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Macrolides for chronic asthma (Review)

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[Intervention Review]

Macrolides for chronic asthma

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ABSTRACT

Background

Asthma is a chronic disease in which inflammation of the airways causes symptomatic coughing, wheezing, and difficult breathing. The inflammation may have different underlying causes, including a reaction to infection in the lungs. Macrolides are antibiotics with antimicrobial and antiinflammatory activities that have been used long-term to control asthma symptoms.

Objectives

To assess the effects of macrolides for managing chronic asthma.

Search methods

We searched the Cochrane Airways Group Specialised Register up to April 2015. We also manually searched bibliographies of previously published reviews and conference proceedings and contacted study authors. We included records published in any language in the search.

Selection criteria

Randomised controlled clinical trials involving both children and adults with chronic asthma treated with macrolides versus placebo for more than four weeks .

Data collection and analysis

Two reviewers independently examined all records identified in the searches then reviewed the full text of all potentially relevant articles before extracting data in duplicate from all included studies.

Main results

Twenty-three studies met the inclusion criteria, randomising a total of 1513 participants to receive macrolide or placebo. The quality of evidence was generally very low due to incomplete reporting of study methodology and clinical data, suspected publication bias, indirectness of study populations, risk of bias and imprecision (because of small numbers of patients and events). Most of the included studies reported data from patients with persistent or severe asthma, but inclusion criteria, interventions and outcomes were highly variable.

Macrolides were not found to be better than placebo for the majority of clinical outcomes including exacerbations requiring hospital admission (odds ratio (OR) 0.98, 95% confidence interval (CI) 0.13 to 7.23; participants = 143; studies = 2; I^2 = 0%) or at least treatment with oral steroids (OR 0.82, 95% CI 0.43 to 1.57; participants = 290; studies = 5; I^2 = 0%). The evidence on asthma control (standardised mean difference (SMD) -0.05, 95% CI -0.26 to 0.15), quality of life (mean difference (MD) 0.06, 95% CI -0.12 to 0.24) and rescue medication use (MD -0.26, 95% CI -0.65 to 0.12) was all of very low quality and did not show a benefit of macrolide treatment. There was some evidence that macrolides led to some improvement on symptom scales (SMD -0.35, 95% CI -0.67 to 0.02), and in lung function (forced expiratory volume in one second (FEV_1): MD 0.08, 95% CI 0.02 to 0.14), although not on all the measures we assessed. Measures of bronchial hyperresponsiveness were too varied to pool, but most studies showed no clear benefit of macrolide over placebo. Two studies recruiting people taking regular oral corticosteroids suggested macrolides may have a steroid-sparing effect in this population. Macrolides were well tolerated with respect to severe adverse events, although less than half of the studies reported the outcome (OR 0.80, 95% CI 0.24 to 2.68; participants = 434; studies = 7; I^2 = 0%). Reporting of specific side effects was too patchy across studies to analyse meaningfully. As already reported in the previous versions of the systematic review, biomarkers of asthma activity, such as sputum and serum level of eosinophil cationic protein (ECP) or sputum and serum eosinophils, were lower in patients treated with macrolides, but this was not associated with clinical benefits.

Two within-study subgroup analyses showed a possible benefit of macrolides for non-eosinophilic asthma, but it was not possible to investigate this further using the data available for this review.

Authors' conclusions

Existing evidence does not show macrolides to be better than placebo for the majority of clinical outcomes. However, they may have a benefit on symptom scales and some measures of lung function, and we cannot rule out the possibility of other benefits or harms because the evidence is of very low quality due to heterogeneity among patients and interventions, imprecision and reporting biases.

The review highlights the need for researchers to report clinically relevant outcomes accurately and completely using guideline definitions of exacerbations and validated scales. The possible benefit of macrolides in patients with non-eosinophilic asthma based on subgroup analyses in two of the included studies may require further investigation.

PLAIN LANGUAGE SUMMARY

Should macrolides be used for chronic asthma?

Main point: Studies do not show that macrolides are better than placebo for most outcomes. There may be a benefit on symptom scales and lung function but the latter depends on how this is measured. The evidence was very low quality so we can't rule out the possibility of other benefits or harms.

Background

Asthma is a chronic disease in which inflammation of the airways leads to coughing, wheezing and breathing problems. There are probably different reasons for this inflammation and why it persists, and these may require different treatments. Infection in the lungs may be one cause, and macrolides are a type of antibiotic that may be used long-term as a way of improving symptoms for these people.

How we answered the question

We looked for studies on adults or children with asthma who were either given a macrolide or placebo for at least four weeks to see if it improved their symptoms and made it less likely for them to have an asthma attack, often referred to as an 'exacerbation'. We carried out our most recent search for studies in April 2015. After finding all of the relevant studies, we pulled out information about asthma attacks requiring hospital admission, asthma attacks that needed to be treated with oral steroids, symptom scales, asthma control, quality of life, several measures of lung function, the need for rescue inhalers, serious side effects and measures of asthma activity in blood and sputum.

What we found

We found 23 studies, including 16 new ones that had been published since the last search was done in 2007. Overall, just over 1500 people received either macrolide or placebo. There were a lot of problems in the way studies were described and how well they reported data, which made us consider the evidence to be very low quality, undermining our confidence in most of the results. The studies were quite different from each other, for example in the severity of people's asthma, the type of macrolide they were given and the length of the treatment period.

Our review did not show that macrolides were better than placebo for most of the important outcomes we looked at. However, they may have some benefits on symptom scales and lung function, and we cannot rule out the possibility that they are helpful for some people or that they cause harm. There were no reports of serious side effects of macrolides, but 16 studies didn't say whether or not any occurred.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Macrolide versus placebo for chronic asthma

Patient or population: adults and children with chronic asthma
Settings: outpatient
Intervention: macrolide
Drugs used were clarithromycin, azithromycin, roxithromycin and troleandomycin. Macrolide was given once or twice daily in most studies for between 6 and 52 weeks (median 8 weeks).
Comparison: placebo
Durations were calculated as weighted means of the studies included in each analysis

Outcomes[a]	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)
	Assumed risk	Corresponding risk			
	Placebo	Macrolide			
'Severe' exacerbation - requiring at least OCS Number of people having one or more exacerbations requiring at least systemic steroids. Classification varied across studies 18 weeks	242 per 1000	208 per 1000 (121 to 334)	**OR 0.82** (0.43 to 1.57)	290 (5 RCTs)	⊕◯◯◯ very low[b,c,d]
Symptom scales 10 weeks	The symptom scales used were different across studies so it was not possible to calculate an assumed risk	The mean symptom scales in the intervention group was **0.35 standard deviations lower** (0.67 lower to 0.02 lower)	-	139 (4 RCTs)	⊕◯◯◯ very low[b,f,g,h]
Asthma control Scored from 0 to 6 (lower scores indicate less impairment)	The mean change in asthma control score in the control group was − **0.21**	The mean asthma control score in the intervention group was **0.05 standard deviations better** (0.26 bet-	-	353 (4 RCTs)	⊕◯◯◯ very low[b,e,i]

17 weeks		ter to 0.15 worse)			
Asthma Quality of Life Questionnaire (AQLQ) Scored from 1 to 7 (higher scores indicate less impairment) 16 weeks	The mean change on the AQLQ scale in the control group was **0.32**	The mean AQLQ score in the intervention group was **0.06 better** (0.12 worse to 0.24 better)	-	389 (5 RCTs)	⊕◯◯◯ very low[b,d,e,i]
Rescue medication, puffs/day 17 weeks	The mean rescue medication use in the control group was **1.08** puffs/day**	The mean rescue medication use in the intervention group was **0.26 puffs/day lower** (0.65 lower to 0.12 higher)	-	314 (4 RCTs)	⊕◯◯◯ very low[b,e,i]
FEV_1 (L) 15 weeks	The mean FEV_1 in the control group was **2.53** L	The mean FEV_1 in the intervention group was **0.08 L lower** (0.02 higher to 0.14 higher)	-	600 (9 RCTs)	⊕◯◯◯ very low[b,j,i,k]
Serious adverse events (including mortality) 16 weeks	23 per 1000	22 per 1000 (6 to 79)	**OR 0.96** (0.25 to 3.68)	359 (7 RCTs)	⊕◯◯◯ very low[e,h,l]

*The basis for the **assumed risk** (e.g. the 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).

**Assumed risk for continuous outcomes were calculated as weighted means of the scores in the control group. NB: Sutherland 2010 could not be included in the rescue medication or quality of life calculations because only mean difference between groups was reported; Brusselle 2013 was not included in the FEV_1 calculation because it was the only change score; Cameron 2012 was not included in the asthma control or quality of life calculations because it was the only study reporting absolute endpoint scores rather than change from baseline

CI: confidence interval; **OCS:** oral corticosteroids; **AQLQ:** Asthma Quality of Life Questionnaire; **FEV_1:** forced expiratory volume in one second

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] Two of the primary outcomes have not been presented. Bronchial hyperresponsiveness could not be pooled in a meta-analysis and has been described narratively in the review. Steroid dose was not well reported in the studies, and there was no data to analyse.

[b] Clinical outcomes were poorly reported across studies, with no more than 9 out of 17 appearing in any efficacy analysis (downgraded one level for publication bias).

[c] Differences in the recruited populations and in the criteria used to define 'severe exacerbations' (downgraded one level for indirectness).

[d] Confidence intervals include an important benefit of macrolide and possible benefit of placebo (downgraded one level for imprecision).

[e] Uncertainties with randomisation procedures, and high risk of attrition bias in some studies included in the analysis (downgraded one level for risk of bias).

[f] High heterogeneity of I^2 = 77% mainly due to one of the cross-over studies (downgraded one level for inconsistency).

[g] Symptom scales were often unvalidated and highly variable across studies, and we chose not to pool most in a meta-analysis using standard mean differences, as this would lead to a result that would have been much more difficult to interpret (downgraded one level for indirectness).

[h] Small number of patients in the analysis; difficult to judge precision due to different scales (downgraded one level for imprecision).

[i] Studies in the analysis recruited different populations with regards to severity of asthma, and one study only recruited smokers (downgraded one level for indirectness)

[j] Four studies that we were unable to properly assess for risk of bias were included in this analysis (downgraded one level for risk of bias), and we were not certain of how and when the measurement was taken in some cases.

[k] Uncertainty in several domains across studies, but the study carrying the majority of the weight was well conducted (no downgrade).

[l] Seven studies reported the outcomes but only three observed events (9 total events), leading to very wide confidence intervals that include important benefit and harm of macrolide treatment (downgraded two levels for imprecision).

BACKGROUND

Description of the condition

Asthma is an inflammatory disease of the airways characterised by chronic inflammation, bronchial hyperresponsiveness and paroxysmal attacks of wheezing. It affects people of every age, but frequently the disease occurs in childhood, especially in those who are atopic. There are different phenotypes of the disease, including one that recognises infection as an important factor in airway inflammation. Current guidelines recommend tailoring asthma treatment according to a stepwise approach, considering severity of symptoms and response to treatment (GINA 2014).

Short-acting bronchodilators are usually effective in controlling intermittent asthma, but persistent asthma may require anti-inflammatory drugs, longer-acting bronchodilators, or both. These are usually administered directly to the lungs via inhalation or orally with the aim of improving respiratory symptoms by reducing airways inflammation (GINA 2014). More recent therapies include anti-leukotrienes in mild-to-moderate asthma, humanised antibodies such as omalizumab, immunosuppressive drugs and inhibitors of specific pathways, which are used only in severe, treatment-resistant asthma (GINA 2014; Olin 2014).

Description of the intervention

Macrolides are a class of antibiotics that are widely used in the treatment of various infectious diseases, including respiratory tract infections (Alvarez-Elcoro 1999). The first studies on macrolides in patients with asthma suggested a steroid-sparing effect (Nelson 1993), while more recent reports have demonstrated an anti-inflammatory effect of this class of antibiotics, whereby macrolides seem to decrease bronchial hyperresponsiveness associated with eosinophilic inflammation (Amayasu 2000). Macrolides are effective in the long-term treatment of cystic fibrosis, diffuse panbronchiolitis and chronic obstructive pulmonary disease, and they are not associated with an increased risk of adverse events (Cai 2011; Spagnolo 2013).

However, a potential drawback of longer-term antibiotic use for asthma is the development of bacterial resistance by strains that normally colonise the airways. Macrolide use in healthy volunteers led to pharyngeal carriage of macrolide-resistant streptococci (Malhotra-Kumar 2007), which is of particular concern for the wider community.

How the intervention might work

Macrolides have anti-inflammatory and antimicrobial properties that may improve asthma symptoms in two ways: by reducing airways inflammation directly and by controlling intracellular infection, which may trigger and maintain inflammation (Black 1997; Black 2000; Kawasaki 1998). Their anti-inflammatory potential has been linked to their action on pro-inflammatory cytokines that cause inflammation, which was highlighted by the results of the previous versions of this systematic review (Richeldi 2002; Richeldi 2005). In vivo and in vitro studies of human and animal models have demonstrated that macrolides suppress the production of cytokines such as interleukins and inhibit the neutrophil adhesion to epithelial cells, the respiratory burst of neutrophils and the secretion of mucus from human airways (Adachi 1996; Konno 1994; Koyama 1998).

The potential benefit of their antimicrobial action for people with asthma was suggested after observational studies identified intracellular bacterial infection (i.e. *Chlamydophilia pneumoniae* or *Mycoplasma pneumoniae)* as a possible trigger of bronchial inflammation (Kraft 1998). Gencay 2001 subsequently demonstrated that people with asthma had a higher frequency of *C. pneumoniae* antibodies than matched controls. Longitudinal studies showed no clear effect of infection with *C. pneumoniae* on the incidence of asthma, but patients who had an infection and developed asthma showed a faster decline in lung function (Pasternack 2005). Furthermore, in children with asthma, *M. pneumoniae* detection in respiratory samples was associated with poorer asthma control (Wood 2013). Recent studies in animal models seems to point out an important role of the infection with *C. pneumoniae* in the early phases of life in the pathogenesis of severe asthma (Essilfie 2015; Hansbro 2014).

Why it is important to do this review

Macrolides represent a relatively inexpensive intervention that may improve control of inflammation and clinical outcomes in patients with chronic asthma.

OBJECTIVES

To assess the effects of macrolides for managing chronic asthma.

METHODS

Criteria for considering studies for this review

Types of studies

We included parallel and cross-over randomised controlled trials (RCT).

Types of participants

Children and adult patients with chronic asthma.

Types of interventions

Macrolides, administered for more than four weeks, versus placebo. We have pooled data from studies comparing different macrolide therapies.

Types of outcome measures

Primary outcomes

- Number of exacerbations requiring hospitalisation and severe exacerbations (requiring emergency room (ER) visits or short-course systemic steroids)
- Asthma symptoms (including symptom scores, asthma control scores and asthma quality of life scores)
- Asthma medication requirements (need for rescue medications)
- Lung function, including morning and evening peak expiratory flow (PEF) and forced expiratory volume in one second (FEV_1)
- Non-specific bronchial hyperreactivity (to histamine or methacholine)
- Lowest tolerated oral corticosteroid dose (in patients requiring oral corticosteroids at baseline)

Secondary outcomes

- Number and type of side effects
- Number of study withdrawals
- Eosinophil count in peripheral blood samples, sputum samples or both
- Eosinophilic cationic protein (ECP) measurements in serum and in sputum.

Search methods for identification of studies

Electronic searches

Search methods used in the previous version of this review are detailed in Appendix 1. The previously published version included searches up to May 2007. The search period for this update is May 2007 to April 2015.

Trials were identified using the Cochrane Airways Group Specialised Register, which is maintained by the Trials Search Coordinator for the Group. The Register is derived from systematic searching of electronic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and CINAHL, and handsearching of respiratory journals and meeting abstracts (see Appendix 2 for more details). Appendix 3 describes the search strategy used in the Specialised Register. We also searched ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO trials portal (www.who.int/ictrp/en/). We searched all databases from their inception to April 2015, with no restriction on language of publication.

Searching other resources

We surveyed review articles and bibliographies identified from the primary papers for additional references and RCTs.

Data collection and analysis

Selection of studies

Two reviewers (KK and GF) independently screened the abstracts of articles identified using the search strategy above, retrieving the full text for articles that appeared to fulfil the inclusion criteria. Two reviewers independently reviewed and categorised each article identified as included or excluded (KK and GF). When there was disagreement or doubt, a third reviewer (KU) assessed the article and helped to reach a consensus. We presented a PRISMA diagram to illustrate the flow of studies through the selection process (Moher 2009).

Data extraction and management

We used a data collection form to collect study characteristics and outcome data. We piloted the form on at least one study in the review. Two review authors (KK and GF) extracted the following study characteristics from included studies, when available.

1. Methods: study design, total duration of study, details of any run-in period, number of study centres and location, study setting, withdrawals and date of study.
2. Participants: n, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria and exclusion criteria.
3. Interventions: intervention, comparison, concomitant medications and excluded medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for trial, and notable conflicts of interest of trial authors.

Two review authors (KK and IK) independently extracted outcome data from included studies. We noted in the 'Characteristics of included studies' table if outcome data was not reported in a usable way. We resolved disagreements by involving a third person (KU). One review author (KK) transferred data into the Review Manager (RevMan) file. Two reviewers (GF and KU) double-checked that data were entered correctly by comparing the data presented in the systematic review with the study reports.

Assessment of risk of bias in included studies

Two review authors (KK and GF) independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We resolved disagreements by discussion and by involving another author (KU). The risk of bias was assessed according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

Each potential source of bias was graded as high, low or unclear and justified with a quote from the study report in the 'Risk of bias' table. The risk of bias judgements across different studies were summarised for each of the domains listed. Blinding was considered separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a patient-reported pain scale). Where information on risk of bias related to unpublished data or correspondence with a trialist, we noted this in the 'Risk of bias' table.

When considering treatment effects, the risk of bias for the studies that contribute to that outcome were taken into account.

Measures of treatment effect

We analysed dichotomous data as odds ratios (OR) and continuous data as mean difference (MD) or standardised mean difference (SMD). We entered data presented as a scale with a consistent direction of effect. We narratively described skewed data reported as medians and interquartile ranges. We analysed data from cross-over trials using generic inverse variance (GIV). We pooled results from cross-over trials and parallel trials. Where raw data and adjusted analyses (e.g. accounting for baseline differences) were presented in the same trial, we used the latter.

We undertook meta-analyses only where meaningful, that is, if the treatments, participants and the underlying clinical question were similar enough for pooling to make sense.

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

If change from baseline and endpoint scores were available for continuous data, we used change from baseline unless the majority of studies reported endpoint scores. If a study reported outcomes at multiple time points, we used the end-of-study measurement.

When both an analysis using only participants who completed the trial and an analysis that imputed data for participants who were randomised but did not provide endpoint data (e.g. last observation carried forward) were available, we used the latter.

Unit of analysis issues

For dichotomous outcomes, we used participants rather than events as the unit of analysis (i.e. number of adults admitted to hospital rather than number of admissions per adult). For continuous data in cross-over trials, we entered data using generic inverse variance from suitable adjusted analyses to account for the trial's design.

Dealing with missing data

We assessed the potential for bias in each trial as a result of participants dropping out of the intervention prematurely. Where this was thought to introduce serious bias, we removed the studies in a sensitivity analysis.

Assessment of heterogeneity

We used the I^2 statistic to measure heterogeneity among the trials in each analysis. If we identified substantial heterogeneity (e.g. I^2 greater than 30%), we reported it and performed a sensitivity analysis with a random-effects model.

Assessment of reporting biases

We were not able to pool more than 10 trials for any of the primary outcomes, so were unable to examine a funnel plot to explore possible small study and publication biases.

Data synthesis

We used a fixed-effect model for all analyses, as we expected variation in effects due to differences in study populations and methods. We performed sensitivity analyses with a random-effects model.

Subgroup analysis and investigation of heterogeneity

We planned subgroup analyses based on serological response or positivity to polymerase chain reaction (PCR) for *C. pneumoniae.*

Sensitivity analysis

We performed sensitivity analyses based on study quality where appropriate.

Summary of findings table

A 'Summary of findings' table was created using the following outcomes: number of exacerbations requiring hospitalisation; severe exacerbations; (requiring short-course systemic steroids); asthma symptoms (including symptom scores, asthma control and asthma

quality of life questionnaire, AQLQ); asthma medication requirements (as reliever); lung function (including FEV_1 and morning and evening PEF); nonspecific bronchial hyperreactivity; serious adverse events and withdrawal; blood and sputum eosinophils and ECP in serum and sputum.

We used 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 contributed data to the meta-analyses for the prespecified outcomes. With the exception of serious adverse events, we did not perform GRADE ratings on the secondary outcomes. We used methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) using GRADEpro software (Brozek 2008). We justified all decisions to down- or up-grade the quality of studies using footnotes and made comments to aid reader's understanding of the review where necessary.

RESULTS

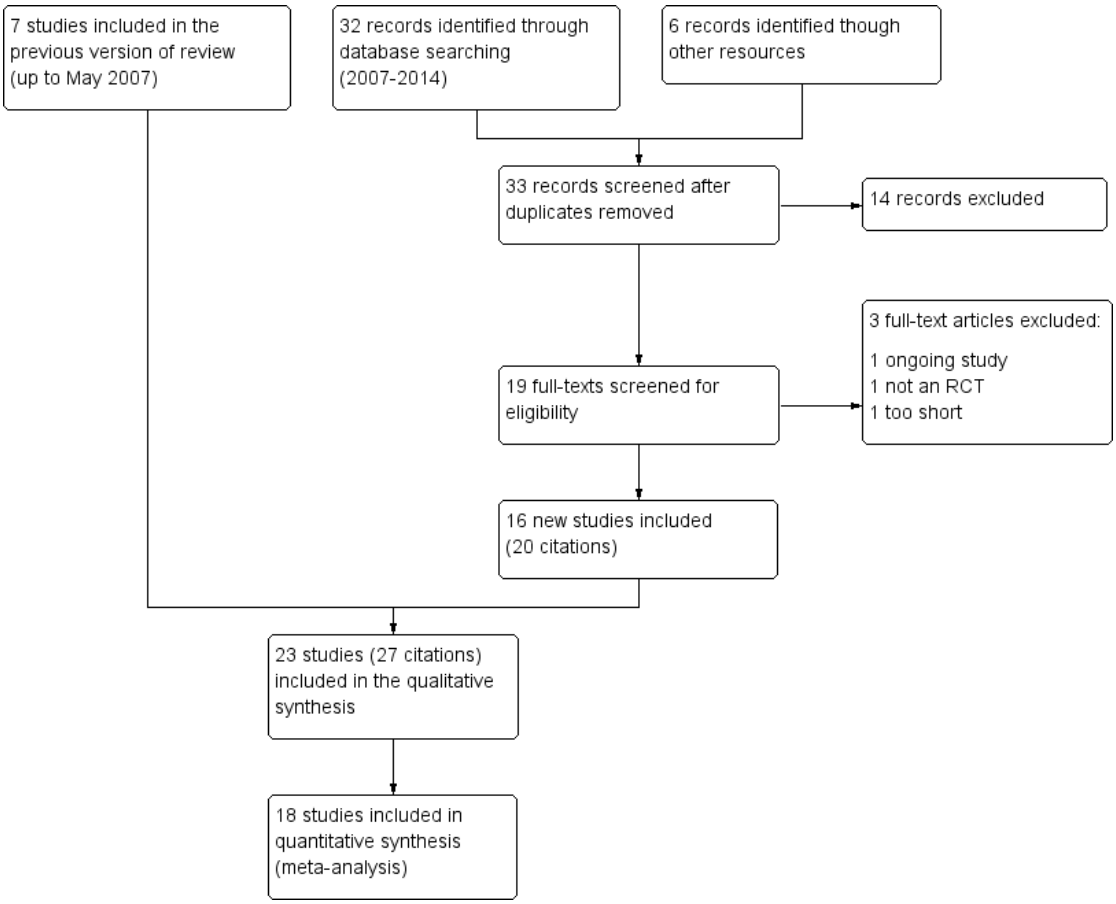
Description of studies

Results of the search

Ninety-nine citations were identified in the literature search of previous versions of this review up to May 2007. Duplicate sifting of the titles and abstracts alone identified 25 potentially eligible studies for inclusion in the systematic review. Among them, reviewers were concordant in identifying seven RCTs that met the inclusion criteria. Five of these were included in the initial version of this review, and two new studies were added in May 2005 (Kostadima 2004; Kraft 2002).

