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Macrolides versus placebo for chronic asthma (Review)

Undela K, Goldsmith L, Kew KM, Ferrara G

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[Intervention Review]

Macrolides versus placebo for chronic asthma

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ABSTRACT

Background

Asthma is a chronic disease in which inflammation of the airways causes symptomatic wheezing, coughing and difficult breathing. Macrolides are antibiotics with antimicrobial and anti-inflammatory activities that have been explored for the long-term control of asthma symptoms.

Objectives

To assess the effects of macrolides compared with placebo for managing chronic asthma.

Search methods

We searched the Cochrane Airways Group Specialised Register up to March 2021. 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

We included randomised controlled clinical trials (RCTs) involving both children and adults with asthma treated with macrolides versus placebo for four or more weeks. Primary outcomes were exacerbation requiring hospitalisation, severe exacerbations (exacerbations requiring emergency department (ED) visits or systemic steroids, or both), symptom scales, asthma control questionnaire (ACQ, score from 0 totally controlled, to 6 severely uncontrolled), Asthma Quality of Life Questionnaire (AQLQ, with score from 1 to 7 with higher scores indicating better QoL), rescue medication puffs per day, morning and evening peak expiratory flow (PEF; litres per minutes), forced expiratory volume in one second (FEV_1; litres), bronchial hyperresponsiveness, and oral corticosteroid dose. Secondary outcomes were adverse events (including mortality), withdrawal, blood eosinophils, sputum eosinophils, eosinophil cationic protein (ECP) in serum, and ECP in sputum.

Data collection and analysis

Two review authors 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. As per protocol, we used a fixed-effect model. We conducted a sensitivity analysis for analyses with high heterogeneity (I^2 greater than 30%). GRADE was used to assess the certainty of the body of evidence.

Main results

Twenty-five studies met the inclusion criteria, randomising 1973 participants to receive macrolide or placebo for at least four weeks. Most of the included studies reported data from adults (mean age 21 to 61 years) with persistent or severe asthma, while four studies included children. All participants were recruited in outpatient settings. Inclusion criteria, interventions and outcomes were highly variable.

The evidence suggests macrolides probably deliver a moderately sized reduction in exacerbations requiring hospitalisations compared to placebo (odds ratio (OR) 0.47, 95% confidence interval (CI) 0.20 to 1.12; studies = 2, participants = 529; moderate-certainty evidence). Macrolides probably reduce exacerbations requiring ED visits and/or treatment with systemic steroids (rate ratio (RaR) 0.65, 95% CI 0.53 to 0.80; studies = 4, participants = 640; moderate-certainty evidence). Macrolides may reduce symptoms (as measured on symptom scales) (standardised mean difference (SMD) −0.46, 95% CI −0.81 to −0.11; studies = 4, participants = 136 ; very low-certainty evidence). Macrolides may result in a little improvement in ACQ (SMD −0.17, 95% CI −0.31 to −0.03; studies = 5, participants = 773; low-certainty evidence). Macrolides may have little to no effect on AQLQ (mean difference (MD) 0.24, 95% CI 0.12 to 0.35; studies = 6, participants = 802; very low-certainty evidence). For both the ACQ and the AQLQ the suggested effect of macrolides versus placebo did not reach a minimal clinically important difference (MCID, 0.5 for ACQ and AQLQ) (ACQ: low-certainty evidence; AQLQ: very low-certainty evidence). Due to high heterogeneity (I^2 > 30%), we conducted sensitivity analyses on the above results, which reduced the size of the suggested effects by reducing the weighting on the large, high quality studies.

Macrolides may result in a small effect compared to placebo in reducing need for rescue medication (MD −0.43 puffs/day, 95% CI −0.81 to −0.04; studies = 4, participants = 314; low-certainty evidence). Macrolides may increase FEV_1, but the effect is almost certainly below a level discernible to patients (MD 0.04 L, 95% CI 0 to 0.08; studies = 10, participants = 1046; low-certainty evidence). It was not possible to pool outcomes for non-specific bronchial hyperresponsiveness or lowest tolerated oral corticosteroid dose (in people requiring oral corticosteroids at baseline). There was no evidence of a difference in severe adverse events (including mortality), although less than half of the studies reported the outcome (OR 0.80, 95% CI 0.49 to 1.31; studies = 8, participants = 854; low-certainty evidence). Reporting of specific adverse effects was too inconsistent across studies for a meaningful analysis.

Authors' conclusions

Existing evidence suggests an effect of macrolides compared with placebo on the rate of exacerbations requiring hospitalisation. Macrolides probably reduce severe exacerbations (requiring ED visit and/or treatment with systemic steroids) and may reduce symptoms. However, 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 results were mostly driven by a well-designed, well powered RCT, indicating that azithromycin may reduce exacerbation rate and improve symptom scores in severe asthma.

The review highlights the need for researchers to report outcomes accurately and according to standard definitions. Macrolides can reduce exacerbation rate in people with severe asthma. Future trials could evaluate if this effect is sustained across all the severe asthma phenotypes, the comparison with newer biological drugs, whether effects persist or wane after treatment cessation and whether effects are associated with infection biomarkers.

PLAIN LANGUAGE SUMMARY

Should macrolides be used for chronic asthma?

Main point: the existing evidence suggests a benefit of macrolides compared to placebo for reducing exacerbations requiring hospitalisation and severe exacerbations (defined as exacerbations requiring emergency department visit/treatment with systemic steroids). The effect of macrolides on other relevant clinical outcomes such as symptom scales and lung function is still unclear.

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 (pretend treatment) 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 March 2021. After finding all the relevant studies, we collected information about asthma attacks requiring hospital admission, asthma attacks that needed to be treated with oral steroids, symptom scores, 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 (mucous).

What we found

We found 25 studies, including two new ones that had been published since the last search was done in 2015. Overall, almost 2000 people received either macrolides or placebo. There were many problems in the way studies were described and how well they reported data, which made us consider the overall evidence to be 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 showed that macrolides were better than placebo in reducing exacerbations and may have benefits for some people in improving asthma symptoms, asthma control, asthma quality of life and some measures of lung function, but how much benefit and for whom are uncertain. Based on one well conducted study, the macrolide azithromycin may have some benefit for people with severe asthma, but overall the findings of this review do not support the use of macrolides for all asthma of any grade or severity. There were no reports of serious side effects of macrolides, but 16 studies did not report whether any occurred.

Summary of findings 1. Macrolides compared to placebo for chronic asthma

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 4–52 weeks (median 8 weeks).
Comparison: placebo

Treatment 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)	Certainty of the evidence	Comments
	Assumed comparator risk**	Corresponding risk				
	Placebo	Macrolide				
Exacerbation requiring hospitalisation Weighted mean study duration: 45 weeks	61 per 1000	29 per 1000 (13 to 68)	**OR 0.47** (0.20 to 1.12)	529 (2 RCTs)	⊕⊕⊕⊖ **Moderate**[b]	—
Severe exacerbations (requiring ED visits or systemic steroids, or both) Number of people having ≥ 1 exacerbations requiring an ED visit or systemic steroids, or both. Classification varied across studies. Weighted mean study duration: 35 weeks	410 per 1000	311 per 1000 (269 to 357)	**Rate ratio 0.65** (0.53 to 0.80)	640 (4 RCTs)	⊕⊕⊕⊖ **Moderate**[b]	—
Asthma symptoms – symptom scales (various scales; lower score = better)	The mean change in symptom scales in the intervention group compared to the control group was a reduction; **0.46 SD lower** (0.81 SD lower to 0.11 SD lower)		—	136 (4 RCTs)	⊕⊖⊖⊖ **Very low**[e,f,g]	The SMD is a Cohen's effect size and can be interpreted as moder-

