase and free neutrophil elastase<br>4. 24-Hour sputum volume<br>5. Sputum purulence<br>6. FEV1, FVC, FEF, mid-expiratory phase<br>7. Exercise capacity<br>8. Leicesters Cough Questionnaire<br>9. St George Respiratory Questionnaire<br>10.Exacerbation<br>11.Adverse effects |

**Murray 2011** *(Continued)*

| | |
|---|---|
| | *Follow-up period:* 3 month treatment-free period (15 months) |
| Notes | Author disclosure: M.P.M. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.R.W.G. was a consultant for Transave Corp ($5,001–$10,000) and was on the Board or Advisory Board for Bayer (up to $1,000). He received grant support from Transave Corp and the Cystic Fibrosis Trust (more than $100,001). C.J.D. was a consultant for Transave Corp ($10,001–$50,000). A.J.S. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. T.S.W. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.D.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. A.P.G. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. C.H. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. A.T.H. was on the Board or Advisory Board for Bayer ($1,001–$5,000) and received lecture fees from GlaxoSmithKline (up to $1,000) |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Unclear how random sequence generation happened |
| Allocation concealment (selection bias) | Unclear risk | Methods not described; randomisation done by study pharmacist |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Participants unmasked because of funding limitations |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Although all study investigators were masked and bronchiectasis specialist nurse was the contact person, participants were not blinded<br><br>Unclear who was responsible for regular assessments and therefore unable to determine likelihood of breaking blinding |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Clear explanation regarding withdrawal from study and missing data<br><br>Reasonable extent of missing data |
| Selective reporting (reporting bias) | Low risk | Reported pre-specified outcomes and addressed missing data |
| Other bias | Low risk | No other biases identified |

**Orriols 1999**

| | |
|---|---|
| Methods | *Country:* Spain<br><br>*Design:* prospective randomised non-blinded pilot<br><br>*Objective/aim:* to investigate long-term effectiveness and safety of inhaled antibiotic treatment in non-cystic fibrosis patients with bronchiectasis and chronic infection by *Pseudomonas aeruginosa*, after standard endovenous and oral therapy for long-term control of infection<br><br>*Study site:* university centres<br><br>*Methods of analysis:* |

**Orriols 1999** *(Continued)*

1. Fisher's exact test
2. Mann-Whitney U test or Wilcoxon test

| | |
|---|---|
| Participants | *Eligible for study:* 17<br><br>*Randomly assigned:* intervention 8, control 9<br><br>*Completed:* intervention 7, control 8<br><br>*Age:* intervention 62.0 ± 8.5, control 61.4 ± 10.3<br><br>*Gender (M/F):* intervention 6/1, control 4/4<br><br>*Bronchiectasis diagnosis criteria:* bronchography, thoracic computed axial tomography or both<br><br>*Recruitment:* not mentioned<br><br>*Co-morbidities:* not mentioned<br><br>*Reasons for participant exclusion:*<br><br>1. Beta-lactam or aminoglycoside sensitivity<br>2. Bacterial resistance on antigram<br>3. Kidney failure<br><br>*Baseline FEV:* intervention FEV1: 1037 mL (386), control FEV1: 866 (225)<br><br>*Baseline exacerbations:* not mentioned |
| Interventions | *Setting:* outpatient<br><br>*Duration of intervention:* 12 months<br><br>*Type of antibiotic(s):* inhalation tobramycin and ceftazidime BD<br><br>*Type of control:* symptomatic treatment |
| Outcomes | *Pre-specified outcomes:*<br><br>1. Number of hospital admissions<br>2. Number of hospital days<br>3. Oral antibiotic use<br>4. FVC, FEV1<br>5. $PaO_2$, $PaCO_2$<br>6. Drug toxicity<br>7. Bacterial resistance<br><br>*Follow-up period:* 12 months |
| Notes | Antibiotic treatment changed to piperacillin and amikacin if clinical impairment and bacterial resistance |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Randomisation mentioned; however, methods not described |
| Allocation concealment (selection bias) | Unclear risk | Not reported |

**Orriols 1999** *(Continued)*

| | | |
|---|---|---|
| Blinding of participants and personnel (performance bias) All outcomes | High risk | Study reported to be non-blinded |
| Blinding of outcome assessment (detection bias) All outcomes | High risk | Study reported to be non-blinded |
| Incomplete outcome data (attrition bias) All outcomes | Unclear risk | Insufficient information to permit a judgement |
| Selective reporting (reporting bias) | Unclear risk | Insufficient information to permit a judgement |
| Other bias | Unclear risk | Insufficient information to permit a judgement |

**Serisier 2013a BLESS**

| | |
|---|---|
| Methods | |
| Participants | *Eligible for study:* 117<br><br>*Randomly assigned:* intervention 59, control 58<br><br>*Completed:* intervention 54, control 53<br><br>*Age:* intervention 61.1 ± 10.5, control 63.5 ± 9.5<br><br>*Gender (M/F):* intervention 21/38, control 25/33<br><br>*Bronchiectasis diagnosis criteria:* bronchiectasis documented by HRCT<br><br>*Recruitment:* regional adult cystic fibrosis centre, other respiratory centres and 2 regional public radio advertisement campaigns<br><br>*Co-morbidities:*<br><br>*Reasons for participant exclusion:*<br><br>1. Cystic fibrosis<br>2. Current mycobacterial disease or bronchopulmonary aspergillosis<br>3. Any reversible cause for exacerbation<br>4. Maintenance oral antibiotic prophylaxis<br>5. Prior macrolide use except short term<br>6. Changes to medications in preceding 4 weeks<br>7. Cigarette smoking within 6 months<br>8. Medications or co-morbidities with potential for important interactions with erythromycin<br><br>*Baseline FEV:* intervention: FEV1 (pre-BD) 1.82 (0.65); %pred 66.9 (17.2); FEV1 (post-BD) 1.93 (0.65); %pred 70.2 (17.2); control: FEV1 (pre-BD) 1.83 (0.77); %pred 70.1 (20.3); FEV1 (post-BD) 1.93 (0.79); %pred 73.6 (20.6)<br><br>*Baseline exacerbations* (> 5/y): intervention: 22 (37.3%); control: 20 (34.5%) |
| Interventions | |

**Serisier 2013a BLESS** *(Continued)*

| | |
|---|---|
| Outcomes | |
| Notes | |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Computer-generated randomisation sequence |
| Allocation concealment (selection bias) | Unclear risk | Central allocation; methods of allocation not described |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Unlikely to have blinding broken; identical shape, appearance and taste of erythromycin and placebo tablets |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Protocol created prospectively and all scripts provided centrally |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Incomplete data explained including missing data |
| Selective reporting (reporting bias) | Low risk | Addressed all pre-specified endpoints from both primary and secondary outcomes |
| Other bias | Low risk | No other biases identified |

**Serisier 2013b ORBIT**

| | |
|---|---|
| Methods | *Country:* Australia, New Zealand<br>*Design:* Phase II multi-centred randomised double-blind placebo-controlled trial<br>*Objective/aim:* to evaluate microbial efficacy of 28 day inhaled dual release ciprofloxacin for inhalation<br>*Study site:* not mentioned<br>*Methods of analysis:*<br>1. Modified intention-to-treat<br>2. Kaplan-Meier survival analysis |
| Participants | *Eligible for study:* 42<br>*Randomised:* intervention 20, control 22<br>*Completed:* intervention 18, control 19<br>*Age:* intervention 70 ± 5.6, control 59.5 ± 13.2<br>*Gender (M/F):* intervention 10/10, control 9/13<br>*Bronchiectasis diagnosis criteria:* clinically stable adults with CT scan proven bronchiectasis |

**Serisier 2013b ORBIT** *(Continued)*

*Recruitment:* not mentioned.

*Co-morbidities:* IHD, hypertension, diabetes , cerebrovascular disease

*Reasons for participant exclusion:*

1. Known local or systemic hypersensitivity to fluoroquinolone or quinolone antibiotics

2. Pulmonary exacerbation during screening phase defined as requiring treatment with inhaled, oral or IV antibiotics before first dose of study drugs

3. Diagnosis of CF

4. Diagnosis of allergic bronchopulmonary aspergillosis

5. Received any IV, oral or inhaled antipseudomonal antibiotic within 28 days before visit 1

6. Used tizanidine within 28 days before visit 1

7. Initiated supplemental oxygen within 28 days before visit 1

8. Used any intravenous or intramuscular corticosteroid or had used oral corticosteroid > 10 mg/d or > 20 mg every other day within 28 days of visit 1

9. Changes in treatment regimen or initiation of treatment with any of the following medications within 28 days before visit 1

a. Azithromycin

b. Hypertonic saline

c. Mucolytics

d. Bronchodilator medications

e. Oral corticosteroid

10. Changes in physiotherapy technique or schedule within 28 days before visit 1

11. History of solid organ (e.g. lung) transplantation

12. History of non-tuberculosis mycobacteria requiring treatment within 12 months before visit 1

13. Serum creatinine levels ≥ 1.5 × upper limit of normal (ULN) at screening visit

14. Serum transaminase levels > 3 × ULN at screening visit

15. Febrile illness within 1 week before visit 1

16. Massive haemoptysis (≥ 300 mL or requiring blood transfusion) within 6 months before visit 1

17. Used any over-the-counter product, herbal product, diet aid, hormone supplement, etc., within 7 days before dosing unless approved by both investigator and sponsor

18. Received investigational drug or device within 28 days before visit 1

19. Any serious or active medical or psychiatric illness, which in the opinion of the investigator, would have interfered with participant's treatment assessment, or compliance with protocol

20. History or suspicion of unreliability, poor co-operation or non-compliance with medical treatment

21. Unable to use nebuliser

22. Unable to understand instruction for use of study drugs or to complete QoL questionnaire at visit 1

23. Previously enrolled in this study

**Serisier 2013b ORBIT** *(Continued)*

| | |
|---|---|
| | 24. Pregnant, planned to become pregnant during study, were nursing mothers or were unwilling to use an acceptable method of contraception for duration of the study<br><br>*Baseline FEV:* intervention 1.57 (0.77), control 1.47 (0.53)<br><br>*Baseline exacerbations:* Both groups were stratified by 2-3 or ≥ 4 exacerbations |
| Interventions | *Setting:* outpatient clinic<br><br>*Duration of intervention:* 24 weeks<br><br>*Type of antibiotic(s):* dual release ciprofloxacin for inhalation (liposomal ciprofloxacin (150 mg in 3 mL) and free ciprofloxacin (60 mg in 3 mL))<br><br>*Type of control:* placebo/matched placebo: control liposomes (15 mg in 3 mL) and normal saline (0.9% in 3 mL) |
| Outcomes | *Pre-specified outcomes:*<br><br>Primary endpoints:<br><br>1. Mean change in sputum *P. aeruginosa* bacterial density<br><br>Secondary endpoints:<br><br>1. Safety<br>2. Time to first pulmonary exacerbation<br>3. FEV<br>4. 6MWT<br>5. SGRQ<br>6. Tolerability<br><br>*Follow-up period:* 24 weeks |
| Notes | This study was funded by Aradigm Corp. |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Stratified by number of exacerbations as per protocol |
| Allocation concealment (selection bias) | Unclear risk | Stratified by number of exacerbations as per protocol |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Matched placebo |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Did not state |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Intention-to-treat analysis |

**Serisier 2013b ORBIT** *(Continued)*

| | | |
|---|---|---|
| Selective reporting (reporting bias) | High risk | SGRQ not reported<br>6MWT not reported |
| Other bias | High risk | Number of participants required met<br>Single participant randomly assigned but not culturing *P. aeruginosa*<br>Limitations stated<br>Moderate sample size: type 1 error<br>Time to exacerbation only conventionally statistically significant<br>Age difference between groups |

**Tsang 1999**

| | |
|---|---|
| Methods | *Country:* Hong Kong<br>*Design:* double-blind randomised placebo-controlled study<br>*Objective/aim:* to evaluate effect of low-dose erythromycin on sputum volume and lung function indices in steady state bronchiectasis<br>*Study site:* outpatient<br>*Methods of analysis:*<br>1. ANOVA<br>2. Paired Student's *t*-test<br>3. Wilcoxon rank sum test |
| Participants | *Eligible for study:* 24<br>*Randomly assigned:* intervention 14, control 10<br>*Completed:* intervention 11, control 10<br>*Age:* intervention 50 ± 15, control 59 ± 16<br>*Gender (M/F):* intervention 3/8, control 2/8<br>*Bronchiectasis diagnosis criteria:* Individuals with proven bronchiectasis, diagnosis by high-resolution computed tomography (HRCT). Origin of bronchiectasis was determined after history taking, examination and investigations including nasal respiratory ciliary beat frequency assessment<br>*Recruitment:* outpatient clinics of University of Hong Kong<br>*Co-morbidities:*<br>1. Thrombocytopaenia<br>2. Bone marrow transplant<br>3. Biliary calculi<br>4. Renal transplant<br>5. Hypertension<br>6. Hepatitis B<br>*Reasons for participant exclusion:*<br>1. Unreliable clinic attendance |

**Tsang 1999** *(Continued)*

| | |
|---|---|
| | 2. Adverse reaction to macrolides<br>3. Females who were lactating<br><br>*Baseline FEV:* intervention 1.06 (0.77 ± 1.47), control 0.99 (0.71 ± 1.39)<br><br>*Baseline exacerbations* (number of exacerbation in previous 12 months): intervention 2.1 ± 1.68, control 2.91 ± 0.2 |
| Interventions | *Setting:* outpatient<br><br>*Duration of intervention:* 8 weeks<br><br>*Type of antibiotic(s):* erythromycin (500 mg BD)<br><br>*Type of control:* placebo (BD) |
| Outcomes | *Pre-specified outcomes:*<br><br>1. Clinical and laboratory assessment<br>2. Sputum collection and assessment of physical character<br>3. Sputum microbiology<br>4. Measurement of sputum pro-inflammatory cytokines and LTB4 concentrations<br><br>*Follow-up period:* 12 months |
| Notes | Study supported by CRCG grant from University of Hong Kong |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Not specified |
| Allocation concealment (selection bias) | Unclear risk | Not specified |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Double-blind but not specified |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Double-blind but not specified |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Primary and secondary endpoints not specified directly but do address aims |
| Selective reporting (reporting bias) | Low risk | Primary and secondary endpoints not specified directly but do address aims; however sputum volume not reported |
| Other bias | Low risk | Inhaled steroids and bronchodilators will change results of PFT; no other biases identified |

