# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEADER</td>
<td>1</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>1</td>
</tr>
<tr>
<td>BACKGROUND</td>
<td>1</td>
</tr>
<tr>
<td>OBJECTIVES</td>
<td>3</td>
</tr>
<tr>
<td>METHODS</td>
<td>3</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>6</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>6</td>
</tr>
<tr>
<td>APPENDICES</td>
<td>8</td>
</tr>
<tr>
<td>CONTRIBUTIONS OF AUTHORS</td>
<td>10</td>
</tr>
<tr>
<td>DECLARATIONS OF INTEREST</td>
<td>10</td>
</tr>
<tr>
<td>SOURCES OF SUPPORT</td>
<td>10</td>
</tr>
</tbody>
</table>

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Macrolide antibiotics for non-cystic fibrosis bronchiectasis (Protocol)  
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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To determine the impact of macrolide antibiotics in the treatment of adults and children with non-cystic fibrosis bronchiectasis.

BACKGROUND

Description of the condition

Bronchiectasis is a chronic respiratory disease characterised by abnormal and irreversible dilatation and distortion of the smaller airways (Pasteur 2010). Bacterial colonisation of the damaged airways leads to chronic cough and sputum production, often with breathlessness and with further structural damage to the airways. Diagnosis is by computed tomography (CT) scanning of the chest when the appropriate clinical symptoms are identified (Chang 2010) but asymptomatic radiological evidence of bronchiectasis is possible (Kwak 2010).

Bronchiectasis has many causes, generally involving either major or repeated insults to the lungs. Severe infections including pneumonia, tuberculosis and pertussis may cause bronchiectasis, particularly if they occur during childhood whilst lungs are still developing. Connective tissue disorders and defects in the immune system are other common causes of bronchiectasis, but many cases are idiopathic. Cystic fibrosis leads to a severe, progressive bronchiectasis and is usually considered a separate entity from 'non-cystic fibrosis' bronchiectasis. This review will exclude bronchiectasis secondary to cystic fibrosis.

Estimates of the prevalence of bronchiectasis vary considerably. Although it has previously been considered a relatively rare disease (Kolbe 1996), more recent studies have suggested an increasing prevalence, particularly in those over 75 years (Weycker 2005), and higher prevalence rates in low-income and middle-income countries (Habesoglu 2011). Prevalence rates per 100,000 were estimated at 0.5 in Finland and 3.7 in New Zealand though these data are more than 10 years old (European Lung White Book 2013). Higher prevalence rates are associated with the over 60s, women, and vary by ethnicity (Chang 2003; Seitz 2012). Recent data suggest that incidence and prevalence in the UK may be higher than previously estimated (Quint 2010). Over a nine-year period to 2013, point prevalence rates per 100,000 rose from 350.5 to...
Mortality rates in England and Wales rose by 3% per year between 2001 to 2007 (Roberts 2010), and hospitalisations also increased by 3% per year over a nine-year period in the US (Seitz 2010). Average mortality rates per 100,000 general population in Europe are estimated at 0.3 in 27 of the 28 countries in the EU (ranging from 0.01 in Germany to 1.18 in the UK) and 0.2 in nine non-EU countries (ranging from 0.01 in Azerbaijan to 0.67 in Kyrgyzstan), based on 2005 to 2009 data (European Lung White Book 2013). The recent UK study reported higher age-adjusted mortality rates, with estimates 2.26 times higher in women and 2.14 times higher in men compared to the general population (Quint 2016).

### Description of the intervention

Chronic airway infection with pathogens such as *Pseudomonas aeruginosa* and *Haemophilus influenzae* and neutrophil-mediated airway inflammation are the key drivers of disease progression and poor outcome in bronchiectasis (Chalmers 2012; Chalmers 2014; Finch 2015). Long-term antibiotic therapy is therefore often prescribed with the intention of suppressing bacterial load and reducing airway inflammation (Chalmers 2012). This in turn aims to reduce exacerbations, improve symptoms and improve quality of life (Haworth 2014). Prolonged antibiotic treatment can be administered in the form of oral or inhaled antibiotics. Inhaled antibiotics have the advantage of delivering a higher dose of the drug directly to the site of bronchiectasis infection, with less potential for collateral damage and resistance, however, they are often time consuming to administer (Brodt 2014). Oral antibiotics by contrast are typically cheaper and easier to administer than inhaled antibiotics.