Weighted mean study duration: 10 weeks						ate (< 0.4 = small, 0.40–0.70 = moderate, > 0.70 = large).
Asthma control (Asthma Control Questionnaire) Scored 0–6 (lower scores indicate improvement in asthma control) Weighted mean study duration: 34 weeks	The mean change in asthma control in the intervention group compared to the mean change in control group was a greater reduction;**0.17 SD lower** (0.31 SD lower to 0.03 SD lower)		—	773 (5 RCTs)	⊕⊕⊖⊖ **Low**[d,h]	The SMD is a Cohen's effect size and can be interpreted as small.
Asthma quality of life (AQLQ) Scored 1–7 (higher scores indicate improvement in quality of life) Weighted mean study duration: 35 weeks	The mean change on the AQLQ scale in the control group was an increase from baseline; **0.31 points higher****	The mean change in AQLQ in the intervention group compared to the mean change in the control group was an increase; **0.24 points higher** (0.12 higher to 0.35 higher)	—	802 (6 RCTs)	⊕⊖⊖⊖ **Very low**[c,d,h]	MCID: 0.5 points
Rescue medication (puffs/day) Weighted mean study duration: 17 weeks	The mean rescue medication use in the control group was **1.08** puffs/day**	The mean change in rescue medication puffs/day in the intervention group compared to the mean change in the control group was reduction; **0.43 fewer puffs** (0.81 fewer to 0.04 fewer)	—	314 (4 RCTs)	⊕⊕⊖⊖ **Low**[d,h]	—
FEV_1 (L) Weighted mean study duration: 28 weeks	The mean FEV_1 in the control group was **2.49** L**	The mean change in FEV_1 (L) the intervention group compared to the control group was an increase; **0.04 L higher** (0 L to 0.08 L higher)	—	1046 (10 RCTs)	⊕⊕⊖⊖ **Low**[h,i,j]	Although there is no universally accepted MCID for FEV_1 in asthma, variability within a single testing session can be up to 0.12 L (data from a mixed pool of respiratory patients; Enright 2004).
Serious adverse events (including mortality)	93 per 1000	76 per 1000 (50 to 118)	**OR 0.80** (0.49 to 1.31)	854 (8 RCTs)	⊕⊕⊖⊖ **Low**[i,k]	—

Weighted mean study duration: 16 weeks				

*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. Note: Sutherland 2010 could not be included in the rescue medication or quality of life calculations because they reported only mean difference between groups; Brusselle 2013 was not included in the FEV_1 calculation because it was the only change score; Cameron 2013 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.

AQLQ: Asthma Quality of Life Questionnaire; **CI:** confidence interval; **ED:** emergency department; **FEV_1:** forced expiratory volume in one second; **MCID:** minimal clinically important difference; **OR:** odds ratio; **RCT:** randomised controlled trial; **SD:** standard deviation.

GRADE domains: study limitations, consistency of effect, imprecision, indirectness and publication bias. GRADE Working Group grades of evidence (Schünemann 2021).
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: 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 certainty: we are very uncertain about the estimate.

[a]Two primary outcomes (morning and evening peak expiratory flow) are not presented. Bronchial hyperresponsiveness could not be pooled in a meta-analysis and is described narratively in the review. Studies did not report lowest tolerated oral corticosteroid dose well and there were no data to analyse.
[b]Downgraded one level for indirectness due to differences in the recruited populations and in the criteria used to define 'severe exacerbations'.
[c]Downgraded one level for imprecision as among the included studies, one reported an important benefit of macrolide and another possible benefit of placebo.
[d]Downgraded one level due to uncertainties with randomisation procedures and high risk of attrition bias in some studies included in the analysis.
[e]Downgraded one level for inconsistency due to high heterogeneity (I^2 = 70%) mainly due to one cross-over study.
[f]Downgraded one level for indirectness. Symptom scales were often invalidated 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.
[g]Downgraded one level for imprecision due to small number of participants in the analysis; it was difficult to judge precision due to different scales.
[h]Downgraded one level for indirectness as studies in the analysis recruited different populations with regard to severity of asthma, and one study only recruited smokers.
[i]Downgraded one level for risk of bias as four studies that we were unable to properly assess for risk of bias were included in this analysis, and we were uncertain of how and when the measurement was taken in some cases.
[j]No change in grade: there was uncertainty in several domains across studies, but the two studies carrying most of the weight were well conducted.
[k]Downgraded one level for imprecision; eight studies reported the outcomes, but only four studies observed events, leading to very wide confidence intervals that included important benefit and harm of macrolide treatment.

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. It is estimated that asthma may affect between 1% and 18% of the general population, and it represents a significant cause of morbidity and costs for healthcare systems. Furthermore, the control of the disease is difficult to achieve in people with severe asthma, and even in people with milder asthma it may be hampered by poor adherence to treatments and lack of access to healthcare (GINA 2021).

Different phenotypes of the disease are recognised and under investigation. Current guidelines recommend tailoring asthma treatment according to a stepwise approach, considering severity of symptoms and response to treatment (GINA 2021).

Recently, the role of short-acting bronchodilators in intermittent asthma was revised, and a combination of inhaled corticosteroids (ICS) and formoterol as needed is now recommended in people with mild asthma. Persistent asthma is treated with regular ICS, longer-acting bronchodilators, or both (GINA 2021). More recent therapies include anti-leukotrienes in mild-to-moderate asthma, humanised antibodies targeting immunoglobulin E (omalizumab), interleukin (IL)-5 (mepolizumab, reslizumab, benralizumab), and IL-4/-13 (dupilumab), which are currently only recommended in severe asthma with markers of a phenotype likely to respond (e.g. raised blood eosinophils for the anti-IL-5 agents) (GINA 2021; 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 people with asthma suggested a steroid-sparing effect (Nelson 1993), while other 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). A host-directed anti-inflammatory effects was also postulated (Spagnolo 2013). Macrolides are effective in the long-term treatment of cystic fibrosis, diffuse panbronchiolitis and chronic obstructive pulmonary disease (COPD), 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. Similar concerns were raised by studies in COPD (Brill 2015). Furthermore, the potential for arrhythmias due to QTc prolongation, potential ototoxicity and hepatotoxicity from macrolide long-term use was highlighted in a British Thoracic Society document (BTS 2020).

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 and chemokines causing inflammation, which was highlighted by the results of the previous versions of this systematic review (Richeldi 2002; Richeldi 2005; Kew 2015). In vivo and in vitro studies of human and animal models have demonstrated that macrolides suppress the production of cytokines such as ILs and inhibit neutrophil adhesion to epithelial cells, the respiratory burst of neutrophils and the secretion of mucous from human airways (Adachi 1996; Hinks 2021; Konno 1994; Koyama 1998).

Older macrolides such as troleandomycin were investigated for a steroid-sparing effect, related to reduced hepatic glucocorticoid metabolism (Nelson 1993).

The potential benefit of their antimicrobial action for people with asthma was suggested after observational studies identified intracellular bacterial infection (i.e. *Chlamydophila 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 people 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). Studies in animal models seem to point to 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 people with chronic asthma.

OBJECTIVES

To assess the effects of macrolides compared with placebo for managing chronic asthma.

METHODS

Criteria for considering studies for this review

Types of studies

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

Types of participants

Children and adults with chronic asthma.

Types of interventions

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

Types of outcome measures

Primary outcomes

- Exacerbations requiring hospitalisation.
- Severe exacerbations (defined as requiring an emergency department (ED) visits or short-course of systemic steroids, or both).
- Asthma symptoms, control and 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 hyperresponsiveness (to histamine or methacholine).
- Lowest tolerated oral corticosteroid dose (in people requiring oral corticosteroids at baseline).

Secondary outcomes

- Number and type of serious adverse events (including mortality).
- Number of study withdrawals.
- Eosinophil count in peripheral blood samples, sputum samples or both.
- Eosinophilic cationic protein (ECP) measurements in serum and 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 April 2015. The search period for this update was April 2015 to 31 March 2021.

We searched the Cochrane Airways Trials Register on 31 March 2021. At that time the Register contained studies identified from:

- monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL), through the Cochrane Register of Studies Online (crso.cochrane.org), all years to Issue 3, 2021;
- weekly searches of MEDLINE (OvidSP), 1946 to 26 March 2021;
- weekly searches of Embase (OvidSP), 1974 to week 12 2021;
- monthly searches of PsycINFO (OvidSP), 1967 to March week 4 2021;
- monthly searches of CINAHL (EBSCO) (Cumulative Index to Nursing and Allied Health Literature), 1937 to 15 March 2021;
- monthly searches of AMED (EBSCO) (Allied and Complementary Medicine), all years to 11 March 2021;
- handsearches of the proceedings of major respiratory conferences.

Studies contained in the Trials Register are identified through search strategies based on the scope of Cochrane Airways. Details of these strategies, as well as a list of handsearched conference proceedings are in Appendix 2. See Appendix 3 for search terms used to identify studies for this review. We did not restrict our search by language or type of publication.

We also searched the following trials registries on 31 March 2021:

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov);
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch).

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 review authors (KU 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 review authors (KU and GF) independently reviewed and categorised each article identified as included or excluded. When there was disagreement or doubt, a third review author (KK) 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 (KU and GF) extracted the following study characteristics from included studies, when available.