**Valery 2013**

| | |
|---|---|
| Methods | *Country:* Australia and New Zealand<br><br>*Design*: multi-centre double-blind randomised parallel-group placebo-controlled trial<br><br>*Objective*: Among indigenous children with bronchiectasis, can long-term (12-24 months) azithromycin treatment reduce the frequency of pulmonary exacerbations compared with placebo?<br><br>Secondary questions: Does long-term azithromycin treatment reduce or lengthen hospitalised pulmonary exacerbations and severity of pulmonary exacerbations, improve growth, decrease school absenteeism, improve respiratory symptoms, improve pulmonary function as measured by FEV1 and sputum characteristics?<br><br>Is azithromycin associated with any serious adverse events or with increased antibiotic resistance in respiratory bacterial pathogens in the nasopharynx?<br><br>*Methods of analysis:*<br><br>1. Intention-to-treat<br>2. Cox proportional hazards regression, Kaplan-Meier estimates<br>3. Chi$^2$ tests<br>4. Fisher's exact test |
| Participants | *Eligible for study:* 92<br><br>*Randomly assigned:* intervention 45, control 44<br><br>*Completed:* intervention 40, control 35<br><br>*Age:* intervention 3.99 ± 2.14, control 4.22 ± 2.30<br><br>*Gender:* intervention M/F 26/19, control M/F 21/23<br><br>*Bronchiectasis diagnosis criteria:* with confirmed HRCT scan diagnosis of bronchiectasis or clinical diagnosis of bronchiectasis (probable bronchiectasis, but no HRCT scan available) after clinical review and other appropriate investigations have been completed (including full blood count, immune function test, sweat test, CXR and, when indicated, contrast videofluoroscopy<br><br>*Recruitment:* outpatient<br><br>*Co-morbidities:*<br><br>*Reasons for participant exclusion:*<br><br>1. Children receiving chemotherapy<br>2. Immunosuppressive treatment<br>3. Long-term antibiotic use<br>4. Identified underlying cause of chronic suppuratives lung disease or bronchiectasis (e.g. CF, primary immunodeficiency, ciliary dyskinesia, primary aspiration)<br>5. Other disorders (e.g. renal or hepatic failure, diabetes, central nervous system or neuromuscular disorder, congenital cardiac abnormality)<br>6. History of macrolide hypersensitivity<br><br>*Baseline FEV:* not mentioned<br><br>*Baseline exacerbations:* not mentioned |
| Interventions | *Setting:* outpatient<br><br>*Duration of intervention:* 12 to 24 months<br><br>*Type of antibiotic(s):* azithromycin (oral 30 mg/kg once a week) |

**Valery 2013** *(Continued)*

| | |
|---|---|
| | *Type of control:* placebo |
| Outcomes | *Pre-specified outcomes:*<br><br>Primary outcome<br><br>1. Pulmonary exacerbation rate as established by medical record review (number of episodes per child/ over study period)<br><br>Secondary outcomes<br><br>1. Time to first pulmonary exacerbation<br>2. Duration of exacerbation episode (discharge date minus admission date plus 1 day)<br>3. Severity (admission to hospital, oxygen supplementation)<br>4. Weight-for-age Z-scores (Z-score at last study clinic minus its value at baseline)<br>5. Respiratory signs and symptoms (assessed by study personnel on history and physical examination)<br>6. Sputum characteristics (using a validated sputum colour chart)<br>7. Bronkotest (Bronkotest, Middlesex, UK)<br>8. School absenteeism<br>9. FEV1 percentage in those 6 years of age and older<br>10. Serious adverse events, antibiotic resistance in bacterial pathogens cultured from deep nasal swabs<br><br>*Follow-up period:* 24 months from study entry |
| Notes | This work is supported by the National Health and Medical Research Council (NHMRC) of Australia (project grant numbers 389837 (clinical component) and 545223 (microbiology component)), the Telstra Foundation (seeding grant – Telstra Community Development Grant, 2004), the Health Research Council of New Zealand (grant no. 08/158) and the Auckland Medical Research Foundation (grant no. 81542). P.C. Valery is supported by an Australian Research Council Future Fellowship (No. 100100511). A.C. is supported by NHMRC fellowship 545216. This work is produced as part of the In-Kind activities of the Lowitja Institute incorporating the Cooperative Research Centre for Aboriginal and Torres Strait Islander Health |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Used computer-generated, permuted-block design |
| Allocation concealment (selection bias) | Low risk | Used sequentially numbered, double-sealed, opaque envelopes |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Used identical packaging and placebo that was the same in appearance, taste and smell to azithromycin |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | Participants, families, health professionals and study personnel unaware of treatment assignment until data analysis was completed |
| Incomplete outcome data (attrition bias)<br>All outcomes | Low risk | Clear explanation regarding missing data and reason for early termination of study |
| Selective reporting (reporting bias) | Unclear risk | Reported pre-specified outcomes |

**Valery 2013** *(Continued)*

| | | |
|---|---|---|
| Other bias | Low risk | No other bias identified |

**Wilson 2013a**

| | |
|---|---|
| Methods | *Country:* Australia, Germany, Spain, Sweden, UK, USA<br><br>*Design:* multi-centre randomised placebo-controlled double-blind study<br><br>*Objective/aim:* to assess safety and efficacy of ciprofloxacin DPI treatment for 28 days, with 56 days of follow-up in individuals with non-CF bronchiectasis, by examining changes in bacterial load and other important clinical outcomes, as well as tolerability<br><br>*Study site:* outpatient<br><br>*Methods of analysis:*<br><br>1. Frequency analysis<br>2. Descriptive analysis<br>3. 2-Way ANCOVA |
| Participants | *Eligible for study:* 277<br><br>*Randomly assigned:* intervention 60, control 64<br><br>*Completed:* 103<br><br>*Age:* intervention 64.7 ± 11.8, control 61.4 ± 11.9<br><br>*Gender (M/F): intervention* 21/39, control 21/43<br><br>*Bronchiectasis diagnosis criteria:*<br><br>adults with proven and documented diagnosis of idiopathic or post-infective non-CF bronchiectasis confirmed by HRCT<br><br>*Recruitment:* not mentioned<br><br>*Co-morbidities:* not mentioned<br><br>*Reasons for participant exclusion:*<br><br>1. Active non-tuberculous mycobacterial infection<br>2. Recent significant haemoptysis (volume requiring clinical intervention, within previous 4 weeks)<br>3. Use of nebulised antibacterials as maintenance treatment or systemic antibacterials for an exacerbation, within 4 weeks before randomisation<br><br>*Baseline FEV:* intervention 57.2 ± 13.7, control 54.6 ± 14.8<br><br>*Baseline exacerbations:* intervention 1 to 2 exacerbations = 30 (50%), 3 to 4 exacerbations = 25 (41.7%), ≥ 5 exacerbations = 5 (8.3%); control 1 to 2 exacerbations = 35 (54.7%), 3 to 4 exacerbations = 26 (40.6%), ≥ 5 exacerbations = 3 (4.7%) |
| Interventions | *Setting:* not mentioned<br><br>*Duration of intervention:* 28 days<br><br>*Type of antibiotic(s):* ciprofloxacin (inhaled 32.5 mg BD)<br><br>*Type of control:* placebo (BD) |
| Outcomes | *Pre-specified outcomes:* |

**Wilson 2013a** *(Continued)*

| | |
|---|---|
| | Primary endpoints:<br>1. To determine effects of ciprofloxacin DPI on total bacterial density of pre-defined potential respiratory pathogens in sputum<br>Secondary endpoints:<br>1. Time to exacerbation<br>2. Emergence of new potential respiratory pathogens - changes in inflammatory biomarkers<br>3. Emergence of resistance among baseline pathogens<br>4. Change in 24 hour sputum volume and colour from baseline<br>5. Changes in FEV1 and FVC<br>6. Health status (SGRQ)<br>7. Adverse effects<br>*Follow-up period:* 84 days |
| Notes | Study was sponsored by Bayer Pharma AG, Germany. R. Wilson and A. De Soyza wish to acknowledge the support of the National Institute for Health Research (NIHR) infrastructure in the form of NIHR Biomedical Research Unit funding (Royal Brompton Hospital, London, UK) and the Comprehensive Local Research Networks funding (other UK centres) |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | Method of allocation sequence not mentioned |
| Allocation concealment (selection bias) | Unclear risk | Not mentioned |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Unclear risk | Delivery of intervention vs control not clear<br>Appearance/packaging, taste of intervention drug and placebo, etc., not mentioned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Unclear risk | Execution of assessment not mentioned<br>Unclear regarding management/protocol for exacerbation while patients were on trial |
| Incomplete outcome data (attrition bias)<br>All outcomes | High risk | Total 74 completed as per Figure 1, but numbers varied as per Tables 2 and 3<br>“N” values from different groups at different stages not available (see Figure 1) |
| Selective reporting (reporting bias) | Unclear risk | Unclear if per protocol or intention-to-treat analysis |
| Other bias | Unclear risk | Many endpoints/outcomes reported with just mean values without SD |

**Wong 2012**

| | |
|---|---|
| Methods | *Country:* New Zealand<br>*Design:* multi-centre double-blind placebo-controlled randomised controlled trial |

**Wong 2012** *(Continued)*

| | |
|---|---|
| | *Objective/aim:* to test whether azithromycin decreases frequency of exacerbations, increases lung function and improves health-related quality of life in patients with non-cystic fibrosis bronchiectasis<br><br>*Study site:* not mentioned<br><br>*Methods of analysis:*<br><br>1. Intention-to-treat analysis<br>2. Poisson regression model (number of exacerbations)<br>3. Cox proportional hazard regression model (time to first exacerbation) |
| Participants | *Eligible for study:* 141<br><br>*Randomly assigned:* intervention 71, control 70<br><br>*Completed:* intervention 67, control 60<br><br>*Age:* intervention 60.9 ± 13.6, control 59.0 ± 13.3<br><br>*Gender (M/F):* intervention 23/48, control 20/50<br><br>*Bronchiectasis diagnosis criteria:* HRCT<br><br>*Recruitment:* 3 centres in New Zealand<br><br>*Co-morbidities:* asthma<br><br>*Reasons for participant exclusion:*<br><br>1. History of cystic fibrosis<br>2. Hypogammaglobulinaemia<br>3. Allergic bronchopulmonary aspergillosis<br>4. Positive culture of non-tuberculous mycobacteria in past 2 years or at screening<br>5. Macrolide treatment for longer than 3 months in past 6 months<br>6. Unstable arrhythmia<br><br>*Baseline FEV:* intervention FEV1 pre-BD: 1.87 (0.74) FEV1 post-BD: 1.94 (0.74), control FEV1 pre-BD: 1.88 (0.69) FEV1 post-BD: 1.95 (0.71)<br><br>*Baseline exacerbations* (in the past year): intervention 3.34 (2.61), control 3.93 (2.49) |
| Interventions | *Setting:* outpatient<br><br>*Duration of intervention:* 6 months<br><br>*Type of antibiotic(s):* azithromycin (oral 500 mg, 3 days a week (M/W/F))<br><br>*Type of control:* placebo |
| Outcomes | *Pre-specified outcomes:*<br><br>Primary endpoints:<br><br>1. Rate of event-based exacerbations in the first 6 months<br>2. Forced expiratory volume in 1 second (FEV1) before bronchodilation<br>3. SGRQ total score at end of treatment period<br><br>Secondary endpoints:<br><br>1. Time to first exacerbation<br>2. Rate of symptom-based exacerbations<br>3. Pre-bronchodilator and post-bronchodilator forced vital capacity (FVC)<br>4. Post-bronchodilator FEV1 |

**Wong 2012** *(Continued)*

| | |
|---|---|
| | 5. Exercise capacity (as measured by 6MWT)<br>6. SGRQ total score at 12 months<br>7. Concentration of C-reactive protein (assessed only at 6 months)<br>8. Sputum cell counts and microbiology<br>9. Adverse events.<br><br>*Follow-up period:* 12 months |
| Notes | Study was funded by Health Research Council of New Zealand and Auckland District Health Board Charitable Trust |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Low risk | Participants randomly assigned in a 1:1 ratio, with permuted block size of 6 and sequential assignment |
| Allocation concealment (selection bias) | Low risk | Eligible participants randomly assigned to receive azithromycin or placebo by a statistician independent of the reporting statistician with a computer-generated random number list |
| Blinding of participants and personnel (performance bias)<br>All outcomes | Low risk | Participants, research assistants and investigators masked to treatment allocation; same protocol applied |
| Blinding of outcome assessment (detection bias)<br>All outcomes | Low risk | No biases identified |
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | Insufficient information |
| Selective reporting (reporting bias) | Low risk | No biases identified |
| Other bias | Unclear risk | One of the secondary outcomes(CRP) was not repeated at the end of the trial |

**Yalçin 2006**

| | |
|---|---|
| Methods | *Country:* Turkey<br><br>*Design:* randomised controlled trial<br><br>*Objective/aim:* to evaluate effects of macrolide antibiotics on process of inflammation (by measuring IL-8, TNF-a, IL-10 levels and cell profiles in BAL fluid), pulmonary function and sputum production in children with steady-state bronchiectasis, secondary to causes other than CF or primary immunodeficiencies<br><br>*Study site:* Department of Paediatric Chest Diseases at Hacettepe University Faculty of Medicine<br><br>*Methods of analysis:*<br><br>1. Wilcoxon signed ranks test<br>2. Mann–Whitney U test was used for comparing per cent changes between the 2 groups |

**Yalçin 2006** *(Continued)*

| | |
|---|---|
| Participants | *Eligible for study:* 34<br><br>*Randomly assigned:* intervention 17, control 17<br><br>*Completed:* intervention 17, control 17<br><br>*Age:* intervention 13.1 ± 2.7, control 11.9 ± 2.9<br><br>*Gender (M/F):* intervention 8/9, control 11/6<br><br>*Bronchiectasis diagnosis criteria:* bronchiectasis, which developed as the result of causes other than CF or primary immunodeficiencies, based on clinical and high-resolution computed tomography (HRCT) findings<br><br>*Recruitment:* outpatient clinics<br><br>*Co-morbidities:* not mentioned<br><br>*Reasons for* participant*exclusion:*<br><br>1. Antibiotic therapy in preceding 4 months<br><br>*Baseline FEV* (% of predicted): intervention 74% predicted, control 79% predicted<br><br>*Baseline exacerbations:* not mentioned |
| Interventions | *Setting:* not mentioned<br><br>*Duration of intervention:* 3 months<br><br>*Type of antibiotic(s):* clarithromycin (15 mg/kg/d)<br><br>*Type of control:* supportive therapy (mucolytics, expectorants, postural drainage) |
| Outcomes | *Pre-specified outcomes:*<br><br>1. Not specifically stated as outcomes but are measured<br>a. Effects on process of inflammation through measurement of IL-8, TNF-a, IL-10, BAL cell profile, PFT, sputum production<br><br>*Follow-up period:* 3 months |
| Notes | SANOVEL Pharmaceuticals Inc. supplied cytokine kits |

***Risk of bias***

| Bias | Authors' judgement | Support for judgement |
|---|---|---|
| Random sequence generation (selection bias) | Unclear risk | No further information available |
| Allocation concealment (selection bias) | Unclear risk | No further information available |
| Blinding of participants and personnel (performance bias)<br>All outcomes | High risk | Placebo was not mentioned |
| Blinding of outcome assessment (detection bias)<br>All outcomes | High risk | No further information available and no pre-specified outcomes for assessment |

**Yalçin 2006** *(Continued)*

| | | |
|---|---|---|
| Incomplete outcome data (attrition bias)<br>All outcomes | Unclear risk | No further information available |
| Selective reporting (reporting bias) | High risk | Majority of results were reported without numerical data.<br>No pre-specified outcomes |
| Other bias | Unclear risk | Insufficient information |

BAL: Bronchoalveolar lavage; CF: Cystic fibrosis; HRCT: High-resolution computed tomography; PA: *Pseudomonas aeruginosa.*