For this updated review, the search extended to April 2015. We identified 32 new references as well as 6 other records by searching reference lists of existing meta-analyses. Five titles referring to abstracts presented at congresses were duplicates of other studies already included in the review, leaving 33 references for screening. We excluded 14 based on the abstract alone and 3 after screening the full-text of the original manuscripts, leaving 16 studies eligible for inclusion in the systematic review and meta-analyses (see 'Characteristics of included studies'; 'Characteristics of excluded studies'). The study flow of the new included studies is presented in Figure 1.

Figure 1. Study flow diagram.



Included studies

For brief descriptions of the included studies, please refer to the 'Characteristics of included studies' table. For a summary of study characteristics and a narrative on the main results of each study, please see Table 1 and Appendix 4.

The 23 included studies reported a great variability in type of patients (ranging from intermittent aspirin-induced asthma to severe asthma), interventions (different type of macrolides, administration scheme and doses in most of the studies) and outcomes recorded. Six studies identified in a previous meta-analysis (Tong 2014) were Chinese trials that were only listed in that country's biomedical databases. The authors of this review were able to confirm key study characteristics in order to include these studies, but we were not able to describe their characteristics and risk of bias in the same detail as for the 17 other included studies.

Design

All the studies were randomised controlled trials using placebo controls, and the majority were described as double-blind. There were 20 parallel group studies and three cross-over studies (Amayasu 2000; Kapoor 2010; Shoji 1999). Median study duration was 8 weeks (range 4 to 52 weeks). Two studies were reported in the form of abstracts from congresses, with a very limited amount of data available (Belotserkovskaya 2007; Kapoor 2010), and six were Chinese studies for which we had only basic information (He 2009; Wang 2012; Wang 2014; Xiao 2013; Yan 2008; Zhang 2013).

Participants

The studies included a total of 1532 participants of which 1513 were relevant to this review (Strunk 2008 included a third group of 18 people receiving a treatment that was not relevant). All participants had an asthma diagnosis, which was generally established

according to the guidelines in use at the time of the studies (ATS 1987, GINA 1995; GINA 2002; GINA 2007; GINA 2010); these are similar to the current international guidelines (GINA 2014).

Three studies assessed the effects of macrolide treatment in paediatric asthma (Kamada 1993; Piacentini 2007; Strunk 2008), and the rest recruited asthma patients over the age of 18 years. The studies varied according to GINA 2014 criteria for asthma severity, and often there was very little information about baseline severity. Most studies included participants with persistent mild-to-severe asthma, while one included participants with intermittent asthma (Amayasu 2000), and one used patients with aspirin-induced intermittent asthma (Shoji 1999).

Three studies investigated the role of macrolides in patients with evidence of *C. pneumoniae* or *M. pneumoniae* infection, based on serological (Black 2001) or molecular (Kraft 2002; Sutherland 2010) methods. The presence of these co-infections or of other concomitant co-infections was not investigated in the remaining studies, although we could not confirm this fact in the non-English language papers. Cameron 2012 investigated the effect of macrolides in adult smokers with persistent asthma, while Brusselle 2013 and Simpson 2008 considered the effect of macrolides in patients with severe non-eosinophilic asthma.

Interventions

Five studies compared roxithromycin with placebo (Black 2001; Kapoor 2010; Shoji 1999; Xiao 2013; Yan 2008); six studies compared clarithromycin with placebo (Amayasu 2000; Kostadima 2004; Kraft 2002; Simpson 2008; Sutherland 2010; Wang 2014); 10 studies investigated the effect of azithromycin (Belotserkovskaya 2007; Brusselle 2013; Cameron 2012; Hahn 2006; Hahn 2012; He 2009; Piacentini 2007; Strunk 2008; Wang 2012; Zhang 2013), and two studies assessed the effects of troleandomycin in addition to oral steroid therapy as part of a steroid tapering protocol (Kamada 1993; Nelson 1993).

Outcomes

Five studies did not appear in any of the quantitative syntheses (Belotserkovskaya 2007; Black 2001; Kapoor 2010; Wang 2012; Zhang 2013), and two more only contributed to the bronchial hyperresponsiveness summary of results and withdrawal (Piacentini 2007; Simpson 2008).

Seven studies considered exacerbations (requiring hospitalisation or emergency room (ER) visit/systemic steroids) as an outcome, but the definition of 'severe' exacerbation was variable and sometimes unclear (Amayasu 2000; Brusselle 2013; Cameron 2012; Hahn 2012; Kostadima 2004; Strunk 2008; Sutherland 2010). Tong 2014 did not include exacerbations as an outcome but explicitly confirmed that the Chinese studies did not report this outcome either. Data from these studies only contributed to one meta-analysis (FEV_1). We narratively summarised data that could not be meta-analysed for the relevant outcomes.

Most studies reported measures of symptoms, asthma control or quality of life, but the analyses were limited by the way data were reported and by the scales that could be reasonably pooled in meta-analysis. We did not consider a meta-analysis of all these measures to be valid or the subsequent results to be interpretable in any meaningful way, so we chose only to meta-analyse those that we knew to be similar. Standardised mean difference had to be used for the 'symptom scale' meta-analysis, which still made the effect and its precision difficult to interpret.

Four studies reported data about change in rescue medication as puffs per day in a way that could be included in meta-analysis (Brusselle 2013; Hahn 2012; Strunk 2008; Sutherland 2010).

Most of the studies reported measures of lung function such as FEV_1, forced vital capacity (FVC) or PEF, but only six reported data for the same measure that could be pooled. There were some issues with selective reporting that prevented studies from being included in the analyses, such as data only being presented graphically or without a measure of variance (e.g. Black 2001). It was often unclear when the measures were taken, (i.e. pre- or post-bronchodilator), but when the information was available, we recorded it in the analysis footnotes. Brusselle 2013 reported percentage FEV_1, but their data could not be combined with the other studies, which reported the outcome in litres. We combined the data made available to us from Tong 2014 for He 2009, Wang 2014, Xiao 2013 and Yan 2008, but we performed a sensitivity analysis without them due to our uncertainties about which measures were used and the unclear risk of bias. We were also provided with data for peak flow for Wang 2014, Xiao 2013 and Yan 2008, but the data were a different order of magnitude to the other studies, and it did not make sense to pool them.

Bronchial hyperresponsiveness was considered in nine studies (Amayasu 2000; Cameron 2012; Kamada 1993; Kostadima 2004; Nelson 1993; Piacentini 2007; Shoji 1999; Simpson 2008; Sutherland 2010) but there was a lot of variation in the measures used and the way the data were reported, which meant it was not possible to meta-analyse the data. The raw data have been presented in a table with information about the measures used.

Adverse events were considered in most of the studies, but serious adverse events were only explicitly reported as an outcome in seven (Amayasu 2000; Brusselle 2013; Cameron 2012; Hahn 2006; Hahn 2012; Kamada 1993; Sutherland 2010). While it was not ideal to include the dichotomous cross-over data without adjusting them to account for matched pairs, no events were observed in Amayasu 2000, so it did not contribute to the pooled effect.

Nine studies (Brusselle 2013; Hahn 2006; Hahn 2012; Kamada 1993; Kostadima 2004; Nelson 1993; Simpson 2008; Strunk 2008; Sutherland 2010) reported study withdrawal.

Eight studies reported the effect of macrolides on markers of inflammation related to asthma activity (Amayasu 2000; Cameron 2012; Kraft 2002; Nelson 1993; Piacentini 2007; Shoji 1999; Simpson 2008; Yan 2008), but they used different measures, which could not be pooled in one analysis. There were also some issues

with data accuracy or incomplete reporting that reduced our confidence in the reliability of the data. The separate analyses include very small participant numbers, mostly from the two cross-over studies.

Two studies considered the steroid-sparing effect of macrolides (Kamada 1993; Nelson 1993).

Excluded studies

We excluded three studies after viewing the full papers. One is an ongoing study (ACTRN12609000197235), one a commentary rather than an RCT (Anon 2009), and one was a paediatric trial that was too short (less than four weeks as set out in the protocol) to be included (Koutsoubari 2012).

We excluded 18 studies after viewing the full texts in the previous version of this review. The most common reason for exclusion was that the study was not a randomised controlled trial (n = 9). We excluded four studies due to the short length of the study period, two because they were in vitro studies, two because the patients did not have asthma and one because it had been terminated prior to completion.

Risk of bias in included studies

There was considerable uncertainty relating to study methodology due to insufficient reporting in the published reports. This was particularly true for the selection bias domains, but also for blinding of outcome assessment and attrition bias. We had concerns about incomplete and selective reporting of the results for most of the studies and generally considered there to be a high risk for publication bias because only a small number of studies reported data in a way that could be pooled in meta-analysis. Summaries of the risk of bias judgements for each study are presented in Figure 2 and Figure 3.

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

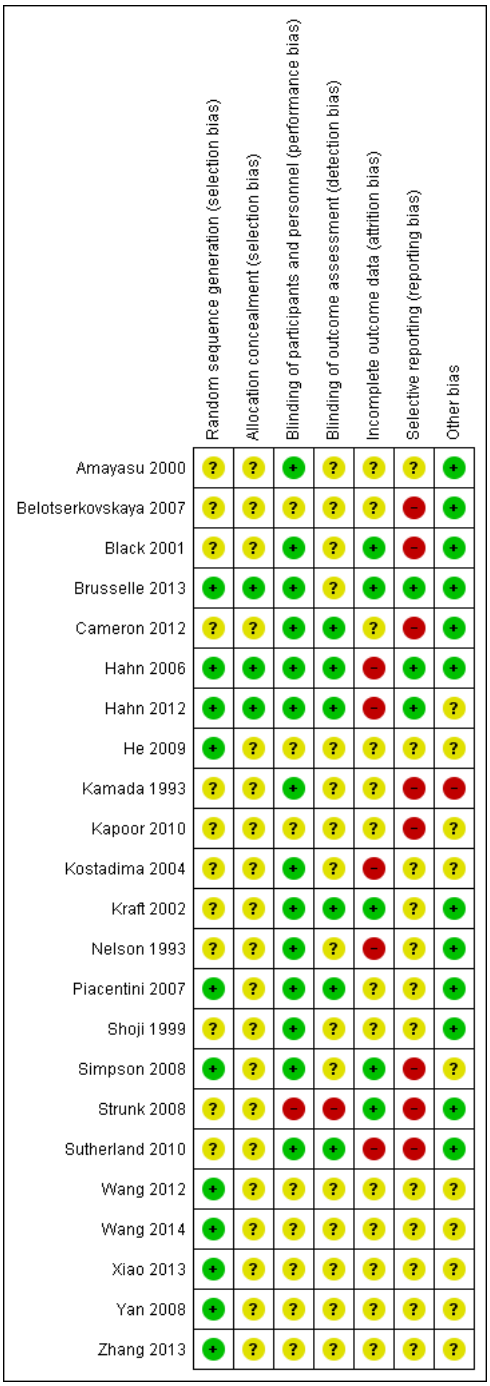
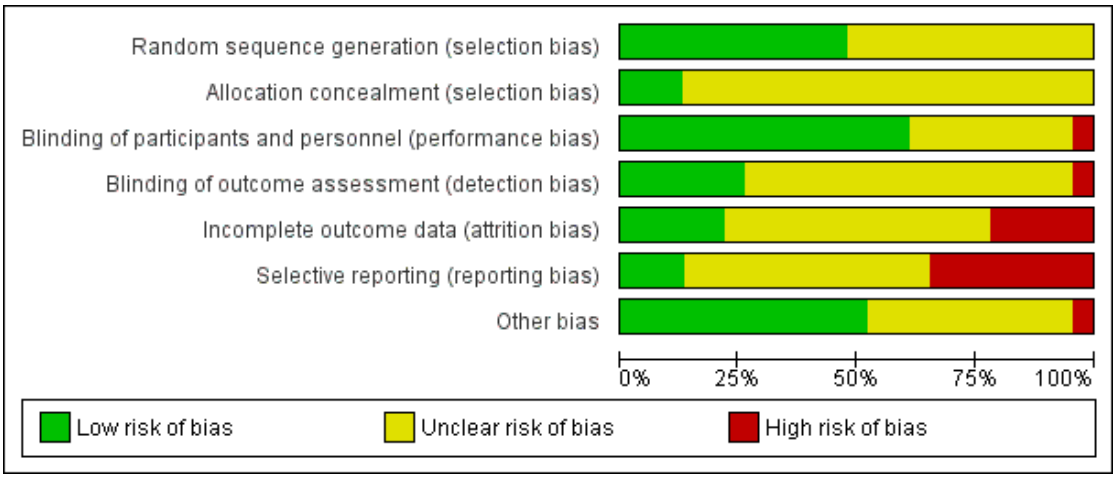


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Pharmaceutical industries financed at least five included studies (Amayasu 2000; Cameron 2012; Hahn 2006; Hahn 2012; Kamada 1993); we could not ascertain this in the non-English language papers. The authors of Tong 2014 provided us with information about study quality for the studies that were not available in English.

Allocation

We deemed 11 studies to be at low risk of bias for random sequence generation, including five of the English language studies (Brusselle 2013; Hahn 2006; Hahn 2012; Piacentini 2007; Simpson 2008) and six that were awarded two points using the Jadad scoring system (Jadad 1996) in Tong 2014. For the rest, allocation bias was unclear.

Only 3 studies were at low risk for adequate allocation concealment (Brusselle 2013; Hahn 2006; Hahn 2012); the 6 studies from the Tong 2014 review were not assessed for this criterion because it is not considered in the Jadad system, so we had to rate those studies as unclear, and the 14 other studies did not adequately describe the methods used.

Blinding

Most of the studies being described as double-blind and placebo-controlled contained adequate descriptions of the blinding of patients and personnel, but methods were unclear in eight studies (including two in an abstract form: Belotserkovskaya 2007; Kapoor 2010). We rated one study as having a high risk of bias (Strunk 2008).

Blinding of outcome assessment was mostly unclear and only judged to be adequate in six studies (Cameron 2012; Hahn 2006; Hahn 2012; Kraft 2002; Piacentini 2007; Sutherland 2010). The same study that we rated high for performance bias also carried a high risk for detection bias (Strunk 2008).

Incomplete outcome data

Five studies had a high risk of attrition bias (Hahn 2006; Hahn 2012; Kostadima 2004; Nelson 1993; Sutherland 2010) and 5 others carried a low risk (Black 2001; Brusselle 2013; Kraft 2002; Simpson 2008; Strunk 2008), while the risk was unclear for the other 13 other studies.

Selective reporting

We judged eight studies (Belotserkovskaya 2007; Black 2001; Cameron 2012; Kamada 1993; Kapoor 2010; Simpson 2008; Strunk 2008; Sutherland 2010) to be at high risk of selective reporting. This was mostly due to insufficient reporting of numerical data, which meant they could not be pooled in meta-analysis. We only considered three to be at low risk of bias (Brusselle 2013; Hahn 2006; Hahn 2012). We rated 12 studies as unclear for this domain, including the 6 non-English language studies, which we could not assess fully.

Overall, it is likely that reporting biases had a significant effect on the completeness of the meta-analyses in this systematic review.

Other potential sources of bias

Kamada 1993 showed significant baseline imbalances between groups, and this may have been an issue in some of the other trials that included very small numbers of participants.

Effects of interventions

See: **Summary of findings for the main comparison** Macrolide compared to placebo for chronic asthma

We present the data in order of outcomes listed in the methods. Evidence quality was mostly very low, with most of the analyses being downgraded for publication bias because so few studies reported clinical data sufficiently well to be included in meta-analysis. We also downgraded most for indirectness due to differences in the study populations and the way outcomes were defined, and for risk of bias due to uncertainty of randomisation procedures and high risk of attrition bias. Appendix 4 presents a narrative on each study, except for the six that we could not assess fully (He 2009; Wang 2012; Wang 2014; Xiao 2013; Yan 2008; Zhang 2013).

Primary outcomes

Exacerbations requiring hospitalisation

Amayasu 2000 and Brusselle 2013 reported on exacerbations requiring hospitalisation, with only four events (all recorded in the Brusselle 2013 study, with two in the treatment and two in the placebo group). Thus, the effect was far too imprecise to interpret meaningfully (OR 0.98, 95% CI 0.13 to 7.23; participants = 143; studies = 2; I^2 = 0%; Analysis 1.1). The evidence was very low quality, being downgraded twice for imprecision and once for publication bias because so few studies could be included in the analysis. Due to the small number of events, we performed a sensitivity analysis using the Peto odds ratio, which did not change the conclusions.

'Severe' exacerbations: exacerbations requiring ER visits/systemic steroids

Five studies reported data on 'severe' exacerbations (Amayasu 2000; Brusselle 2013; Hahn 2006; Kostadima 2004; Strunk 2008), and none showed a benefit of macrolides over placebo (OR 0.82, 95% CI 0.43 to 1.57; participants = 290; studies = 5; I^2 = 0%; Analysis 1.2). The data suggest 34 fewer people per 1000 would have an exacerbation while taking a macrolide compared with placebo over 18 weeks, but the 95% confidence intervals range from 121 fewer to 92 more. The evidence was very low quality, being downgraded for publication bias, indirectness and imprecision. It was not always clear how the studies had defined 'severe' exacerbations, which further reduced our confidence in the result.

Symptoms and quality of life

Symptom scales used across studies varied and were mostly not validated. Data from four studies that could be combined in meta-analysis (Amayasu 2000; Hahn 2006; Hahn 2012; Kamada 1993) suggested a modest benefit of macrolides compared with placebo (SMD -0.35, 95% CI -0.67 to -0.02; participants = 156; studies = 4; I^2 = 77%; Analysis 1.3). We downgraded the evidence for publication bias, risk of bias, heterogeneity, and indirectness and imprecision, meaning it was very low quality, and we had very little confidence in the result. We did not have information on the scales used in the Chinese studies, so we were not able to confirm whether they were similar enough to pool.

A meta-analysis of four studies (Brusselle 2013; Cameron 2012; Hahn 2012; Sutherland 2010) reporting measures of asthma control, mostly the Asthma Control Questionnaire, did not show any benefit of macrolide over placebo (SMD − 0.05, 95% CI − 0.26 to 0.15; participants = 353; studies = 4; I^2 = 0%; Analysis 1.4), and the same was true for quality of life on the Asthma Quality of Life Questionnaire AQLQ (MD 0.06, 95% CI − 0.12 to 0.24; participants = 389; studies = 5 (as above plus Hahn 2006); I^2 = 18%; Analysis 1.5). We considered evidence for both of these outcomes to be very low quality after downgrading it for publication bias, risk of bias and indirectness; in addition, we downgraded the evidence on asthma control for imprecision.

Need for rescue medications

A meta-analysis of data from Brusselle 2013, Cameron 2012, Hahn 2006 and Sutherland 2010 did not show a difference between macrolides and placebo in reducing need for rescue medications (MD − 0.26, 95% CI − 0.65 to 0.12; participants = 314; studies = 4; I^2 = 26%; Analysis 1.6). Again, the evidence was very low quality, being downgraded for publication bias, risk of bias and indirectness.

Morning and evening PEF

The data for morning and evening PEF did not suggest a benefit of macrolide over placebo, but the evidence was very low quality (Morning PEF: MD 2.22, 95% CI − 9.73 to 14.17; participants = 289; studies = 4; I^2 = 0%; Analysis 1.7; data from Brusselle 2013; Cameron 2012; Kamada 1993; Sutherland 2010). Evening PEF: MD 1.97, 95% CI − 12.68 to 16.62; participants = 212; studies = 3; I^2 = 0%; Analysis 1.8; data from Brusselle 2013; Kamada 1993; Sutherland 2010). The evidence for both measures was downgraded due to issues with risk of bias, indirectness, imprecision and suspected publication bias. Data for three additional studies were provided by Tong 2014, but it was not clear if they were morning

or evening measurements (Wang 2014; Xiao 2013; Yan 2008). Moreover, the data were in a different order of magnitude to the other studies and had been combined using standardised mean difference, so we could not combine them. These three studies all showed a benefit of macrolide over placebo, but the method of analysis meant it was difficult to quantify.

FEV_1

There was a small benefit of macrolide over placebo on FEV_1 in litres (MD 0.08, 95% CI 0.02 to 0.14; participants = 600; studies = 9; Analysis 1.9). We deemed the evidence to be of very low quality after downgrading it for publication bias, indirectness and risk of bias. It was not always clear whether the measurement was taken before or after a bronchodilator. We performed a sensitivity analysis, removing the data included from the studies we were unable to extract and assess ourselves, and the effect was smaller, no longer showing a benefit of macrolide over placebo (MD 0.02, 95% CI − 0.07 to 0.11).

Bronchial hyperresponsiveness

We could not compare the results reported for bronchial hyperresponsiveness in nine studies due to differences in the challenge agent (e.g. methacholine, hypertonic solution) and measurement (histamine provocative concentration causing a 20% (PC_{20}) or 15% (PC_{15}) drop in FEV_1, results expressed as log) in the different studies. We present the unpooled data in Analysis 1.10. Amayasu 2000, Kostadima 2004 and Sutherland 2010 reported a significant effect of macrolides in reducing bronchial hyperresponsiveness compared to placebo, while Cameron 2012, Kamada 1993, Nelson 1993, Piacentini 2007, Simpson 2008 and Shoji 1999 reported no effect compared with placebo.

Oral corticosteroid dose

Most studies either excluded patients taking oral corticosteroids or recruited people who did not take them regularly. Two studies that recruited participants taking regular oral corticosteroids reported that macrolides had a steroid-sparing benefit (Analysis 1.11). However, there was a baseline imbalance in corticosteroid dose in Nelson 1993, which overstated the difference at endpoint. We chose not to combine the study results because it was not clear if the ways the doses were calculated were sufficiently similar for pooling to make sense (see footnotes).