- 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.
- Participants: number, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion criteria and exclusion criteria.
- Interventions: intervention, comparison, concomitant medications and excluded medications.
- Outcomes: primary and secondary outcomes specified and collected, and time points reported.
- Notes: funding for trial, and notable conflicts of interest of trial authors.

Two review authors (KU and GF) independently extracted outcome data from included studies. We noted in the Characteristics of included studies table if outcome data were not reported in a usable way. We resolved disagreements by involving a third review author (KK). Two review authors (KK and KU) transferred data into the Review Manager 5 (Review Manager 2014). Three review authors (KU, LG and GF) 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 review author (KU). We assessed risk of bias according to the following domains.

- Random sequence generation.
- Allocation concealment.
- Blinding of participants and personnel.
- Blinding of outcome assessment.
- Incomplete outcome data.
- Selective outcome reporting.
- 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. We summarised the risk of bias judgements across different studies for each of the domains listed. We considered blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different from for a participant-reported pain scale). Where information on risk of bias related to unpublished data or correspondence with a trial list, we noted this in the risk of bias table.

For treatment effects, we considered the risk of bias for the studies that contributed to that outcome.

Measures of treatment effect

We analysed dichotomous data as odds ratios (OR), incidence rate data as rate ratio (RaR) and continuous data as mean difference (MD; where studies used the same scales) or standardised mean difference (SMD; where studies used different scales). 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 studies presented raw data and adjusted analyses (e.g. accounting for baseline differences), we used the adjusted analyses.

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 and made decisions about this by consensus among review authors.

Where a trial reported multiple arms, we included only the relevant arms but reported all arms in the Characteristics of included studies table. 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 most studies reported endpoint scores. If a study reported outcomes at multiple time points, we used the end-of-study treatment 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

We combined events data using ORs or RaRs (number of participants or number of events) according to which measure would allow us to include the most studies. We used ORs for exacerbations requiring hospitalisation, serious adverse events (including mortality) (Peto OR) and withdrawal. We used RaRs for severe exacerbations (defined as exacerbations requiring ED visits or systemic steroids, or both). For continuous data in cross-over trials, we entered data using GIV 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 high 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 unable 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 limited variation in effects due to differences in study populations and methods.

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 a sensitivity analysis with a random-effects model in case of high heterogeneity (I^2 greater than 30%).

Summary of findings and assessment of the certainty of the evidence

The summary of findings table included the following outcomes: number of exacerbations requiring hospitalisation; severe exacerbations (requiring ED visits or short-course systemic steroids, or both); asthma symptoms (including symptom scores, asthma control and Asthma Quality of Life Questionnaire (AQLQ)); asthma medication requirements (as reliever); lung function (including morning and evening PEF and FEV_1); non-specific bronchial hyperresponsiveness; serious adverse events; 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 certainty of the body of evidence as it related to the studies that contributed data to the meta-analyses for the prespecified outcomes. Except for 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 (GRADEpro GDT). We justified all decisions to downgrade or upgrade the certainty of the evidence using footnotes and made comments to aid reader's understanding of the review where necessary.

RESULTS

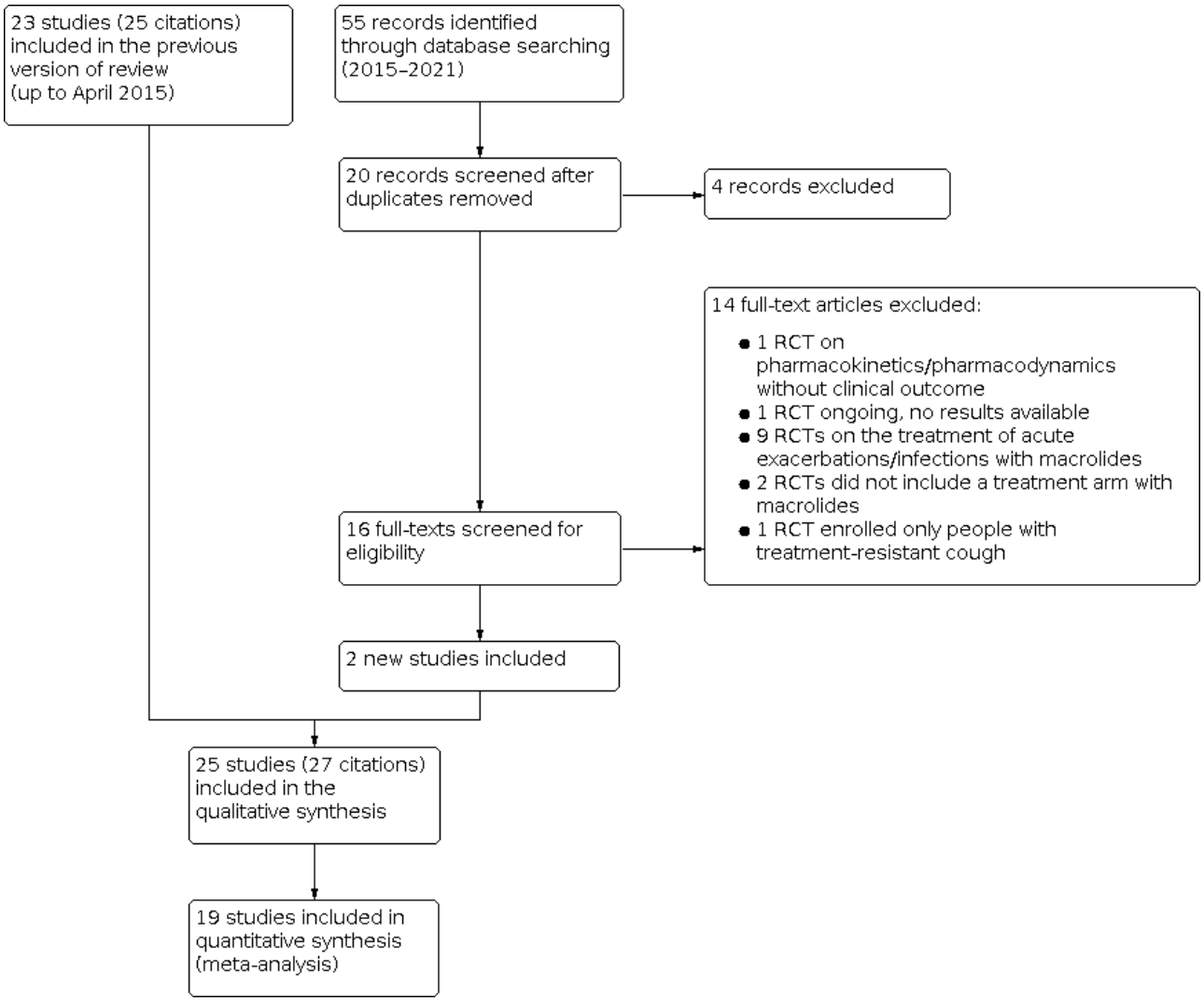
Description of studies

Results of the search

The literature search of previous versions of this review up to April 2015 identified 137 citations. Out of the 38 references identified in the search between 2007 and 2015, duplicate sifting of the titles and abstracts alone identified 33 potentially eligible studies for inclusion in the systematic review. Among them, review authors were concordant in identifying 16 RCTs to be included in the previous update of the systematic review (Kew 2015). Six of the 16 RCTs were identified in a previous meta-analysis (Tong 2015); these Chinese trials were only listed in China's biomedical databases. The authors of this review were able to confirm key study characteristics in order to include them, although risk of bias could not be properly assessed.

For this updated review, the search extended to March 2021. We identified 55 new references. Seven titles referring to abstracts presented at congresses were duplicates of other studies already included in the review, while one title (Gibson 2019) was a subgroup analysis of another RCT (Gibson 2017) included in this update, leaving 20 references for screening. We excluded four based on the abstract alone and 13 after screening the full-text of the original manuscripts, leaving two new studies eligible for inclusion in the systematic review and meta-analyses (Wan 2016; Gibson 2017). One study is ongoing, no results available. See Characteristics of included studies, Characteristics of excluded studies, and Characteristics of ongoing studies tables. The study flow of the new included studies is presented in Figure 1.

Figure 1. Study flow diagram.