Oral antibiotics may be given at lower dose than those used to treat acute infections, with the aim to reduce adverse effects and promote compliance (Haworth 2014). Macrolide antibiotics are antibacterial agents with anti-inflammatory and immunomodulatory properties (Haworth 2014). Long-acting macrolide antibiotics such as azithromycin can be given intermittently rather than requiring daily dosing. Penicillins, tetracyclines and macrolides have all been tested as prolonged therapy in bronchiectasis (Pasteur 2010). National guidelines for bronchiectasis, such as those from the British Thoracic Society suggest considering the use of long-term antibiotic treatment in patients with three or more exacerbations per year (Pasteur 2010). Long-term use of macrolides in bronchiectasis is supported by their ease of administration, their effectiveness in cystic fibrosis and other neutrophilic lung diseases and their reported anti-inflammatory properties (Saiman 2003). Balanced against this is the potential for macrolides to induce antibiotic resistance, the potential for antibiotic-related adverse effects, hearing impairment and cardiotoxicity (Serisier 2013).

### How the intervention might work

Exacerbations, symptoms and quality of life are directly linked to bacterial infection and airway inflammation in bronchiectasis (Chalmers 2012; Chalmers 2014). Macrolides are given as both antibacterial and anti-inflammatory drugs, although it is unclear which of these properties is primarily responsible for the clinical effect observed in cystic fibrosis or bronchiectasis. Macrolides bind reversibly to the 50s ribosomal subunit, preventing bacterial protein synthesis (Haworth 2014). They therefore have broad activity against Gram-positive organisms such as *Staphylococci* and *Streptococci*, and a degree of activity against Gram-negative organisms such as *Haemophili*. Interestingly, they show no bacteriocidal activity against *Pseudomonas* but may modify virulence by interfering with quorum sensing and virulence factors (Kohler 2010). The anti-inflammatory effects of macrolides have been known for decades, classically demonstrated in their effectiveness against diffuse panbronchiolitis (Amsden 2005). Macrolides contain a macrocyclic lactone ring that is thought to be responsible for the majority of the anti-inflammatory effects (Haworth 2014). Macrolides are classified according to the number of lactone rings as 14-, 15- and 16-member ring macrolides. Macrolides have potentially beneficial effects at every level of the ‘vicious cycle’ of bronchiectasis. They reduce the secretion of pro-inflammatory cytokines from epithelial cells, inhibit leukocyte recruitment to the airway, inhibit neutrophil activation and reduce oxidative stress (Zarogoulidis 2012).

Thus potential benefits of macrolides will include the suppression of bacterial infection, leading to reduced exacerbations, reduced cough and sputum production and improved lung function and quality of life.

### Why it is important to do this review

Non-cystic fibrosis bronchiectasis is associated with a mortality rate more than twice that of the general population; 2.26 times higher in women and 2.14 times higher in men (Quint 2016). Frequent exacerbations impair quality of life and lead to progressive lung damage with permanent loss of lung function (Martinez-Garcia 2007). Drug interventions which are effective in reducing the frequency of exacerbations should therefore be of both short- and long-term benefit to patients with bronchiectasis. A Cochrane review of short-term antibiotics showed there was little evidence on which to base a recommendation, with one small trial showing evidence of global improvement and pathogen eradication.
A further Cochrane review of long-term antibiotic therapy included 18 trials of moderate quality and provided evidence of a reduction in exacerbation frequency and hospitalisation, but an increase in drug resistance (Hnin 2015). Neither of these reviews examined effects by class of antibiotics and did not specifically subgroup by macrolide therapy. A Cochrane overview concluded that further evidence is required on the efficacy of antibiotics in terms of eradication of specific bacterial colonisation and the extent of antibiotic resistance (Welsh 2015). The importance of this question was further reinforced by recent recommendations from the European Task Force on bronchiectasis that named research on macrolide therapy as one of the key priorities in bronchiectasis (Aliberti 2016). Macrolides may potentially reduce bronchiectasis exacerbations. Given their drawbacks, particularly cardiac toxicity (Ray 2012) and the potential for selecting for antibiotic-resistant organisms (Leclercq 2002), robust evidence for their effectiveness is needed for them to be used with confidence for this indication.

This review is being conducted alongside two other closely related reviews: ‘Dual antibiotics for non-cystic fibrosis bronchiectasis’ and ‘Head to head trials of antibiotics for non-cystic fibrosis bronchiectasis.’