Secondary outcomes

Drug tolerability and serious adverse events

In general, macrolides were well tolerated, and there were no recorded deaths due to treatment with macrolides. A meta-analysis of seven studies (Amayasu 2000; Brusselle 2013; Cameron 2012; Hahn 2006; Hahn 2012; Kamada 1993; Sutherland 2010) did not show a clear difference in the likelihood of serious adverse events in the treatment and placebo groups, but the effect was very imprecise due to the rarity of events (OR 0.80, 95% CI 0.24 to 2.68; participants = 434; studies = 7; I^2 = 0%; Analysis 1.12). Again, we rated the evidence to be of very low quality due to very serious imprecision in the estimate, risk of bias issues, and possible indirectness. Due to the small number of events, we performed a sensitivity analysis using the Peto odds ratio, which did not change the conclusions.

Withdrawal/dropouts

Pooled data from nine studies (Brusselle 2013; Hahn 2006; Hahn 2012; Kamada 1993; Kostadima 2004; Nelson 1993; Simpson 2008; Strunk 2008; Sutherland 2010) suggested the likelihood of withdrawal from the studies was similar between participants taking macrolide and placebo (OR 0.95, 95% CI 0.59 to 1.52; participants = 563; studies = 9; I^2 = 0%; Analysis 1.13).

Blood and sputum eosinophils

One new study (Yan 2008) reported no difference between macrolide and placebo in blood eosinophils, but analysed data were only available as standardised mean difference, so we did not enter it with the two existing studies (Amayasu 2000; Shoji 1999). These small cross-over studies showed a reduction of eosinophils in the blood of asthmatic patients treated with macrolides (MD − 33.50, 95% CI − 36.11 to − 30.90; participants = 62; studies = 2; Analysis 1.14). Cameron 2012, another new study, investigated the effect of macrolides in sputum eosinophils in current smokers with asthma, and it showed a vastly different result from the two trials previously included in the analysis. The highly significant heterogeneity suggested that there was a data error (I^2 = 98%). For this reason, data for the three studies have been displayed but not pooled (Analysis 1.15).

Serum and sputum ECP

No new data were added by the new studies included in the meta-analysis; macrolides appear to significantly reduce the concentration of ECP both in serum (MD − 12.84, 95% CI − 15.67 to − 10.00; participants = 62; Analysis 1.16) and sputum (MD − 1.45, 95% CI − 1.78 to − 1.11; participants = 62; Analysis 1.17), according to previous results from two studies (Amayasu 2000 and Shoji 1999).

Subgroup analysis

Subgroup analysis based on serological response or positivity to PCR for *C. pneumoniae* was not possible due to the scarcity and heterogeneity of data and methods.

DISCUSSION

Summary of main results

Twenty-three studies, involving a total of 1513 participants given macrolide or placebo, met the inclusion criteria. The quality of evidence was generally very low due to incomplete reporting of study methodology and clinical data, suspected publication bias, indirectness of study populations, risk of bias and imprecision caused by small numbers of patients and events. Most of the included studies reported data from patients with persistent or severe asthma, but inclusion criteria, interventions and outcomes were highly variable.

For the most part, macrolides did not lead to better clinical outcomes than placebo, including for exacerbations requiring hospital admission (OR 0.98, 95% CI 0.13 to 7.23; participants = 143; studies = 2; I^2 = 0%) or treatment with oral steroids (OR 0.82, 95% CI 0.43 to 1.57; participants = 290; studies = 5; I^2 = 0%). The evidence on asthma control (SMD -0.05, 95% CI -0.26 to 0.15), quality of life (MD 0.06, 95% CI -0.12 to 0.24), and rescue medication use (MD -0.26, 95% CI -0.65 to 0.12) was all of very low quality and did not show a benefit of macrolide treatment. There was limited evidence that macrolides led to some improvement on symptom scales (SMD -0.35, 95% CI -0.67 to -0.02) and lung function (FEV_1: MD 0.08, 95% CI 0.02 to 0.14), although not on all the measures we assessed. Measures of bronchial hyperresponsiveness were too varied to pool, but most studies showed no clear benefit of macrolide over placebo. Two studies recruiting people taking regular oral corticosteroids suggested macrolides may have a steroid-sparing effect in this population. Macrolides were well tolerated with respect to severe adverse events, although less than half of the studies reported the outcome (OR 0.80, 95% CI 0.24 to 2.68; participants = 434; studies = 7; I^2 = 0%). Reporting of specific side effects was too patchy across studies to analyse meaningfully. As already reported in the previous versions of the systematic review, biomarkers of asthma activity such as sputum and serum ECP, sputum and serum eosinophils were lower in patients treated with macrolides, but this was not associated with clinical benefits.

Two within-study subgroup analyses showed a possible benefit of macrolides for non-eosinophilic asthma, but it was not possible to investigate this further using the data available for this review.

Overall completeness and applicability of evidence

The available data do not support any generalised use of macrolides in clinical practice to improve clinical outcomes in patients with persistent asthma, but we cannot rule out the possibility of benefit due to several shortcomings in the evidence base. The potential benefit of macrolides in selected phenotypes in particular (i.e. non-eosinophilic asthma) is not yet confirmed.

The interpretation of the available data from the 23 RCTs included in the present review are difficult to interpret for several reasons. Firstly, four different types of macrolides were used across the studies (roxithromycin, clarithromycin, azithromycin and troleandomycin), often with differences in dosage and frequency of administration. Secondly, participants with different severities of asthma were included: the oldest studies included participants who were taking long-term oral steroids (Kamada 1993; Nelson 1993), which could reflect a severe population or outdated prescribing practice. One study included patients with aspirin-intolerant asthma (Shoji 1999), one included patients with intermittent allergic asthma (Amayasu 2000), and another exclusively recruited smokers with asthma (Cameron 2012); all the other studies enrolled patient with mild-to-severe persistent asthma, and we could not properly assess the patient populations of six Chinese studies. Four studies (Black 2001; Kraft 2002; Simpson 2008; Strunk 2008) tested participants for *C. pneumoniae* or*M. pneumoniae* infection, but all with different techniques and very different results. The scarcity of data in the primary analyses precluded any meaningful subgroup analyses to assess the possible effect of these factors.Thirdly and perhaps most importantly, the outcomes measured were heterogeneous; reporting of exacerbations and definitions for severe exacerbations varied across the studies; asthma symptoms were recorded using a variety of non-validated scales as well as the ACQ and AQLQ, with a great variability across the studies. Lung function and bronchial hyperresponsiveness were often assessed and reported using different methodologies or parameters.

Two studies showing some effect on symptoms and markers of eosinophil inflammation were unusual both in the participants they recruited and in their design. Both were cross-over studies, one recruiting patients with allergic intermittent asthma (Amayasu 2000; Shoji 1999), and the other enrolling patients whose asthma was aspirin-induced.

Only three studies investigated the role of macrolides in children with asthma (Kamada 1993; Piacentini 2007; Strunk 2008); unfortunately the great variability in the interventions, measurements and outcomes makes any firm conclusion on the role of macrolides in children impossible. Kamada 1993 suggested a potential role for troleandomycin as steroid-sparing agent, while Strunk 2008 seems instead to exclude any role of macrolides used in this way.

Despite these limitations, our systematic review and meta-analysis did not show a benefit of macrolides over placebo on rates of exacerbations, quality of life or participants' need for rescue med-

ications. As discussed, this does not rule out the possibility for significant benefit or harm of macrolides given the shortcomings of the evidence described above, and there may be a small benefit on symptom scales and some measures of lung function. The results of this review might change if well-designed and appropriately powered RCTs are conducted, but at present the evidence is not promising enough to support further investigation in similar cohorts of patients. There is a suggestion that research targeted at specific phenotypes (i.e. non-eosinophilic asthma) may be warranted.

Antibiotic resistance is of increasing concern and only one included study investigated this (Brusselle 2013), reporting that 87% of azithromycin-treated patients were colonised with erythromycin-resistant streptococci, a statistically significant increase from baseline and in comparison with the placebo group. These results suggest that spread of resistant strain is a real concern, and any further research should clearly measure and report resistance as an outcome. Alongside this, the case for macrolide therapy contributing to better outcomes in those testing positive for *C. pneumoniae* or *M. pneumoniae* infection was mostly unconvincing (Belotserkovskaya 2007; Black 2001; Kraft 2002; Strunk 2008; Sutherland 2010). The number of patients testing positive was much lower than expected in several studies, and subgroup analyses were often underpowered or post hoc.

Quality of the evidence

The overall quality of the evidence is very low. We had serious concerns about publication bias and underreporting or variation of study results; there was a lot of uncertainty regarding allocation procedures and blinding of outcome assessment, and all but three of the trials recruited fewer than 100 people.

We downgraded most of the analyses for publication bias because so few studies reported clinical data well enough to be included in meta-analysis. Some studies reported outcomes of interest but not in a format that allowed the data to be combined with other studies, and other studies focused on non-clinical outcomes when the use of macrolides was being tested to assess their mechanism of action and effect on biomarkers. Most outcomes were also downgraded for indirectness because some studies focused on specific populations, such as smokers or those with asthma of a particular severity, which varied across studies. Inconsistencies in the scales used or description of outcomes also made it difficult to meta-analyse the data and reduced our confidence in the conclusions that could be drawn. Risk of bias was also an issue across most of the analyses, largely due to uncertainty as a result of insufficient reporting of methodology, but also as a result of failure to prevent or account for high or unbalanced dropout.

Evidence for outcomes such as exacerbations requiring hospitalisation and serious adverse events was very imprecise due to the length of the studies and the rarity of this sort of events, so it was difficult to reach meaningful conclusions for these outcomes. For other outcomes such as symptoms, quality of life and FEV_1, the reporting made it difficult for us to assess the amount of variation in scales, properties, time of measurement, etc., and this uncertainty made the data difficult to interpret.

Potential biases in the review process

We did not contact most trial authors to obtain unpublished data or to clarify methodology. Only nine of the studies were conducted in the last five years, and seven were conducted over 10 years ago. We judged that the time taken to contact all authors and the anticipated low response rate due to study age would delay the publication of this update.

We found six studies listed in an existing systematic review conducted in China (Tong 2014) that did not appear in our searches. While we did not limit our searches by language, they did not cover studies that are indexed in non-English language databases. Since the Tong 2014 systematic review was published in English, we were able to contact the authors and extract sufficient information to confirm the eligibility of these trials. However, we did not have the resources to personally extract data or assess for risk of bias in these studies, and the information we were able to include were kindly provided by the authors of that systematic review and not directly from the studies themselves. The review authors were able to answer questions we had about outcomes the studies and their outcomes, but these studies could not be assessed as rigorously as the other 17 included studies and we could not be certain that all of the data relevant to this review were included. For peak flow and blood eosinophils, some of these studies could not be pooled with the others because a different unit of analysis had been used. In these cases we reported the results alongside the meta-analysis results narratively. The main benefit of including these studies is the completeness of the evidence base, and checking study lists of existing meta-analyses is part of the standard search procedures for Cochrane reviews. Subtle differences in the methods between our own review and that of Tong 2014 (e.g. the way data were extracted, application of trial eligibility criteria) may also have introduced a potential bias, meaning we cannot be sure that all studies relevant to our review were picked up and analysed in the same way. We considered the overall benefit of inclusion to outweigh the potential biases in light of the help provided to us by Hon Fang and the other authors of that review (Fan 2015 [pers comm]).

Current methodology has enriched this updated review. These changes, including the use of the Cochrane 'Risk of bias' tool rather than Jadad (Jadad 1996) and the introduction of GRADE, resulted in differences to the original protocol but should nonetheless reduce the possibility for internal biases.

Agreements and disagreements with other studies or reviews

Two other recent meta-analyses have evaluated the treatment of asthma with long-term macrolides (Reitner 2013; Tong 2014). There are noticeable differences across all three in the conclusions drawn, and this is likely a reflection of the choice of outcomes and methods of analysis. In particular, we chose not to pool results where we were uncertain of scale or measurement similarity in order to make the results as clinically meaningful as possible. Furthermore, more subtle differences in the eligibility criteria and the way scores were aggregated are likely to have contributed to differences in the results and conclusions, such as using standardised mean difference or mean difference, fixed or random effects, change from baseline or endpoint scores, merging multiple relevant study arms, etc. These differences entail difficulties with meta-analysing and interpreting the body of evidence, which is quite heterogenous.

The analysis by Reitner 2013 included 12 RCTs with a minimum duration of three weeks, and reported a positive effect of macrolides on symptoms scores, quality of life, peak flow and bronchial hyperresponsiveness. Tong 2014 included 18 studies, including the 6 Chinese studies that were not identified by our search, and it reports a positive effect on several measures of lung function (FEV_1, PEF, FVC) and airways hyperresponsiveness, but not on other measures of lung function (percentage predicted FEV_1 and FVC), symptoms, or quality of life. Neither review formally assessed exacerbations, either because they were not included as an outcome (Tong 2014) or because the data were considered insufficient to do so (Reitner 2013). The lack of exacerbation data is a major shortcoming of the evidence base, considering that reducing the frequency of asthma exacerbations is the main premise of long-term macrolides treatment.

AUTHORS' CONCLUSIONS

Implications for practice

Existing evidence does not show that macrolides are better than placebo for most clinical outcomes. They may have a benefit on symptom scales and some measures of lung function, and we cannot rule out the possibility of other benefits or harms because the evidence is of very low quality due to heterogeneity among patients and interventions, imprecision and reporting biases.

Implications for research

The review highlights the need for researchers to report clinically relevant outcomes accurately and completely using guideline definitions of exacerbations and validated scales. The possible benefit of macrolides in patients with non-eosinophilic asthma based on subgroup analyses in two of the included studies may require further investigation.

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Rebecca Normansell was the Editor for this review and commented critically on its development.

The background and methods section of this updated review is based on a standard template used by Cochrane Airways Group.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Amayasu 2000

Methods	**Design**: randomised controlled, double-blind, placebo-controlled, cross-over study Statistical analysis: Student's paired T-test **Duration**: 8 weeks per treatment with 4-week washout Conducted in Yokohama, Japan, and Boston, USA
Participants	**Population**: 17 participants were randomised to the two treatment sequences (clarithromycin-placebo and placebo-clarithromycin) **Baseline characteristics**: reported for population as a whole, since the study was a cross-over design % male: 52.9 Mean age: 38.5 % on maintenance ICS: 0 % on maintenance LABA/ICS: 0 Mean % predicted FEV_1: 76.2 Mean daily ICS dose, µg: 0 *Chlamydophila* infection: not reported **Inclusion criteria**: non-smokers, aspirin tolerant, with mild or moderate asthma diagnosed according to the criteria of the American Thoracic Society. All were in stable condition and had been free of symptoms for respiratory infections for at least 6 weeks **Exclusion criteria**: patients using oral or inhaled corticosteroids, theophylline, any anti-leukotriene drug, any other anti-inflammatory agents or clarithromycin
Interventions	**Run-in**: wash-out period of at least 4 weeks between cross-over **Intervention**: clarithromycin 200 mg twice a day **Control**: matching placebo
Outcomes	Blood eosinophils, blood neutrophils, serum ECP, sputum eosinophils, sputum neutrophils, sputum ECP, symptom score, FVC, FEV_1, methacholine challenge
Notes	**Funding**: Aoki International Co, Ltd **Study ID(s)**: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly assigned, no details
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo of identical appearance used; described as double-blind

Amayasu 2000 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of dropouts
Selective reporting (reporting bias)	Unclear risk	Reported outcomes could be used in analysis, but unclear if others were missing (protocol registration not reported)
Other bias	Low risk	None noted

Belotserkovskaya 2007

Methods	**Design**: parallel randomised trial (blinding and type of control unclear) **Duration**: 8 weeks Location unclear
Participants	**Population**: 51 adult participants with chronic stable asthma were randomised to azithromycin (28) or 'control' (23) **Baseline characteristics**: none reported **Inclusion criteria**: adults with chronic stable asthma. No other details. **Exclusion criteria**: not described
Interventions	**Run-in**: 24 week open-label period before randomisation **Intervention**: azithromycin (dose not reported) **Control**: 'control' not described
Outcomes	FEV_1 and PEF (not suitable for analysis)
Notes	**Funding**: not stated **Study ID(s)**: not stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Abstract only, no information
Allocation concealment (selection bias)	Unclear risk	Abstract only, no information
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No mention of blinding

Belotserkovskaya 2007 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention of blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of withdrawals not given
Selective reporting (reporting bias)	High risk	No full text found; minimal information about methodology and no analysable results
Other bias	Low risk	None noted

Black 2001

Methods	**Design**: parallel randomised, double-blind, placebo-controlled, multicentre, multinational study **Duration**: 6 weeks of treatment with 24 week follow-up Conducted in Australia, New Zealand, Italy and Argentina
Participants	**Population**: 219 asthmatic participants were randomised to roxithromycin (105) or placebo (114) **Baseline characteristics** % male: roxithromycin, 44.8; placebo, 50.0 Mean age (SD): roxithromycin, 40 (11.6); placebo, 42 (11.9) % on maintenance ICS: roxithromycin, 77.1; placebo, 84.2 % on maintenance LABA/ICS: not reported Mean % predicted FEV_1 (SD): roxithromycin, 79.0 (19.3); placebo, 75.3 (17.4) Mean daily ICS dose, µg: not reported *Chlamydophila* infection: reported according to serological tests **Inclusion criteria**: 18 to 60 years of age, physician diagnosis of asthma, FEV_1 at least 50% of predicted and either > 15% increase in FEV_1 following inhaled salbutamol or a > 15% diurnal variation in PEF on 7 of 14 days during the run-in period. Participants also needed to have IgG titres to *C. pneumonia* > 1:64,or IgA titres > 1:16, and a daytime symptom score of at least 2 or nighttime symptom score of at least 1, on 7 of the 14 days of the run-in period **Exclusion criteria**: Treatment with any macrolide, quinolone or tetracycline in the 4 weeks before study entry or over more than 3 weeks in the preceding 4 months. Other medicines that were not permitted were ergot alkaloids, terfenadine and astemizole. Patients also excluded if they had a smoking history of > 20 pack-years, bronchiectasis, any other serious systemic diseases, hypersensitivity to macrolides or any significant change in asthma medication in the previous month, including a course of oral corticosteroids. In addition, they were not eligible if they had a respiratory tract infection during the run-in or if they had abnormal liver function tests or serum creatinine > 200 μmol/L
Interventions	**Run-in**: 2 weeks **Intervention**: roxithromycin 150 mg twice a day **Control**: matching placebo Treatments for asthma other than oral corticosteroids were permitted if the dose had not

Black 2001 (*Continued*)

	changed in the previous month
Outcomes	Symptoms, PEF, FEV_1, reliever medication
Notes	**Funding**: not stated **Study ID(s)**: not stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised but methods not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Described as double-blind, with matching placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	The analysis was on an intention-to-treat basis. This did not include 12 patients who withdrew from the study within a few days of randomisation, without recording any diary card data, or a thirteenth subject who was withdrawn because of nausea and vomiting and did not record any diary card data after the first 10 days of treatment. Does not state from which groups but represents less than 6% of overall population
Selective reporting (reporting bias)	High risk	Outcomes were poorly reported. FEV_1, PEF morning and evening, symptoms and quality of life all reported without variance
Other bias	Low risk	None noted

Brusselle 2013

Methods	**Design**: parallel, randomised, double-blind, placebo-controlled, multicentre study **Duration**: 26 weeks Locations not described in details; appears to be mostly conducted Belgium

Brusselle 2013 (*Continued*)

Participants	**Population**: 109 participants were randomised to azithromycin (55) and placebo (54) **Baseline characteristics** % male: azithromycin, 47; placebo, 30 Median age: azithromycin, 53; placebo, 53 % on maintenance ICS: not reported % on maintenance LABA/ICS: azithromycin, 100; placebo, 100 Mean % predicted FEV_1 (SD): azithromycin, 80.1 (21.9); placebo, 84.8 (20.7) Mean daily ICS dose, µg: azithromycin, 2000; placebo, 2000 *Chlamydophila* infection: not reported **Inclusion criteria**: 18 to 75 years of age; diagnosis of persistent asthma; history consistent with Global Initiative for Asthma step 4 or 5 clinical features; received high doses of ICS ($\geq$ 1000 mg fluticasone or equivalent) plus inhaled LABA for at least 6 months prior to screening and had at least two independent severe asthma exacerbations requiring systemic corticosteroids, LRTI requiring antibiotics or both within the previous 12 months; never smokers or ex-smokers with a smoking history of $\leq$ 10 pack-years; FeNO level was below the upper limit of normal **Exclusion criteria**: Prolonged corrected QT interval, severe bronchiectasis, significant medical conditions or significant laboratory abnormalities that might interfere with the study conduct or patient's safety, pregnancy or breastfeeding, prohibited concomitant medication including anti-IgE treatment and treatment with macrolide antibiotics within the last 3 months
Interventions	**Run-in**: 2 weeks **Intervention**: azithromycin 250 mg per day for 5 days and then 1 capsule 3 times a week **Control**: matching placebo All patients received high-dose combination therapy of ICS and LABA for at least 6 months prior to study entry and continued this treatment throughout the study
Outcomes	ACQ, AQLQ, rescue medication use, FEV_1, morning and evening PEF, adverse events, withdrawals Severe asthma exacerbations were defined as deterioration in asthma leading to at least one of the following: hospitalisation, emergency room visit, or need for systemic corticosteroids for at least 3 days
Notes	**Funding**: academic trial, no industry funding. Agency for Innovation by Science and Technology **Study ID(s)**: NCT00760838

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned in a 1:1 ratio to receive add-on treatment with azithromycin or placebo using a central web-based randomisation tool

Brusselle 2013 (*Continued*)

Allocation concealment (selection bias)	Low risk	Web-based randomisation and the concealment of allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind design (presumably participants and investigators)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout in both groups, but higher in placebo (3.6% vs 9.3%). ITT analysis used
Selective reporting (reporting bias)	Low risk	All outcomes stated in the prospectively registered protocol were well reported
Other bias	Low risk	None noted

Cameron 2012

Methods	**Design**: parallel, randomised, double-blind, placebo-controlled trial **Duration**: 12 weeks Conducted at 2 hospitals in the UK
Participants	**Population**: 77 participants were randomised to azithromycin (39) and placebo (38) **Baseline characteristics** % male: azithromycin, 51.3; placebo, 44.7 Mean age (SD): azithromycin, 46.4 (8.8); placebo, 42.8 (9.4) % on maintenance ICS: azithromycin, 89.7; placebo, 81.6 % on maintenance LABA/ICS: azithromycin, 38.5; placebo, 47.4 Mean % predicted FEV_1: 78.3 (pre-bronchodilator) Mean daily ICS dose, µg (SD): azithromycin, 603 (457); placebo, 709 (564) *Chlamydophila* infection: not reported **Inclusion criteria**: All subjects were aged 18 to 70 years, were current smokers (≥ 5 pack-years history) with chronic asthma (> 1 year duration) and had been free of exacerbations and respiratory tract infections for at least 6 weeks. Able to maintain asthma without exacerbations during run-in period and able to wean off other asthma medication **Exclusion criteria**: Ex-smokers or never smokers; planning to quit smoking during duration of trial; patients with unstable asthma; patients with current epilepsy, psychosis or history of significant atrial or ventricular tachyarrhythmia; corrected QT interval greater than 450 ms in women or 430 ms in men; low potassium levels (if this can be corrected, screening can continue with confirmation of normal levels prior to taking study medication); liver disease (levels for ALT, AST or both 2 or more times ULN); significant renal disease (creatinine or urea levels 2 or more times ULN); any previous severe adverse reactions to macrolides; patients known to have specific IgE sensitivity or skin test positivity to grass pollen and a history of worsening of asthma due to hay fever will not be recruited from mid-May to the end of July; upper or lower respiratory tract infection

	in the 4 weeks prior to randomisation (run-in period can be prolonged in this situation to have 4 weeks with no respiratory infection prior to randomisation); patients who require medications known to interact with azithromycin; on other immunosuppressants or chronic antibiotics; weight under 45 kg; frequent asthma exacerbations (greater than 4) requiring OCS in the year prior to randomisation; current or past diagnosis of allergic-bronchopulmonary-aspergillosis; pregnancy and breastfeeding; mental impairment or language difficulties that makes informed consent impossible
Interventions	**Run-in**: 4 weeks (on inhaled corticosteroid therapy equivalent to 400 µg beclomethasone ± a LABA) **Intervention**: azithromycin 250 mg per day **Control**: matching placebo
Outcomes	Change in ACQ, AQLQ, LCQ, diary symptom score, change in morning PEF, airways responsiveness methacholine PC_{20}, differential cell counts, colony counts, antibody status, FeNO, exacerbation rates
Notes	**Funding**: Medical Research Council UK and supported financially by NHS Research Scotland (NRS), through the Scottish Primary Care Research Network. Study medication (budesonide Easyhalers; Orion Pharma, Newbury, UK) was purchased with an educational grant from AstraZeneca (London, UK) **Study ID(s)**: NCT00852579