Included studies

We included 25 RCTs (Amayasu 2000; Belotserkovskaya 2007; Black 2001; Brusselle 2013; Cameron 2013; Gibson 2017; Hahn 2006; Hahn 2012; He 2009; Kamada 1993; Kapoor 2010; Kostadima 2004; Kraft 2002; Nelson 1993; Piacentini 2007; Shoji 1999; Simpson 2008; Strunk 2008; Sutherland 2010; Wan 2016; Wang 2012; Wang 2014; Xiao 2013; Yan 2008; Zhang 2013). For brief descriptions of the included studies, refer to the Characteristics of included studies table. For a summary of study characteristics and a narrative on the main results of each study, see Table 1 and Appendix 4.

The 25 included studies reported a great variability in type of participants (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.

Design

All studies were RCTs using placebo controls, and most were described as double-blind. There were 22 parallel group studies and three cross-over studies (Amayasu 2000; Kapoor 2010; Shoji 1999). Median study duration was 15.2 weeks (range four 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); the results of one new included study could not be used due to very poor reporting (Wan 2016), and only basic information was available from six Chinese studies (He 2009; Wang 2012; Wang 2014; Xiao 2013; Yan 2008; Zhang 2013) included in the previous version of this review (Kew 2015).

Participants

The studies included 1991 participants of whom 1973 were relevant to this review (Strunk 2008 included a third group of 18 people receiving a treatment that was outside the protocol of this review). 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; GINA 2014); these are similar to the current international guidelines for what concerns main diagnosis and grading of severity of asthma (GINA 2021).

Four studies assessed the effects of macrolide treatment in children with asthma (Kamada 1993; Piacentini 2007; Strunk 2008; Wan 2016), and the rest recruited adults with asthma (aged over 18 years). The studies varied according to GINA 2014/GINA 2020/GINA 2021 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 mild asthma (step 1 according to GINA 2021) (Amayasu 2000), and one used people with aspirin-induced intermittent asthma (Shoji 1999).

Five studies investigated the role of macrolides in people with evidence of *C pneumoniae* or *M pneumoniae* infection, based on serological (Black 2001; Hahn 2006; Wan 2016) or molecular (Kraft 2002; Sutherland 2010) methods. The remaining studies did not investigate the presence of these co-infections or of other concomitant co-infections, although we could not confirm this in the non-English language papers. Cameron 2013 investigated the effect of macrolides in adult smokers with persistent asthma, while Brusselle 2013, Simpson 2008, and Gibson 2017 considered the effect of macrolides in people with eosinophilic and non-eosinophilic asthma.

Interventions

Five studies compared roxithromycin with placebo (Black 2001; Kapoor 2010; Shoji 1999; Xiao 2013; Yan 2008); seven studies compared clarithromycin with placebo (Amayasu 2000; Kostadima 2004; Kraft 2002; Simpson 2008; Sutherland 2010; Wang 2014; Wan 2016); 11 studies investigated the effect of azithromycin (Belotserkovskaya 2007; Brusselle 2013; Cameron 2013; Gibson 2017; 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

Six studies did not appear in any of the quantitative syntheses (Belotserkovskaya 2007; Black 2001; Kapoor 2010; Wan 2016; Wang 2012; Zhang 2013), and two more only contributed to the bronchial hyperresponsiveness summary of results and withdrawal (Piacentini 2007; Simpson 2008).

Two studies reported data on exacerbations requiring hospitalisation (Brusselle 2013; Gibson 2017), and four on severe exacerbations (defined as exacerbations requiring ED visits or systemic steroids, or both) as an outcome, but the definition of 'severe exacerbation' used in the different studies was variable and sometimes unclear (Brusselle 2013; Gibson 2017; Kostadima 2004; Strunk 2008). The meta-analysis of Tong 2015 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 use of different scales. 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 would be similar. We used SMDs 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; Cameron 2013; Hahn 2006; Sutherland 2010).

Most of the studies reported measures of lung function such as FEV_1 or PEF, but only 10 reported data for FEV_1 (Amayasu 2000; Cameron 2013; Gibson 2017; He 2009; Kraft 2002; Shoji 1999; Sutherland 2010; Wang 2014; Xiao 2013; Yan 2008), four reported morning PEF (Brusselle 2013; Cameron 2013; Kamada 1993; Sutherland 2010), and three reported for evening PEF (Brusselle 2013; Kamada 1993; Sutherland 2010) 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; Wan

2016). 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 2015 for He 2009, Wang 2014, Xiao 2013, and Yan 2008. 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.

Nine studies considered bronchial hyperresponsiveness, but there was variation in the measures used and the way the data were reported, which meant it was not possible to meta-analyse the data (Amayasu 2000; Cameron 2013; Kamada 1993; Kostadima 2004; Nelson 1993; Piacentini 2007; Shoji 1999; Simpson 2008; Sutherland 2010).

Most studies considered adverse events, but only eight explicitly reported serious adverse events (Amayasu 2000; Brusselle 2013; Cameron 2013; Gibson 2017; 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, there were no events in Amayasu 2000, so it did not contribute to the pooled effect.

Ten studies reported study withdrawal (Brusselle 2013; Gibson 2017; Hahn 2006; Hahn 2012; Kamada 1993; Kostadima 2004; Nelson 1993; Simpson 2008; Strunk 2008; Sutherland 2010).

Eight studies reported the effect of macrolides on markers of inflammation related to asthma activity, but they used different measures, which could not be pooled in one analysis (Amayasu 2000; Cameron 2013; Kraft 2002; Nelson 1993; Piacentini 2007; Shoji 1999; Simpson 2008; Yan 2008). 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 14 studies from the review after viewing the full papers. Reasons for exclusion are reported in the Characteristics of excluded studies table and Figure 1.

Previous versions of this systematic review excluded 17 studies after reading the full papers (Kew 2015; Richeldi 2005), so a total of 31 studies are excluded.

Studies awaiting classification

There are no studies awaiting classification.

Ongoing studies

We found one ongoing study (NCT02517099).

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 bias because only a few 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.

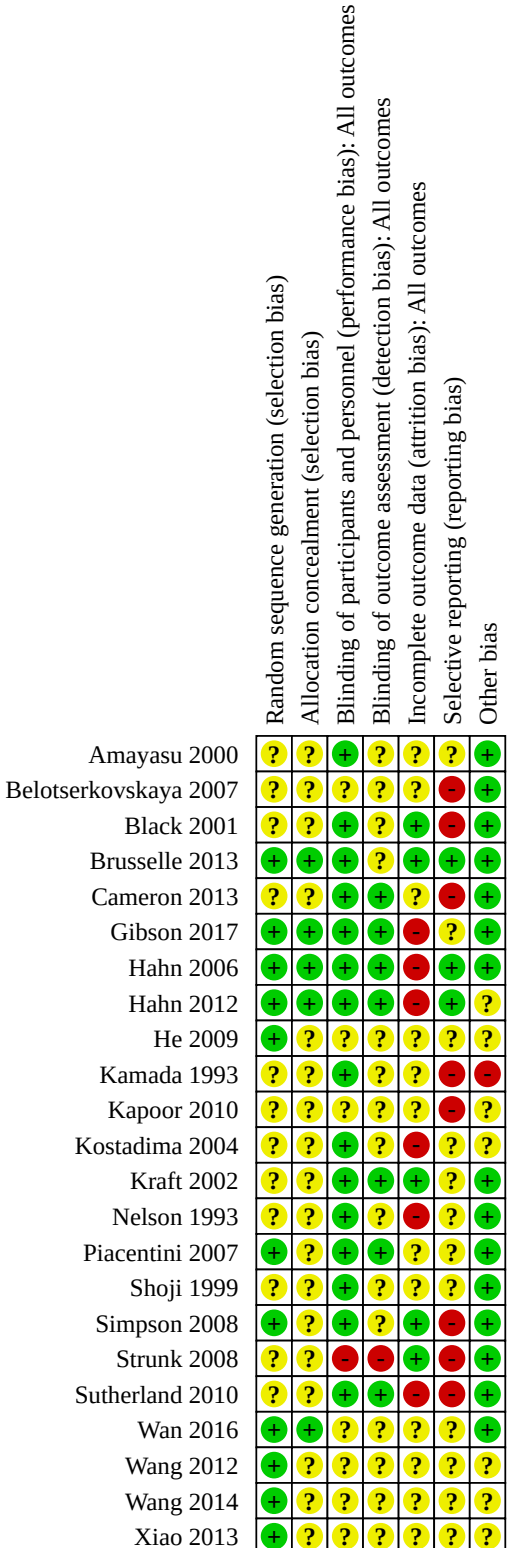


Figure 2. (Continued)