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

| Study | Reason for exclusion |
|---|---|
| Adachi 1988 | Not all patients with bronchiectasis |
| Al Mobeireek 1998 | Full review not possible; however no particular intervention was used |
| Alberto 1968 | Not all patients with bronchiectasis |
| Alekseenko 1978 | No prolonged antibiotics |
| Allen 1988 | No prolonged antibiotics, 1 week duration |
| Allen 1990 | No prolonged antibiotics |
| Alora 1978 | No bronchiectasis |
| Anwar 2008 | Not an RCT |
| Barach 1952 | Not an RCT |
| Begg 2000 | No prolonged antibiotics |
| Bergogne 1982 | No prolonged antibiotics |
| Bergogne 1985 | No antibiotics |
| Bevilacqua 1973 | Not all patients with bronchiectasis |
| Bilton 2006 | Study recruited participants when they experienced an exacerbation |
| Bilton 2013 | No antibiotics |
| Bradley 2011 | No antibiotics |
| Brambilla 1992 | Not all patients with bronchiectasis |
| Bruninx 1973 | Not all patients with bronchiectasis |
| Chan 1996 | No prolonged antibiotics |
| Chang 2010 | Not all patients with bronchiectasis |

| Study | Reason for exclusion |
|---|---|
| Chang 2012 | No prolonged antibiotics |
| Cherniack 1959 | Not all patients with bronchiectasis |
| Cherniack 1966 | Not an RCT |
| Choi 1996 | No bronchiectasis |
| Chonabayashi 1988 | No bronchiectasis |
| Chonabayashi 1988a | No bronchiectasis |
| Chuchalin 1997 | Not all patients with bronchiectasis |
| Clarke 1981 | Not an RCT |
| Crowther 1999 | No patients with non-CF bronchiectasis |
| Cseri 1975 | Not all patients with bronchiectasis |
| Currie 1987 | Not an RCT |
| Czako 1968 | No antibiotics |
| Danesi 1985 | Not an RCT |
| Davies 1983 | No prolonged antibiotics |
| Dobrev1990 | No prolonged antibiotics |
| Douglas 1957 | Not an RCT |
| Doutsu 1988 | Full review not possible; however drug not used in clinical practice |
| Finelgold 1981 | Not all patients with bronchiectasis |
| Foweraker 1993 | Not all patients with bronchiectasis |
| Franklin 1953 | Not an RCT |
| Garcia 1984 | Not all patients with bronchiectasis |
| Grau 1992 | Not an RCT |
| Haidl 2013 | No non-CF bronchiectasis |
| Hara 1997 | Not an RCT |
| Harada 1988 | No prolonged antibiotics and not all patients with bronchiectasis |
| Hayashi 1989 | Not an RCT |
| Helm 1956 | Not an RCT |
| Hernandez 2002 | No prolonged antibiotics |

| Study | Reason for exclusion |
|---|---|
| Hill 1986 | Not an RCT |
| Hill 1988 | Not an RCT |
| Hill 1992 | Full review not possible; however drug not used in clinical practice |
| Hill 1994 | No prolonged antibiotics |
| Hossain 2010 | Full review of abstract not possible |
| Howie 1976 | Not an RCT |
| Hughes 1973 | No bronchiectasis |
| Hughes 1973a | No bronchiectasis |
| Ida 1988 | Not all patients with bronchiectasis |
| Iino 1993 | Not an RCT |
| Inoue 1989 | Not an RCT |
| Ip 1993 | Not an RCT |
| Ip 1998 | No prolonged antibiotics |
| Irabu 1989 | Not an RCT |
| Irabu 1992 | Not an RCT |
| Izumi 1994 | Not an RCT |
| Izumikawa 1988 | Not an RCT |
| Jia 2010 | No bronchiectasis |
| Kaji 1988 | Not an RCT |
| Kanaij, 1963 | Not an RCT |
| Karachalios 1985 | Not an RCT |
| Kawai 1988 | Not an RCT |
| Kawai 1996 | Not an RCT |
| Kawano 1974 | Not an RCT |
| Kawashima 1989 | Not all patients with bronchiectasis |
| Kellett 2011 | No antibiotics |
| Kikuchi 1991 | Not an RCT |
| Knox 1955 | Not an RCT |

| Study | Reason for exclusion |
|---|---|
| Kobayashi 1984 | Not an RCT |
| Kobayashi 1995 | Not an RCT |
| Koh 2000 | No antibiotics |
| Koyama 1992 | Not an RCT |
| Krawczyk 1981 | Not an RCT |
| Krofton 1971 | No bronchiectasis |
| Kudo 1988 | Full review not possible; however drug not used in clinical practice |
| Kudo 1992 | Not an RCT |
| Kulpati 1990 | No bronchiectasis and not an RCT |
| Kurasawa 1988 | No bronchiectasis |
| Kurishima 1992 | Not an RCT |
| Kuze 1988 | Not an RCT |
| Lam 1986a | No prolonged antibiotics |
| Lam 1989 | No prolonged antibiotics, trial of 10 days duration |
| Lam 2006 | No prolonged antibiotics |
| Lamotte 1981 | Not an RCT |
| Ledson 2000 | Not an RCT |
| Lin 1996 | No control group; comparison of erithromycin vs amoxicillin |
| Lin 1997 | No prolonged antibiotics, trial of 3 days duration |
| Lin 2006 | No antibiotics for bronchiectasis |
| Lioberes 1990 | Does not fulfil inclusion criteria |
| Lunacharskaia 1968 | Not all patients with bronchiectasis |
| Maekawa 1967 | No bronchiectasis |
| Mahashur 1993 | Not an RCT |
| Mahashur 2002 | Not all patients with bronchiectasis |
| Masekela 2013 | Not all patients with bronchiectasis |
| Masuno 1992 | Not an RCT |
| Matsumoto 1983 | Not an RCT |

| Study | Reason for exclusion |
|---|---|
| Matsumoto 1984 | Not an RCT |
| Matsumoto 1984a | Full review not possible; however drug not used in clinical practice |
| Matsumoto 1986 | Full review not possible; however drug not used in clinical practice |
| Matsumoto 1992 | Full review not possible; however drug not used in clinical practice |
| Matsushima 1988 | Full review not possible; however drug not used in clinical practice |
| Matsuura 1993 | Not an RCT |
| Matzeu 1981 | Not an RCT |
| May 1972 | Not all patients with bronchiectasis |
| May 1974 | Not all patients with bronchiectasis |
| Mazzei 1993 | Not all patients with bronchiectasis |
| McVay 1953 | Not an RCT |
| Mehta 1991 | No prolonged antibiotics |
| Messens 1973 | Not all patients with bronchiectasis |
| Mijuskovic 1972 | No prolonged antibiotics |
| Milcev 1985 | Not all patients with bronchiectasis |
| Min 1988 | Not an RCT |
| Minami 1996 | Not an RCT |
| Ming 2005 | Not all prolonged antibiotics |
| Miyamoto 1984 | Full review not possible; however drug not used in clinical practice |
| Molodtsova 1980 | Full review not possible; however drug not used in clinical practice |
| Morrone 1989 | Not all patients with bronchiectasis |
| Murayama 1992 | Not all patients with bronchiectasis |
| Music 1989 | No bronchiectasis |
| Nagy 1968 | Not an RCT |
| Nakagawa 1993 | Not an RCT |
| Nakagawa 1995 | No bronchiectasis and no prolonged antibiotics |
| Nakamori 1992 | Not an RCT |
| Nakamura 2007 | No prolonged antibiotics |

| Study | Reason for exclusion |
|---|---|
| Nakatani 1993 | Not an RCT |
| Nasu 1988 | Not an RCT |
| Neumayr 1963 | Not an RCT |
| Nobuoka 1985 | Not an RCT |
| O'Donovan, 1987 | No prolonged antibiotics |
| Oishi 1994 | Not an RCT |
| Oizumi 1978 | Not an RCT |
| Oki 1993 | Not an RCT |
| Ovcharenko 1991 | No prolonged antibiotics |
| Patterson 2005 | No antibiotics; this study randomly assigned participants between airway clearance techniques with no antibiotic regimens |
| Patterson 2007 | No prolonged antibiotics |
| Pezza 1983 | No bronchiectasis |
| Pines 1967 | Not all patients with bronchiectasis |
| Pines 1979 | No prolonged antibiotics |
| Pines 1981 | Not all patients with bronchiectasis |
| Piovano 1997 | No prolonged antibiotics |
| Popov 1988 | Not an RCT |
| Prigogine 1988 | No prolonged antibiotics |
| Ramer 1981 | No prolonged antibiotics |
| Rayner 1994 | Not an RCT |
| Rimoldi 1987 | Not all patients with bronchiectasis |
| Saito 1993 | Full review not possible; however drug not used in clinical practice |
| Saito 1999 | Full review not possible; however drug not used in clinical practice |
| Saito 2002 | Not all patients with bronchiectasis |
| Santiveri 1995 | No prolonged antibiotics |
| Sawae 1991 | Not all patients with bronchiectasis |
| Sawae 1995 | No prolonged antibiotics |

| Study | Reason for exclusion |
|---|---|
| Sawaki 1986 | Not an RCT |
| Schulz 1972 | Not all patients with bronchiectasis |
| Serisier 2011a | Not an RCT |
| Serisier 2011b | No antibiotics |
| Shewsbury 2004 | Published rationale and methodology |
| Shigeno 1984 | Full review not possible; however drug not used in clinical practice |
| Shimada 1996 | No prolonged antibiotics |
| Shimada K 1988 | Full review not possible; however drug not used in clinical practice |
| Shimokata 1990 | Not an RCT |
| Shimokata 1992 | Exclusion criteria (panbronchiolitis) |
| Shirai 1995 | Exclusion criteria (panbronchiolitis) |
| Shishido 1988 | Not all patients with bronchiectasis |
| Shishido 1995 | Exclusion criteria (panbronchiolitis) |
| Singleton 2007 | Full review not possible; intervention not available to be determined based on abstract |
| Singleton 2008 | Not an RCT |
| Soejima 1988 | No prolonged antibiotics |
| Stass 2013 | Not all patients with bronchiectasis |
| Stockley 1984 | Not an RCT |
| Stockley 1985 | Not an RCT |
| Suga 1988 | Full review not possible; however drug not used in clinical practice |
| Suyama 1988 | No prolonged antibiotics |
| Tagaya 2002 | No prolonged antibiotics |
| Tageldin 1994 | Not an RCT |
| Takamoto 1994 | Not all patients with bronchiectasis |
| Tamura 1992 | Full review not possible; however drug not used in clinical practice |
| Tanimoto 1992 | No prolonged antibiotics |
| Tanimoto 1993 | No prolonged antibiotics |
| Taskar 1992 | Review of bromhexine, not antibiotics |

| Study | Reason for exclusion |
|---|---|
| Tsang 1993 | No prolonged antibiotics |
| Tsang 1994 | No prolonged antibiotics |
| Tsang 1999a | No prolonged antibiotics |
| Unoura 1988 | Exclusion criteria (panbronchiolitis) |
| Vergnon 1985 | No prolonged antibiotics |
| Watanabe 1982 | No prolonged antibiotics |
| Watanabe 1989 | Exclusion criteria (panbronchiolitis) |
| Watanabe 1991 | Exclusion criteria (panbronchiolitis) |
| Watanabe 1994 | No control group; comparison of 2 antibiotics and no prolonged antibiotics |
| Watanabe 1995 | Exclusion criteria (panbronchiolitis) |
| Watanabe 2001 | Not all patients with bronchiectasis |
| Yamada 1993 | Not all patients with bronchiectasis |
| Yamaki 1988 | Not all patients with bronchiectasis |
| Young Whan 1993 | Effect of long-term erythromycin on diffuse panbronchiolitis, not non-CF bronchiectasis |
| Zhang 2003 | No prolonged antibiotics |

For additional details on excluded studies, see additional tables.

### Characteristics of studies awaiting assessment *[ordered by study ID]*

#### Aksamit 2017

| |
|---|
| Methods |
| Participants |
| Interventions |
| Outcomes |
| Notes |

#### Alder 2012

| |
|---|
| Methods |
| Participants |

**Alder 2012** *(Continued)*

| |
|---|
| Interventions |
| Outcomes |
| Notes |

**Altenburg 2016**

| |
|---|
| Methods |
| Participants |
| Interventions |
| Outcomes |
| Notes |

**Altenburg 2016a**

| |
|---|
| Methods |
| Participants |
| Interventions |
| Outcomes |
| Notes |

**Altenburg 2016b**

| |
|---|
| Methods |
| Participants |
| Interventions |
| Outcomes |
| Notes |

**Barker 2014**

| |
|---|
| Methods |
| Participants |

**Barker 2014** *(Continued)*

| | |
|---|---|
| Interventions | |
| Outcomes | |
| Notes | |

**Burr 2015**

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Burr 2016**

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Chalmers 2012**

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Chang 2013**

| | |
|---|---|
| Methods | Randomised double-blind double-dummy placebo-controlled parallel-group trial |
| Participants | n = 170 children from 6 Australian and New Zealand centres |

**Chang 2013** *(Continued)*

| | |
|---|---|
| Interventions | Group 1 will receive azithromycin (5 mg/kg daily) with placebo amoxycillin-clavulanate, and group 2 will receive amoxycillin-clavulanate (22.5 mg/kg twice daily) with placebo azithromycin for 21 days as treatment for non-severe respiratory exacerbations |
| Outcomes | Exacerbations<br>Parent proxy cough-specific quality of life (PC-QOL) questionnaire<br>Time to next exacerbation<br>Hospitalisation<br>Duration of exacerbation<br>Spirometry data<br>Descriptive viral and bacteriological data from nasal samples and blood inflammatory markers |
| Notes | Based on published protocol |

**Chen 2014**

| |
|---|
| Methods |
| Participants |
| Interventions |
| Outcomes |
| Notes |

**De Soyza 2016**

| |
|---|
| Methods |
| Participants |
| Interventions |
| Outcomes |
| Notes |

**Dimakou 2014**

| |
|---|
| Methods |
| Participants |
| Interventions |

**Dimakou 2014** *(Continued)*

| | |
|---|---|
| Outcomes | |
| Notes | |

**Hare 2015**

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Haworth 2013**

| | |
|---|---|
| Methods | Randomised controlled trial |
| Participants | n = 54 (weeks 0 and 12); n = 31 (week 26), for each arm |
| Interventions | Nebulised colistimethate sodium 1 MIU/mL for ≤ 6 months |
| Outcomes | St George's Respiratory Questionnaire (SGRQ) across 3 domains (symptoms, activity, impact) |
| Notes | Based on abstract |

**Haworth 2013a**

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Haworth 2014**

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | |

**Haworth 2014** *(Continued)*

| | |
|---|---|
| Outcomes | |
| Notes | |

**Juthong 2011**

| | |
|---|---|
| Methods | Randomised double-blind placebo-controlled trial |
| Participants | 20 bronchiectatic patients, mean age 56 years, participated in this study. Nine participants were randomly assigned to roxithromycin 300 mg, and 11 participants received placebo once daily |
| Interventions | Roxithromycin 300 mg once daily for 8 weeks |
| Outcomes | Symptom score<br>Quality of life (SGRQ)<br>Pulmonary function test<br>Sputum culture<br>Adverse events |
| Notes | Contacted study author for further information, but not available at time of completion of this review |

**Kobbernagel 2016**

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Liu 2012a**

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

### Liu 2014

| |
|---|
| Methods |
| Participants |
| Interventions |
| Outcomes |
| Notes |

### Lourdesamy 2014

| |
|---|
| Methods |
| Participants |
| Interventions |
| Outcomes |
| Notes |

### New Study

| |
|---|
| Methods |
| Participants |
| Interventions |
| Outcomes |
| Notes |

### O'Donnell 2016

| |
|---|
| Methods |
| Participants |
| Interventions |
| Outcomes |
| Notes |

**O'Donnell 2016a**

| |
|---|
| Methods |
| Participants |
| Interventions |
| Outcomes |
| Notes |

**Orriols 2015**

| |
|---|
| Methods |
| Participants |
| Interventions |
| Outcomes |
| Notes |

**Rogers 2014**

| |
|---|
| Methods |
| Participants |
| Interventions |
| Outcomes |
| Notes |

**Tabernero 2014**

| |
|---|
| Methods |
| Participants |
| Interventions |
| Outcomes |
| Notes |

**Tabernero 2015**

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Terpstra 2016**

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | |
| Outcomes | |
| Notes | |