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised but no details of sequence generation
Allocation concealment (selection bias)	Unclear risk	Not stated
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Masking: double-blind (subject, caregiver, investigator, outcomes assessor)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Masking:double-blind (subject, caregiver, investigator, outcomes assessor)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	6 patients dropped out, but details not mentioned
Selective reporting (reporting bias)	High risk	Exacerbations were not reported in either of the published reports. Other outcomes were well reported at each of the stated time points
Other bias	Low risk	None noted

Hahn 2006

Methods	**Design**: community-based, parallel multisite, double-blind, randomised, placebo-controlled trial **Duration**: 6 weeks of treatment; outcomes measured at 3 months Conducted in community-based healthcare settings located in 4 US states and 1 Canadian province
Participants	**Population**: 45 participants were randomised to azithromycin (24) and placebo (21) **Baseline characteristics** % male: azithromycin, 33; placebo, 67 Mean age (SD): azithromycin, 50 (14); placebo, 45 (12) % on maintenance ICS: azithromycin, 83; placebo, 76 % on maintenance LABA/ICS: not reported Mean % predicted FEV_1: not reported Mean daily ICS dose, µg: not reported *Chlamydophila* infection: azithromycin, 33%; placebo, 52% **Inclusion criteria**: 18 or older with a diagnosis of current asthma that was persistent, stable, and present for more than 3 months prior to enrolment. Stability was assessed during a 2 to 3 week run-in period, during which eligible patients remained in the same severity class (mild, moderate, or severe) and had no acute exacerbations. Documented objective evidence for reversible airway obstruction, either spontaneously or after treatment, was also required prior to randomisation, either FEV_1 change of 12% (and > 200 mL) or PEF change of 25% (and > 60 L/min) **Exclusion criteria**: ingestion of any macrolide, tetracycline or quinolone in the 6 weeks before randomisation; macrolide allergy; any unstable illness or other cause for symptoms; use of coumadin, anticonvulsants or digoxin; and pregnancy or lactation Note: Asthma was defined as variable symptoms of wheeze, chest tightness, cough, or shortness of breath triggered by a variety of stimuli
Interventions	**Run-in**: 2- to 3-week run-in period, during which eligible patients remained in the same severity class (mild, moderate or severe) and had no acute exacerbations **Intervention**: azithromycin, one 600 mg tablet daily for 3 days, followed by 600 mg weekly for an additional 5 weeks **Control**: matching placebo All patients continued to receive usual care for asthma from their primary physician, who was blinded to treatment allocation
Outcomes	Symptoms, adverse events, withdrawals
Notes	**Funding**: Pfizer **Study ID(s)**: NCT00245908

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	At randomisation, participants meeting final eligibility criteria were allocated to study medication bottles that were coded centrally using a computerised 1:1 alloca-

Hahn 2006 (*Continued*)

		tion ratio blocked by site. Block size was n = 6. An independent statistician, who had no further contact with study conduct, generated the randomisation sequences
Allocation concealment (selection bias)	Low risk	Study physicians, research staff, participants, and data analysts were unaware of allocation due to central randomisation and coding. Emergency unblinding envelopes were available, but study sites did not report opening any of them
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Blinded (patient, physician, data collector, data analyst). Bulk study medication tablets were bottled, labelled and distributed by an independent pharmaceutical service that had no further role in study conduct
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded (patient, physician, data collector, data analyst)
Incomplete outcome data (attrition bias) All outcomes	High risk	We employed the 'intention-to-treat' principle. We did not impute values for missing data. Approximate 20% dropout in both groups unaccounted for
Selective reporting (reporting bias)	Low risk	Prospectively registered pilot study. Specified outcomes were reported
Other bias	Low risk	None noted

Hahn 2012

Methods	**Design**: parallel, randomised, placebo-controlled, double-blind trial **Duration**: 12 weeks of treatment with 1 year off-treatment follow-up Conducted in the USA. Study clinician members, staff of 5 practice-based research networks and one community-based allergist enrolled patients from their practices for this study
Participants	**Population**: 75 participants were randomised to azithromycin (38) and placebo (37) **Baseline characteristics** % male: azithromycin, 29; placebo, 35 Mean age (SD): azithromycin, 45.7 (15.5); placebo, 47.4 (14.2) % on maintenance ICS: azithromycin, 63; placebo, 81 % on maintenance LABA/ICS: azithromycin, 37; placebo, 70 Mean % predicted FEV_1: not reported Mean daily ICS dose, µg: not reported

	Chlamydophila infection: not reported **Inclusion criteria**: adults 18 years of age or older with physician-diagnosed asthma (symptomatic > 2 days per week, > 2 nights per month, in exacerbation, or a combination of these characteristics); objective evidence for reversible airway obstruction (> 12% and > 200 mL change in FEV_1, a 25% and 60 L/min change in PEF or both) either spontaneously or after treatment; asthma for at least 6 months before enrolment **Exclusion criteria**: not English literate or has no email address or Internet access; macrolide allergy; pregnant or lactating; 4 weeks of continuous use of macrolides, tetracyclines, or quinolones within 6 months of randomisation; asthma symptoms less than 6 months' duration; unstable asthma requiring immediate emergency care; comorbidities likely to interfere with study assessments or follow-up (e.g. cystic fibrosis, obstructive sleep apnoea requiring CPAP, cardiomyopathy, congestive heart failure, terminal cancer, alcoholism or other substance addiction, or any other serious medical condition that, in the opinion of the study physician, would seriously interfere with or preclude assessment of study outcomes or completion of study assessments); medical conditions for which macrolide administration may possibly be hazardous (e.g. acute or chronic hepatitis, cirrhosis, or other liver disease; chronic kidney disease; history of prolonged cardiac repolarisation and QT interval or torsades de pointes); specified medications for which close monitoring has been recommended in the setting of macrolide administration (digoxin, theophylline, warfarin, ergotamine or dihydroergotamine, triazolam, carbamazepine, cyclosporine, hexobarbital, or phenytoin)
Interventions	**Run-in**: unclear **Intervention**: azithromycin 600 mg, 1 tablet daily for 3 days followed by 1 tablet weekly for 11 weeks **Control**: matching placebo
Outcomes	Symptoms, ACQ, changes in asthma medications, withdrawals, quality of life, exacerbations Exacerbations were recorded separately for those requiring a steroid burst, an unscheduled or emergency visit or a hospitalisation for asthma
Notes	**Funding**: Pfizer, Inc., donated identical matching azithromycin and placebo. The Wisconsin Academy of Family Physicians; the American Academy of Family Physicians Foundation, under the auspices of the Joint Grant Awards Program; the Dean Foundation for Health Research and Education; and private donors provided financial support for direct costs of AZMATICS trial **Study ID(s)**: NCT00266851

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	An independent statistician prepared the randomisation codes used for subject assignment to the azithromycin or placebo study arms

Hahn 2012 (*Continued*)

Allocation concealment (selection bias)	Low risk	The investigators, study subjects and study site personnel were blinded to treatment allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Each study site received coded study medication bottles (1:1 allocation) in blocks of 6 and was instructed to distribute them (numbered 1 to 6) in numerical ascending order to eligible consenting study subjects
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The investigators, study subjects, and study site personnel were blinded to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	High risk	All analyses were by intention-to-treat, and no subjects with available data were excluded from any analysis. Withdrawal was high and quite uneven between groups (42% and 30%)
Selective reporting (reporting bias)	Low risk	Prospectively registered outcomes reported fully
Other bias	Unclear risk	More participants in the control group were taking regular ICS or ICS/LABA combination

He 2009

Methods	**Design**: randomised controlled trial (assumed parallel assignment; unconfirmed) **Duration**: 12 weeks Conducted in China
Participants	**Population**: 40 participants were randomised to azithromycin (20) and placebo (20) **Baseline characteristics** % male: not reported Mean age (SD): azithromycin, 35 (7.3); placebo, 34 (5.6) % on maintenance ICS: not reported % on maintenance LABA/ICS: not reported Mean % predicted FEV_1 : not reported Mean daily ICS dose, µg: not reported *Chlamydophila* infection: not reported **Inclusion criteria**: We were not able to detail the specific inclusion and exclusion criteria for this trial because it was included from an existing systematic review (Tong 2014) . The inclusion criteria of the review required that the study be designed to evaluate the "efficacy of prolonged treatment with macrolide antibiotics in adult patients with asthma"

He 2009 (*Continued*)

	Exclusion criteria: not reported
Interventions	**Run-in**: unknown **Intervention**: azithromycin 250 mg twice weekly **Control**: placebo
Outcomes	FEV_1, FEV_1/FVC, symptoms
Notes	**Funding**: unknown **Study ID(s)**: unknown

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Tong 2014 awarded 2 points for this domain, suggesting well reported and acceptable methods of random sequence generation
Allocation concealment (selection bias)	Unclear risk	Information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Tong 2014 noted that methods of blinding were not adequately described in the study, although a placebo control was used
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Tong 2014 noted that methods of blinding were not adequately described in the study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Tong 2014 noted that withdrawals and dropouts were not adequately described in the study
Selective reporting (reporting bias)	Unclear risk	Information was not available.
Other bias	Unclear risk	Information was not available.

Kamada 1993

Methods	**Design**: parallel, randomised, double-blind, placebo-controlled trial **Duration**: 12 weeks Conducted in Denver, USA
Participants	**Population**: 19 participants were randomised to troleandomycin + methylprednisolone (6), troleandomycin + prednisone (8), and placebo + methylprednisolone (5) **Baseline characteristics** % male: troleandomycin + methylprednisolone, 16.7; troleandomycin + prednisone,

	100; placebo + methylprednisolone, 60 Mean age (SD): troleandomycin + methylprednisolone, 14.3 (2.9); troleandomycin + prednisone, 11.9 (2.6); placebo + methylprednisolone, 11.3 (2.7) % on maintenance ICS: troleandomycin + methylprednisolone, 100; troleandomycin + prednisone, 100; placebo + methylprednisolone, 100 % on maintenance LABA/ICS: not reported Mean % predicted FEV_1: not reported Mean daily ICS dose, µg: not reported *Chlamydophila* infection: not reported **Inclusion criteria**: patients aged 6 to 17 meeting ATS criteria for reversible obstructive airways disease, requiring prednisone in doses of at least 20 mg every other day, using inhaled bronchodilators at least 4 times a day, taking theophylline with daytime peak serum concentrations > 10 µg/mL, and having previously failed treatment with or were receiving cromolyn sodium at the time of screening **Exclusion criteria**: patients with evidence of pregnancy, smoking, viral upper respiratory infection within 4 weeks of enrolment
Interventions	**Run-in**: single-blind run-in period of at least 1 week **Intervention 1**: troleandomycin (250 µg) + methylprednisolone once daily **Intervention 2**: troleandomycin (250 µg) + prednisolone once daily **Control**: placebo + methylprednisolone once daily All patients required OCS, given as part of the randomised treatment. The mean daily dose was 34.2 mg, 21.3 mg and 23.5 mg in intervention 1, intervention 2 and control groups, respectively
Outcomes	Symptoms score, methacholine PD_{20}, glucocorticoid dose reduction, FEV_1, PEF
Notes	**Funding**: FDA grant FD-R 000278 **Study ID(s)**: not stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation was stratified on 2 levels of severity of asthma. Methods unclear
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All patients received identically appearing study medications in the form of 2 blue capsules, which contained either prednisolone or methylprednisolone, and one white capsule, which contained either troleandomycin or placebo, daily Described as double-blind. Investigators who were not blinded to data tapered doses as tolerated by patients on the recommendations of investigators who were blinded

Kamada 1993 (*Continued*)

		to data
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear who measured outcomes and whether they were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	2 patients dropped out of the troleandomycin-prednisone group, 1 of whom could not be included in the final analysis (representing 14% dropout due to small randomisation numbers)
Selective reporting (reporting bias)	High risk	Several measures were only reported graphically and could not be analysed
Other bias	High risk	Baseline characteristics were unbalanced due to the very small numbers per group

Kapoor 2010

Methods	**Design**: cross-over, randomised, double-blind, placebo-controlled trial **Duration**: 6 weeks per treatment with 3-week washout Conducted in India
Participants	**Population**: 40 participants were randomised to the two treatment sequences (roxithromycin-placebo and placebo-roxithromycin) **Baseline characteristics**: none reported **Inclusion criteria**: stable, mild-to-moderate asthma **Exclusion criteria**: not described
Interventions	**Run-in**: not described **Intervention**: roxithromycin 150 mg once daily **Control**: matching placebo
Outcomes	Asthma control test, spirometric indices, impulse oscillometry parameters
Notes	**Funding**: not stated **Study ID(s)**: not stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Not described
Allocation concealment (selection bias)	Unclear risk	Not described

Kapoor 2010 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Described as double-blind, no other details
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not described
Selective reporting (reporting bias)	High risk	Only abstract available, no published report. Minimal details of study characteristics, participants or outcomes
Other bias	Unclear risk	Impossible to assess

Kostadima 2004

Methods	**Design**: parallel, randomised, double-blind, placebo-controlled trial **Duration**: 8 weeks Conducted in Greece
Participants	**Population**: 75 participants were randomised to clarithromycin twice daily (25), 3 times daily (25) and placebo (25) **Baseline characteristics** % male: clarithromycin twice daily, 72.7; clarithromycin 3 times daily, 40; placebo, 28.6 Mean age (SD): clarithromycin twice daily, 48 (16); clarithromycin 3 times daily, 42 (12); placebo, 41 (16) % on maintenance ICS: clarithromycin twice daily, 100; clarithromycin 3 times daily, 100; placebo, 100 % on maintenance LABA/ICS: not reported Mean % predicted FEV_1 (SD): clarithromycin twice daily, 85 (14); clarithromycin 3 times daily, 85 (13); placebo, 86 (14) Mean daily ICS dose, µg: not reported *Chlamydophila* infection: not reported **Inclusion criteria**: Aged 18 to 70 yrs; established diagnosis of bronchial asthma for 1 year; treatment with budesonide 400 mg twice daily and salbutamol 200 mg taken as needed less than twice weekly for at least 1 month prior to recruitment; a PD_{20} of < 2 mg. **Exclusion criteria**: history of allergic rhinitis or occupational asthma; a history of smoking (past or current); treatment with systemic corticosteroids or a history of URTI over the 4 weeks prior to participation in the trial; FEV_1 of < 50% of the predicted value or of < 1 L at baseline; URTI or asthma exacerbation during the study period; a history of systemic diseases (i.e. heart attack or stroke in the previous 3 months, uncontrolled hypertension, known aortic aneurysm, epilepsy requiring drug treatment or peptic ulcer disease); treatment with beta-blockers; and pregnancy or lactation

Kostadima 2004 (*Continued*)

Interventions	**Run-in**: not described **Intervention 1**: clarithromycin 250 mg twice daily **Intervention 2**: clarithromycin 250 mg 3 times daily **Control**: matching placebo dextrose During the study, patients continued their treatment with budesonide and salbutamol. No other medication was allowed
Outcomes	Methacholine PD_{20}
Notes	**Funding**: not stated **Study ID(s)**: not stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No specific details
Allocation concealment (selection bias)	Unclear risk	Randomised to one of the study groups by a research nurse who played no further role in the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Patients and investigators were blinded with regard to the type of treatment received
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear who measured outcomes
Incomplete outcome data (attrition bias) All outcomes	High risk	Patients who dropped out were not represented in the analysis; varied across groups from 12% to 20%
Selective reporting (reporting bias)	Unclear risk	Several key outcomes were not reported; report does not give details of a study protocol to check that all outcomes were reported
Other bias	Unclear risk	% male was unbalanced across groups, but other measures were well balanced (included age and baseline lung function)

Kraft 2002

Methods	**Design**: parallel, randomised, double-blind, placebo-controlled trial **Duration**: 6 weeks Conducted in Denver, USA
Participants	**Population**: 55 participants were randomised to clarithromycin (26) and placebo (26); 3 withdrew due to scheduling conflicts (n = 1 participant) and non-compliance (n = 2) **Baseline characteristics**: reported for the population as a whole, not for each group % male: 49.1 Mean age (SD): 33.4 (8.9) % on maintenance ICS: 32.7 % on maintenance LABA/ICS: 100 Mean % predicted FEV_1 (SD): 69.3 (15.6) Mean daily ICS dose, µg : not reported *Chlamydophila* infection: 56.4% had evidence of *C. pneumoniae* or *M. pneumoniae* infection **Inclusion criteria**: Participants fulfilled criteria for asthma, exhibiting a provocative concentration of methacholine causing a 20% decline in FEV_1 of < 8 mg/mL, and reversibility of lung function by at least 12% with bronchodilator **Exclusion criteria**: inpatient status; upper or lower respiratory tract infection within previous 3 months; use of macrolides, tetracyclines or quinolones within previous 3 months; smoking history > 5 pack-years or any cigarettes within the previous 2 years; and significant non-asthma pulmonary disease or other medical problems
Interventions	**Run-in**: not described **Intervention**: clarithromycin 500 mg twice daily **Control**: matching placebo
Outcomes	Lung function, cytokine in situ production
Notes	**Funding**: not stated **Study ID(s)**: not stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised, not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind randomisation to treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blind randomisation to treatment. The individual who performed the analysis was blinded to participants' *Mycoplasma/ Chlamydophila* status, and those counting

Kraft 2002 (*Continued*)

		were blinded to treatment status
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 subjects (treatment groups unknown) underwent analysis for *Mycoplasma and Chlamydophila* but were excluded from the treatment analysis due to scheduling difficulties (n = 1) and noncompliance (n = 2)
Selective reporting (reporting bias)	Unclear risk	Mostly non-clinical outcomes. No preregistered protocol mentioned to cross-check
Other bias	Low risk	None noted

Nelson 1993

Methods	**Design**: prospective, parallel, randomised, double-blind, placebo-controlled trial **Duration**: 1 to 2 years (variable) Conducted in Denver, USA
Participants	**Population**: 75 participants were randomised to troleandomycin + methylprednisolone (37) and placebo + methylprednisolone (38) **Baseline characteristics** % male: troleandomycin + methylprednisolone, 36.7; placebo + methylprednisolone, 29.6 Age range: troleandomycin + methylprednisolone, 21 to 75; placebo + methylprednisolone, 22 to 62 % on maintenance ICS: not reported % on maintenance LABA/ICS: not reported Mean % predicted FEV_1: not reported Mean daily ICS dose, µg: not reported *Chlamydophila* infection: not reported **Inclusion criteria**: All patients had a diagnosis of asthma with demonstrated fluctuation in the FEV_1 of 15% or more of the predicted value occurring either spontaneously or as a result of therapy. They were required to have received a minimum of 15 mg prednisone per day or an equivalent dose of another corticosteroid over the preceding 3 months with a history that lower doses resulted in deterioration of asthma control and pulmonary function. They were also required to be unable to achieve alternate-day corticosteroid therapy, be receiving theophylline, if tolerated, with a peak serum value of greater than 10 µg/mL and inhaled b-adrenergic bronchodilator therapy at least 4 times daily **Exclusion criteria**: Patients who were employing inhaled sodium cromolyn or ICS were required to discontinue these medications before enrolment. Patients who otherwise qualified were not enrolled if they were receiving anticonvulsant therapy, had significant hepatic disease or were current smokers. Women of child-bearing age were required to have a negative pregnancy test and agree to avoid pregnancy during the duration of possible troleandomycin therapy
Interventions	**Run-in**: Before entry, each patient's medication was optimally adjusted and often had received a transient increase in corticosteroid dose. Therefore, each patient's asthma was under good control when they were randomised, and steroids were tapered only in a way

Nelson 1993 (*Continued*)

	consistent with maintenance of continued good control **Intervention**: troleandomycin 250 µg once daily + methylprednisolone **Control**: matching placebo + methylprednisolone All patients required OCS, which were given as part of the randomised treatment. Mean daily doses were 30.8 mg and 32.0 mg for intervention and control, respectively
Outcomes	Symptoms score, corticosteroid dose, blood eosinophil count, IgG, fasting blood sugar, methacholine PD_{20}
Notes	**Funding**: grant from the Clinical Investigation Committee, National Jewish Centre for Immunology and Respiratory Medicine **Study ID(s)**: not stated

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised; no details
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind (presumably patients and personnel/investigators)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear who performed the evaluations
Incomplete outcome data (attrition bias) All outcomes	High risk	Dropout higher in placebo group; data not accounted for
Selective reporting (reporting bias)	Unclear risk	Most outcome data are reported; study predates requirement to register a protocol
Other bias	Low risk	None noted

Piacentini 2007

Methods	**Design**: parallel, randomised, double-blind, placebo-controlled trial **Duration**: 8 weeks Conducted at the residential house of the Istituto Pio XII for asthma in Italy
Participants	**Population**: 16 participants were randomised to azithromycin (8) and placebo (8) **Baseline characteristics** % male: azithromycin, 75; placebo, 75 Mean age (SD): azithromycin, 13.9 (2.4); placebo 12.9, (2.4) % on maintenance ICS: azithromycin, 100; placebo, 100

	% on maintenance LABA/ICS: not reported Mean % predicted FEV_1: azithromycin, 73.5; placebo, 84.3 Mean daily ICS dose, µg: not reported *Chlamydophila* infection: not reported **Inclusion criteria**: children with asthma (age not specified) according to ATS criteria **Exclusion criteria**: not described in detail
Interventions	**Run-in**: not stated **Intervention**: azithromycin once a day for 3 consecutive days every week, at the dosage of 10 mg/kg body weight **Control**: matching placebo All of the patients continued their long-term treatment for asthma with a low dose of ICS: either fluticasone, 100 to 200 μg/day, or beclomethasone dipropionate, 200 to 400 μg/day. Oral steroids were not allowed in the 3 months preceding enrolment
Outcomes	Lung function, bronchial hyperresponsiveness expressed as the DRS of FEV_1 fall after hypertonic saline inhalation and induced sputum
Notes	**Funding**: not stated **Study ID(s)**: not stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Active or placebo treatment was randomly attributed using a computer-generated randomisation code
Allocation concealment (selection bias)	Unclear risk	No details
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Active treatment and placebo were stored in identical bottles, and nursing staff not involved in any part of the study administered the drug to the children
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Active treatment and placebo were stored in identical bottles, and nursing staff not involved in any part of the study administered the drug to the children
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No mention of dropout
Selective reporting (reporting bias)	Unclear risk	No trial registration number reported; cannot check if outcomes are missing
Other bias	Low risk	None noted