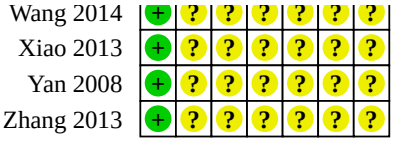
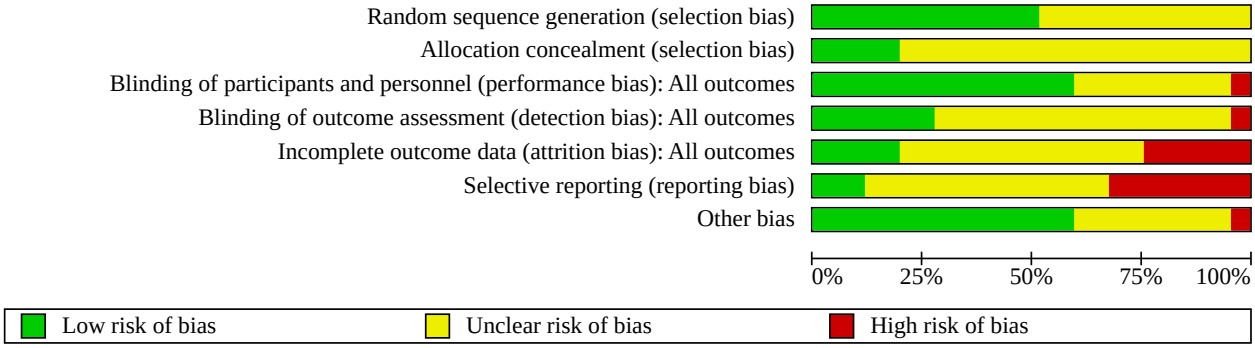


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Pharmaceutical industries financed at least five included studies (Amayasu 2000; Cameron 2013; Hahn 2006; Hahn 2012; Kamada 1993); which could raise the risk of publication bias; this could not be ascertained in the non-English language papers. The authors of Tong 2015 provided us with information about study quality for the studies that were not available in English.

Allocation

We deemed 13 studies at low risk of bias for random sequence generation, including seven of the English language studies (Brusselle 2013; Gibson 2017; Hahn 2006; Hahn 2012; Piacentini 2007; Simpson 2008; Wan 2016) and six in Tong 2015 (He 2009; Wang 2012; Wang 2014; Xiao 2013; Yan 2008; Zhang 2013). For the rest, the methods for random sequence generation was unclear.

Only five studies were at low risk for adequate allocation concealment (Brusselle 2013; Gibson 2017; Hahn 2006; Hahn 2012; Wan 2016); the studies from the Tong 2015 review were not assessed for this criterion because it is not considered in the Jadad 1996 system, so we had to rate those studies as unclear, and the 14 other studies did not adequately describe the methods used.

Blinding

Most studies described as double-blind and placebo-controlled contained adequate descriptions of the blinding of participants and personnel, but methods were unclear in nine studies (He 2009; Wan 2016; Wang 2012; Wang 2014; Xiao 2013; Yan 2008; Zhang 2013, including two in an abstract form: Belotserkovskaya 2007; Kapoor 2010). Blinding of outcome assessment was adequate in seven studies (Cameron 2013; Gibson 2017; 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

Six studies had a high risk of attrition bias (Gibson 2017; Hahn 2006; Hahn 2012; Kostadima 2004; Nelson 1993; Sutherland 2010), five carried a low risk (Black 2001; Brusselle 2013; Kraft 2002; Simpson 2008; Strunk 2008), and the risk was unclear for the other 14 studies.

Selective reporting

We considered three studies at low risk of bias (Brusselle 2013; Hahn 2006; Hahn 2012). We judged eight studies at high risk of selective reporting (Belotserkovskaya 2007; Black 2001; Cameron 2013; Kamada 1993; Kapoor 2010; Simpson 2008; Strunk 2008; Sutherland 2010). This was mostly due to insufficient reporting of numerical data, which meant they could not be pooled in meta-analysis. We rated 14 studies as unclear for this domain, including the six 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

We judged Kamada 1993 to be at high risk of bias because the report showed significant baseline imbalances between groups, and this may have been an issue in some of the other trials that included very small number of participants. We judged eight studies to be at unclear risk of bias (Hahn 2012; He 2009; Kapoor 2010; Kostadima 2004; Wang 2012; Wang 2014; Xiao 2013; Yan 2008; Zhang 2013).

Effects of interventions

See: **Summary of findings 1** Macrolides compared to placebo for chronic asthma

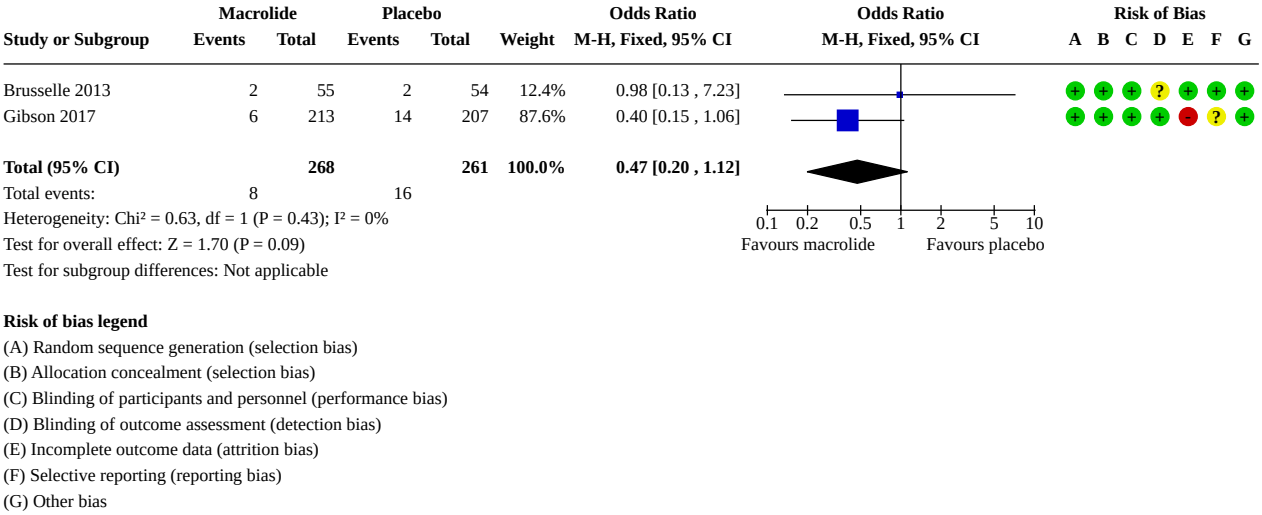
We present the data with the order of outcomes listed in the methods. Evidence certainty was varied. We downgraded most for indirectness due to differences in the study populations and the way outcomes were defined, and for risk of bias due to uncertainty of randomisation procedures and high risk of 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

Two studies reported exacerbations requiring hospitalisation, with 24 events (four recorded in Brusselle 2013; 20 recorded in Gibson 2017). The meta-analysis suggests macrolides make a moderately sized but non-significant reduction in exacerbation requiring hospitalisation compared to placebo (OR 0.47, 95% CI 0.20 to 1.12; I^2 = 0%; participants = 529; Analysis 1.1; Figure 4) (95% CI cross the line of zero effect). One study is equivocal and this effect is driven by the larger study. The evidence was of moderate certainty.

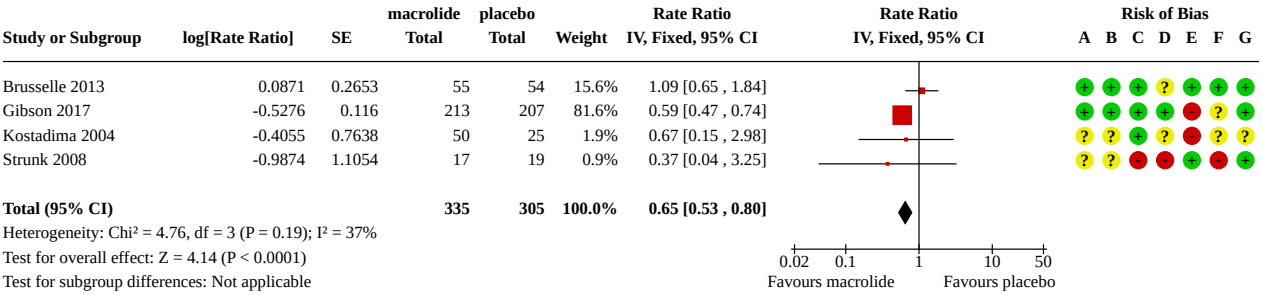
Figure 4. Forest plot of comparison: 1 Macrolide versus placebo, outcome: 1.1 Exacerbation requiring hospitalisation.