**Twiss 2008**

| | |
|---|---|
| Methods | Randomised double-blind placebo-controlled cross-over (2 × 3 month treatment period) |
| Participants | 15 participants 5 to 15 years of age |
| Interventions | Trial of 80 mg gentamicin nebulised twice daily |
| Outcomes | Monthly spirometry<br>Symptom scores<br>Hospitalisation<br>Antibiotic history<br>Sputum samples for microbiology |
| Notes | Based on abstract |

**Yalcin 2006**

| | |
|---|---|
| Methods | |
| Participants | |
| Interventions | |
| Outcomes | |

**Yalcin 2006** *(Continued)*

Notes

## DATA AND ANALYSES

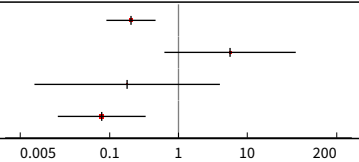
### Comparison 1. Continuous antibiotics versus standard treatment with or without added placebo (parallel groups)

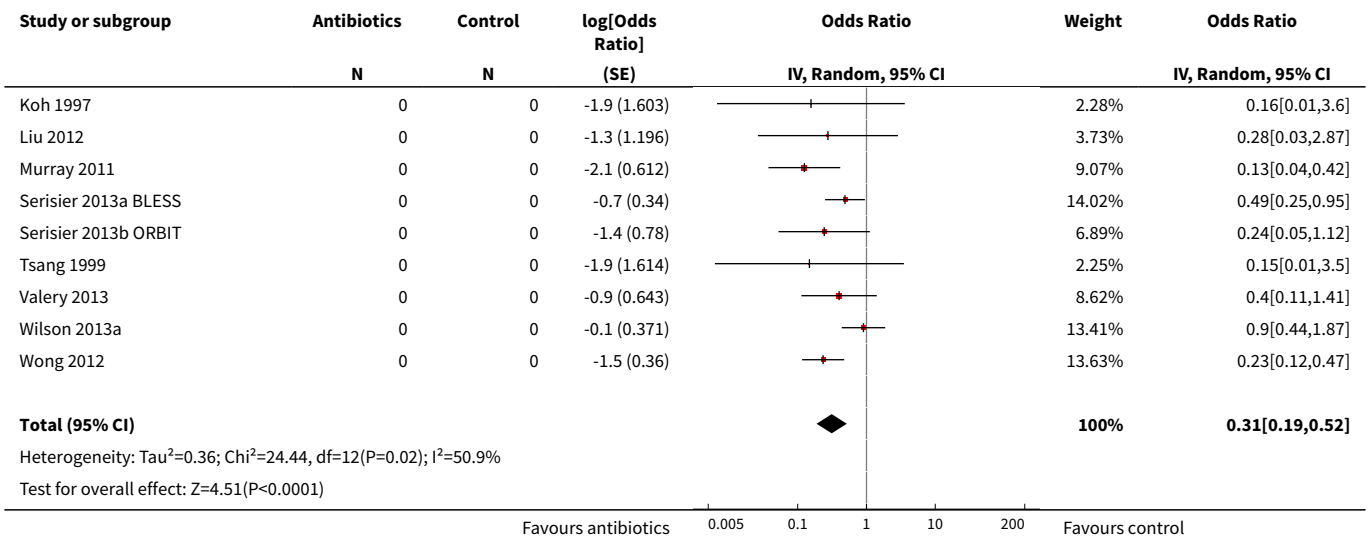
| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Exacerbations | 13 | | Odds Ratio (Random, 95% CI) | 0.31 [0.19, 0.52] |
| 2 Hospitalisations | 7 | 643 | Odds Ratio (M-H, Random, 95% CI) | 0.40 [0.14, 1.11] |
| 3 Response rates | 2 | 110 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.30 [0.14, 0.63] |
| 4 Lung function | 8 | | Std. Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 4.1 $FEV_1$ % predicted | 5 | 338 | Std. Mean Difference (IV, Random, 95% CI) | -0.12 [-0.34, 0.10] |
| 4.2 Change in $FEV_1$ | 3 | 84 | Std. Mean Difference (IV, Random, 95% CI) | -0.07 [-0.84, 0.70] |
| 4.3 $FEV_1$ | 2 | 36 | Std. Mean Difference (IV, Random, 95% CI) | -0.36 [-1.03, 0.30] |
| 5 Sputum leucocytes | 3 | 165 | Mean Difference (IV, Random, 95% CI) | -0.39 [-0.87, 0.09] |
| 6 Erythrocyte sedimentation rate (ESR) | 2 | 87 | Mean Difference (IV, Random, 95% CI) | -2.47 [-9.76, 4.82] |
| 7 Adverse events | 10 | | Peto Odds Ratio (Peto, Fixed, 95% CI) | Subtotals only |
| 7.1 Withdrawals (intolerable side effects) | 10 | 683 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.91 [0.56, 1.49] |
| 7.2 Diarrhoea | 3 | 231 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 3.33 [1.50, 7.37] |
| 7.3 Rash | 3 | 140 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 1.98 [0.67, 5.80] |
| 7.4 Wheeze | 1 | 74 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 8.56 [1.63, 44.93] |
| 7.5 Dyspnoea | 1 | 74 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 4.41 [1.43, 13.61] |
| 7.6 Chest pain/palpitations | 3 | 274 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 5.21 [1.35, 20.14] |
| 7.7 Increased cough | 2 | 198 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 1.12 [0.48, 2.61] |
| 7.8 Nausea | 4 | 275 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 1.01 [0.45, 2.26] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 7.9 Fatigue | 2 | 157 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.99 [0.30, 3.33] |
| 7.10 Hemoptysis | 3 | 310 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.87 [0.45, 1.70] |
| 7.11 Fever | 1 | 74 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.63 [0.17, 2.38] |
| 7.12 Increased sputum | 1 | 74 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 1.74 [0.53, 5.71] |
| 7.13 Abdominal pain | 2 | 195 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 5.10 [1.38, 18.86] |
| 7.14 Headache | 2 | 122 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.22 [0.05, 1.01] |
| 7.15 Bronchospasm | 2 | 189 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 2.19 [0.76, 6.33] |
| 7.16 Vomiting | 1 | 112 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 4.37 [0.07, 290.15] |
| 7.17 Acute sinusitis | 1 | 117 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 0.50 [0.05, 4.89] |
| 8 Deaths | 7 | 595 | Peto Odds Ratio (Peto, Fixed, 95% CI) | 1.48 [0.28, 7.85] |
| 9 Emergence of resistance | 6 | 431 | Odds Ratio (M-H, Random, 95% CI) | 3.48 [1.20, 10.07] |
| 10 Exercise capacity (6MWD) | 2 | 96 | Std. Mean Difference (IV, Random, 95% CI) | 0.18 [-0.22, 0.58] |
| 11 Change in St George Respiratory Questionnaire | 5 | | Mean Difference (IV, Random, 95% CI) | Subtotals only |
| 11.1 Symptoms | 2 | 147 | Mean Difference (IV, Random, 95% CI) | -14.16 [-40.22, 11.90] |
| 11.2 Total | 5 | 315 | Mean Difference (IV, Random, 95% CI) | -2.75 [-7.08, 1.57] |
| 12 Number of participants with exacerbations | 10 | 654 | Odds Ratio (M-H, Random, 95% CI) | 0.36 [0.19, 0.69] |
| 13 Exacerbation rates - continuous | 3 | 230 | Std. Mean Difference (IV, Random, 95% CI) | -0.80 [-1.32, -0.29] |

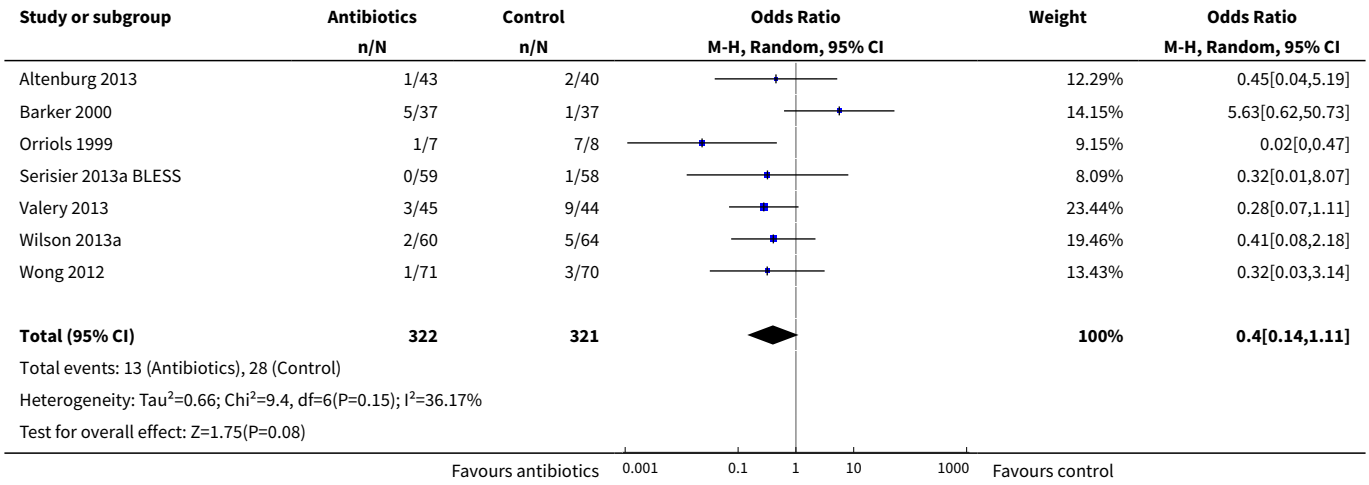
**Analysis 1.1. Comparison 1 Continuous antibiotics versus standard treatment with or without added placebo (parallel groups), Outcome 1 Exacerbations.**

| Study or subgroup | Antibiotics | Control | log[Odds Ratio] | Odds Ratio | Weight | Odds Ratio |
|---|---|---|---|---|---|---|
| | N | N | (SE) | IV, Random, 95% CI | | IV, Random, 95% CI |
| Altenburg 2013 | 0 | 0 | -1.6 (0.42) | | 12.43% | 0.2[0.09,0.46] |
| Barker 2000 | 0 | 0 | 1.7 (1.122) | | 4.12% | 5.62[0.62,50.73] |
| Currie 1990 | 0 | 0 | -1.7 (1.584) | | 2.32% | 0.18[0.01,4] |
| De Diego 2013 | 0 | 0 | -2.6 (0.75) | | 7.23% | 0.08[0.02,0.33] |

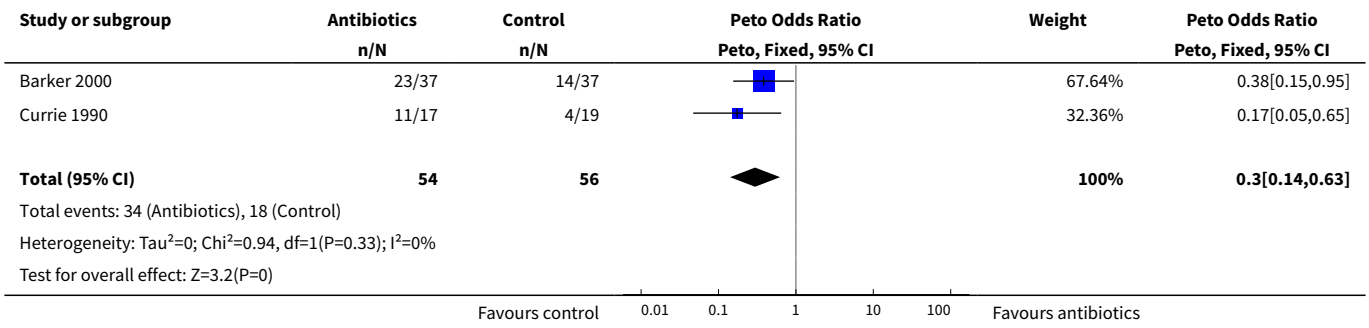





## Analysis 1.2. Comparison 1 Continuous antibiotics versus standard treatment with or without added placebo (parallel groups), Outcome 2 Hospitalisations.

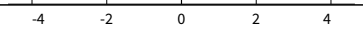



## Analysis 1.3. Comparison 1 Continuous antibiotics versus standard treatment with or without added placebo (parallel groups), Outcome 3 Response rates.



## Analysis 1.4. Comparison 1 Continuous antibiotics versus standard treatment with or without added placebo (parallel groups), Outcome 4 Lung function.

| Study or subgroup | Control N | Control Mean(SD) | Antibiotics N | Antibiotics Mean(SD) | Std. Mean Difference Random, 95% CI | Weight | Std. Mean Difference Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **1.4.1 FEV1 % predicted** | | | | | | | |
| Koh 1997 | 12 | 85 (8) | 13 | 86 (7) | | 7.75% | -0.13[-0.91,0.66] |
| Murray 2011 | 27 | 68.1 (31.4) | 30 | 64.3 (42.6) | | 17.34% | 0.1[-0.42,0.62] |
| Orriols 1999 | 8 | 56.1 (45.3) | 7 | 61.7 (61.1) | | 4.67% | -0.1[-1.11,0.92] |
| Serisier 2013a BLESS | 58 | -4 (6.6) | 59 | -1.6 (4.6) | | 33.82% | -0.42[-0.79,-0.05] |
| Wilson 2013a | 60 | 0.1 (8.4) | 64 | -0.4 (10.1) | | 36.42% | 0.05[-0.3,0.4] |
| **Subtotal ***** | **165** | | **173** | | | **100%** | **-0.12[-0.34,0.1]** |
| Heterogeneity: $Tau^2$=0; $Chi^2$=4.14, df=4(P=0.39); $I^2$=3.42% | | | | | | | |
| Test for overall effect: Z=1.08(P=0.28) | | | | | | | |
| **1.4.2 Change in FEV1** | | | | | | | |
| De Diego 2013 | 14 | 0 (0) | 16 | 0.1 (0) | | 34.72% | -0.75[-1.5,-0.01] |
| Orriols 1999 | 8 | -0.1 (0.6) | 7 | -0.1 (0.2) | | 27.2% | 0.09[-0.93,1.1] |
| Serisier 2013b ORBIT | 20 | 0 (0.1) | 19 | -0 (0.1) | | 38.08% | 0.44[-0.19,1.08] |
| **Subtotal ***** | **42** | | **42** | | | **100%** | **-0.07[-0.84,0.7]** |
| Heterogeneity: $Tau^2$=0.3; $Chi^2$=5.8, df=2(P=0.06); $I^2$=65.49% | | | | | | | |
| Test for overall effect: Z=0.17(P=0.86) | | | | | | | |
| **1.4.3 FEV1** | | | | | | | |
| Orriols 1999 | 8 | 803 (610) | 7 | 932 (1097) | | 42.55% | -0.14[-1.16,0.88] |
| Tsang 1999 | 10 | 0.9 (0.4) | 11 | 1.2 (0.5) | | 57.45% | -0.53[-1.4,0.35] |
| **Subtotal ***** | **18** | | **18** | | | **100%** | **-0.36[-1.03,0.3]** |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0.32, df=1(P=0.57); $I^2$=0% | | | | | | | |
| Test for overall effect: Z=1.07(P=0.28) | | | | | | | |
| Test for subgroup differences: $Chi^2$=0.49, df=1 (P=0.78), $I^2$=0% | | | | | | | |




## Analysis 1.5. Comparison 1 Continuous antibiotics versus standard treatment with or without added placebo (parallel groups), Outcome 5 Sputum leucocytes.

| Study or subgroup | Antibiotics N | Antibiotics Mean(SD) | Control N | Control Mean(SD) | Mean Difference Random, 95% CI | Weight | Mean Difference Random, 95% CI |
|---|---|---|---|---|---|---|---|
| Altenburg 2013 | 43 | 7.6 (2.6) | 40 | 7.5 (2.7) | | 17.36% | 0.1[-1.04,1.24] |
| Koh 1997 | 13 | 1.3 (0.5) | 12 | 1.8 (0.8) | | 78.44% | -0.52[-1.06,0.02] |
| Murray 2011 | 27 | 7.1 (5.6) | 30 | 7.1 (2.7) | | 4.2% | 0[-2.32,2.32] |
| **Total ***** | **83** | | **82** | | | **100%** | **-0.39[-0.87,0.09]** |
| Heterogeneity: $Tau^2$=0; $Chi^2$=1.04, df=2(P=0.59); $I^2$=0% | | | | | | | |
| Test for overall effect: Z=1.61(P=0.11) | | | | | | | |

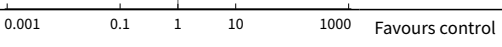
## Analysis 1.6. Comparison 1 Continuous antibiotics versus standard treatment with or without added placebo (parallel groups), Outcome 6 Erythrocyte sedimentation rate (ESR).