Shoji 1999

Methods	**Design**: cross-over, randomised, double-blind, placebo-controlled trial Statistical analysis: Student's paired T-test **Duration**: 8 weeks per treatment with 4-week washout Conducted at a single centre in Japan
Participants	**Population**: 14 participants were randomised to the two treatment sequences (roxithromycin-placebo and placebo-roxithromycin) **Baseline characteristics:** presented for the population as a whole due to the cross-over design % male: 42.9 Mean age: 39.6 % on maintenance ICS: 0 % on maintenance LABA/ICS: 0 Mean % predicted FEV_1: 75 Mean daily ICS dose, µg: 0 *Chlamydophila* infection: Not reported **Inclusion criteria**: adult patients with clinical histories of aspirin-intolerant asthma. Positive sulpyrine or lysine aspirin provocation test. Non-smokers diagnosed with mild or moderate asthma according to ATS criteria. The patients were in a stable condition and had been free of symptoms of respiratory infection for at least 6 weeks **Exclusion criteria**: patients using oral or inhaled corticosteroids, theophylline, any anti-leukotriene drug, such as pranlukast, or any other anti-allergic agents as well as roxithromycin
Interventions	**Run-in**: washout period of at least 4 weeks **Intervention**: roxithromycin 150 mg twice daily **Control**: matching placebo
Outcomes	Blood eosinophils, blood neutrophils, serum ECP, sputum eosinophils, sputum neutrophils, sputum ECP, symptom score, FVC, FEV_1, methacholine challenge
Notes	**Funding**: grants-in-aid from Aoki International Co Ltd for Dr T Shoji **Study ID(s)**: not stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomised, no details
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind (presumably patients and personnel); matching placebo

Shoji 1999 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear who performed the assessments and whether they were blind
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details of dropout
Selective reporting (reporting bias)	Unclear risk	Outcomes were well reported. No details of trial registration to cross-check
Other bias	Low risk	None noted

Simpson 2008

Methods	**Design**: parallel, randomised, double-blind, placebo-controlled trial **Duration**: 8 weeks Participants were recruited from the Ambulatory Care Service of the Department of Respiratory and Sleep Medicine at the John Hunter Hospital, New Lambton, Australia
Participants	**Population**: 45 participants were randomised to clarithromycin (23) and placebo (22) **Baseline characteristics** % male: clarithromycin, 43.5; placebo, 54.5 Mean age (SD): clarithromycin, 60; placebo, 55 % on maintenance ICS: not reported % on maintenance LABA/ICS: clarithromycin, 83; placebo, 82 Mean % predicted FEV_1 (SD): clarithromycin, 73.6 (15.8); placebo, 67.6 (18.8) Mean daily ICS dose, µg: clarithromycin, 2000; placebo, 2000 *Chlamydophila* infection: not reported **Inclusion criteria**: non-smoking adults with symptomatic refractory asthma according to GINA **Exclusion criteria**: Participants were excluded if they had smoked more than 5 pack-years or if they had any known sensitivity to macrolide antibiotics. Antihistamine therapies were ceased for the duration of the study
Interventions	**Run-in**: mentioned but not described **Intervention**: clarithromycin 500 mg twice daily **Control**: matching placebo During the study, participants continued with their baseline medications as prescribed by their physician
Outcomes	Sputum IL-8 concentration, sputum neutrophil numbers and concentrations of neutrophil elastase and matrix metalloproteins (MMP)-9, lung function, airway hyperresponsiveness to hypertonic saline, asthma control, quality of life, and symptoms
Notes	**Funding**: not stated **Study ID(s)**: ACTR12605000318684

Risk of bias

Simpson 2008 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A random-numbers table was computer generated for treatment allocation using permuted blocks of 4. Randomisation was stratified according to those with high (≥ 61%) and low neutrophil proportions at screening. Treatment was assigned randomly for each group separately to ensure equal numbers of subjects with high neutrophil proportions in each of the 2 treatment groups
Allocation concealment (selection bias)	Unclear risk	A blinded staff member, who took no further part in the study, performed randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The placebo and active medication were packaged identically by the hospital pharmacy department, which dispensed treatments according to the random-numbers table
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not described
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts reported in the study
Selective reporting (reporting bias)	High risk	Data reported in the paper could not be meta-analysed (median IQR)
Other bias	Unclear risk	None noted

Strunk 2008

Methods	**Design**: parallel, randomised, double-blind, placebo-controlled multicentre trial **Duration**: 30 weeks, depending on asthma control Recruited from five CARE Network centres in the USA
Participants	**Population**: 55 patients were randomised to azithromycin (17), placebo (19), and one other group not relevant to this review (19, Montelukast) **Baseline characteristics:** presented for the population as a whole % male: 58.2 Mean age (SD): 11.2 (2.6) % on maintenance ICS: not reported % on maintenance LABA/ICS: 100 Mean % predicted FEV_1 (SD): 101.9 (13.7)

	Mean daily ICS dose, µg: 60% were taking 800 µg of budesonide a day at randomisation *Chlamydophila* infection: nasal washes were obtained at randomisation, at week 18 and at end of trial (either after the last planned visit or at time of treatment failure) **Inclusion criteria**: Aged 6 to 17 years, and demonstration of moderate-to-severe persistent asthma. Pre-bronchodilator values of FEV_1 had to be $\geq$ 80% predicted for consideration of step-down at enrolment, or $\geq$ 50% predicted if inadequately controlled and step-up planned. All children demonstrated ability to perform reproducible spirometry and had airway lability demonstrated either by an improvement in FEV_1 of $\geq$ 12% after 4 puffs of albuterol or airway hyperresponsiveness, reflected by a $\geq$ 20% fall in FEV_1 after a methacholine dose of $\leq$ 12.5 mg/mL. **Exclusion criteria**: very severe asthma, as indicated by more than 3 hospitalisations in the preceding 12 months, history of intubation or mechanical ventilation within the last year, or any history of hypoxic seizure due to asthma; history of severe sinusitis requiring sinus surgery within the past 12 months; use of maintenance oral or systemic antibiotics for treatment of an ongoing condition; contraindication for use of azithromycin or montelukast; presence of lung disease other than asthma; use of digoxin, ergotamine or dihydroergotamine, triazolam, carbamazepine, cyclosporine, hexobarbital, phenytoin, and other macrolides
Interventions	**Run-in**: budesonide-stable period of 6 weeks (with salmeterol 50 µg). During the run-in, participants demonstrated evidence of inadequate control on ICS plus salmeterol, with subsequent documentation that step-up to a higher dose of ICS (to a maximum of 1600 µg daily, again with salmeterol) established control. Participants were excluded if they were unable to use the study drug delivery systems or to adhere to $\geq$ 80% of days with use of salmeterol Diskus and oral capsules and of diary card completion during the run-in (pre-randomisation) period **Intervention**: azithromycin 250 mg (25 to 40 kg) or 500 mg (> 40 kg) once daily plus placebo montelukast tablet **Control**: 1 or 2 placebo azithromycin capsules once daily plus 1 placebo montelukast tablet The treatment arms were stratified according to clinical centre and dose of budesonide (800 µg/day vs 1600 µg/day) that achieved asthma control during run-in Participants were provided with albuterol MDI (Ventolin, GSK), prednisone (10 mg tablets) and a written asthma action plan
Outcomes	Exacerbations requiring oral corticosteroids, PEF, nocturnal awakenings, rescue medication use
Notes	**Funding**: not stated **Study ID(s)**: not stated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation was stratified according to clinical centre and dose of budesonide (800 µg/day vs 1600 µg/day) that achieved asthma control during run-in. Sequence

Strunk 2008 (*Continued*)

		generation was not described
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	High risk	Double-masked. After the lowest dose was achieved and control maintained for an additional 6 weeks, the active study medication was changed to placebo (blinded to participant). Investigators appear not to be blind after this stage
Blinding of outcome assessment (detection bias) All outcomes	High risk	Double-masked, as above
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout in active and placebo groups
Selective reporting (reporting bias)	High risk	Registration number not reported. Outcomes could not be included in meta-analysis, and several were reported for the population as a whole so groups could not be compared
Other bias	Low risk	None noted

Sutherland 2010

Methods	**Design**: parallel, randomised, double-blind, placebo-controlled trial **Duration**: 16 weeks Recruited from 10 hospitals and medical centres in the USA
Participants	**Population**: 92 patients were randomised to clarithromycin (47) and placebo (45) **Baseline characteristics:** % male: clarithromycin, 42.6; placebo, 44.4 Mean age (SD): clarithromycin, 41.3 (12.5); placebo, 37.5 (10.5) % on maintenance ICS: not reported % on maintenance LABA/ICS: not reported Mean % predicted FEV_1: 76.0 (whole population) Mean daily ICS dose, µg: not reported *Chlamydophila* infection: 6 clarithromycin and 6 placebo patients were PCR positive for *M. pneumoniae* or *C. pneumoniae* **Inclusion criteria**: history of physician-diagnosed asthma; methacholine PC_{20} less than or equal to 16 mg/mL, FEV_1 improvement greater than or equal to 12% in response to 180 µg albuterol, or both; stable asthma for at least 6 weeks prior to study entry; FEV_1 greater than or equal to 60% of predicted result following 180 µg albuterol; Juniper ACQ score greater than or equal to 1.5 (optimal ACQ score cut-off point for asthma that is 'not well controlled' by NIH/GINA guidelines); non-smoker (less than

	10 pack-per-year lifetime smoking history and no smoking in the year prior to study entry); able to perform spirometry, as per ATS criteria; 75% adherence with diary cards, fluticasone (monitored with Doser), and placebo pill trial (monitored electronically with electronic Drug Exposure Monitor (eDEM) pill dose counter) for the final 2 weeks of the 4-week run-in period; at visit 1, in steroid-naive participants, no significant adrenal suppression, defined as a plasma cortisol concentration less than 5 μg/dL (if adrenal suppression occurs, a 250 μg corticotropin (ACTH) stimulation test was performed. Plasma cortisol levels were collected at baseline, and 30 and 60 minutes after the ACTH stimulation test. Participants must have a cortisol concentration greater than 20 μg/dL on at least one of the post-ACTH time points); absence of bronchoscopy-induced exacerbation (if bronchoscopy-induced exacerbation has occurred, prednisone therapy must have stopped at least 6 weeks prior to study entry); absence of respiratory tract infection (if infection has occurred, infection-related symptoms must have stopped at least 6 weeks prior to study entry); has experienced no more than two exacerbations or respiratory tract infections prior to study entry; if female and able to conceive, willing to utilise two medically acceptable forms of contraception (one non-barrier method with single barrier method or a double barrier method) **Exclusion criteria**: presence of lung disease other than asthma; presence of vocal cord dysfunction, due to potential confounding of ACQ score; significant medical illness other than asthma; history of atrial or ventricular tachyarrhythmia; use of any medication that has a significant interaction with clarithromycin, including herbal or alternative therapies; asthma exacerbation within 6 weeks of the screening visit or during the run-in period prior to bronchoscopy; use of systemic steroids or change in dose of controller therapy within 6 weeks of the screening visit; inability, in the opinion of the study investigator, to coordinate use of dry powder or metred-dose inhaler or to comply with medication regimens; inability or unwillingness to perform required study procedures; prolonged heart rate corrected QT interval (greater than 450 ms in women and greater than 430 ms in men) on ECG at study entry; low potassium or magnesium levels (based on local Asthma Clinical Research Network laboratory definitions); abnormal elevation of liver function tests (AST, ALT, total bilirubin or alkaline phosphatase); abnormal prothrombin time (PT) or partial thromboplastin time (PTT) results; reduced creatinine clearance; contraindication to bronchoscopy, as determined by medical history or physical examination; regular consumption of grapefruit or grapefruit juice; pregnant or breastfeeding
Interventions	**Run-in**: 4-week run-in period, in which participants were treated with CFC-fluticasone propionate MDI, 88 μg inhaled regularly twice daily, and inhaled CFC-albuterol sulfate, 180 μg as needed every 4 to 6 hours for relief of acute symptoms. If, at the end of the four week run-in period, participants demonstrated an ACQ score of $\geq$ 1.25, they were eligible to proceed to fibreoptic bronchoscopy for the purposes of endobronchial biopsy for characterisation of lower airway PCR status for *M. pneumoniae* or *C. pneumoniae.* **Intervention**: clarithromycin 500 mg twice daily + fluticasone propionate 88 μg twice daily (Flovent HFA 44 μg 2 puffs twice daily) **Control**: placebo + fluticasone propionate 88 μg twice daily (Flovent HFA 44 μg two puffs twice daily)
Outcomes	ACQ total score and MCID for treatment response, rescue albuterol use, morning and evening PEF, FEV_1, PC_{20}, change in exacerbation number and frequency PC_{20} and change in FeNO

Notes	**Funding**: Milton S Hershey Medical Center with collaboration from the National Heart, Lung, and Blood Institute (NHLBI) **Study ID(s)**: NCT00318708

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Based on the results of PCR testing, participants were stratified into 2 groups, either PCR positive or PCR negative for both *M. pneumoniae* and *C. pneumoniae*. Within these two strata, participants were randomly allocated in a 1:1 distribution to the addition of either clarithromycin, 500 mg capsule by mouth twice daily, or matched placebo
Allocation concealment (selection bias)	Unclear risk	Not described
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both participants and study personnel were blinded to treatment allocation
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Masking: double-blind (participant, caregiver, investigator, outcomes assessor)
Incomplete outcome data (attrition bias) All outcomes	High risk	All analyses invoked the intention-to-treat paradigm, with truncation at the time of exacerbation or treatment failure in relevant analyses. Dropout was 17% and 11% in clarithromycin and placebo groups, respectively, and the primary outcome reported on ClinicalTrials.gov does not appear to have imputed for missing participants
Selective reporting (reporting bias)	High risk	Only group contrasts available for some outcomes in the published paper, and only the primary outcome and adverse events have been uploaded to ClinicalTrials.gov
Other bias	Low risk	None noted

Wang 2012

Methods	**Design**: randomised controlled trial (assumed parallel assignment; unconfirmed) **Duration**: 8 weeks Conducted in China
Participants	**Population**: 45 patients were randomised to clarithromycin (23) and placebo (22) **Baseline characteristics:** % male: not reported Mean age: not reported % on maintenance ICS: not reported % on maintenance LABA/ICS: not reported Mean % predicted FEV_1: not reported Mean daily ICS dose, µg: not reported *Chlamydophila* infection: not reported **Inclusion criteria**: We were not able to detail the specific inclusion and exclusion criteria for this trial because it was included from an existing systematic review (Tong 2014) . The inclusion criteria of the review required that the study be designed to evaluate the "efficacy of prolonged treatment with macrolide antibiotics in adult patients with asthma" **Exclusion criteria**: not reported
Interventions	**Run-in**: unknown **Intervention**: clarithromycin 500 mg twice daily **Control**: placebo
Outcomes	Trough FEV_1, cell counts, symptoms
Notes	**Funding**: unknown **Study ID(s)**: unknown

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Tong 2014 awarded 2 points for this domain, suggesting well reported and acceptable methods of random sequence generation
Allocation concealment (selection bias)	Unclear risk	Information was not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Tong 2014 noted that methods of blinding were reported but not in detail. A placebo control was used
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Tong 2014 noted that methods of blinding were not adequately described in the study

Wang 2012 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Tong 2014 noted that withdrawals and dropouts were not adequately described in the study
Selective reporting (reporting bias)	Unclear risk	Information was not available.
Other bias	Unclear risk	Information was not available.

Wang 2014

Methods	**Design**: randomised controlled trial (assumed parallel assignment; unconfirmed) **Duration**: 52 weeks Conducted in China
Participants	**Population**: 58 patients were randomised to azithromycin (29) and placebo (29) **Baseline characteristics:** % male: not reported Mean age (SD): azithromycin, 28.4 (16.0); placebo 29.6 (14.2) % on maintenance ICS: not reported % on maintenance LABA/ICS: not reported Mean % predicted FEV_1 (SD): not reported Mean daily ICS dose, µg (SD): not reported *Chlamydophila* infection: not reported **Inclusion criteria**: We were not able to detail the specific inclusion and exclusion criteria for this trial because it was included from an existing systematic review (Tong 2014) . The inclusion criteria of the review required that the study be designed to evaluate the "efficacy of prolonged treatment with macrolide antibiotics in adult patients with asthma" **Exclusion criteria**: not reported
Interventions	**Run-in**: unknown **Intervention**: azithromycin 250 mg twice weekly **Control**: placebo
Outcomes	FEV_1, PEF
Notes	**Funding**: unknown **Study ID(s)**: unknown

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Tong 2014 awarded 2 points for this domain, suggesting well reported and acceptable methods of random sequence generation

Wang 2014 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Information was not available
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Tong 2014 noted that methods of blinding were not adequately described in the study, although a placebo control was used
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Tong 2014 noted that methods of blinding were not adequately described in the study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Tong 2014 noted that withdrawals and dropouts were not adequately described in the study
Selective reporting (reporting bias)	Unclear risk	Information was not available.
Other bias	Unclear risk	Information was not available.

Xiao 2013

Methods	**Design**: randomised controlled trial (assumed parallel assignment - unconfirmed) **Duration**: 12 weeks Conducted in China
Participants	**Population**: 210 patients were randomised to roxithromycin (106) and placebo (104) **Baseline characteristics:** % male: Not reported Mean age (SD): roxithromycin, 34.5 (7.2); placebo, 33.7 (8.3) % on maintenance ICS: not reported % on maintenance LABA/ICS: not reported Mean % predicted FEV_1: not reported Mean daily ICS dose, µg: not reported *Chlamydophila* infection: not reported **Inclusion criteria**: We were not able to detail the specific inclusion and exclusion criteria for this trial because it was included from an existing systematic review (Tong 2014) . The inclusion criteria of the review required that the study be designed to evaluate the "efficacy of prolonged treatment with macrolide antibiotics in adult patients with asthma" **Exclusion criteria**: Not reported
Interventions	**Run-in**: unknown **Intervention**: roxithromycin 150 mg twice daily **Control**: placebo
Outcomes	FEV_1, FVC, PEF
Notes	**Funding**: unknown **Study ID(s)**: unknown

Xiao 2013 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Tong 2014 awarded 2 points for this domain, suggesting well reported and acceptable methods of random sequence generation
Allocation concealment (selection bias)	Unclear risk	Information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Tong 2014 noted that methods of blinding were not adequately described in the study, although a placebo control was used
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Tong 2014 noted that methods of blinding were not adequately described in the study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Information was not available.
Selective reporting (reporting bias)	Unclear risk	Information was not available.
Other bias	Unclear risk	Information was not available.

Yan 2008

Methods	**Design**: randomised controlled trial (assumed parallel assignment; unconfirmed) **Duration**: 4 weeks Conducted in China
Participants	**Population**: 40 patients were randomised to roxithromycin (20) and placebo (20) **Baseline characteristics:** % male: not reported Mean age: not reported % on maintenance ICS: not reported % on maintenance LABA/ICS: not reported Mean % predicted FEV_1: not reported Mean daily ICS dose, µg: not reported *Chlamydophila* infection: not reported **Inclusion criteria**: We were not able to detail the specific inclusion and exclusion criteria for this trial because it was included from an existing systematic review (Tong 2014) . The inclusion criteria of the review required that the study be designed to evaluate the "efficacy of prolonged treatment with macrolide antibiotics in adult patients with asthma" **Exclusion criteria**: not reported

Yan 2008 (*Continued*)

Interventions	**Run-in**: unknown **Intervention**: roxithromycin 150 mg twice daily **Control**: placebo
Outcomes	Trough FEV_1, FEV_1, PEF, cell counts, symptoms
Notes	**Funding**: unknown **Study ID(s)**: unknown

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Tong 2014 awarded 2 points for this domain suggesting well reported and acceptable methods of random sequence generation
Allocation concealment (selection bias)	Unclear risk	Information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Tong 2014 noted that methods of blinding were not adequately described in the study, although a placebo control was used
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Tong 2014 noted that methods of blinding were not adequately described in the study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Tong 2014 noted that there was a detailed report of withdrawals and dropouts in the study, but we were unable to assess the level of dropout and how this might have affected the results
Selective reporting (reporting bias)	Unclear risk	Information was not available.
Other bias	Unclear risk	Information was not available.

Zhang 2013

Methods	**Design**: randomised controlled trial (assumed parallel assignment; unconfirmed) **Duration**: 60 days (8.7 weeks) Conducted in China
Participants	**Population**: 60 patients were randomised to azithromycin (30) and placebo (30) **Baseline characteristics:** % male: not reported Mean age: not reported

	% on maintenance ICS: not reported % on maintenance LABA/ICS: not reported Mean % predicted FEV_1: not reported Mean daily ICS dose, µg: not reported *Chlamydophila* infection: not reported **Inclusion criteria**: We were not able to detail the specific inclusion and exclusion criteria for this trial because it was included from an existing systematic review (Tong 2014) . The inclusion criteria of the review required that the study be designed to evaluate the "efficacy of prolonged treatment with macrolide antibiotics in adult patients with asthma" **Exclusion criteria**: not reported
Interventions	**Run-in**: unknown **Intervention**: azithromycin 100 mg once daily **Control**: placebo
Outcomes	Trough FEV_1
Notes	**Funding**: unknown **Study ID(s)**: unknown

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Tong 2014 awarded 2 points for this domain, suggesting well reported and acceptable methods of random sequence generation
Allocation concealment (selection bias)	Unclear risk	Information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Tong 2014 noted that methods of blinding were not adequately described in the study, although a placebo control was used
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Tong 2014 noted that methods of blinding were not adequately described in the study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Tong 2014 noted that withdrawals and dropouts were not adequately described in the study
Selective reporting (reporting bias)	Unclear risk	Information was not available.
Other bias	Unclear risk	Information was not available.

ACQ: Asthma Control Questionnaire; **ACT**: Asthma Control Test; **ACTH**; adrenocorticotropic hormone; **ALT**: alanine aminotransferase; **AQLQ**: Asthma Quality of Life Questionnaire; **AST**: aspartate aminotransferase; **ATS**: American Thoracic Society; **CFC**: chloro fluorocarbon; **CPAP**: continuous positive airway pressure; **DRS**: dose-response slope; **ECG**: electrocardiography; **ECP**: eosinophil cationic protein; **FDA**: Food and Drug Administration (USA); **FeNO**: fractional exhaled nitric oxide; **FEV_1** : forced expiratory volume in one second; **FVC**: forced vital capacity; **GINA**: Global Initiative for Asthma; **ICS**: inhaled corticosteroids; **IgA**: immunoglobulin A; **IgE**: immunoglobulin E; **IgG**: immunoglobulin G; **IL-8**: interleukin 8; **IQR**: interquartile range; **ITT**: intention-to-treat; **LABA**: long-acting $beta_2$-agonist; **LCQ**: Leicester Cough Questionnaire; **LRTI**: lower respiratory tract infection; **NIH**: National Institutes of Health (USA) **MCID**: minimal clinically important difference; **MDI**: metred dose inhaler; **MPN**: methylprednisolone; **OCS**: oral corticosteroids; **PC_{20}** or **PD_{20}** : provocative concentration (or dose) causing a 20% fall in forced expiratory volume in 1 second (FEV_1); **Log PC_{20}** : logarithm to the base 10 of PC_{20}; **PCR**: polymerase chain reaction; **PEF**: peak expiratory flow; **PBRN**: practice-based research network; **QT interval**: measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle; **SD**: standard deviation; **ULN**: upper limit normal; **URTI**: upper respiratory tract infections.