Severe exacerbations

Four studies reported data on severe exacerbations (defined as exacerbations requiring ED visits or short-course of systemic steroids, or both) (Brusselle 2013; Gibson 2017; Kostadima 2004; Strunk 2008). The pooled effect of these studies showed a benefit of macrolides over placebo (RaR 0.65, 95% CI 0.53 to 0.80; I^2 = 37%; participants = 640; Analysis 1.2; Figure 5). The results were mostly driven by the data from Gibson 2017 (weight 81.6%). Apart from this study, the evidence from the other studies was very low quality, being downgraded for indirectness and imprecision. Overall the evidence was of moderate certainty.

Figure 5. Forest plot of comparison: 1 Macrolide versus placebo, outcome: 1.2 Severe exacerbations: exacerbations requiring emergency department visits/systemic steroids.

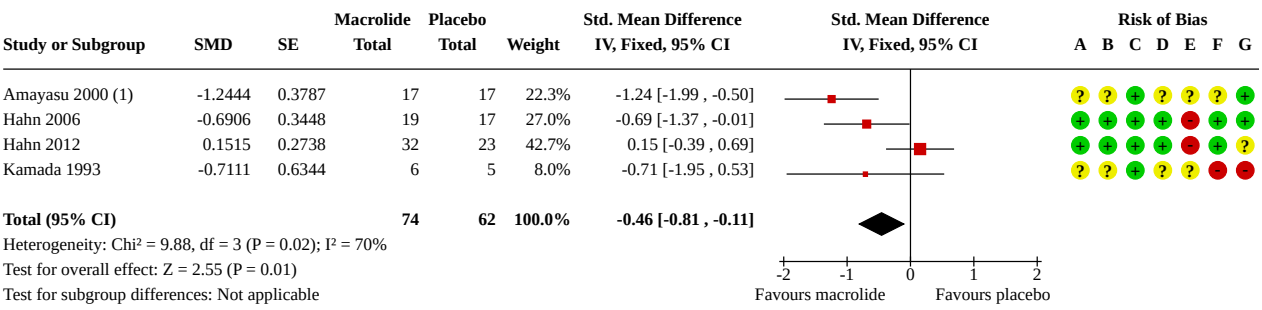


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Asthma symptoms, control and quality of life scores

Symptom scales used across studies varied and were mostly not psychometrically validated. Data from four studies could be combined in meta-analysis (Amayasu 2000; Hahn 2006; Hahn 2012; Kamada 1993). There was suggestion of a benefit of macrolides compared with placebo (SMD −0.46, 95% CI −0.81 to −0.11; I^2 = 70%; participants = 156; Analysis 1.3; Figure 6). We downgraded the evidence for high heterogeneity (I^2 = 70%), use of scales that were not psychometrically validated and small numbers in the analysis, meaning the evidence was of very low certainty.

Figure 6. Forest plot of comparison: 1 Macrolide versus placebo, outcome: 1.3 Symptom scales.

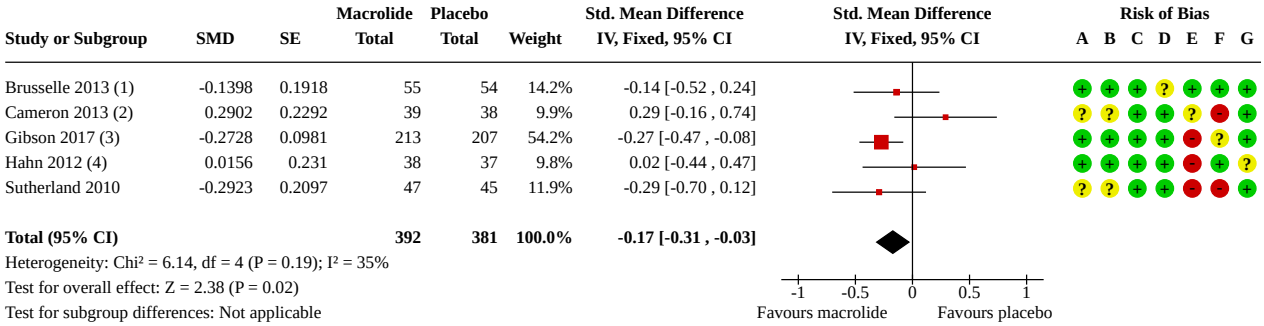


Footnotes
(1) Cross-over study including 17 participants who received macrolide and placebo in random order.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Five studies reported measures of asthma control, mostly the Asthma Control Questionnaire (ACQ) (Brusselle 2013; Cameron 2013; Gibson 2017; Hahn 2012; Sutherland 2010). There was a small benefit of macrolide over placebo in reducing symptoms (SMD −0.17, 95% CI −0.31 to −0.03; I^2 = 35%; participants = 773; Analysis 1.4; Figure 7), although the decrease in the symptom score did not reach the minimal clinically important difference (MCID) (0.5 for the ACQ, Juniper 2005). We considered the evidence to be low after downgrading for uncertainties with randomisation procedures and different populations with regards to severity of asthma.

Figure 7. Forest plot of comparison: 1 Macrolide versus placebo, outcome: 1.4 Asthma Control.



Footnotes

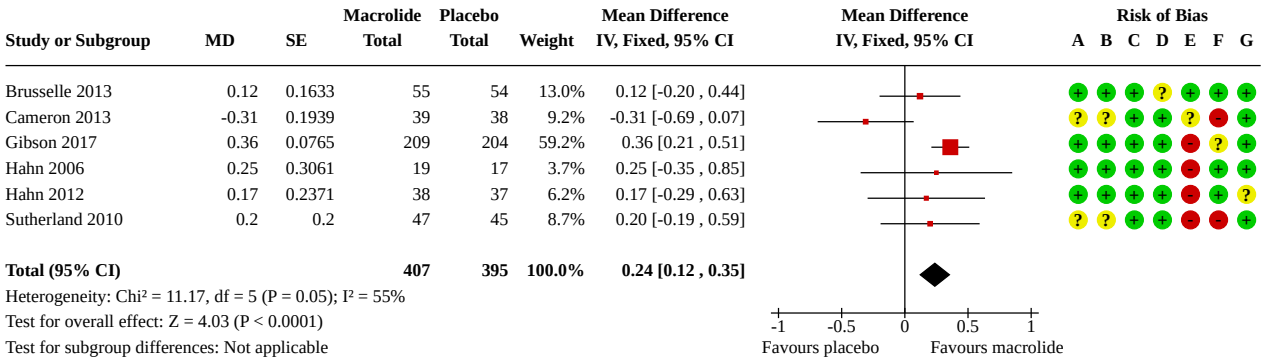
(1) Adjusted change in Asthma Control Questionnaire (ACQ) score, baseline to week 26.
(2) Adjusted change in 7-point ACQ score, baseline to week 12.
(3) Adjusted ACQ6 score end of treatment difference vs placebo.
(4) Adjusted change in asthma control, from baseline to week 12.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Six studies reported quality of life measured with the AQLQ (Brusselle 2013; Cameron 2013; Gibson 2017; Hahn 2006; Hahn 2012; Sutherland 2010). There was an improvement of quality of life with macrolides over placebo, but it was under the MCID (MD 0.24, 95% CI 0.12 to 0.35; I^2 = 55%; participants = 802; Analysis 1.5; Figure 8) (MCID: 0.5; Juniper 1994). We considered the evidence to be very low certainty after downgrading it for imprecision, uncertainties with randomisation procedures and different populations with regards to severity of asthma.

Figure 8. Forest plot of comparison: 1 Macrolide versus placebo, outcome: 1.5 Asthma Quality of Life Questionnaire (AQLQ).