### Objectives

To determine the impact of macrolide antibiotics in the treatment of adults and children with non-cystic fibrosis bronchiectasis.

### Methods

#### Criteria for considering studies for this review

**Types of studies**

We will include randomised controlled trials (RCTs) of at least four weeks duration. We will include cross-over studies, but will only use data from the first pre-cross-over phase to eliminate potentially irreversible carry-over effects (e.g. antibiotic resistance). We will include studies reported as full-text, those published as abstract only, and unpublished data.

**Types of participants**

We will include adult and paediatric participants diagnosed with bronchiectasis by bronchography, plain film chest radiograph, or high-resolution computed tomography who report daily sputum expectoration for at least three months. We will not exclude participants diagnosed by radiography alone. When a study includes participants with different respiratory conditions, we will only include that study if there is a separate subgroup analysis conducted for participants with bronchiectasis. Studies will be excluded if participants have been receiving continuous or high-dose antibiotics immediately before the study, or if they have received a diagnosis of cystic fibrosis, sarcoidosis or allergic bronchopulmonary aspergillosis. We will define the paediatric population as those from six months to 18 years of age.

**Types of interventions**

We will include studies comparing macrolide antibiotics with placebo, standard care or non-macrolide antibiotics in the long-term management of stable bronchiectasis. These different comparisons will be considered separately. We will exclude studies looking at short-term macrolides for the treatment (as opposed to prevention) of exacerbations of bronchiectasis.

**Types of outcome measures**

Where possible we will assess exacerbation and hospitalisation rates at 12 months. We will estimate annual rates in studies reporting shorter follow-up times. We will collect outcome data at a range of follow-up points that will best reflect the available evidence from included studies, e.g. end of study, end of follow-up, change from baseline.

#### Primary outcomes

1. Exacerbations (defined using study authors’ criteria).
2. Hospitalisation (defined using study authors’ criteria).
3. Adverse events and serious adverse events using the definitions from Hansen 2015 as follows.
   i) Adverse events are unwanted outcomes undetectable by the patient; usually identified by laboratory tests (e.g. biochemical, haematological, immunological, radiological, pathological tests) or by clinical investigations (e.g. gastrointestinal endoscopy, cardiac catheterisation).
   ii) Serious adverse events are those that result in death or life-threatening events; requirement for hospitalisation or prolongation of existing hospitalisation; persistent or significant disability; or congenital anomalies, or are events that are considered medically important.

#### Secondary outcomes

1. Sputum volume and purulence.
2. Measures of lung function (e.g. forced expiratory volume in one second (FEV<sub>1</sub>)).
3. Systemic markers of infection (e.g. leucocyte count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR)).
4. Adverse events (e.g. cardiac arrhythmias, gastrointestinal symptoms, hearing impairment).
5. Mortality (we will extract and report whether this is defined as all-cause or bronchiectasis-related in the individual studies).
6. Emergence of resistance to antibiotics.
7. Exercise capacity (e.g. the Six-Minute Walk Distance test (6MWD)).
8. Quality of life (e.g. St George Respiratory Questionnaire (SGRQ)).

Reporting one or more of the outcomes listed here in the study will not be an inclusion criterion for the review.

Search methods for identification of studies

Electronic searches
We will identify studies from the Cochrane Airways Group’s Specialised Register (CAGR), which is maintained by the Information Specialist 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, CINAHL (Cumulative Index to Nursing and Allied Health Literature), AMED (Allied and Complementary Medicine), and PsycINFO, and handsearching of respiratory journals and meeting abstracts (please see Appendix 1 for further details). We will search all records in the CAGR using the search strategy in Appendix 2.

We will also conduct a search of the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch).

We will search all databases from their inception to the present, and we will impose no restriction on language of publication.

Searching other resources
We will check reference lists of all primary studies and review articles for additional references. We will search relevant manufacturers’ websites for study information.

We will search for errata or retractions from included studies published in full-text on PubMed (www.ncbi.nlm.nih.gov/pubmed) and report the date this was done within the review.

Data collection and analysis

Selection of studies
Two review authors (James Chalmers (JC) and David Evans (DE)) will independently screen titles and abstracts for inclusion of all the potential studies we identify as a result of the search and code them as ‘retrieve’ (eligible or potentially eligible/unclear) or ‘do not retrieve’. We will retrieve the full-text study reports/publication and two review authors (JC and DE) will independently screen the full-text, identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third review author (Sally Spencer (SS) or Stephen J Milan (SJM)). We will identify and exclude duplicates and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail so as to complete a PRISMA flow diagram and Characteristics of excluded studies table (Moher 2009).