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

Study	Reason for exclusion
Andrade 1983	Study period too short (6 days) and randomisation method not adequate
Anon 2009	Commentary. Not an RCT
Ball 1990	Study period too short (2 weeks)
Cogo 1994	Study of inadequate duration
Ebling 1984	Basic science study
Feldman 1997	Basic science in vitro study
Gotfried 2004	The study was suspended because the slow enrolment of patients. The clarithromycin and placebo groups were unequal in size, and the final analysis was performed only within the treatment group, analysing data before and after the macrolide therapy within the same patients. Therefore the study was excluded because there were no between-study comparisons
Hueston 1991	Patients not affected by asthma
Itkin 1970	Short (2 weeks) duration
Kaplan 1958	Not an RCT
Koh 1997	Patients are children with bronchiectasis; 7 children had asthma and insufficient data were reported for these children separately
Koutsoubari 2012	Acute exacerbations in children, trial less than 4 weeks
Spector 1974	Not an RCT
Szefler 1980	Not an RCT

(*Continued*)

Szefler 1982a	Not an RCT
Szefler 1982b	Not an RCT
Takamura 2001	Not an RCT
Wald 1986	Not an RCT
Weinberger 1977	Not an RCT
Zeiger 1980	Not an RCT

RCT: randomised controlled trial.

Characteristics of studies awaiting assessment *[ordered by study ID]*

ACTRN12609000197235

Methods	Large-scale, parallel, multicentre, double-blind, placebo-controlled randomised trial
Participants	Patients with symptomatic stable asthma with ACQ > 0.75, confirmed variable airflow obstruction, maintenance combination therapy. Minimum age 18 years, males and females. Target sample size 420
Interventions	Azithromycin 500 mg (2 x 250 mg tablets to be administered by the oral route) 3 times weekly for 48 weeks Placebo 3 times weekly for 48 weeks
Outcomes	Asthma exacerbations, Juniper Asthma Quality of Life Questionnaire, safety, Juniper Asthma Control Questionnaire, Symptom diary data
Notes	Recruitment status: recruiting Government funded in Australia Trial ID: ACTRN12609000197235

ACQ: Asthma Control Questionnaire.

DATA AND ANALYSES

Comparison 1. Macrolide versus placebo

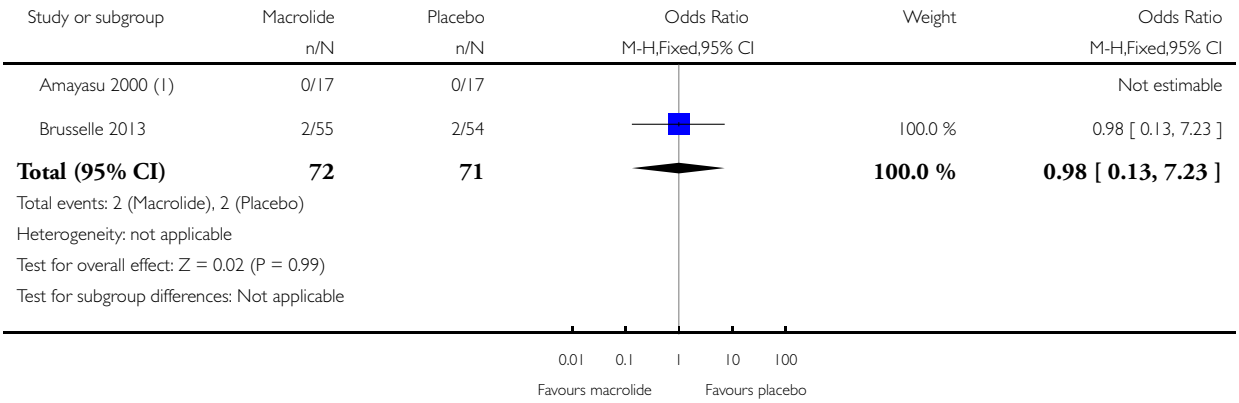
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Exacerbation requiring hospitalisation	2	143	Odds Ratio (M-H, Fixed, 95% CI)	0.98 [0.13, 7.23]
2 'Severe' exacerbation - requiring at least OCS	5	290	Odds Ratio (M-H, Fixed, 95% CI)	0.82 [0.43, 1.57]
3 Symptom scales	4	156	Std. Mean Difference (Fixed, 95% CI)	-0.35 [-0.67, -0.02]
4 Asthma Control	4	353	Std. Mean Difference (Fixed, 95% CI)	-0.05 [-0.26, 0.15]
5 Asthma Quality of Life Questionnaire (AQLQ)	5	389	Mean Difference (Fixed, 95% CI)	0.06 [-0.12, 0.24]
6 Rescue medication puffs/day	4	314	Mean Difference (Fixed, 95% CI)	-0.26 [-0.65, 0.12]
7 Morning PEF (L/min)	4	289	Mean Difference (Fixed, 95% CI)	2.22 [-9.73, 14.17]
8 Evening PEF (L/min)	3	212	Mean Difference (Fixed, 95% CI)	1.97 [-12.68, 16.62]
9 FEV_1 (L)	9	631	Mean Difference (Fixed, 95% CI)	0.08 [0.02, 0.14]
10 Bronchial hyperresponsiveness (BHR)			Other data	No numeric data
11 Oral corticosteroid dose	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
12 Serious adverse events (incl mortality)	7	434	Odds Ratio (M-H, Fixed, 95% CI)	0.80 [0.24, 2.68]
13 Withdrawal	9	563	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.59, 1.52]
14 Blood eosinophils	2		Mean Difference (Fixed, 95% CI)	-33.50 [-36.11, -30.90]
15 Sputum eosinophils	3		Mean Difference (Fixed, 95% CI)	Totals not selected
16 ECP in serum	2		Mean Difference (Fixed, 95% CI)	-12.84 [-15.67, -10.00]
17 ECP in sputum	2		Mean Difference (Fixed, 95% CI)	-1.45 [-1.78, -1.11]

Analysis 1.1. Comparison 1 Macrolide versus placebo, Outcome 1 Exacerbation requiring hospitalisation.

Review: Macrolides for chronic asthma

Comparison: 1 Macrolide versus placebo

Outcome: 1 Exacerbation requiring hospitalisation



(1) Crossover trial - no events occurred in either phase. Participants have not been split to avoid double counting as the study does not contribute to the effect estimate.

Analysis 1.2. Comparison 1 Macrolide versus placebo, Outcome 2 'Severe' exacerbation - requiring at least OCS.

Review: Macrolides for chronic asthma

Comparison: 1 Macrolide versus placebo

Outcome: 2 'Severe' exacerbation - requiring at least OCS

Study or subgroup	Macrolide n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Amayasu 2000 (1)	0/17	0/17			Not estimable
Brusselle 2013 (2)	26/55	26/54		68.6 %	0.97 [0.46, 2.05]
Hahn 2006	0/19	0/17			Not estimable
Kostadima 2004 (3)	4/50	3/25		18.2 %	0.64 [0.13, 3.10]
Strunk 2008 (4)	1/17	3/19		13.2 %	0.33 [0.03, 3.55]
Total (95% CI)	**158**	**132**		**100.0 %**	**0.82 [0.43, 1.57]**

Total events: 31 (Macrolide), 32 (Placebo)

Heterogeneity: $Chi^2 = 0.83$, df = 2 (P = 0.66); $I^2 = 0.0\%$

Test for overall effect: Z = 0.59 (P = 0.55)

Test for subgroup differences: Not applicable

(1) Crossover trial - no events occurred in either phase. Participants have not been split to avoid double counting as the study does not contribute to the effect estimate.

(2) Defined as those requiring hospitalisation/ER visit/systemic corticosteroids/LRTI requiring antibiotics

(3) Two dose groups merged. Exacerbation not defined.

(4) Exacerbation defined as requiring oral steroids

Analysis 1.3. Comparison 1 Macrolide versus placebo, Outcome 3 Symptom scales.

Review: Macrolides for chronic asthma

Comparison: 1 Macrolide versus placebo

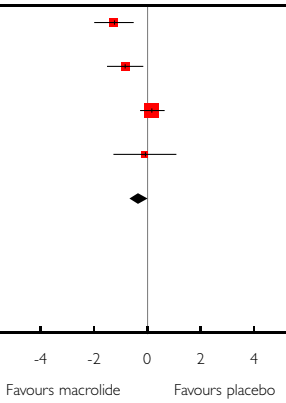
Outcome: 3 Symptom scales

Study or subgroup	Macrolide N	Placebo N	Std. Mean Difference (SE)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
Amayasu 2000 (1)	17	17	-1.26 (0.377)		19.2 %	-1.26 [-2.00, -0.52]
Hahn 2006	19	17	-0.8307 (0.3496)		22.3 %	-0.83 [-1.52, -0.15]
Hahn 2012 (2)	38	37	0.1734 (0.2314)		51.0 %	0.17 [-0.28, 0.63]
Kamada 1993	6	5	-0.097 (0.6061)		7.4 %	-0.10 [-1.28, 1.09]
Total (95% CI)	**80**	**76**			**100.0 %**	**-0.35 [-0.67, -0.02]**

Heterogeneity: Chi² = 13.01, df = 3 (P = 0.005); I² =77%

Test for overall effect: Z = 2.10 (P = 0.036)

Test for subgroup differences: Not applicable



(1) 4-point scale. This is a crossover study including 17 participants who received macrolide and placebo in a random order.

(2) 0-4 scale (lower is better)

Analysis 1.4. Comparison 1 Macrolide versus placebo, Outcome 4 Asthma Control.

Review: Macrolides for chronic asthma

Comparison: 1 Macrolide versus placebo

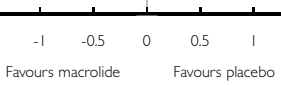
Outcome: 4 Asthma Control

Study or subgroup	Macrolide N	Placebo N	Std. Mean Difference (SE)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
Brusselle 2013 (1)	55	54	-0.12 (0.1633)		40.9 %	-0.12 [-0.44, 0.20]
Cameron 2012 (2)	39	38	0.1877 (0.2285)		20.9 %	0.19 [-0.26, 0.64]
Hahn 2012 (3)	38	37	0.0109 (0.231)		20.4 %	0.01 [-0.44, 0.46]
Sutherland 2010	47	45	-0.24 (0.2476)		17.8 %	-0.24 [-0.73, 0.25]
Total (95% CI)	**179**	**174**			**100.0 %**	**-0.05 [-0.26, 0.15]**

Heterogeneity: Chi^2 = 1.92, df = 3 (P = 0.59); I^2 =0.0%

Test for overall effect: Z = 0.48 (P = 0.63)

Test for subgroup differences: Not applicable



(1) ACQ adjusted mean difference as change from baseline

(2) ACQ

(3) ACQ

Analysis 1.5. Comparison 1 Macrolide versus placebo, Outcome 5 Asthma Quality of Life Questionnaire (AQLQ).

Review: Macrolides for chronic asthma

Comparison: 1 Macrolide versus placebo

Outcome: 5 Asthma Quality of Life Questionnaire (AQLQ)

Study or subgroup	Macrolide N	Placebo N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Brusselle 2013 (1)	55	54	0.12 (0.1633)		31.9 %	0.12 [-0.20, 0.44]
Cameron 2012	39	38	-0.31 (0.1939)		22.6 %	-0.31 [-0.69, 0.07]
Hahn 2006	19	17	0.25 (0.3042)		9.2 %	0.25 [-0.35, 0.85]
Hahn 2012	38	37	0.17 (0.2371)		15.1 %	0.17 [-0.29, 0.63]
Sutherland 2010	47	45	0.2 (0.2)		21.2 %	0.20 [-0.19, 0.59]
Total (95% CI)	**198**	**191**			**100.0 %**	**0.06 [-0.12, 0.24]**

Heterogeneity: Chi^2 = 4.87, df = 4 (P = 0.30); I^2 =18%

Test for overall effect: Z = 0.64 (P = 0.52)

Test for subgroup differences: Not applicable

(1) Mean change from baseline

Analysis 1.6. Comparison 1 Macrolide versus placebo, Outcome 6 Rescue medication puffs/day.

Review: Macrolides for chronic asthma

Comparison: 1 Macrolide versus placebo

Outcome: 6 Rescue medication puffs/day

Study or subgroup	Macrolide N	Placebo N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Brusselle 2013	55	54	-0.16 (0.3674)		28.4 %	-0.16 [-0.88, 0.56]
Cameron 2012	39	38	-0.3 (0.5102)		14.7 %	-0.30 [-1.30, 0.70]
Hahn 2006	19	17	0.59 (0.5196)		14.2 %	0.59 [-0.43, 1.61]
Sutherland 2010	47	45	-0.6 (0.3)		42.6 %	-0.60 [-1.19, -0.01]
Total (95% CI)	**160**	**154**			**100.0 %**	**-0.26 [-0.65, 0.12]**

Heterogeneity: Chi^2 = 4.04, df = 3 (P = 0.26); I^2 =26%

Test for overall effect: Z = 1.34 (P = 0.18)

Test for subgroup differences: Not applicable

Analysis 1.7. Comparison 1 Macrolide versus placebo, Outcome 7 Morning PEF (L/min).

Review: Macrolides for chronic asthma

Comparison: 1 Macrolide versus placebo

Outcome: 7 Morning PEF (L/min)

Study or subgroup	Macrolide N	Placebo N	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Brusselle 2013	55	54	3.96 (9.8777)		38.1 %	3.96 [-15.40, 23.32]
Cameron 2012	39	38	-10.3 (18.7759)		10.5 %	-10.30 [-47.10, 26.50]
Kamada 1993 (1)	6	5	52.1 (57.1487)		1.1 %	52.10 [-59.91, 164.11]
Sutherland 2010	47	45	2.4 (8.6)		50.2 %	2.40 [-14.46, 19.26]
Total (95% CI)	**147**	**142**			**100.0 %**	**2.22 [-9.73, 14.17]**

Heterogeneity: Chi^2 = 1.24, df = 3 (P = 0.74); I^2 =0.0%

Test for overall effect: Z = 0.36 (P = 0.72)

Test for subgroup differences: Not applicable

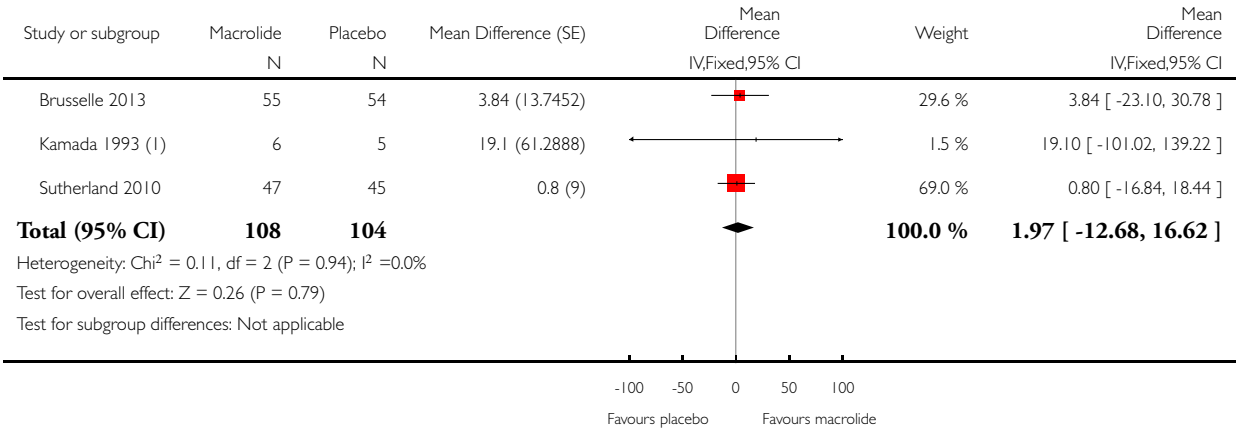
(1) PEF pre-dose

Analysis 1.8. Comparison 1 Macrolide versus placebo, Outcome 8 Evening PEF (L/min).

Review: Macrolides for chronic asthma

Comparison: 1 Macrolide versus placebo

Outcome: 8 Evening PEF (L/min)



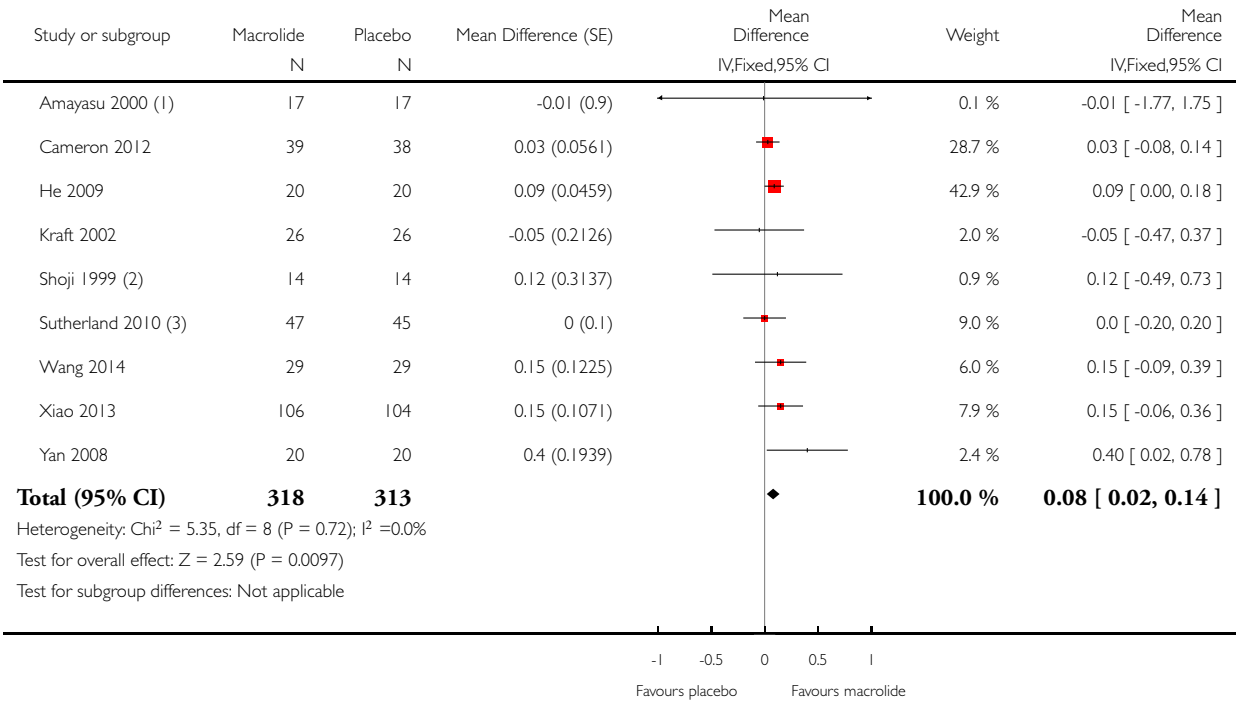
(1) PEF post-dose

Analysis 1.9. Comparison 1 Macrolide versus placebo, Outcome 9 FEV1 (L).

Review: Macrolides for chronic asthma

Comparison: 1 Macrolide versus placebo

Outcome: 9 FEV_1 (L)



(1) This is a crossover study including 17 participants who received macrolide and placebo in a random order.

(2) Crossover study with 14 participants who received both treatments.

(3) Pre-bronchodilator

Analysis 1.10. Comparison 1 Macrolide versus placebo, Outcome 10 Bronchial hyperresponsiveness (BHR).

Bronchial hyperresponsiveness (BHR)

Study	Measure of BHR (units)	Results	Conclusions
Amayasu 2000	Methacoline challenge test (log PC_{20})	Clarithromycin: 2.96 ± 0.57 Placebo: 2.60 ± 0.51 (P < 0.01)	Clarithromycin significantly reduced BHR in patients with allergic intermittent asthma
Cameron 2012	Methacoline challenge test (log PC_{20})	Azithromycin: 0.20 ± 1.52 Placebo: 0.19 ± 1.29 (P < 0.93)	No effect of azithromycin in smokers with persistent asthma

Bronchial hyperresponsiveness (BHR) (*Continued*)

Kamada 1993	Methacoline challenge test (PC_{20})	16 of the 19 patients took test at the beginning and at the end of the analysis. Data are reported graphically and not included in the main analysis	No significant difference at the end of the treatment was recorded among the 3 arms of the study
Kostadima 2004	Methacoline challenge test (PC_{20})	Median interquartile range (IQR) before and after the treatment: Clarithromycin 250 mg twice daily: 0.3 mg (0.1 to 1) and 1.3 mg (0.6 to 2) mg (P < 0.001) Clarithromycin 250 mg 3 times-daily: 0.4 mg (0.1 to 0.9) mg (P < 0.001) Placebo: 0.4 mg (0.1 to 0.9) and 0.3 mg (0.1 to 0.6) mg (P not significant)	Compared to the baseline, there was a significant increase in the median PC_{20} in the 2 macrolide groups but not in the placebo group
Nelson 1993	Methacoline challenge test (PC_{20})	11 out of 27 placebo group patients and 13 out of 30 troleandomycin group patients took the test at the start and end of the study. Troleandomycin: +1.89 mg/mL Placebo: +0.55 mg/mL	No significant effect of troleandomycin was recorded in comparisons within and between the study groups
Piacentini 2007	Hypertonic saline challenge (dose-response slope)	Azithromycin: 2.75 ± 2.12 to 1.42 ± 1.54 (P < 0.02) Placebo: 1.48 ± 1.75 to 1.01 ± 1.38 (P = 0.21)	The reduction of BHR in the treatment group was driven by the change from the baseline in 3 out of 9 patients. No significant difference was observed in a comparison between the groups. Study in children
Shoji 1999	Sulpyrine inhalation testing (log PC_{20}-sulpyrine)	Roxitrhromycin: 1.18 ± 0.40 Placebo: 1.15 ± 0.43	No significant improvement of BHR was recorded within and between group comparisons
Simpson 2008	Hypertonic saline challenge (dose-response slope; DSR)	DSR before: 1.8 (0.6 to 6.4) and after clarithromycin: 1 (0.5 to 4.2) DSR before: 1 (0.6 to 3.2) and after placebo: 1 (0.5 to 3.3)	No significant improvement of BHR was recorded within and between group comparisons
Sutherland 2010	Methacoline challenge test (PC_{20} doubling dose) Analysis stratified for (polymerase chain reaction) PCR positivity for *M. pneumoniae* or *C. pneumonia*.	Difference between clarithromycin and placebo groups: Irrespective of PCR status: + 1.2 ± 0.5, P = 0.01; In patients with positive PCR status: + 0.9 ± 1.8, P = 0.6;	BHR was significantly improved by clarithromycin compared to placebo in the whole population and in the PCR negative groups, but not among the PCR positive patients

		In patients with negative PCR status: + 1.2 ± 0.5, P = 0.02.	