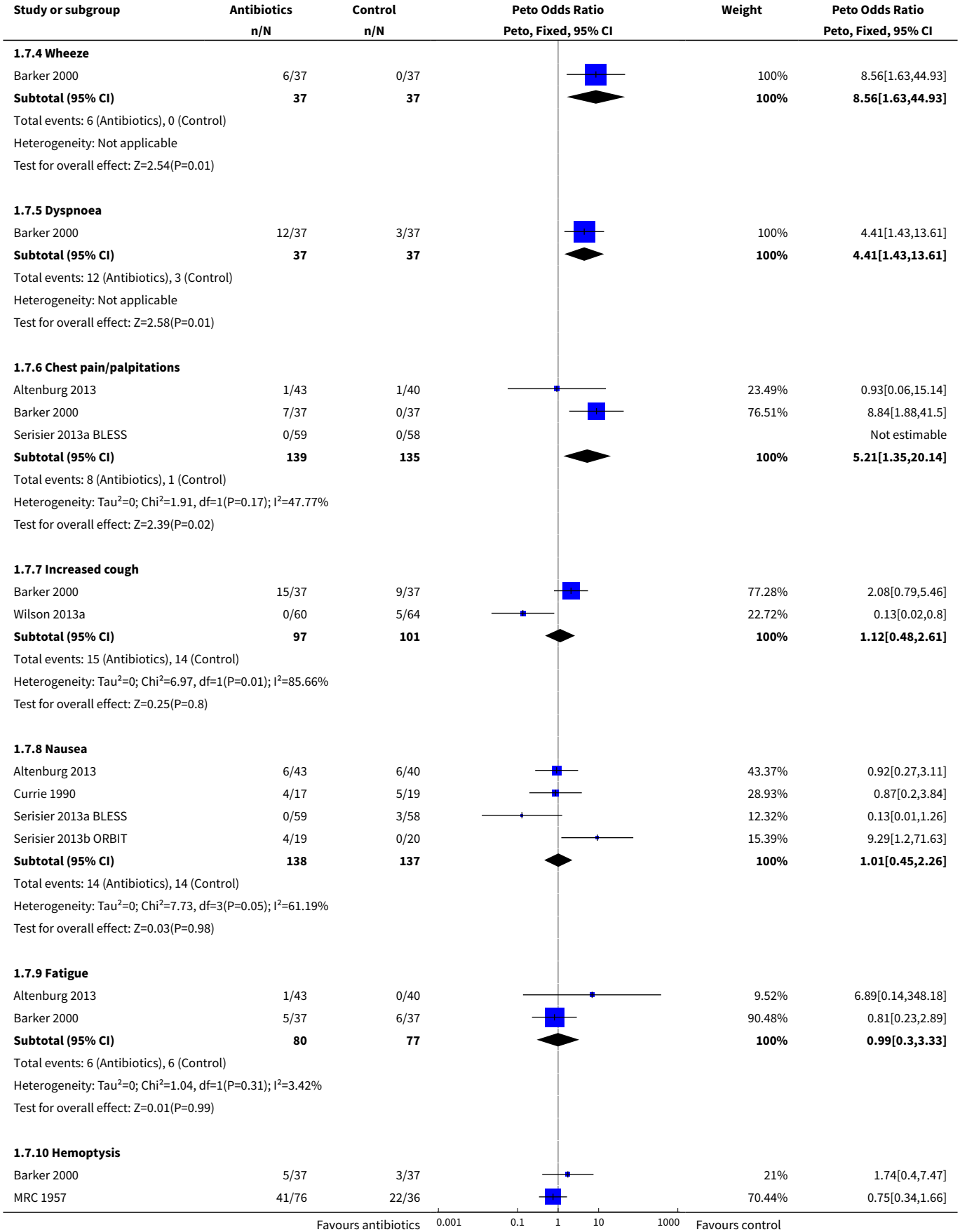
| Study or subgroup | Antibiotic N | Antibiotic Mean(SD) | Control N | Control Mean(SD) | Mean Difference Random, 95% CI | Weight | Mean Difference Random, 95% CI |
|---|---|---|---|---|---|---|---|
| De Diego 2013 | 16 | -14 (4) | 14 | -9 (12) | | 68.38% | -5[-11.58,1.58] |
| Murray 2011 | 27 | 17 (24) | 30 | 14 (20.1) | | 31.62% | 3[-8.56,14.56] |
| **Total ***** | **43** | | **44** | | | **100%** | **-2.47[-9.76,4.82]** |
| Heterogeneity: $Tau^2$=8.95; $Chi^2$=1.39, df=1(P=0.24); $I^2$=27.98% | | | | | | | |
| Test for overall effect: Z=0.66(P=0.51) | | | | | | | |

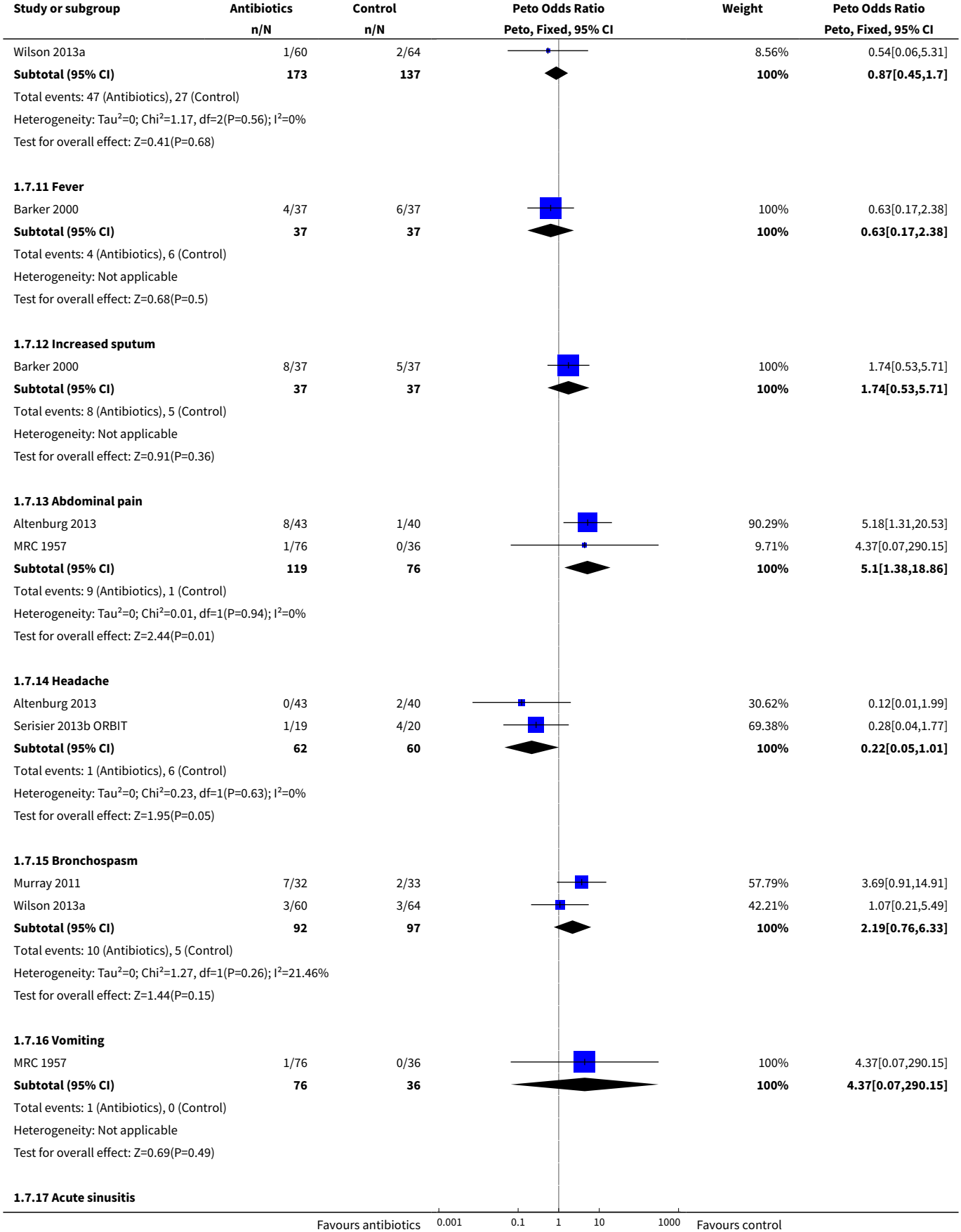


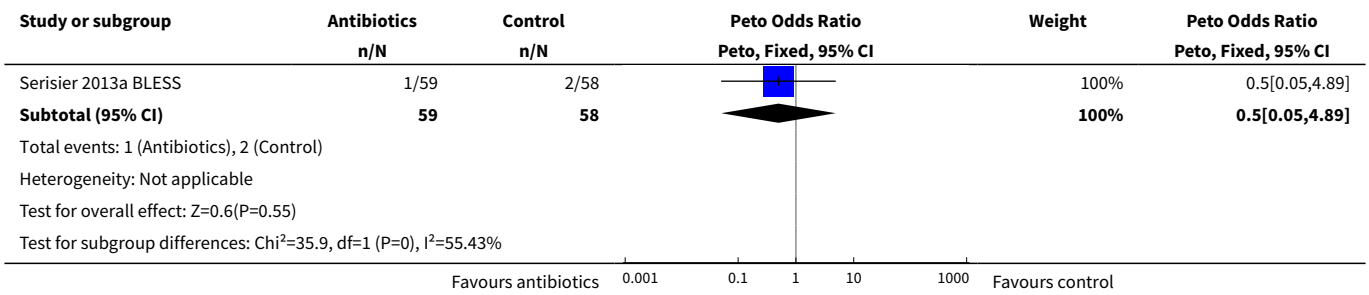

## Analysis 1.7. Comparison 1 Continuous antibiotics versus standard treatment with or without added placebo (parallel groups), Outcome 7 Adverse events.

| Study or subgroup | Antibiotics n/N | Control n/N | Peto Odds Ratio Peto, Fixed, 95% CI | Weight | Peto Odds Ratio Peto, Fixed, 95% CI |
|---|---|---|---|---|---|
| **1.7.1 Withdrawals (intolerable side effects)** | | | | | |
| Altenburg 2013 | 1/43 | 1/40 | | 3.08% | 0.93[0.06,15.14] |
| Barker 2000 | 5/37 | 8/37 | | 16.96% | 0.58[0.18,1.89] |
| Currie 1990 | 2/17 | 1/19 | | 4.4% | 2.29[0.22,23.61] |
| MRC 1957 | 2/76 | 0/36 | | 2.7% | 4.42[0.22,87.19] |
| Murray 2011 | 2/27 | 2/30 | | 5.89% | 1.12[0.15,8.41] |
| Orriols 1999 | 1/8 | 1/9 | | 2.92% | 1.13[0.06,19.96] |
| Serisier 2013a BLESS | 5/59 | 5/58 | | 14.4% | 0.98[0.27,3.57] |
| Serisier 2013b ORBIT | 1/20 | 2/22 | | 4.44% | 0.55[0.05,5.59] |
| Tsang 1999 | 1/11 | 0/10 | | 1.56% | 6.75[0.13,341.54] |
| Wilson 2013a | 19/60 | 23/64 | | 43.66% | 0.83[0.39,1.74] |
| **Subtotal (95% CI)** | **358** | **325** | | **100%** | **0.91[0.56,1.49]** |
| Total events: 39 (Antibiotics), 43 (Control) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=3.57, df=9(P=0.94); $I^2$=0% | | | | | |
| Test for overall effect: Z=0.37(P=0.71) | | | | | |
| **1.7.2 Diarrhoea** | | | | | |
| Altenburg 2013 | 9/43 | 1/40 | | 36.57% | 5.58[1.5,20.76] |
| Currie 1990 | 7/17 | 3/19 | | 30.46% | 3.42[0.81,14.45] |
| MRC 1957 | 8/76 | 2/36 | | 32.97% | 1.83[0.46,7.32] |
| **Subtotal (95% CI)** | **136** | **95** | | **100%** | **3.33[1.5,7.37]** |
| Total events: 24 (Antibiotics), 6 (Control) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=1.31, df=2(P=0.52); $I^2$=0% | | | | | |
| Test for overall effect: Z=2.97(P=0) | | | | | |
| **1.7.3 Rash** | | | | | |
| Altenburg 2013 | 8/43 | 4/40 | | 78.2% | 1.99[0.59,6.71] |
| Currie 1990 | 1/17 | 0/19 | | 7.51% | 8.31[0.16,421.42] |
| Tsang 1999 | 1/11 | 1/10 | | 14.29% | 0.9[0.05,15.59] |
| **Subtotal (95% CI)** | **71** | **69** | | **100%** | **1.98[0.67,5.8]** |
| Total events: 10 (Antibiotics), 5 (Control) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0.8, df=2(P=0.67); $I^2$=0% | | | | | |
| Test for overall effect: Z=1.24(P=0.21) | | | | | |