Assessment of risk of bias in included studies
Two review authors (Nicola Relph (NR) and LF) will independently assess risk of bias for each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011). We will resolve any disagreements by discussion or by involving another review author (SS or SJM). We will assess the risk of bias according to the following domains.
1. Random sequence generation.
Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations form it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will analyse dichotomous data as odds ratios and continuous data as mean difference or standardised mean difference. We will analyse hospitalisation and exacerbation rates as rate ratios where possible. We will enter data presented as a scale with a consistent direction of effect.

We will undertake meta-analyses only where this is meaningful i.e. if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense.

We will narratively describe skewed data reported as medians and interquartile ranges.

Where multiple trial arms are reported in a single trial, we will include only the relevant arms. If two comparisons (e.g. drug A versus placebo and drug B versus placebo) are combined in the same meta-analysis, we will halve the control group to avoid double-counting.

Unit of analysis issues

In all included studies the unit of analysis will be the participant. In terms of exacerbation rates and admission rates we plan to focus on the number of events experienced by the participant during the trial. Where cross-over trials are included we will only use data from the first pre-cross-over phase to minimise potential bias from carry-over effects.

Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as abstract only). Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis.

Assessment of heterogeneity

We will use the I² statistic to measure heterogeneity among the studies in each analysis. If we identify substantial heterogeneity we will report it and explore possible causes by prespecified subgroup analysis.

Assessment of reporting biases

If we are able to pool more than 10 studies, we will create and examine a funnel plot to explore possible small study and publication biases.

Data synthesis

Outcomes will be included in meta-analyses where the study designs, interventions and outcomes are similar. Where substantial heterogeneity (> 50%) is identified we will report outcomes in the test, giving direction and size of the effect along with the strength of the evidence (risk of bias). It is likely that antibiotic studies will vary by population, design and outcomes, therefore meta-analysis using a random-effects model would be most appropriate. However, where there are few studies or the effects of interventions across studies are not randomly distributed (for example, with publication bias), the estimates from a random-effects model may be unreliable or biased. It is likely that this review will only include a small number of low powered studies, therefore we will use a fixed-effect model, reported with 95% confidence intervals (CI), and evaluate the impact of model choice using a sensitivity analysis. We will synthesise and report dichotomous and continuous data separately for each outcome (e.g. exacerbation/no exacerbation or exacerbation duration). Where end-of-study point estimates and change from baseline scores are reported we will analyse these separately.

'Summary of findings' table

We will create a 'Summary of findings' table using the following primary and secondary outcomes: exacerbations, hospitalisation, serious adverse events, deaths, quality of life. We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies which contribute
data to the meta-analyses for the prespecified outcomes. We will use methods and recommendations described in Section 8.5 and Chapter 12 of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011) using GRADEProGDT software (GRADEproGDT). We will justify all decisions to downgrade or upgrade the quality of studies using footnotes and we will make comments to aid the reader’s understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses.

1. Children versus adults.
2. Macrolides versus other classes of long-term antibiotics.
3. Type of macrolide.
4. Dose and frequency.
5. Duration.

We will use the following outcomes in subgroup analyses.

1. Exacerbations.
2. Hospitalisation.
3. Serious adverse events.

Sensitivity analysis

We plan to evaluate the effects of methodological study quality by removing those at high or unclear risk of bias for the domains of random sequence generation or allocation concealment. We will also conduct a separate analysis including only those comparing macrolides with a placebo-controlled group.

ACKNOWLEDGEMENTS

We would like to thank Edge Hill University for their support for this review. We would also like to thank Cochrane Airways for their support.

Rebecca Normansell was the Editor and commented critically on the protocol.

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

REFERENCES

Additional references

Aliberti 2016

Amsden 2005
Amsden GW. Anti-inflammatory effects of macrolides-an under appreciated benefit in the treatment of community-acquired respiratory tract infections and chronic inflammatory pulmonary conditions!.