Analysis 1.11. Comparison 1 Macrolide versus placebo, Outcome 11 Oral corticosteroid dose.

Review: Macrolides for chronic asthma

Comparison: 1 Macrolide versus placebo

Outcome: 11 Oral corticosteroid dose

Study or subgroup	Macrolide N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Kamada 1993 (1)	6	4.9 (2.45)	5	11.5 (5.5902)		-6.60 [-11.88, -1.32]
Nelson 1993 (2)	29	6.3 (7.0007)	27	10.4 (6.755)		-4.10 [-7.70, -0.50]

(1) Lowest tolerated mg/day in prednisolone equivalent during the 12 week study

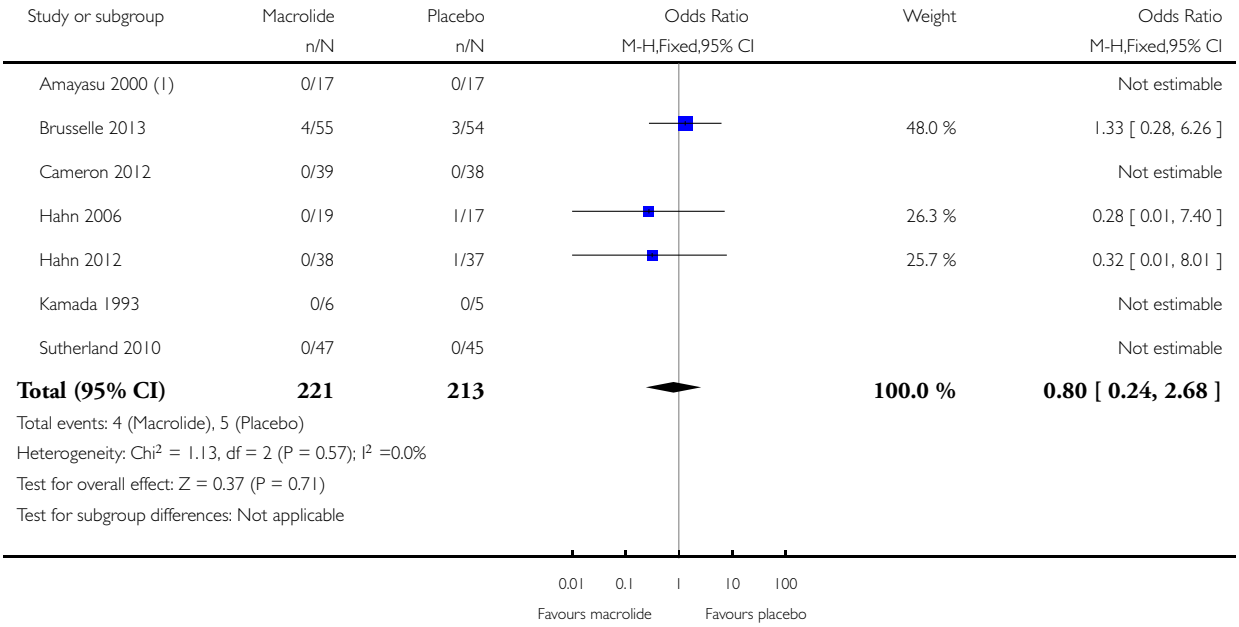
(2) Lowest stable dose (mg/day of methylprednisolone) achieved between study entry and 12 month follow-up

Analysis 1.12. Comparison 1 Macrolide versus placebo, Outcome 12 Serious adverse events (incl mortality).

Review: Macrolides for chronic asthma

Comparison: 1 Macrolide versus placebo

Outcome: 12 Serious adverse events (incl mortality)



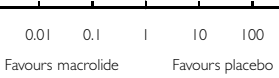
(1) Crossover trial - no events occurred in either phase. Participants have not been split to avoid double counting as the study does not contribute to the effect estimate.

Analysis 1.13. Comparison 1 Macrolide versus placebo, Outcome 13 Withdrawal.

Review: Macrolides for chronic asthma
Comparison: 1 Macrolide versus placebo
Outcome: 13 Withdrawal

Study or subgroup	Macrolide n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Brusselle 2013	2/55	5/54		13.9 %	0.37 [0.07, 1.99]
Hahn 2006	5/24	4/21		9.7 %	1.12 [0.26, 4.86]
Hahn 2012	16/38	11/37		18.5 %	1.72 [0.66, 4.47]
Kamada 1993	0/6	0/5			Not estimable
Kostadima 2004 (1)	8/50	4/25		12.8 %	1.00 [0.27, 3.70]
Nelson 1993	7/37	11/38		25.2 %	0.57 [0.19, 1.69]
Simpson 2008	0/23	1/22		4.3 %	0.30 [0.01, 7.89]
Strunk 2008	2/17	1/19		2.4 %	2.40 [0.20, 29.13]
Sutherland 2010	5/47	5/45		13.1 %	0.95 [0.26, 3.54]
Total (95% CI)	**297**	**266**		**100.0 %**	**0.95 [0.59, 1.52]**

Total events: 45 (Macrolide), 42 (Placebo)
Heterogeneity: $Chi^2 = 4.58$, df = 7 (P = 0.71); $I^2 = 0.0\%$
Test for overall effect: Z = 0.23 (P = 0.82)
Test for subgroup differences: Not applicable



(1) Two dose groups merged

Analysis 1.14. Comparison 1 Macrolide versus placebo, Outcome 14 Blood eosinophils.

Review: Macrolides for chronic asthma

Comparison: 1 Macrolide versus placebo

Outcome: 14 Blood eosinophils

Study or subgroup	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Amayasu 2000 (1)	-35.5 (1.704)		60.8 %	-35.50 [-38.84, -32.16]
Shoji 1999	-30.4 (2.1225)		39.2 %	-30.40 [-34.56, -26.24]
Total (95% CI)			**100.0 %**	**-33.50 [-36.11, -30.90]**

Heterogeneity: $Chi^2 = 3.51$, df = 1 (P = 0.06); $I^2 = 72\%$

Test for overall effect: Z = 25.21 (P < 0.00001)

Test for subgroup differences: Not applicable

(1) Amayasu 2000 and Shoji 1999 are both crossover studies including 17 and 14 participants respectively who received macrolide and placebo in a random order.

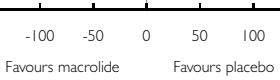
Analysis 1.15. Comparison 1 Macrolide versus placebo, Outcome 15 Sputum eosinophils.

Review: Macrolides for chronic asthma

Comparison: 1 Macrolide versus placebo

Outcome: 15 Sputum eosinophils

Study or subgroup	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Amayasu 2000 (1)	-77 (8.852)		-77.00 [-94.35, -59.65]
Cameron 2012	3.5 (3.9479)		3.50 [-4.24, 11.24]
Shoji 1999	-80 (8.9642)		-80.00 [-97.57, -62.43]



(1) Amayasu 2000 and Shoji 1999 are both crossover studies including 17 and 14 participants respectively who received macrolide and placebo in a random order.

Analysis 1.16. Comparison 1 Macrolide versus placebo, Outcome 16 ECP in serum.

Review: Macrolides for chronic asthma
Comparison: 1 Macrolide versus placebo
Outcome: 16 ECP in serum

Study or subgroup	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Amayasu 2000 (1)	-14.4 (2.021)		51.2 %	-14.40 [-18.36, -10.44]
Shoji 1999	-11.2 (2.07)		48.8 %	-11.20 [-15.26, -7.14]
Total (95% CI)			**100.0 %**	**-12.84 [-15.67, -10.00]**

Heterogeneity: Chi² = 1.22, df = 1 (P = 0.27); I² =18%
Test for overall effect: Z = 8.88 (P < 0.00001)
Test for subgroup differences: Not applicable

(1) Amayasu 2000 and Shoji 1999 are both crossover studies including 17 and 14 participants respectively who received macrolide and placebo in a random order.

Analysis 1.17. Comparison 1 Macrolide versus placebo, Outcome 17 ECP in sputum.

Review: Macrolides for chronic asthma
Comparison: 1 Macrolide versus placebo
Outcome: 17 ECP in sputum

Study or subgroup	Mean Difference (SE)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Amayasu 2000 (1)	-1.6 (0.2448)		48.9 %	-1.60 [-2.08, -1.12]
Shoji 1999	-1.3 (0.2397)		51.1 %	-1.30 [-1.77, -0.83]
Total (95% CI)			**100.0 %**	**-1.45 [-1.78, -1.11]**

Heterogeneity: Chi² = 0.77, df = 1 (P = 0.38); I² =0.0%
Test for overall effect: Z = 8.45 (P < 0.00001)
Test for subgroup differences: Not applicable

(1) Amayasu 2000 and Shoji 1999 are both crossover studies including 17 and 14 participants respectively who received macrolide and placebo in a random order.

ADDITIONAL TABLES

Table 1. Summary characteristics of included studies at baseline

Study ID	Country	Number of participants	Design	Duration (weeks)	Macrolide dose and schedule	Mean age	% male	% on ICS	% Predicted FEV_1
Amayasu 2000	Japan and USA	17	C, R, DB, PC	8	Clarithromycin 200 mg twice daily	38.5	52.9	0.0	76.2
Belotserkovskaya 2007	Russia	51	P, R	8	Azithromycin (unknown dose)	NR	NR	NR	NR
Black 2001	Multinational	219	P, R, DB, PC	6	Roxithromycin 150 mg twice daily	41.0	47.5	80.8	77.1
Brusselle 2013	Belgium	109	P, R, DB, PC	26	Azithromycin 250 mg once daily for 5 days then three times daily	53.0 (median)	38.5	100[a]	82.5
Cameron 2012	UK	77	P, R, DB, PC	12	Azithromycin 250 mg once daily	44.6	48.1	85.7	78.3
Hahn 2006	USA, Canada	45	P, R, DB, PC	6	Azithromycin 600 mg once daily for 3 days then weekly	47.7	48.9	80.0	NR
Hahn 2012	USA	75	P, R, DB, PC	12	Azithromycin 600 mg once daily for 3 days then weekly	46.6	32.0	72.0	NR

Table 1. Summary characteristics of included studies at baseline (*Continued*)

He 2009	China	40	P, R, PC	12	Azithromycin 250 mg twice weekly	34.5	NR	NR	NR
Kamada 1993	USA	19	P, R, DB, PC	12	Troleandomycin 250 µg once daily + OCS	12.5	63.2	100	NR
Kapoor 2010	India	40	C, R, DB, PC	6	Roxithromycin 150 mg once daily	NR	NR	NR	NR
Kostadima 2004	Greece	75	P, R, DB, PC	8	Clarithromycin 250 mg twice daily or three times daily	43.7	47.1	100	85.3
Kraft 2002	USA	55	P, R, DB, PC	6	Clarithromycin 500 mg twice daily	33.4	49.1	32.7	69.3
Nelson 1993	USA	75	P, R, DB, PC	52	Troleandomycin 250 mg once daily + OCS	NR	33.3	0	NR
Piacentini 2007	Italy	16	P, R, DB, PC	8	Azithromycin 10mg/kg once daily 3 days per week	13.4	75	100	78.9
Shoji 1999	Japan	14	C, R, DB, PC	8	Roxithromycin 150 mg twice daily	39.6	42.9	0.0	75.0
Simpson 2008	Australia	45	P, R, DB, PC	8	Clarithromycin	57.6	48.9	NR[b]	70.7

Table 1. Summary characteristics of included studies at baseline (*Continued*)

					500 mg twice daily				
Strunk 2008	USA	55[c]	P, R, DB, PC	30	Azithromycin 250 or 500 mg once daily	11.2	58.2	100[a]	101.9
Sutherland 2010	USA	92	P, R, DB, PC	16	Clarithromycin 500 mg twice daily	39.4	43.5	NR	76.0
Wang 2012	China	45	P, R, PC	8	Clarithromycin 500 mg twice daily	NR	NR	NR	NR
Wang 2014	China	58	P, R, PC	52	Azithromycin 250 mg twice weekly	29.0	NR	NR	NR
Xiao 2013	China	210	P, R, PC	12	Roxithromycin 150 mg twice daily	34.1	NR	NR	NR
Yan 2008	China	40	P, R, PC	4	Roxithromycin 150 mg twice daily	38.5	NR	NR	NR
Zhang 2013	China	60	P, R, PC	9	Azithromycin 100 mg once daily	NR	NR	NR	NR

C: cross-over; **DB**: double-blind; **NR**: not reported; **OCS**: oral corticosteroids; **P**: parallel; **PC**: placebo-controlled; **R**: randomised.

[a] All patients were taking LABA + ICS combination.

[b] 82.2% were taking LABA + ICS combination.

[c] 19 of these participants were not included in the review because they were randomised to a third group who received montelukast.

APPENDICES

Appendix 1. Search methods up to May 2007

Trials were identified using the Cochrane Airways Group Specialised Register, which is derived from systematic searching of electronic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE and CINAHL, and handsearching of respiratory journals and meeting abstracts. All records in the Specialised Register coded as 'asthma' were searched using the following terms:
macrolide* OR clarithromycin OR troleandomycin OR erythromycin OR josamycin OR azithromycin OR roxithromycin
Review articles and bibliographies identified from these primary papers were surveyed for additional citations and RCTs.
The most recent search was run in May 2007.

Appendix 2. Sources and search methods for the Cochrane Airways Group Specialised Register (CAGR)

Electronic searches: core databases

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

Hand-searches: 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

(*Continued*)

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

Asthma search

1. exp Asthma/
2. asthma$.mp.
3. (antiasthma$ or anti-asthma$).mp.
4. Respiratory Sounds/
5. wheez$.mp.
6. Bronchial Spasm/
7. bronchospas$.mp.
8. (bronch$ adj3 spasm$).mp.
9. bronchoconstrict$.mp.
10. exp Bronchoconstriction/
11. (bronch$ adj3 constrict$).mp.
12. Bronchial Hyperreactivity/
13. Respiratory Hypersensitivity/
14. ((bronchial$ or respiratory or airway$ or lung$) adj3 (hypersensitiv$ or hyperreactiv$ or allerg$ or insufficiency)).mp.
15. ((dust or mite$) adj3 (allerg$ or hypersensitiv$)).mp.
16. or/1-15

Filter to identify RCTs

1. exp "clinical trial [publication type]"/
2. (randomised or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11

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

Appendix 3. Search strategy for Cochrane Airways Group Register

#1 AST:MISC1
#2 MeSH DESCRIPTOR Asthma Explode All
#3 asthma*:ti,ab
#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 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13
#15 #4 and #14
[In search line #1, MISC1 denotes the field where the reference has been coded for condition, in this case, asthma]

Appendix 4. Narrative of individual study results

Study ID	Detail of results
Amayasu 2000	15 of the 17 patients improved their symptom score; 2 reported no improvement. The mean symptom score decreased significantly after treatment with clarithromycin (1.64 SD 0.48 vs 0.88 SD 0.72 P < 0.05). FVC and FEV_1 did not show a significant variation during the time of clarithromycin therapy. This study failed to confirm the bronchodilating effect of the macrolide. Blood eosinophil count as well as serum and sputum ECP levels were significantly decreased after clarithromycin treatment (blood eosinophils 46.3 SD 6.9 vs 12.0 SD 2.4 P < 0.1, sputum eosinophils 90 SD 32 vs 11 SD 6 P < 0.05, both serum and sputum ECP P < 0.05, 15.2 SD 7.3 vs 3.7 SD 1.5 and 1.7 SD 0.9 vs 0.4 SD 0.1, respectively). Methacholine provocation test caused an obstructive reaction in all patients independently of the treatment. PC_{20}-methacholine was higher in the clarithromycin than in the placebo group (mean log PC_{20} methacholine was 2.96 SD 0.57 in clarithromycin vs 2.60 SD 0.51 in placebo P < 0.01). No statistically significant association was found between increased PC_{20} methacholine and ECP levels. No adverse reaction was reported during the treatment with clarithromycin. The authors concluded that clarithromycin has not only antibacterial, but also an anti-inflammatory activity, associated with a reduction of the eosinophilic infiltration in patients with asthma. It is able to improve symptoms and bronchial hyperresponsiveness, but further trials are needed to investigate its clinical utility
Belotserkovskaya 2007	Only an abstract from the ERS congress 2007 is available for this study. Data are only partially reported. No significant difference was reported for FEV_1, PEF, rescue medications and symptoms between the azithromycin and the placebo group. A subgroup analysis for the patients treated with azithromycin and with serologic positivity for *C. pneumoniae* showed a statistically significant improvement from the baseline for FEV_1 and PEF (from 1.99 L to 2.25 L, P = 0.01, and from 305.1 to 348 L/min, P = 0.03 respectively)

(*Continued*)

Black 2001	At the end of the 6 weeks of treatment, the increase of the mean values of morning PEF was significantly higher in the treated group (14 L/min) compared to the placebo group (8 L/min). There was a subsequent increase of the morning PEF values in both groups over the following 6 months after the end of treatment, where the improvement over baseline was 18 L/min in the roxithromycin group, compared to 12 L/min in the placebo group (P = NS). For evening PEF values, roxithromycin significantly improved PEF values (15 L/min vs 3 L/min in the placebo group) at the end of the treatment (P = 0.02), but not at later time points. Both the daytime and the nighttime symptom scores showed a non-significant improvement in the treated group compared to the placebo group over the 6-month study period. There was a non-significant trend for improved AQLQ score with treatment. No statistically significant difference was recorded for the daytime and nighttime symptoms scores. No difference was found for rescue medications or for *Chlamydophila* antibody titres measured during the study. No difference was reported for side effects between the 2 groups. Only mild and reversible liver function test alterations were recorded in 2 patients treated with roxithromycin. The authors concluded that the (not statistically significant) trend of improvement of pulmonary function test as seen in the 3 months following end of treatment in the roxithromycin group compared to the placebo group, suggest that the effect of the macrolide therapy on PEF values could be due more to the antimicrobial effect than to the antiinflammatory effect of the drug, and that the onset time and persistence of the effect could be due to a suppression more than a eradication of the *C. pneumoniae* infection. The authors also suggested a study with the use of 2 antibiotics active against *C. pneumoniae*.
Brusselle 2013	No difference was found between the treatment arms in the primary endpoint (i.e. rate of severe asthma exacerbations, defined as need for hospitalisation, need for systemic steroids for at least 3 days or ER visits) or in lower respiratory tract infections requiring antibiotics No effect of azithromycin compared with placebo was demonstrated after 26 weeks for lung function (FEV_1 and morning and evening PEF), or for the ACQ. The AQLQ score was significantly improved after 26 weeks from the baseline in the azithromycin group, but not in the placebo group; no significant difference were found between the azithromycin and placebo group when comparing the AQLQ score after 26 weeks of treatment No differences were found in the rate of adverse events in the azithromycin and placebo group over the study. A significantly higher proportion of patients treated with azithromycin compared with the patients treated with placebo had macrolide resistant strains of streptococci at the end of the study (87% vs 35%, P < 0.001) A predefined subgroup analysis for the main outcome showed a statistically significant reduction in the rate of exacerbations in patients with non-eosinophilic severe asthma (defined as blood eosinophils $\leq 200/\mu L$) treated with macrolides vs the same type of patients receiving placebo (0.44 primary endpoint rate, 95% CI 0.25 to 0.78 vs 1.03 primary endpoint rate, 95% CI 0.72 to 1.48, P = 0.01 respectively). Conversely, a higher primary endpoint rate was recorded in the group treated with azithromycin (0.96, 95% CI 0.66 to 1.41) compared with the placebo group (0.50, 95% CI 0.28 to 0.88) among the patients with severe asthma and blood eosinophils > $200/\mu L$)
Cameron 2012	The study did not show any significant difference between the arm treated with azithromycin and the placebo group The primary outcome (change from the baseline of the morning PEF) was not different in the 2 treatment arms, with a mean difference of -10.3, 95% CI -47.1 to 26.5 $L*min^{-1}$, P = 0.58. No difference was recorded

(*Continued*)

	for FEV_1 at 12 weeks (pre-albuterol, 2.41 ± 0.77 L/s in the azithromycin groups vs 2.46 ± 0.75 L/s in the placebo group. P = NS) or for the bronchial hyperreactivity (0.20 ± 1.52 Log PC_{20} mg/mL in the azithromycin groups vs 0.19 ± 1.29 Log PC_{20} mg/mL in the placebo group, P = NS). No significant effect of macrolides was observed for the use of rescue medications (2.7 ± 2.5 times/day in the azithromycin group vs 3.0 ± 4.0 times/day in the placebo group, P = NS), for the scores of ACQ (1.75 ± 0.83 vs 1.58 ± 0.96, P = NS), AQLQ (5.2 ± 1.06 vs 5.42 ± 1.31, P = NS) or for the count of eosinophils in the induced sputum ($10.3 \pm 20.1*10^4$ vs $6.8 \pm 13.9*10^4$, P = NS, in the azithromycin and placebo group, respectively) after the 12-week study period No adverse events were recorded in either of the treatment arms during the study
Hahn 2006	No significant difference was observed at 3 months after the completion of the 6 week-treatment for the outcomes Juniper AQLQ (0.59 ± 0.8 vs 0.34 ± 1.0, P = NS) and rescue medications (0.43 ± 1.8 times/day vs − 0.16 ± 1.3, P = NS) in the azithromycin group compared with the placebo group, respectively. Symptoms and daily activities, recorded with a homemade scale from 0 = no symptoms to 4 = worse than ever, were significantly improved in patients treated with azithromycin compared with placebo (0.55 ± 0.7 vs − 0.13 ± 0.9, P = 0.04) 3 patients per group withdrew consent during the study, while 1 patient in the azithromycin group discontinued the study No adverse events were recorded among the patients in the azithromycin group. 1 serious adverse event occurred in the placebo group, with a patient who died for asthma-related causes
Hahn 2012	Only data from the randomised treatment arm and the placebo arm were considered in the systematic review/meta-analysis, while the open label arm was excluded. Of 304 screened patients, 97 (32%) were enrolled: 38 were randomised to azithromycin, 37 to placebo and 22 were allocated to the elected open label treatment No significant difference was observed for severe exacerbations across the study groups, but rates in the different groups were not reported No significant difference was observed for symptoms with a home scale from 0 = no symptoms to 4 = worse than ever (− 0.31 ± 0.74 vs − 0.48 ± 1.16, P = NS), for the ACQ score (− 0.40 ± 0.8 vs − 0.41 ± 1.1, P = NS) and in the Juniper AQLQ (0.67 ± 1.10 vs 0.50 ± 0.95) between the randomised azithromycin and placebo group, respectively, 1 year after randomisation Withdrawal was high and quite uneven between groups (19 patients (50%) and 12 (32.4%) at the 12-month-follow-up in the randomised azithromycin and placebo groups, respectively) One subject in the placebo group discontinued the study because of acute coronary syndrome; another patient in the placebo group discontinued the study because of side effects. Mild side effects were common among patients treated with azithromycin (nausea, 33% vs 9% for placebo, stomach pain, 42% vs 12% for placebo and diarrhoea, 42% vs 15% for placebo), but none of them discontinued medications because of the side effects
Kamada 1993	A significant glucocorticoid dosage reduction was recorded in all 3 groups. The maximum tolerated percentage dosage reductions were 80% ± 6% in the troleandomycin-methyl prednisone group (P < 0.001) , 55% ± 8% (P < 0.001) for the troleandomycin-prednisone group, 44% ± 14% (P = 0.04) for methyl prednisone group. A significant difference was present only between troleandomycin-methyl prednisone group and methyl prednisone group. No statistically significant difference was reported for days of supplemental prednisone for exacerbations. Symptom score was reduced by nearly 50% in patients receiving troleandomycin-methyl prednisone (P = 0.03). There were no significant differences in the other two groups. Pulmonary function tests were slightly reduced in all groups, with a significant reduction of pre-bronchodilator FEV_1 and FEF25- 75