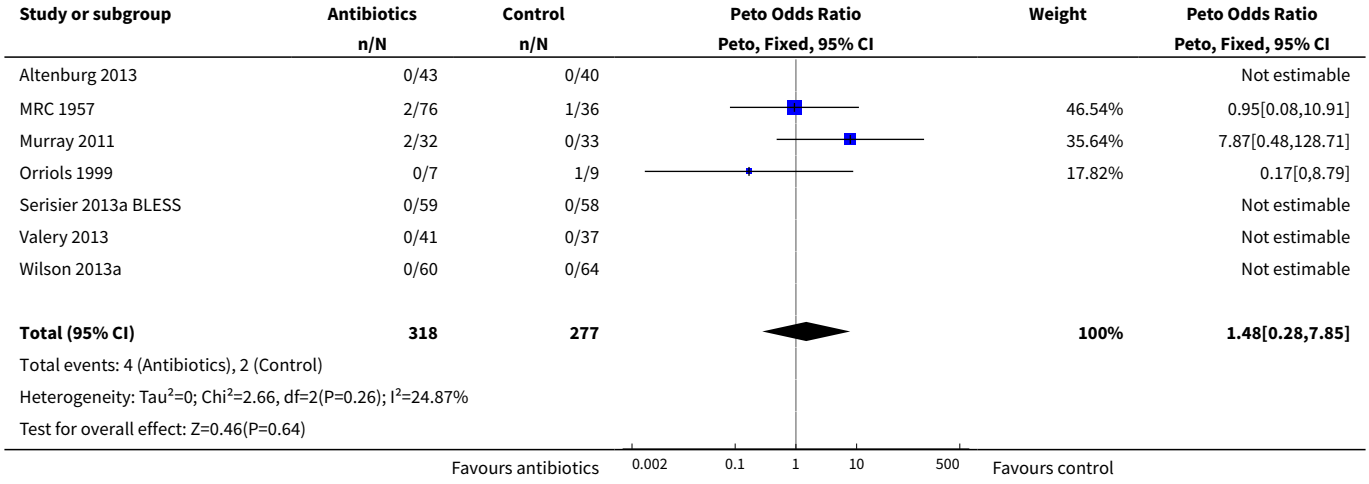




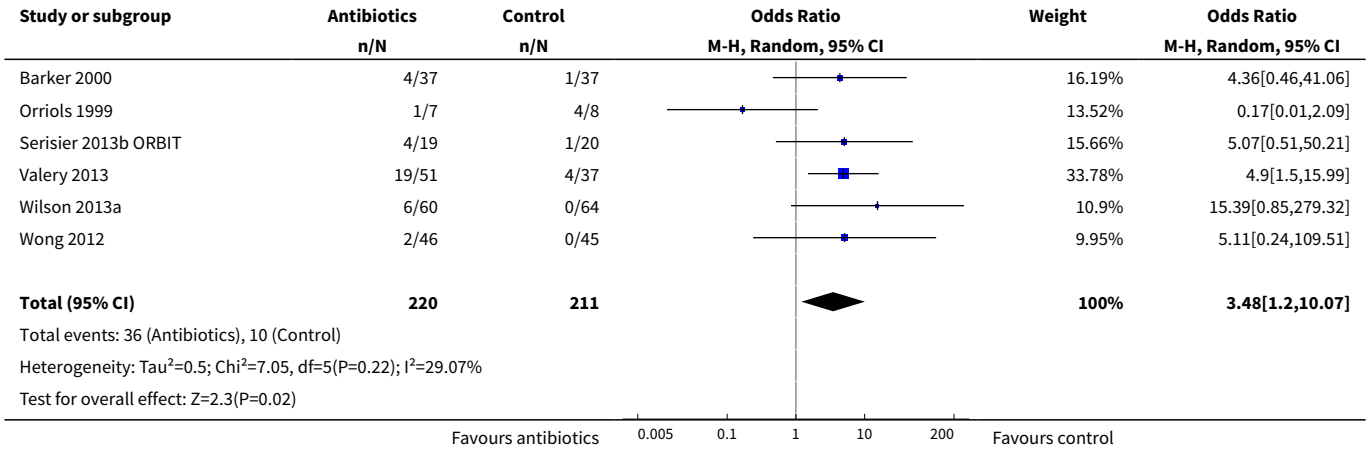





## Analysis 1.8. Comparison 1 Continuous antibiotics versus standard treatment with or without added placebo (parallel groups), Outcome 8 Deaths.

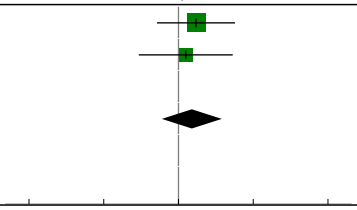



## Analysis 1.9. Comparison 1 Continuous antibiotics versus standard treatment with or without added placebo (parallel groups), Outcome 9 Emergence of resistance.



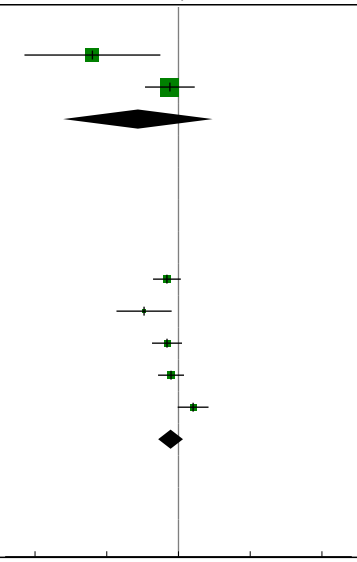
## Analysis 1.10. Comparison 1 Continuous antibiotics versus standard treatment with or without added placebo (parallel groups), Outcome 10 Exercise capacity (6MWD).

| Study or subgroup | Antibiotic N | Antibiotic Mean(SD) | Control N | Control Mean(SD) | Std. Mean Difference Random, 95% CI | Weight | Std. Mean Difference Random, 95% CI |
|---|---|---|---|---|---|---|---|
| Murray 2011 | 27 | 510 (404.5) | 30 | 415 (395) | | 59.18% | 0.23[-0.29,0.76] |
| Serisier 2013b ORBIT | 19 | 0.6 (71.6) | 20 | -7.6 (92.3) | | 40.82% | 0.1[-0.53,0.73] |
| **Total ***** | **46** | | **50** | | | **100%** | **0.18[-0.22,0.58]** |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0.11, df=1(P=0.74); $I^2$=0% | | | | | | | |
| Test for overall effect: Z=0.87(P=0.38) | | | | | | | |



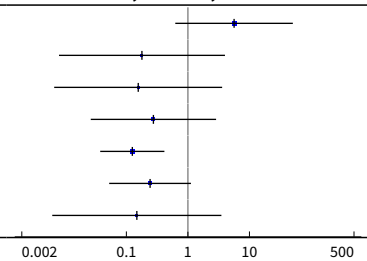

## Analysis 1.11. Comparison 1 Continuous antibiotics versus standard treatment with or without added placebo (parallel groups), Outcome 11 Change in St George Respiratory Questionnaire.

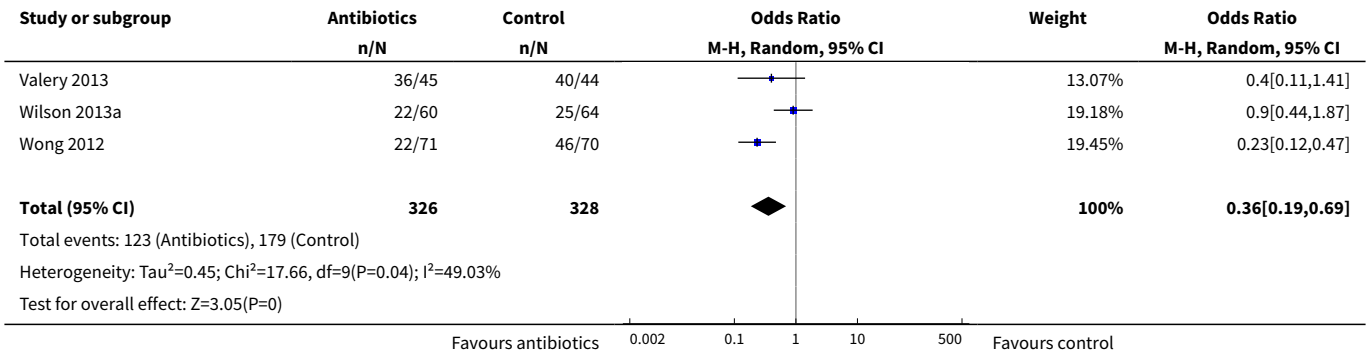
| Study or subgroup | Antibiotics N | Antibiotics Mean(SD) | Control N | Control Mean(SD) | Mean Difference Random, 95% CI | Weight | Mean Difference Random, 95% CI |
|---|---|---|---|---|---|---|---|
| **1.11.1 Symptoms** | | | | | | | |
| De Diego 2013 | 16 | -20 (20) | 14 | 10 (41.2) | | 41.33% | -30[-53.68,-6.32] |
| Serisier 2013a BLESS | 59 | -6 (23.5) | 58 | -3 (24.3) | | 58.67% | -3[-11.66,5.66] |
| **Subtotal ***** | **75** | | **72** | | | **100%** | **-14.16[-40.22,11.9]** |
| Heterogeneity: $Tau^2$=281.73; $Chi^2$=4.4, df=1(P=0.04); $I^2$=77.29% | | | | | | | |
| Test for overall effect: Z=1.06(P=0.29) | | | | | | | |
| **1.11.2 Total** | | | | | | | |
| Altenburg 2013 | 43 | -6.1 (13) | 40 | -2.1 (9.3) | | 22.32% | -4.03[-8.87,0.81] |
| De Diego 2013 | 16 | -7.9 (12.4) | 14 | 4.1 (14.2) | | 12.25% | -12[-21.61,-2.39] |
| Liu 2012 | 24 | -14 (9) | 22 | -10 (9.1) | | 21.33% | -4[-9.22,1.22] |
| Serisier 2013a BLESS | 59 | -3.9 (10) | 58 | -1.3 (14.5) | | 23.14% | -2.6[-7.12,1.92] |
| Serisier 2013b ORBIT | 19 | -1.3 (7.2) | 20 | -6.4 (9.8) | | 20.97% | 5.1[-0.27,10.47] |
| **Subtotal ***** | **161** | | **154** | | | **100%** | **-2.75[-7.08,1.57]** |
| Heterogeneity: $Tau^2$=15.76; $Chi^2$=12.13, df=4(P=0.02); $I^2$=67.02% | | | | | | | |
| Test for overall effect: Z=1.25(P=0.21) | | | | | | | |
| Test for subgroup differences: $Chi^2$=0.72, df=1 (P=0.4), $I^2$=0% | | | | | | | |



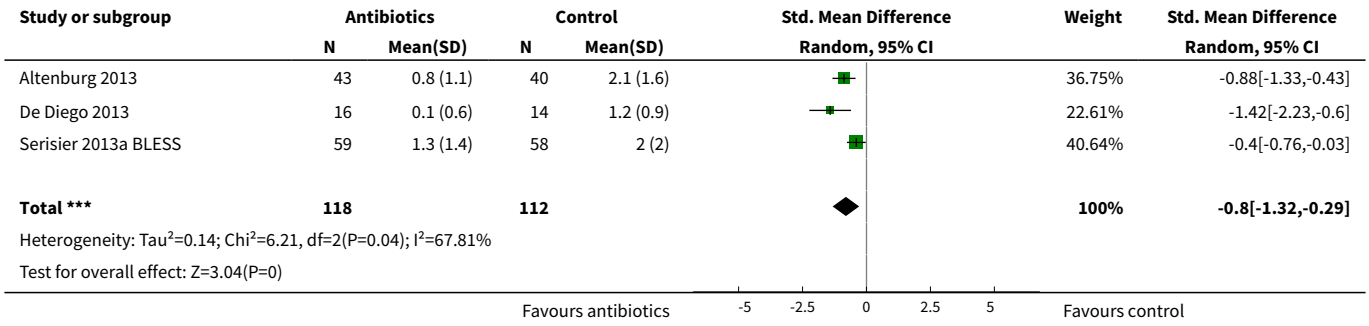

## Analysis 1.12. Comparison 1 Continuous antibiotics versus standard treatment with or without added placebo (parallel groups), Outcome 12 Number of participants with exacerbations.

| Study or subgroup | Antibiotics n/N | Control n/N | Odds Ratio M-H, Random, 95% CI | Weight | Odds Ratio M-H, Random, 95% CI |
|---|---|---|---|---|---|
| Barker 2000 | 5/37 | 1/37 | | 6.62% | 5.63[0.62,50.73] |
| Currie 1990 | 17/19 | 19/19 | | 3.83% | 0.18[0.01,4] |
| Koh 1997 | 0/13 | 2/12 | | 3.75% | 0.16[0.01,3.6] |
| Liu 2012 | 1/24 | 3/22 | | 6.02% | 0.28[0.03,2.87] |
| Murray 2011 | 9/27 | 24/30 | | 13.68% | 0.13[0.04,0.42] |
| Serisier 2013b ORBIT | 11/19 | 17/20 | | 10.68% | 0.24[0.05,1.12] |
| Tsang 1999 | 0/11 | 2/10 | | 3.71% | 0.15[0.01,3.5] |






### Analysis 1.13. Comparison 1 Continuous antibiotics versus standard treatment with or without added placebo (parallel groups), Outcome 13 Exacerbation rates - continuous.




## Comparison 2. Sensitivity analysis (fixed effect): continuous antibiotics versus standard treatment with or without added placebo (parallel groups)

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 1 Exacerbations | 13 | | Odds Ratio (Fixed, 95% CI) | 0.34 [0.25, 0.46] |
| 2 Hospitalisations | 7 | 643 | Odds Ratio (M-H, Fixed, 95% CI) | 0.44 [0.23, 0.87] |
| 3 Lung function | 8 | | Std. Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 3.1 $FEV_1$ % predicted | 5 | 338 | Std. Mean Difference (IV, Fixed, 95% CI) | -0.12 [-0.34, 0.09] |
| 3.2 Change in $FEV_1$ | 3 | 84 | Std. Mean Difference (IV, Fixed, 95% CI) | -0.03 [-0.47, 0.40] |
| 3.3 $FEV_1$ | 2 | 36 | Std. Mean Difference (IV, Fixed, 95% CI) | -0.36 [-1.03, 0.30] |
| 4 Sputum leucocytes | 3 | 165 | Mean Difference (IV, Fixed, 95% CI) | -0.39 [-0.87, 0.09] |
| 5 Erythrocyte sedimentation rate (ESR) | 2 | 87 | Mean Difference (IV, Fixed, 95% CI) | -3.04 [-8.76, 2.68] |

| Outcome or subgroup title | No. of studies | No. of participants | Statistical method | Effect size |
|---|---|---|---|---|
| 6 Emergence of resistance | 6 | 431 | Odds Ratio (M-H, Fixed, 95% CI) | 3.65 [1.74, 7.64] |
| 7 Exercise capacity (6MWD) | 2 | 96 | Std. Mean Difference (IV, Fixed, 95% CI) | 0.18 [-0.22, 0.58] |
| 8 Change in St George Respiratory Questionnaire | 5 | | Mean Difference (IV, Fixed, 95% CI) | Subtotals only |
| 8.1 Symptoms | 2 | 147 | Mean Difference (IV, Fixed, 95% CI) | -6.19 [-14.32, 1.95] |
| 8.2 Total | 5 | 315 | Mean Difference (IV, Fixed, 95% CI) | -2.29 [-4.69, 0.10] |