Chang 2003

Chang 2010

European Lung White Book 2013

Finch 2015
Macrolide antibiotics for non-cystic fibrosis bronchiectasis (Protocol)

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Seitz 2012

Serisier 2013

Welsh 2015

Weycker 2005

Wurzel 2011

Zarogoulidis 2012

* Indicates the major publication for the study

**APPENDICES**

Appendix 1. Sources and search methods for the Cochrane Airways Group’s Specialised Register (CAGR)

Electronic searches: core databases

<table>
<thead>
<tr>
<th>Database</th>
<th>Frequency of search</th>
</tr>
</thead>
<tbody>
<tr>
<td>CENTRAL (the Cochrane Library)</td>
<td>Monthly</td>
</tr>
<tr>
<td>MEDLINE (Ovid)</td>
<td>Weekly</td>
</tr>
<tr>
<td>Embase (Ovid)</td>
<td>Weekly</td>
</tr>
<tr>
<td>PsycINFO (Ovid)</td>
<td>Monthly</td>
</tr>
<tr>
<td>CINAHL (EBSCO)</td>
<td>Monthly</td>
</tr>
<tr>
<td>AMED (EBSCO)</td>
<td>Monthly</td>
</tr>
</tbody>
</table>

Handsearches: core respiratory conference abstracts
<table>
<thead>
<tr>
<th>Conference</th>
<th>Years searched</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Academy of Allergy, Asthma and Immunology (AAAAI)</td>
<td>2001 onwards</td>
</tr>
<tr>
<td>American Thoracic Society (ATS)</td>
<td>2001 onwards</td>
</tr>
<tr>
<td>Asia Pacific Society of Respirology (APSR)</td>
<td>2004 onwards</td>
</tr>
<tr>
<td>British Thoracic Society Winter Meeting (BTS)</td>
<td>2000 onwards</td>
</tr>
<tr>
<td>Chest Meeting</td>
<td>2003 onwards</td>
</tr>
<tr>
<td>International Primary Care Respiratory Group Congress (IPCRG)</td>
<td>2002 onwards</td>
</tr>
<tr>
<td>Thoracic Society of Australia and New Zealand (TSANZ)</td>
<td>1999 onwards</td>
</tr>
</tbody>
</table>

**MEDLINE search strategy used to identify trials for the CAGR**

**Bronchiectasis search**
1. exp Bronchiectasis/
2. bronchiect$.mp.
3. bronchoect$.mp.
4. cartagener$.mp.
5. (ciliary adj3 dyskinesia).mp.
6. (bronchial$ adj3 dilat$).mp.
7. or/1-6

**Filter to identify randomised controlled trials (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 (Lefebvre 2011) are adapted to identify trials in other electronic databases.
Appendix 2. Search strategy to identify relevant trials from the CAGR

#1 BRONCH:MISC1
#2 MeSH DESCRIPTOR Bronchiectasis Explode All
#3 bronchiect*  
#4 #1 or #2 or #3
#5 MeSH DESCRIPTOR Macrolides Explode 1 2 3  
#6 macrolide*  
#7 azithromycin*  
#8 clarithromycin*  
#9 erythromycin*  
#10 roxithromycin*  
#11 spiramycin*  
#12 telithromycin*  
#13 troleandomycin*  
#14 josamycin*  
#15 Midecamycin*  
#16 Oleandomycin*  
#17 Solithromycin*  
#18 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17
#19 #4 AND #18  
(Note: in search line #1, MISC1 denotes the field in the record where the reference has been coded for condition, in this case, bronchiectasis)

Contributions of Authors
All authors contributed to the Background section.
Stephen J Milan and Sally Spencer contributed to the Methods section.

Declarations of Interest
Sally Spencer, Carol Kelly and Nicola Relph are named co-investigators on a study funded by Edge Hill University to develop a series of reviews on bronchiectasis and Lambert Felix is supported by that funding. No funding was received for this systematic review by any of the other authors.

James D Chalmers declares grant support from Pfizer, AstraZeneca and GlaxoSmithKline. In addition he is part of an innovative medicines initiative consortium that includes Novartis and Basilea. He has participated in advisory boards for Bayer Healthcare, Chiesi and Raptor Pharmaceuticals. He has received fees for speaking from Napp, AstraZeneca, BI and Pfizer. None of these conflicts of interest are related to the work of this review and are unrelated to the topic of the review.

Sources of Support
Internal sources

• Edge Hill University, UK.
Funded Lambert Felix to provide support for a series of reviews on bronchiectasis.

External sources

• National Institute for Health Research (NIHR), UK.
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