(*Continued*)

	in the troleandomycin-prednisone group (P = 0.03 and P = 0.01, respectively). Methacholine PC_{20} was significantly reduced only in the troleandomycin-methyl prednisone group and slightly increased in the troleandomycin-prednisone group, but the difference may be a reflection of glucocorticoid dosage taper and supplemental prednisone before the final evaluation. Safety aspects: 13 patients received troleandomycin. 1 patient in the troleandomycin-prednisone group experienced an elevation of liver enzymes that was resolved by the discontinuation of troleandomycin. Another patient, in the troleandomycin-methyl prednisone group, reported a mild elevation of liver enzymes, which resolved spontaneously without discontinuation of the treatment. No significant alteration of serum and urine cortisol concentrations were observed, whereas an increase was observed in the methyl prednisone group. Bone density was unchanged in all groups. A slightly decrease (NS) in bone density was observed in the two groups receiving troleandomycin. One patient, in the troleandomycin-prednisone group, was severely osteopenic before the start of the study and experienced a vertebral compression fracture that was attributed to her previous glucocorticoid exposure. Another patient in the troleandomycin-prednisone group developed marked striae on the arms and trunk. She was also affected by Marfan syndrome. The authors concluded that, despite the absence of a control group with only prednisone and the poor number of subjects for each group, some conclusions could be drawn from this study: it is not possible to improve lung function by tapering the steroid dose; the only goal reached is to keep the same level of lung function when reducing the dose of steroids, without severe adverse effect
Kapoor 2010	This study was presented in the form of abstract at the ERS Congress 2010 in Barcelona A significant improvement from the baseline was reported for the ACT score in both the roxithromycin and the placebo group, but no difference was observed when comparing the improvements between the 2 groups after the 6 weeks of treatment (2.68 ± 3.17 vs 1.80 ± 2.83, P = NS in the roxithromycin and in the placebo group, respectively). No significant difference between the groups were reported for FEV_1 at the end of the study. Only very limited information on patients' characteristics and randomisation are available. No data are reported for withdrawal or adverse events, and data on lung function and impulse oscillometry are described only as not significantly different in the 2 groups
Kostadima 2004	A significant increase of the FEV1% was reported only in the group B (from 85±13 at the baseline to 88±12 at the end of the study period, P<0.05). In the other 2 groups the predicted values were 85±14 and 86±14 at the baseline and 85±12 and 88±15 in group A and C, respectively, differences not statistically significant. Compared to the baseline, there was a significant increase in the median PD_{20} in groups A and B (receiving the macrolide) but not in the placebo group. Median (interquartile range) in the 3 groups were before and after the treatment were: group A: 0.3 (0.1-1) and 1.3 (0.6-2) mg (P<0.001); group B: 0.4 (0.1-0.9) mg (P<0.001); and group C: 0.4 (0.1-0.9) and 0.3 (0.1-0.6) mg (P=NS). No side effects were clearly reported, but a patient in the group B withdrawn for a gastrointestinal disorder (no further details were reported). Cortisol levels were measured in 40 patients, no alteration was found at the baseline and after the treatment with the macrolide
Kraft 2002	Out of 55 patients included in the study, 3 were not randomised due to scheduling difficulties (n = 1) and noncompliance (n = 2). The clarithromycin group included 26 randomised patients, as did the control group. Fourteen patients in the treatment group and 13 patients in the placebo group showed a positive PCR for *M. pneumoniae* or *C. pneumoniae* at the baseline on samples obtained via bronchoscopy. No change in the FEV_1 mean values between clarithromycin and placebo was reported at the end of the

(*Continued*)

	treatment (2.64 ± 0.14 L vs 2.69 ± 0.16, respectively, P = 0.75). A subanalysis for PCR status the subjects with a positive PCR for *M. pneumoniae* or*C. pneumoniae* showed a significant increase from their baseline after the therapy with clarithromycin (from a FEV_1 mean value of 2.50 ± 0.16 to 2.69 ± 0.16, P = 0.05, n = 14), whilst this change was not observed in subjects with a positive or negative PCR who received placebo (data are not reported in the paper) or with a negative PCR who received the macrolide (baseline FEV_1 mean value 2.59 ± 0.24 L vs 2.54 ± 0.18 L after the treatment, P = 0.85, n = 12) The study was also designed to investigate the modulation of inflammatory cytokines in BAL and bronchial biopsies during the treatment with clarithromycin. A significant reduction in the expression of TNF-alpha, IL-5 and IL-12 mRNA in BAL and TNF-alpha in airways tissue among the PCR-positive patients treated with macrolides and the PCR-negative patients receiving clarithromycin, showed a significant reduction in the expression of TNF-alphaand IL-12 mRNA in BAL and TNF-alpha in airways tissue. No significant difference in the cytokines expression was noted among subjects receiving placebo It is unclear why the patients underwent a sinus CT evaluation if they were not affected by chronic sinusitis and if one of the exclusion criteria was a history of upper airways infection in the last 3 months before the study No data on adverse events were available.
Nelson 1993	Significant reduction in the requirement for hospitalisation and steroid boost relative to the year before the study were reported in both active and placebo groups. Similar results were reported during the 2 years of follow-up, with non-significant differences between the 2 groups. Data were expressed as rate/year, not as number of events. The authors remarked that the tapering of steroid dose was performed only in situations of complete symptom control and that symptom control was not an evaluable outcome. Corticosteroid dose: the mean steroid dose at enrolment was not significantly different between the 2 groups. The mean dose reported in the placebo group during the year preceding the study entry was significantly higher than in the troleandomycin group (22.8 mg/day, SD 1.9 mg/day vs 17.6 mg/day SD 1.5 mg/day P = 0.02). A significant reduction from the previous corticosteroid usage was reported for the lowest stable dose in both groups, with troleandomycin treated patients reaching a lower dose (10.4 mg/day SD 1.3 mg/day vs 6.3 mg/day SD 1.3 mg/day P = 0.03). Neither the 1-year nor the 2-year reduction of the dose was significantly different in the 2 groups. Corticosteroid effects: eosinophil counts were significantly increased at the time of the 1-year evaluation in both groups. Similarly, the 60-minute stimulated cortisol levels rose during the study, and after 1 year the difference was significant in both groups, but not between groups. Dual-photon densitometry of the L2-4 vertebrae showed a continued decline in both groups of bone density when adjusted for age-matched controls. The mean decline over 1 and 2 years was twice as great, but significant only in the troleandomycin group (1 year P = 0.01, 2 years P = 0.001). Significant differences between the 2 groups were reported for the following 3 parameters: Mean IgG level decreased in the troleandomycin group, and this change was not observed in the placebo group (2 years P = 0.03). Fasting blood sugar increased in the troleandomycin group and decreased in the placebo group (2 years P = 0.02). Mean cholesterol level increased in the troleandomycin group, although not significantly; it was lower in the placebo group after 1 and 2 years (P = 0.03 and P = 0.01, respectively), with a significant difference between the 2 groups (P = 0.02 and P = 0.03 in the 1- and 2-year groups, respectively). Methacholine challenge was performed in only 11 patients in the placebo and in 13 in the treatment

(*Continued*)

	group. The dose producing a 20% fall in FEV_1 rose in the troleandomycin group, indicating less airway responsiveness (0.55 mg/mL in the placebo vs 1.86 mg/mL in the macrolides group, P = 0.08). 3 subjects died during the study, 2 in the treated group and 1 in the placebo group, none for asthma Number of dropouts at 1 year of the study were higher in the placebo group (n = 11, 28.9%) than in the treatment group (n = 7, 18.9%). The authors highlighted the importance of adequately educating the patients regarding the use of anti-asthma drugs, especially steroids. Although the study showed a significant difference in the lower stable dose reached in the troleandomycin group, the increase in indicators of side effects such as cholesterol and fasting blood sugar, and a less significant reduction in the bone densitometry, did not confirm the utility of the steroid sparing effect of troleandomycin but showed a detrimental action with increasing the potential for adverse effects of steroid treatment
Piacentini 2007	8 patients were randomised to receive azithromycin and 8 were randomised to the control group The study did not show any statistically significant variation for FEV_1 within and between the study groups (azithromycin FEV_1 % of reference value 73.5 ± 12.90 at time point 0 and 74.62 ± 9.76 after the treatment, P = NS; placebo FEV_1 % of reference value 84.25 ± 9.58 at time point 0 and 86.00 ± 9.85, P = NS, comparison between azithromycin and placebo group at the end of the study not statistically significant) Bronchial hyperresponsiveness was assessed with a hypertonic saline challenge and expressed not as PD_{15} but as dose-response slope (DRS), reflecting the fall of FEV_1 per unit of substance inhaled. A significant reduction from the baseline in the DSR was observed in the azithromycin group at the end of the study (2.75 ± 2.12 to 1.42 ± 1.54, P = 0.02), but not in the placebo group (1.48 ± 1.75 to 1.01 ± 1.38, P = NS). No differences were shown with between-group comparisons Sputum analysis was conducted in 6 patients in the treatment group and in 7 patients in the placebo group. The percentage of neutrophils in the sputum was significantly decreased from the baseline in the azithromycin group (10% ± 5% to 2.2% ± 2.4%, P < 0.01) but not in the placebo group (7.2% ± 4.2% to 3.2% ± 3.6%, P = NS). No differences were shown with between-group comparisons This study did not report data on dropouts and adverse events
Shoji 1999	Symptom score significantly decreased after roxithromycin treatment (1.63 ± 0.48 vs 0.87 ± 0.70 P < 0.05) . No statistically significant differences were observed in the FEV_1 between roxithromycin and placebo treated patients after the 8 weeks (2.37 ± 0.30 to 2.25 ± 0.26 respectively, P = NS) or for the provocation test with sulpyrine (PC_{20} sulpyrine 1.18 ± 0.40 in the roxithromycin group, 1.15 ± 0.43 for the placebo group at the end of the study, P = NS). No difference was found in the leukotriene E_4 elimination in the urine after the treatment within and between groups. Mean ECP and eosinophils count both in serum and sputum showed a significant decrease after the 8 weeks period of treatment with the antibiotic (blood eosinophils from 43.36 ± 7.3 to 12.4 ± 2.3*10^4/mL, P < 0.01; sputum eosinophils from 94 ± 28 to 10 ± 6*10^4/mL; serum ECP 15.8 ± 6.3 to 3.6 ± 1.4 mg/L, P < 0.05; sputum ECP 1.8 ± 0.4 to 0.4 ± 0.1 mg/L P < 0.05) Dropouts were not reported. None of the patients reported any adverse effects
Simpson 2008	This study was designed and powered primarily to detect a difference in the IL-8 expression in sputum supernatants of patients with refractory asthma after treatment with macrolides. Results were reported as median and interquartile range for most of the descriptive statistics The levels of IL-8 were significantly reduced from the baseline within the clarithromycin group, with 6.

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	6 ng/mL (2.7 to 11.9) before and 3.9 ng/mL (1.8 to 5.4) after the treatment (P = 0.001). A statistically significant difference (with a cut-off point of 0.05 used to determine significance) was also observed when IL-8 levels in the treatment group at the end of the study were compared with the results in the placebo group, where 6.3 ng/mL (3.1 to 17.3) and 6.4 ng/mL (3.7 to 11.3) were measured at the beginning and at the end of the study period, respectively The number of neutrophils in the sputum was significantly reduced (P < 0.04) in the clarithromycin group from the baseline at the end of the treatment, from $142.9*10^4$/mL to $66.7*10^4$/mL, respectively, but no significant difference was found when comparing the results with the placebo group No effect of clarithromycin was demonstrated on FEV_1 % within the treatment arm (73.6 ± 15.8 at time point 0 and 74.6 ± 17.1 at the end of treatment period, P = NS) or in comparison with the placebo group (P = NS) No effect of clarithromycin was demonstrated on bronchial hyperresponsiveness within the treatment arm, with dose-related slope in the hypertonic saline challenge 1.8 (0.6 to 6.4) at time points 0 and 1 (0.5 to 4. 2) at the end of treatment period, P = NS, or in comparison with the placebo group (P = NS) The total score for the AQLQ was significantly improved in the clarithromycin group from the baseline (score 5.5, IQR 4.8 to 6.4) after the treatment period (score 6.2, IQR 5.4 to 6.6, P = 0.014), but not in comparison with the placebo group (score 6.4, IQR 5.2 to 6.7 at time point 0 and score 6.4, IQR 5.7 to 6.8, P = NS both within the placebo group and for the comparison with the treatment arm) The total asthma control score was not significantly improved in the clarithromycin group from the baseline (score 1.6 ± 0.6) after the treatment period (score 1.3 ± 0.7, P = NS); no difference was found in the comparison with and within the placebo group (score 1.3 ± 1.0 at time point 0 and score 1.2 ± 0.8, P = NS both within the placebo group and for the comparison with the treatment arm) A predefined subanalysis showed that most of the significant differences for IL-8 levels, MMP-9 and AQLQ were driven by the effect of macrolides in a subgroup of patients with non-eosinophilic asthma defined as proportion of neutrophils in induced sputum ≥ 61%
Strunk 2008	This study was designed to test a potential inhaled steroid-sparing effect of azithromycin compared with an arm with montelukast and a placebo arm, in children with persistent to severe asthma. After a run-in period of 6 weeks, when patients were treated with salmeterol and an increasing dose of inhaled budesonide to obtain good control of asthma, patients were randomised to azithromycin or montelukast or placebo, holding the same dose of inhaled steroids for 6 weeks. Inhaled steroids were then reduced according to a predefined protocol every 6 weeks Only 55 (19%) of 292 patients enrolled for inclusion in the study reached the randomisation. Out of the 55 patients randomised, 35 (63.6%) reached inadequately controlled status of asthma within a median of 5.1 weeks (range 2.4 to 23.4 weeks) after randomisation. The study was prematurely terminated by the Data Safety Monitoring Board No difference was found in time regarding inadequate control among the 3 groups (median (weeks, 95% CI)): azithromycin, 8.4 (4.3, 17.3); montelukast, 13.9 (4.7, 20.6); placebo, 19.1 (11.7, infinity). A futility analysis with the available data indicated that the study might have shown negative results even if the planned sample size of 210 children was reached PCR for *C. pneumoniae* or *M. pneumoniae* showed no evidence of infection in 140 samples collected from the 55 patients randomised to the treatment arms
Sutherland 2010	The study investigated the role of clarithromycin in adults with mild-to-moderate persistent asthma not optimally controlled by inhaled steroids and analysed the results according to the PCR status for *M. pneumoniae* and *C. Pneumonia* on bronchoscopy samples. A sample size of at least 72 patients for PCR status was required to achieve a 90% power to detect a difference of 0.5 in the primary outcome, the ACQ score

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	Of 253 patients meeting the criteria for inclusion in the study, only 92 were randomised in the 2 treatment arms (clarithromycin and placebo) due to suboptimal asthma control during the 4-week run-in period. Among them, 12 (13%) demonstrated a positive PCR for *M. pneumoniae* or *C. pneumoniae*, while 80 (87%) showed a negative PCR. The original purpose to reach 72 patients with evidence of infection was judged as not feasible, and further enrolment stopped The ACQ score was not significantly improved in any comparison within and between the treatment arms and PCR status at the end of the study period: - difference in ACQ score between the clarithromycin and placebo groups irrespective of PCR status (n = 92): 0.2 ± 0.2, P = 0.2; - difference in ACQ score between the clarithromycin and placebo groups in patients with a positive PCR status (n = 12): 0.3 ± 0.5, P = 0.6; - difference in ACQ score between the clarithromycin and placebo groups in patients with a negative PCR status (n = 80): 0.2 ± 0.2, P = 0.3 FEV_1 (pre-albuterol) was not significantly improved in any comparison at the end of the study period: • difference in FEV_1 (L) between the clarithromycin and placebo groups irrespective of PCR status (n = 92): 0.0 ± 0.1, P = 0.8; • difference in FEV_1 (L) between the clarithromycin and placebo groups in patients with a positive PCR status (n = 12): 0.4 ± 0.2, P = 0.9; • difference in FEV_1 (L) between the clarithromycin and placebo groups in patients with a negative PCR status (n = 80): − 0.2 ± 0.1, P = 0.8. Similar results were obtained for FEV_1 %, morning and evening PEF and rescue medications, with no statistically significant differences shown for any within and between groups analyses, even in the PCR status comparisons Bronchial hyperresponsiveness was significantly improved by clarithromycin compared to placebo in the whole population and in the PCR negative groups, but not among the PCR positive patients: • difference in PC_{20} doubling dose between the clarithromycin and placebo groups irrespective of PCR status (n = 92): + 1.2 ± 0.5, P = 0.01; • difference in PC_{20} doubling dose between the clarithromycin and placebo groups in patients with a positive PCR status (n = 12): + 0.9 ± 1.8, P = 0.6; • difference PC_{20} doubling dose between the clarithromycin and placebo groups in patients with a negative PCR status (n = 80): + 1.2 ± 0.5, P = 0.02. The incidence of adverse events was not different between the clarithromycin and placebo group; no severe adverse event was recorded

ACQ: Asthma Control Questionnaire; **ACT**: Asthma Control Test; **AQLQ**: Asthma Quality of Life Questionnaire; **BAL**: bronchoalveolar lavage; **CI**: confidence interval; **CT**: computed tomography; **DRS**: dose-response slope; **ECP**: eosinophil cationic protein; **ER**: emergency room; **ERS**: European Respiratory Society; **FEF25-75**: the average forced expiratory flow during the mid (25% to 75%) portion of the FVC; **FEV_1** : forced expiratory volume in one second; **FVC**: forced vital capacity; **IgG**: immunoglobulin G; **IL**: interleukin; **MMP**: matrix metallopeptidase; **NS**: not significant; **PEF**: peak expiratory flow; **PC_{20}** or **PD_{20}** : provocative concentration (or dose) causing a 20% fall in forced expiratory volume in 1 second (FEV_1); **PCR**: polymerase chain reaction; **SD**: standard deviation;**TNF-alpha**: tumour necrosis factor alpha.

FEEDBACK

Feedback concerning presentation of data, 16 April 2016

Summary

As primary author of two RCTs included in your recent review of macrolides for asthma, I would like to question the presentation of data from one of my studies (Hahn 2006) that I feel may affect the interpretation of review findings for two outcomes.
The symptom scale forest plot (Analysis 1.3) placed the central point for overall symptoms for our RCT on the "favors placebo" side whereas our results favored macrolide, as stated in our abstract and as illustrated in our Figure 2. It is possible the problem arose during the examination of Table 2 in which we described a symptom change score difference with a (+) result indicating improvement, as noted in our footnote. We also reported that the overall symptom score change favoring azithromycin was statistically significant (0.68, 95% CI 0.1 to 1.3).
The AQLQ forest plot (Analysis 1.5) likewise placed the central point for AQLQ change score for our RCT (2) on the "Favors placebo" side whereas our results favored macrolide, as stated in our abstract. In this case the sign of the positive result was not changed because a positive score already reflected improvement. The review accurately presented the midpoint data from our Table 2 but report different confidence intervals.
I advocate for Analyses 1.3 & 1.5 to be amended in the interest of correct data.
Highest regards for the work you do,
Dr. Hahn.

Reply

Dear Dr Hahn,
We are very grateful for your helpful feedback regarding the accuracy of data pertaining to your study (Hahn 2006).
Regarding Analysis 1.3, we agree data from your study have been misinterpreted, causing the effect to lie in the opposite direction. This has now been amended in the review to correctly represent your symptom scale data in the meta-analysis, and in the interpretation of the results. There may be differences between the methods we have used and your own which make the data look slightly different. For example, we had to use a standardised mean difference analysis because the scales were not the same across studies, meaning your raw data were transformed and displayed as standard deviation units. Importantly, the pooled result for symptom scales now favours macrolide.
Regarding Analysis 1.5, while the effect for Hahn 2006 lies to the right of the line of no difference, this indicates 'favours macrolide' on the forest plot. As is standard practice for scales where higher scores indicate improvement, the labels of the plot were swapped to represent correctly the direction of effect. As above, the confidence intervals may differ slightly as a result of the method of analysis used. We used the mean change scores and standard deviations presented in Table 2 (0.59 (0.8) n = 19 azithromycin; 0.34 (1.0) n = 17 placebo), entered in a generic inverse variance (GIV) analysis in RevMan. We have not altered this analysis but hope this clarification satisfies you that these data have been interpreted correctly.
Many thanks again for the time and consideration taken to submit these comments.
Kayleigh Kew on behalf of the authors for the review.

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WHAT'S NEW

Last assessed as up-to-date: 15 April 2015.

Date	Event	Description
13 May 2016	Feedback has been incorporated	Hahn 2006 data corrected in Symptom scales analysis 1.3 after receiving feedback. New pooled result carried through text. Overall conclusions not affected

HISTORY

Protocol first published: Issue 1, 2000

Review first published: Issue 3, 2001

Date	Event	Description
15 April 2015	New citation required and conclusions have changed	Sixteen new RCTs have been included. No real advantage of the use of macrolides in patients with asthma was demonstrated The review was redrafted for this update. We added a 'Summary of findings' table and used the current methodology recommended by Cochrane. We re-extracted data from primary studies for the studies included in the previous version, including applying the new 'Risk of bias' tool
15 April 2015	New search has been performed	New literature search run
7 August 2008	Amended	Converted to new review format.
6 June 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Kayleigh Kew: data extraction, entry and analysis, drafting of the review.

Krishna Undela: data extraction, drafting of the review.

Ioanna Kotortsi: data extraction.

Giovanni Ferrara: data extraction, entry, interpretation, and drafting of the review.

DECLARATIONS OF INTEREST

None of the authors has conflict of interest for issues related to the review.

SOURCES OF SUPPORT

Internal sources

- Kayleigh Kew, UK.

St George's, University of London

External sources

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

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

This update of the review has been brought up to date with current methodology, which meant changing some of the methods from those stated in the original protocol. GRADE was used to assess the quality of the evidence for the primary outcomes, and a 'Summary of findings' table has been added. Methods for data synthesis have been explained in more detail, and we replaced Jadad with the Cochrane 'Risk of bias' tool (Jadad 1996).

The planned subgroup and sensitivity analyses were not appropriate given the small number of studies in the analyses.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [*therapeutic use]; Anti-Inflammatory Agents [*therapeutic use]; Asthma [*drug therapy]; Chronic Disease; Disease Progression; Macrolides [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Adult; Child; Humans