**Analysis 2.1. Comparison 2 Sensitivity analysis (fixed effect): continuous antibiotics versus standard treatment with or without added placebo (parallel groups), Outcome 1 Exacerbations.**

| Study or subgroup | Antibiotics N | Control N | log[Odds Ratio] (SE) | Odds Ratio IV, Fixed, 95% CI | Weight | Odds Ratio IV, Fixed, 95% CI |
|---|---|---|---|---|---|---|
| Altenburg 2013 | 0 | 0 | -1.6 (0.42) | | 14% | 0.2[0.09,0.46] |
| Barker 2000 | 0 | 0 | 1.7 (1.122) | | 1.96% | 5.62[0.62,50.73] |
| Currie 1990 | 0 | 0 | -1.7 (1.584) | | 0.98% | 0.18[0.01,4] |
| De Diego 2013 | 0 | 0 | -2.6 (0.75) | | 4.39% | 0.08[0.02,0.33] |
| Koh 1997 | 0 | 0 | -1.9 (1.603) | | 0.96% | 0.16[0.01,3.6] |
| Liu 2012 | 0 | 0 | -1.3 (1.196) | | 1.73% | 0.28[0.03,2.87] |
| Murray 2011 | 0 | 0 | -2.1 (0.612) | | 6.58% | 0.13[0.04,0.42] |
| Serisier 2013a BLESS | 0 | 0 | -0.7 (0.34) | | 21.36% | 0.49[0.25,0.95] |
| Serisier 2013b ORBIT | 0 | 0 | -1.4 (0.78) | | 4.06% | 0.24[0.05,1.12] |
| Tsang 1999 | 0 | 0 | -1.9 (1.614) | | 0.95% | 0.15[0.01,3.5] |
| Valery 2013 | 0 | 0 | -0.9 (0.643) | | 5.97% | 0.4[0.11,1.41] |
| Wilson 2013a | 0 | 0 | -0.1 (0.371) | | 17.97% | 0.9[0.44,1.87] |
| Wong 2012 | 0 | 0 | -1.5 (0.36) | | 19.1% | 0.23[0.12,0.47] |
| **Total (95% CI)** | | | | | **100%** | **0.34[0.25,0.46]** |
| Heterogeneity: Tau²=0; Chi²=24.44, df=12(P=0.02); I²=50.9% | | | | | | |
| Test for overall effect: Z=6.84(P<0.0001) | | | | | | |



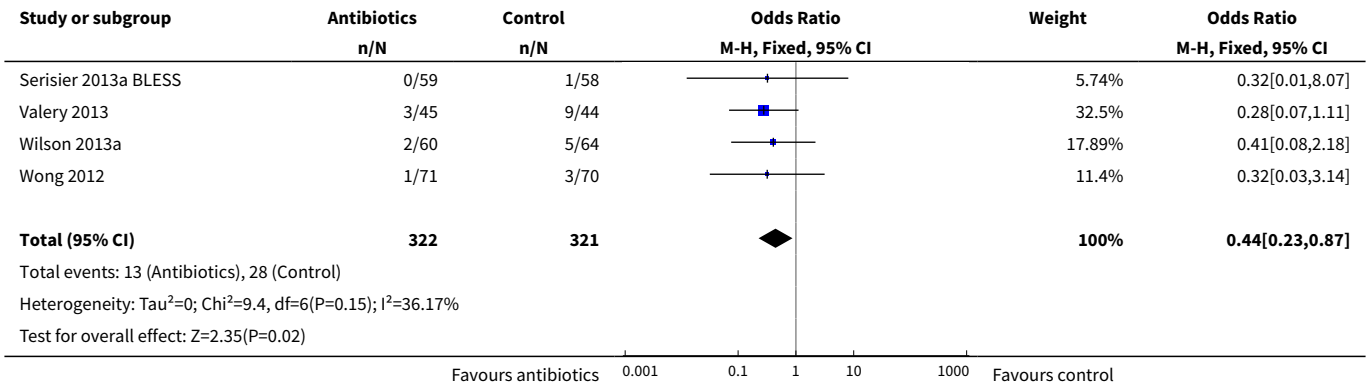

Favours antibiotics — Favours control

**Analysis 2.2. Comparison 2 Sensitivity analysis (fixed effect): continuous antibiotics versus standard treatment with or without added placebo (parallel groups), Outcome 2 Hospitalisations.**

| Study or subgroup | Antibiotics n/N | Control n/N | Odds Ratio M-H, Fixed, 95% CI | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| Altenburg 2013 | 1/43 | 2/40 | | 7.74% | 0.45[0.04,5.19] |
| Barker 2000 | 5/37 | 1/37 | | 3.31% | 5.63[0.62,50.73] |
| Orriols 1999 | 1/7 | 7/8 | | 21.42% | 0.02[0,0.47] |



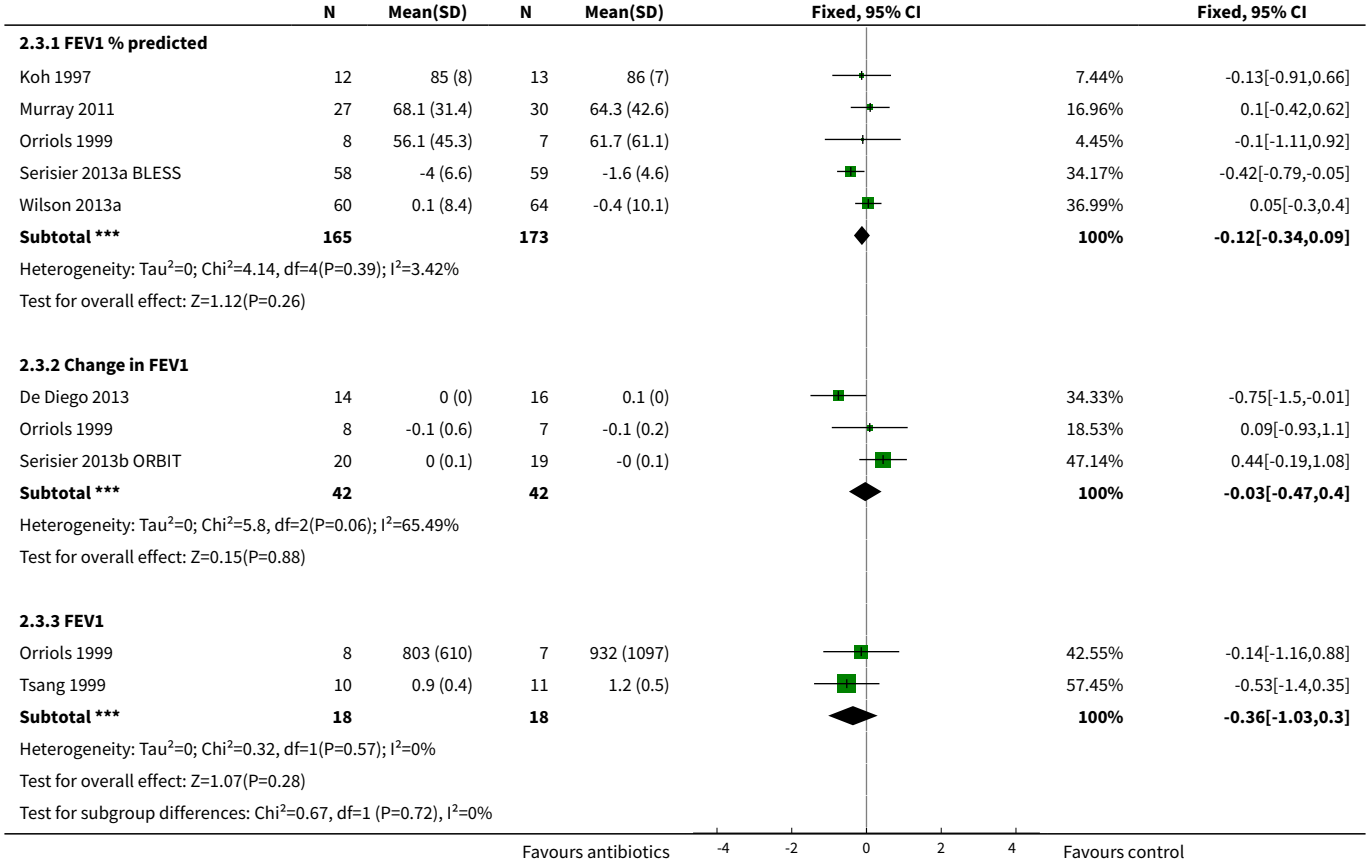

Favours antibiotics — Favours control



| Study or subgroup | Antibiotics n/N | Control n/N | Odds Ratio M-H, Fixed, 95% CI | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| Serisier 2013a BLESS | 0/59 | 1/58 | | 5.74% | 0.32[0.01,8.07] |
| Valery 2013 | 3/45 | 9/44 | | 32.5% | 0.28[0.07,1.11] |
| Wilson 2013a | 2/60 | 5/64 | | 17.89% | 0.41[0.08,2.18] |
| Wong 2012 | 1/71 | 3/70 | | 11.4% | 0.32[0.03,3.14] |
| **Total (95% CI)** | **322** | **321** | | **100%** | **0.44[0.23,0.87]** |
| Total events: 13 (Antibiotics), 28 (Control) | | | | | |
| Heterogeneity: Tau²=0; Chi²=9.4, df=6(P=0.15); I²=36.17% | | | | | |
| Test for overall effect: Z=2.35(P=0.02) | | | | | |



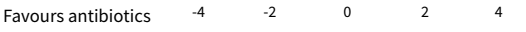
## Analysis 2.3. Comparison 2 Sensitivity analysis (fixed effect): continuous antibiotics versus standard treatment with or without added placebo (parallel groups), Outcome 3 Lung function.



| Study or subgroup | Control N | Control Mean(SD) | Antibiotics N | Antibiotics Mean(SD) | Std. Mean Difference Fixed, 95% CI | Weight | Std. Mean Difference Fixed, 95% CI |
|---|---|---|---|---|---|---|---|
| **2.3.1 FEV1 % predicted** | | | | | | | |
| Koh 1997 | 12 | 85 (8) | 13 | 86 (7) | | 7.44% | -0.13[-0.91,0.66] |
| Murray 2011 | 27 | 68.1 (31.4) | 30 | 64.3 (42.6) | | 16.96% | 0.1[-0.42,0.62] |
| Orriols 1999 | 8 | 56.1 (45.3) | 7 | 61.7 (61.1) | | 4.45% | -0.1[-1.11,0.92] |
| Serisier 2013a BLESS | 58 | -4 (6.6) | 59 | -1.6 (4.6) | | 34.17% | -0.42[-0.79,-0.05] |
| Wilson 2013a | 60 | 0.1 (8.4) | 64 | -0.4 (10.1) | | 36.99% | 0.05[-0.3,0.4] |
| **Subtotal ***** | **165** | | **173** | | | **100%** | **-0.12[-0.34,0.09]** |
| Heterogeneity: Tau²=0; Chi²=4.14, df=4(P=0.39); I²=3.42% | | | | | | | |
| Test for overall effect: Z=1.12(P=0.26) | | | | | | | |
| **2.3.2 Change in FEV1** | | | | | | | |
| De Diego 2013 | 14 | 0 (0) | 16 | 0.1 (0) | | 34.33% | -0.75[-1.5,-0.01] |
| Orriols 1999 | 8 | -0.1 (0.6) | 7 | -0.1 (0.2) | | 18.53% | 0.09[-0.93,1.1] |
| Serisier 2013b ORBIT | 20 | 0 (0.1) | 19 | -0 (0.1) | | 47.14% | 0.44[-0.19,1.08] |
| **Subtotal ***** | **42** | | **42** | | | **100%** | **-0.03[-0.47,0.4]** |
| Heterogeneity: Tau²=0; Chi²=5.8, df=2(P=0.06); I²=65.49% | | | | | | | |
| Test for overall effect: Z=0.15(P=0.88) | | | | | | | |
| **2.3.3 FEV1** | | | | | | | |
| Orriols 1999 | 8 | 803 (610) | 7 | 932 (1097) | | 42.55% | -0.14[-1.16,0.88] |
| Tsang 1999 | 10 | 0.9 (0.4) | 11 | 1.2 (0.5) | | 57.45% | -0.53[-1.4,0.35] |
| **Subtotal ***** | **18** | | **18** | | | **100%** | **-0.36[-1.03,0.3]** |
| Heterogeneity: Tau²=0; Chi²=0.32, df=1(P=0.57); I²=0% | | | | | | | |
| Test for overall effect: Z=1.07(P=0.28) | | | | | | | |
| Test for subgroup differences: Chi²=0.67, df=1 (P=0.72), I²=0% | | | | | | | |

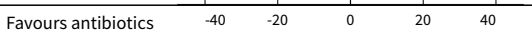
### Analysis 2.4. Comparison 2 Sensitivity analysis (fixed effect): continuous antibiotics versus standard treatment with or without added placebo (parallel groups), Outcome 4 Sputum leucocytes.

| Study or subgroup | Antibiotics N | Antibiotics Mean(SD) | Control N | Control Mean(SD) | Mean Difference Fixed, 95% CI | Weight | Mean Difference Fixed, 95% CI |
|---|---|---|---|---|---|---|---|
| Altenburg 2013 | 43 | 7.6 (2.6) | 40 | 7.5 (2.7) | | 17.36% | 0.1[-1.04,1.24] |
| Koh 1997 | 13 | 1.3 (0.5) | 12 | 1.8 (0.8) | | 78.44% | -0.52[-1.06,0.02] |
| Murray 2011 | 27 | 7.1 (5.6) | 30 | 7.1 (2.7) | | 4.2% | 0[-2.32,2.32] |
| **Total ***** | **83** | | **82** | | | **100%** | **-0.39[-0.87,0.09]** |
| Heterogeneity: $Tau^2$=0; $Chi^2$=1.04, df=2(P=0.59); $I^2$=0% | | | | | | | |
| Test for overall effect: Z=1.61(P=0.11) | | | | | | | |



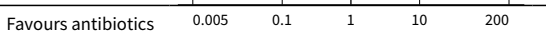

### Analysis 2.5. Comparison 2 Sensitivity analysis (fixed effect): continuous antibiotics versus standard treatment with or without added placebo (parallel groups), Outcome 5 Erythrocyte sedimentation rate (ESR).

| Study or subgroup | Antibiotic N | Antibiotic Mean(SD) | Control N | Control Mean(SD) | Mean Difference Fixed, 95% CI | Weight | Mean Difference Fixed, 95% CI |
|---|---|---|---|---|---|---|---|
| De Diego 2013 | 16 | -14 (4) | 14 | -9 (12) | | 75.52% | -5[-11.58,1.58] |
| Murray 2011 | 27 | 17 (24) | 30 | 14 (20.1) | | 24.48% | 3[-8.56,14.56] |
| **Total ***** | **43** | | **44** | | | **100%** | **-3.04[-8.76,2.68]** |
| Heterogeneity: $Tau^2$=0; $Chi^2$=1.39, df=1(P=0.24); $I^2$=27.98% | | | | | | | |
| Test for overall effect: Z=1.04(P=0.3) | | | | | | | |




### Analysis 2.6. Comparison 2 Sensitivity analysis (fixed effect): continuous antibiotics versus standard treatment with or without added placebo (parallel groups), Outcome 6 Emergence of resistance.

| Study or subgroup | Antibiotics n/N | Control n/N | Odds Ratio M-H, Fixed, 95% CI | Weight | Odds Ratio M-H, Fixed, 95% CI |
|---|---|---|---|---|---|
| Barker 2000 | 4/37 | 1/37 | | 10.27% | 4.36[0.46,41.06] |
| Orriols 1999 | 1/7 | 4/8 | | 36.86% | 0.17[0.01,2.09] |
| Serisier 2013b ORBIT | 4/19 | 1/20 | | 8.86% | 5.07[0.51,50.21] |
| Valery 2013 | 19/51 | 4/37 | | 33.51% | 4.9[1.5,15.99] |
| Wilson 2013a | 6/60 | 0/64 | | 4.98% | 15.39[0.85,279.32] |
| Wong 2012 | 2/46 | 0/45 | | 5.51% | 5.11[0.24,109.51] |
| **Total (95% CI)** | **220** | **211** | | **100%** | **3.65[1.74,7.64]** |
| Total events: 36 (Antibiotics), 10 (Control) | | | | | |
| Heterogeneity: $Tau^2$=0; $Chi^2$=7.05, df=5(P=0.22); $I^2$=29.07% | | | | | |
| Test for overall effect: Z=3.43(P=0) | | | | | |



**Analysis 2.7. Comparison 2 Sensitivity analysis (fixed effect): continuous antibiotics versus standard treatment with or without added placebo (parallel groups), Outcome 7 Exercise capacity (6MWD).**

| Study or subgroup | Antibiotic N | Antibiotic Mean(SD) | Control N | Control Mean(SD) | Std. Mean Difference Fixed, 95% CI | Weight | Std. Mean Difference Fixed, 95% CI |
|---|---|---|---|---|---|---|---|
| Murray 2011 | 27 | 510 (404.5) | 30 | 415 (395) | | 59.18% | 0.23[-0.29,0.76] |
| Serisier 2013b ORBIT | 19 | 0.6 (71.6) | 20 | -7.6 (92.3) | | 40.82% | 0.1[-0.53,0.73] |
| **Total ***** | **46** | | **50** | | | **100%** | **0.18[-0.22,0.58]** |
| Heterogeneity: $Tau^2$=0; $Chi^2$=0.11, df=1(P=0.74); $I^2$=0% | | | | | | | |
| Test for overall effect: Z=0.87(P=0.38) | | | | | | | |




**Analysis 2.8. Comparison 2 Sensitivity analysis (fixed effect): continuous antibiotics versus standard treatment with or without added placebo (parallel groups), Outcome 8 Change in St George Respiratory Questionnaire.**

| Study or subgroup | Antibiotics N | Antibiotics Mean(SD) | Control N | Control Mean(SD) | Mean Difference Fixed, 95% CI | Weight | Mean Difference Fixed, 95% CI |
|---|---|---|---|---|---|---|---|
| **2.8.1 Symptoms** | | | | | | | |
| De Diego 2013 | 16 | -20 (20) | 14 | 10 (41.2) | | 11.8% | -30[-53.68,-6.32] |
| Serisier 2013a BLESS | 59 | -6 (23.5) | 58 | -3 (24.3) | | 88.2% | -3[-11.66,5.66] |
| **Subtotal ***** | **75** | | **72** | | | **100%** | **-6.19[-14.32,1.95]** |
| Heterogeneity: $Tau^2$=0; $Chi^2$=4.4, df=1(P=0.04); $I^2$=77.29% | | | | | | | |
| Test for overall effect: Z=1.49(P=0.14) | | | | | | | |
| **2.8.2 Total** | | | | | | | |
| Altenburg 2013 | 43 | -6.1 (13) | 40 | -2.1 (9.3) | | 24.58% | -4.03[-8.87,0.81] |
| De Diego 2013 | 16 | -7.9 (12.4) | 14 | 4.1 (14.2) | | 6.23% | -12[-21.61,-2.39] |
| Liu 2012 | 24 | -14 (9) | 22 | -10 (9.1) | | 21.07% | -4[-9.22,1.22] |
| Serisier 2013a BLESS | 59 | -3.9 (10) | 58 | -1.3 (14.5) | | 28.15% | -2.6[-7.12,1.92] |
| Serisier 2013b ORBIT | 19 | -1.3 (7.2) | 20 | -6.4 (9.8) | | 19.97% | 5.1[-0.27,10.47] |
| **Subtotal ***** | **161** | | **154** | | | **100%** | **-2.29[-4.69,0.1]** |
| Heterogeneity: $Tau^2$=0; $Chi^2$=12.13, df=4(P=0.02); $I^2$=67.02% | | | | | | | |
| Test for overall effect: Z=1.87(P=0.06) | | | | | | | |
| Test for subgroup differences: $Chi^2$=0.81, df=1 (P=0.37), $I^2$=0% | | | | | | | |




## ADDITIONAL TABLES

**Table 1. Search history**

| Search years | Detail |
|---|---|
| All years to January 2003 | N citations retrieved: 447<br>N studies included: 6 |
| January 2003 to January 2004 | No new studies identified |
| January 2004 to January 2005 | No new studies identified |
| January 2005 to January 2007 | N citations retrieved: 11 |

**Table 1. Search history** *(Continued)*

| | |
|---|---|
| | N retrieved: 4<br>N included: 3 |

**Table 2. Description of characteristics of included studies**

| Study ID | Design | Country | Age (mean ± SD) | | Participants (N) | | Follow-up (weeks) |
|---|---|---|---|---|---|---|---|
| | | | Int | Cont | Int | Cont | |
| Valery 2013 | RCT | Australia/NZ | 3.99 ± 2.14 | 4.22 ± 2.30 | 45 | 44 | 96 |
| De Diego 2013 | RCT | Spain | 57 ± 11 | 61 ± 12 | 16 | 14 | NA |
| Serisier 2013a | RCT | Australia | 61.1 ± 10.5 | 63.5 ± 9.5 | 59 | 58 | 52 |
| Serisier 2013b | RCT | Australia/NZ | 70 ± 5.6 | 59.5 ± 13.2 | 20 | 22 | 24 |
| Altenburg 2013 | RCT | Netherlands | 59.9 ± 12.3 | 64.6 ± 9.1 | 46 | 44 | 52 |
| Wilson 2013a | RCT | Aust; Germany; Spain; Sweden; UK; USA | 64.7 ± 11.8 | 61.4 ± 11.9 | 60 | 64 | 8 |
| Liu 2012 | RCT | China | NA | NA | 24 | 22 | NA |
| Wong 2012 | RCT | NZ | 60.9 ± 13.6 | 59.0 ± 13.3 | 71 | 70 | 52 |
| Murray 2011 | RCT | Scotland | 58 (53-67)‡ | 64 (55.7-69)‡ | 32 | 33 | 64 |
| Yalçin 2006 | RCT | Turkey | 13.1 ± 2.7 | 11.9 ± 2.9 | 17 | 17 | 52 |
| Cymbala 2005 | COT | USA | 70.8 ± 9.7 | 70.8 ± 9.7 | 11 | 11 | 52 to 56 |
| Drobnic 2005 | COT | Spain | 64.5 (38-75)† | 64.5 (38-75)† | 30 | 30 | 52 |
| Barker 2000 | RCT | USA | 66.6 | 63.2 | 37 | 37 | 6 |
| Orriols 1999 | RCT | Spain | 62.0 ± 8.5¶ | 61.4 ± 10.3¶ | 8 | 9 | 52 |
| Tsang 1999 | RCT | China | 50 ± 15 | 59 ± 16 | 14 | 10 | 52 |
| Koh 1997 | RCT | Korea | 13.3 ± 2.5 | 12.9 ± 2.6 | 13 | 12 | 12 |
| Currie 1990 | RCT | UK | 54* | 51* | 19 | 19 | 52 |
| MRC 1957 | RCT | UK | Int 1: 34.3; Int 2: 32.3 | 32.6 | Int 1: 36; Int 2: 44 | 40 | 52 |

* = median; † = mean and range; ‡ = median and IQR; ¶ = mean + SE.

**Table 3. Types of interventions and status of *Pseudomonas aeruginosa***

| Study ID | Patients with PA (baseline) | Patients with PA (end of intervention) | Antibiotics | Control | Delivery mode | Int duration (weeks) | Follow-up (weeks) |
|---|---|---|---|---|---|---|---|
| Altenburg 2013 | 6/43 on intervention, 6/40 on placebo | 5/43 on intervention, 4/40 on placebo | Azithromycin | Placebo | Oral | 52 | 52 |
| De Diego 2013 | 7/16 on intervention, 5/14 on control | 0/16 on intervention | Azithromycin | Usual care | Oral | 12 | 12# |
| Serisier 2013 BLESS | 23/59 on intervention, 18/58 on placebo | 17/59 on intervention, 17/58 on placebo | Erythromycin | Placebo | Oral | 52 | 52 |
| Valery 2013 | 0/45 on intervention, 0/44 on placebo | 0/45 on intervention, 0/44 on placebo | Azithromycin | Placebo | Oral | 82.8 (mean) | 96 |
| Liu 2012 | NA | NA | Roxithromycin | Placebo | Oral | 24 | 24 |
| Wong 2012 EM-BRACE | 9/71 on intervention, 8/70 on placebo | 5/46 on intervention, 5/45 on placebo* | Azithromycin | Placebo | Oral | 24 | 52 |
| Yalçin 2006 | NA | NA | Clarithromycin | Usual care | Oral | 12 | 52 |
| Cymbala 2005 | NA | NA | Azithromycin | Usual care | Oral | 26 | 52 to 56 |
| Tsang 1999 | NA | 10/11 on intervention, 6/10 on placebo | Erthromycin | Placebo | Oral | 8 | 52 |
| Koh 1997 | NA | NA | Roxithromycin | Placebo | Oral | 12 | 12 |
| Currie 1990 | 8/17 on intervention, 7/19 on placebo | 5/17 on intervention, 4/19 on placebo | Amoxycillin | Placebo | Oral | 32 | 52 |
| MRC 1957 | NA | NA | Int 1: penicillin | Placebo | Oral | 52 | 52 |
| | | | Int 2: oxytetracycline | | | | |
| Serisier 2013 ORBIT | 20/20 on intervention, 22/22 on placebo | 8/20 on intervention, 19/22 on placebo† | Ciprofloxacin | Placebo | Inhaled | 24 | 24 |

**Table 3. Types of interventions and status of *Pseudomonas aeruginosa*** *(Continued)*

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Wilson 2013a | 32/60 on intervention, 35/64 on placebo | 14/40 on intervention, 4/49 on placebo‡ | Ciprofloxacin | Placebo | Inhaled | 4 | 8 |
| Drobnic 2005 | 30/30 on intervention, 30/30 on placebo | 26/30 on intervention§ | Tobramycin | Placebo | Nebulised | 26 | 52 |
| Barker 2000 | 37/37 on intervention, 37/37 on placebo | 13/37 on intervention, 0/37 on placebo* | Tobramycin | Placebo | Nebulised | 4 | 6 |
| Orriols 1999 | 7/7 on intervention, 8/8 on control | 7/7 on intervention, 8/8 on control | Ceftazidime/to-bramycin | Symptomatic treatment | Nebulised | 52 | 52 |
| Murray 2011 | 13/27 on intervention, 11/30 on placebo | 4/13 on intervention* | Gentamicin | Placebo | Nebulised | 52 | 64 |

PA = *Pseudomonas aeruginosa*. *Eradicated. †At day 28. ‡Negative bacterial culture at end of intervention. §Transient disappearance of *Pseudomonas* in culture. #Actual follow-up period was not reported.

# APPENDICES

## Appendix 1. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

**Electronic searches: core databases**

| Database | Frequency of search |
|---|---|
| CENTRAL | 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 |
| 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**

***Bronchiectasis search***

1. exp Bronchiectasis/

2. bronchiect$.mp.

3. bronchoect$.mp.

4. kartagener$.mp.

5. (ciliary adj3 dyskinesia).mp.

6. (bronchial$ adj3 dilat$).mp.

7. or/1-6

***Filter to identify RCTs***

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

2. (randomized 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 2. Search strategy for the Cochrane Airways Group Register

**2013 search**

#1 BRONCH:MISC1

#2 MeSH DESCRIPTOR Bronchiectasis Explode All

#3 bronchiect*

#4 #1 or #2 or #3

#5 MeSH DESCRIPTOR Anti-Bacterial Agents Explode 1

#6 antibiotic* or anti-biotic*

#7 anti-bacteri* or antibacteri*

#8 *cillin

#9 *mycin

#10 *oxacin

#11 *tetracycline

#12 macrolide*

#13 quinolone*

#14 trimethoprim

#15 ceph*

#16 sulpha*

#17 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16

#18 #4 and #17

*[In search line #1, MISC1 denotes the field where the reference has been coded for condition, in this case, bronchiectasis]*

***Previous search (used until 2011)***

*cillin OR antibiotic* OR *tetracycline OR *mycin OR macrolide* OR quinolone* OR *oxacin OR trimethoprim OR *sulpha OR *ceph or antibacteri* or "anti bacteri*"

[Limited to bronchiectasis records]

## WHAT'S NEW

| Date | Event | Description |
|---|---|---|
| 9 August 2017 | Amended | New literature search run to assess the need to update this review. Twenty eight potentially eligible studies identified and added to Studies awaiting classification. |

## HISTORY

Protocol first published: Issue 2, 2000
Review first published: Issue 4, 2003

| Date | Event | Description |
|---|---|---|
| 21 February 2014 | New search has been performed | Literature search run |
| 21 February 2014 | New citation required and conclusions have changed | 9 additional studies identified (total now: n = 18); stronger evidence base available with clear benefit in terms of reduced hospitalisation and exacerbations |
| 14 January 2011 | New search has been performed | New literature search run. No new studies identified. Minor copy-edits made to 'Risk of bias' table and layout of review |
| 18 August 2008 | Amended | Converted to new review format |
| 4 January 2008 | New search has been performed | Literature search re-run. New excluded study: Bilton 2006 |
| 20 February 2007 | New citation required and conclusions have changed | New studies: Cymballa 2005; Drobnic 2005; Yalcin 2006<br><br>These 3 studies used a cross-over design and brought additional data on quality of life, lung function, exacerbation rates and adverse events<br><br>As differences in the design of these studies prevented us from pooling their findings with those of the other trials included in the review, they have not had a significant impact on the conclusions of the review<br><br>Additional trials needed in children |

## CONTRIBUTIONS OF AUTHORS

KH updated the protocol, selected RCTs for inclusion, assessed the quality of papers and risk of bias, extracted data, described the studies, conducted data analysis and assisted in manuscript preparation.

CN selected RCTs for inclusion, assessed the quality of papers, performed risk of bias assessments and extracted data.

KVC updated the protocol, performed data analysis and assisted in manuscript preparation.

DE updated the previous version of this review and were involved in manuscript preparation for this update.

BS updated the protocol and assisted in manuscript preparation.

## DECLARATIONS OF INTEREST

None known.

## SOURCES OF SUPPORT

### Internal sources

- Department of Respiratory and Sleep Service, Flinders Medical Centre, Australia.
- Department of Respiratory Medicine, The Queen Elizabeth Hospital, Australia.

### External sources

- No sources of support supplied

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The presence of clinical heterogeneity between treatments used in this review precluded the assumption of a fixed-effect model (with a single treatment effect for all studies). As such, the primary analyses were changed to a random-effects model, with a fixed-effect model included as a sensitivity analysis.

The small number of paediatric studies and the presence of high heterogeneity between them led to the decision that pre-specified subgroup analyses for paediatric versus adult populations would not be performed.

The order of the outcomes was changed. Acute exacerbations and hospitalisations was added as a primary outcome. Methods were updated to the latest Cochrane methodological expectations, and a 'Summary of findings' table, a 'Characteristics of included studies' table and a table reporting types of interventions and status of *Pseudomonas aeruginosa* were added.

## NOTES

We selected outcomes for Summary of findings for the main comparison on the basis of what respiratory clinicians (KH, CN and BJS) believed to be the most relevant clinical outcomes that would likely be used to inform patient care.

## INDEX TERMS

### Medical Subject Headings (MeSH)

Anti-Bacterial Agents [*administration & dosage] [adverse effects]; Bronchiectasis [*drug therapy] [microbiology]; Diarrhea [chemically induced]; Disease Progression; Drug Resistance, Bacterial; Hospitalization [statistics & numerical data]; Odds Ratio; Randomized Controlled Trials as Topic; Time Factors

### MeSH check words

Adult; Child; Humans; Middle Aged