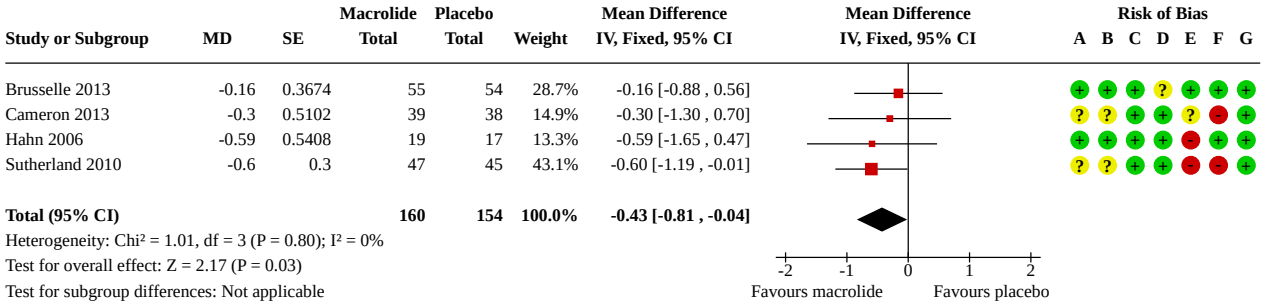
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Need for rescue medications

Four studies reported need for rescue medication (Brusselle 2013; Cameron 2013; Hahn 2006; Sutherland 2010). Analysis indicated macrolides reduced in the need for rescue medications compared to placebo (MD −0.43 puffs per day, 95% CI −0.81 to −0.04; I^2 = 0%; participants = 314; Analysis 1.6; Figure 9). The evidence was low certainty, being downgraded for uncertainties in the randomisation procedure and indirectness.

Figure 9. Forest plot of comparison: 1 Macrolide versus placebo, outcome: 1.6 Rescue medication puffs/day.

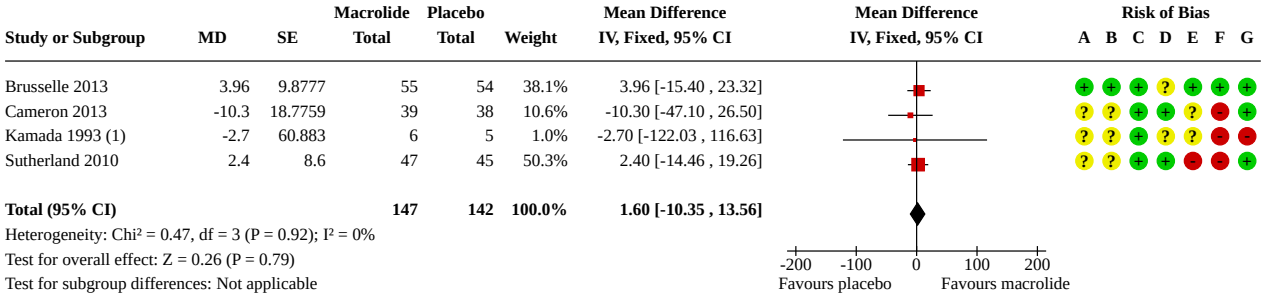


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Lung function (morning and evening peak expiratory flow and forced expiratory volume in one second)

Four studies reported morning PEF (Brusselle 2013; Cameron 2013; Kamada 1993; Sutherland 2010), and three studies reported evening PEF (Brusselle 2013; Cameron 2013; Kamada 1993; Sutherland 2010). The data for morning and evening PEF did not suggest a benefit of macrolide over placebo, and the evidence was very low certainty (morning PEF: MD 1.60 L/minute, 95% CI −10.35 to 13.56; I^2 = 0%; participants = 289; Analysis 1.7; Figure 10; evening PEF: MD 1.00, 95% CI −13.65 to 15.65; I^2 = 0%; participants = 212; Analysis 1.8; Figure 11). The evidence for both measures was downgraded due to issues with risk of bias, indirectness and imprecision.

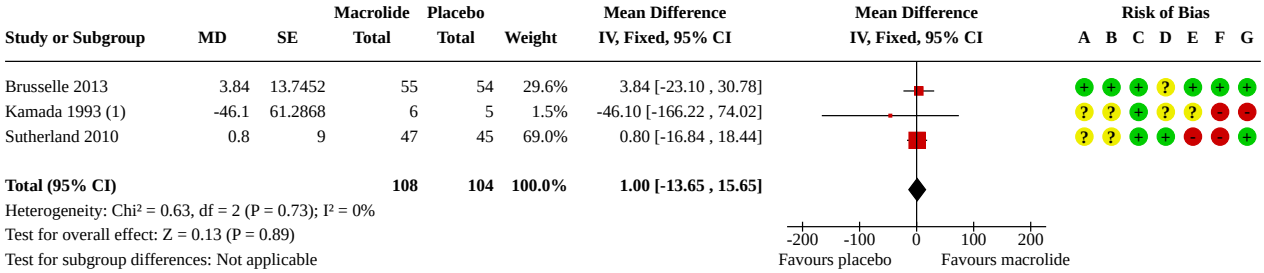
Figure 10. Forest plot of comparison: 1 Macrolide versus placebo, outcome: 1.7 Morning PEF (L/minute).



Footnotes
(1) PEF predose.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Figure 11. Forest plot of comparison: 1 Macrolide versus placebo, outcome: 1.8 Evening PEF (L/minute).



Footnotes

(1) PEF postdose.

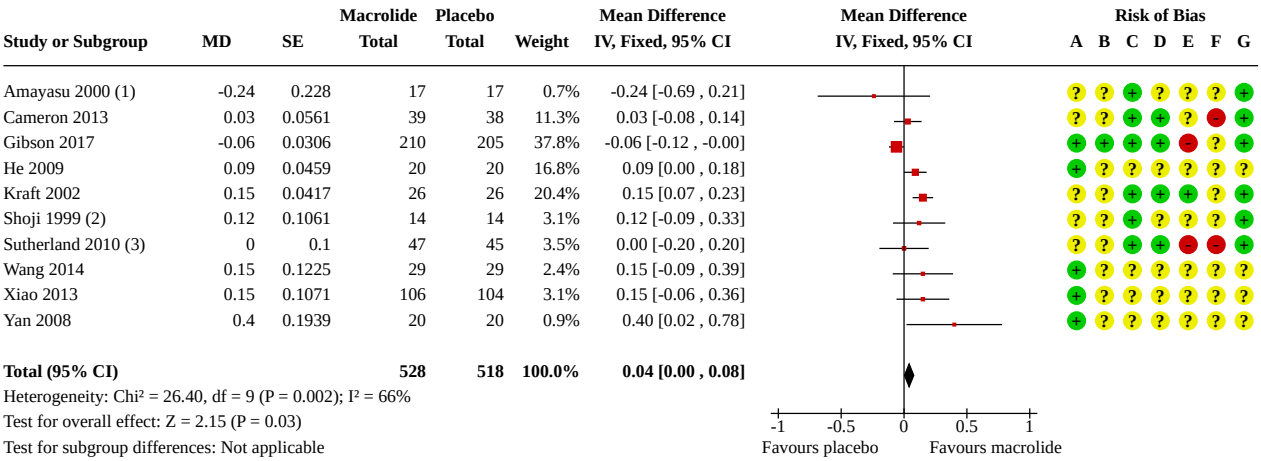
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Tong 2015 provided data for three additional studies, 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 SMD, so we could not combine them. These three studies showed a benefit of macrolide over placebo, but the method of analysis meant it was difficult to contextualise.

Ten studies reported data on $FEV_{1,}$ that could be aggregated in a meta-analysis (Amayasu 2000; Cameron 2013; Gibson 2017; He 2009; Kraft 2002; Shoji 1999; Sutherland 2010; Wang 2014; Xiao 2013; Yan 2008). There was a benefit of macrolide over placebo on FEV_1 (MD 0.04 L, 95% CI 0 to 0.008; I^2 = 66%; participants = 1046; Analysis 1.9; Figure 12). The evidence was of low certainty due to indirectness and four studies for which we were unable to properly assess risk of bias. It was not always clear whether the measurement was taken before or after a bronchodilator.

Figure 12. Forest plot of comparison: 1 Macrolide versus placebo, outcome: 1.9 FEV_1 (L).



Footnotes

(1) Cross-over study including 17 participants who received macrolide and placebo in random order.
(2) Cross-over study with 14 participants who received both treatments.
(3) Prebronchodilator.

Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

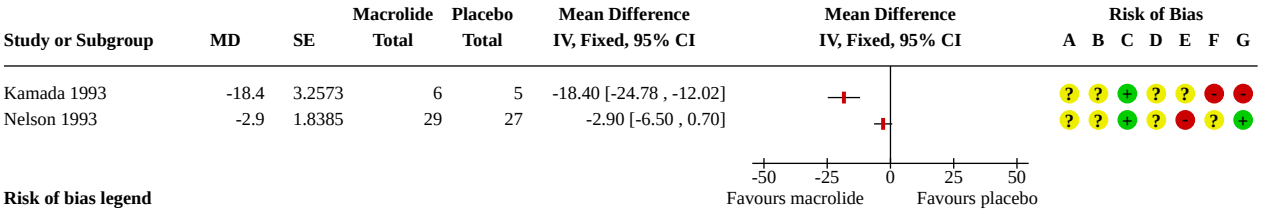
Non-specific bronchial hyperresponsiveness

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. Three studies reported an effect of macrolides in reducing bronchial hyperresponsiveness compared to placebo (Amayasu 2000; Kostadima 2004; Sutherland 2010), while six studies reported no effect compared with placebo (Cameron 2013; Kamada 1993; Nelson 1993; Piacentini 2007; Shoji 1999; Simpson 2008).

Lowest tolerated oral corticosteroid dose (in people requiring oral corticosteroids at baseline)

Most studies either excluded people taking oral corticosteroids or recruited people who did not take them regularly. Two studies that recruited people taking regular oral corticosteroids reported that macrolides had a steroid-sparing benefit (Analysis 1.11; Figure 13; Kamada 1993; Nelson 1993). 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 unclear if the ways the doses were calculated were sufficiently similar for pooling to make sense.

Figure 13. Forest plot of comparison: 1 Macrolide versus placebo, outcome: 1.11 Oral corticosteroid dose.



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Secondary outcomes

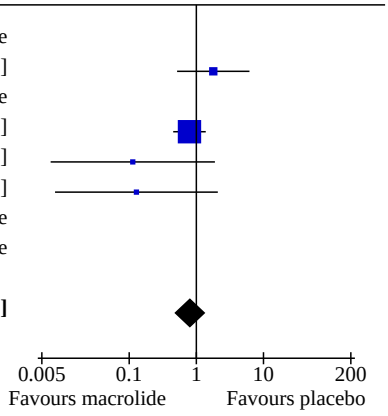
Serious adverse events

In general, macrolides were well tolerated, and there were no recorded deaths due to treatment with macrolides. Eight studies reported SAEs (Amayasu 2000; Brusselle 2013; Cameron 2013; Gibson 2017; Hahn 2006; Hahn 2012; Kamada 1993; Sutherland 2010). Meta-analysis found no clear difference in the likelihood of SAEs in the treatment and placebo groups, but the effect was imprecise due to the rarity of events (Peto OR 0.80, 95% CI 0.49 to 1.31; I^2 = 41%; participants = 854; Analysis 1.12; Figure 14).

Figure 14. Forest plot of comparison: 1 Macrolide versus placebo, outcome: 1.12 Serious adverse events (including mortality).

Study or Subgroup	Macrolide Events	Macrolide Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Amayasu 2000 (1)	0	17	0	17		Not estimable
Brusselle 2013	7	55	4	54	15.8%	1.79 [0.52 , 6.18]
Cameron 2013	0	39	0	38		Not estimable
Gibson 2017	26	213	31	207	78.0%	0.79 [0.45 , 1.38]
Hahn 2006	0	19	2	17	3.1%	0.11 [0.01 , 1.89]
Hahn 2012	0	38	2	37	3.1%	0.13 [0.01 , 2.09]
Kamada 1993	0	6	0	5		Not estimable
Sutherland 2010	0	47	0	45		Not estimable
Total (95% CI)		**434**		**420**	**100.0%**	**0.80 [0.49 , 1.31]**
Total events:	33		39			

Heterogeneity: Chi² = 5.12, df = 3 (P = 0.16); I² = 41%
Test for overall effect: Z = 0.89 (P = 0.38)
Test for subgroup differences: Not applicable



Footnotes
(1) Cross-over trial; no events in either phase. Participants not split to avoid double-counting as study did not contribute to effect estimate.

We rated the evidence to be of low certainty due to very serious imprecision in the estimate, risk of bias issues and possible indirectness.

Study withdrawals/dropouts

Ten studies reported withdrawals/dropouts (Brusselle 2013; Gibson 2017; Hahn 2006; Hahn 2012; Kamada 1993; Kostadima 2004; Nelson 1993; Simpson 2008; Strunk 2008; Sutherland 2010). Analysis suggested the likelihood of withdrawal from the studies was similar between participants taking macrolide and placebo (OR 1.06, 95% CI 0.76 to 1.48; I^2 = 0%; participants = 984; Analysis 1.13).

Eosinophil counts in blood and sputum

One study reported blood eosinophils (Yan 2008). There was no difference between macrolide and placebo in blood eosinophils, but analysed data were only available as SMD, so we did not enter it with the two existing studies (Amayasu 2000; Shoji 1999). A meta-analysis of these two small cross-over studies showed a reduction of eosinophils in the blood of people with asthma

treated with macrolides (MD −32.16, 95% CI −34.77 to −29.56; I^2 = 12%; participants = 62; Analysis 1.14). Cameron 2013 investigated the effect of macrolides in sputum eosinophils in current smokers with asthma, and found 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 = 97%). For this reason, data for the three studies have been displayed but not pooled (Analysis 1.15).

Eosinophil cationic protein in serum and sputum

Two studies reported serum and sputum ECP (Amayasu 2000; Shoji 1999). Macrolides appear to reduce the concentration of ECP both in serum and sputum (serum: MD −12.07, 95% CI −14.90 to −9.24; I^2 = 0%; participants = 62; Analysis 1.16; sputum: MD −1.35, 95% CI −1.69 to −1.01; I^2 = 0%; participants = 62; Analysis 1.17).

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.

Sensitivity analysis

Primary or secondary outcomes with high heterogeneity (I^2 greater than 30%) were taken into the consideration for conducting the sensitivity analysis with a random-effects model. The outcomes with high heterogeneity that suggested a beneficial effect of macrolide in primary analyses such as severe exacerbations: exacerbations requiring ED visits/systemic steroids (Analysis 1.2 versus Analysis 2.1), symptom scales (Analysis 1.3 versus Analysis 2.2), asthma control (Analysis 1.4 versus Analysis 2.3), AQLQ (Analysis 1.5 versus Analysis 2.4), and FEV_1 (Analysis 1.9 versus Analysis 2.5) became analyses in which the 95% CIs crossed the line of no effect by changing the model to random-effects. The reason for the change in effect estimate is decreasing the weighting of large studies such as Gibson 2017 (Analysis 2.1; Analysis 2.3; Analysis 2.4) and Hahn 2012 (Analysis 2.2) by changing the model to random effects.

DISCUSSION

Summary of main results

Twenty-five studies, involving 1973 participants given macrolide or placebo, met the inclusion criteria. The certainty of the evidence was generally low due to incomplete reporting of study methodology and clinical data, indirectness of study populations, risk of bias, and imprecision caused by small numbers of participants and events. Most studies reported data from people with persistent or severe asthma, but inclusion criteria, interventions and outcomes were highly variable, and there may have been selective or incomplete reporting.

Macrolides led to a moderately sized but non-significant improvement compared to placebo when this was defined as exacerbations requiring hospital admission (OR 0.47, 95% CI 0.20 to 1.12; I^2 = 0%; studies = 2, participants = 529), but this was driven by one study and the 95% CIs did not exclude the possibility of no effect. Not considering the heterogeneity among the studies, macrolides appeared beneficial compared to placebo for severe exacerbations (defined as requiring ED visits or systemic steroids, or both) (RaR 0.65, 95% CI 0.53 to 0.80; I^2 = 37%; studies = 4, participants = 640), improvement on symptom scales (SMD −0.46, 95% CI −0.81 to −0.11; I^2 = 70%, studies = 4, participants = 136), rescue medication use (MD −0.43 puffs per day, 95% CI −0.81 to −0.04), ACQ (SMD −0.17, 95% CI −0.31 to −0.03) and AQLQ (MD 0.24, 95% CI 0.12 to 0.35), although the variation in ACQ and AQLQ did not reach the MCID (for both scores, MCID = 0.50) (Juniper 2005; Juniper 1994). The improvement in FEV_1 (MD 0.04 L, 95% CI 0.03 to 0.08) was very small and of doubtful clinical relevance. There is no agreed MCID for FEV_1 but this is below any likely MCID. The other outcomes such as lung function were of very low quality and did not show a benefit of macrolide treatment (morning PEF: MD 1.60 L/minute, 95% CI −10.35 to 13.56; evening PEF: MD 1.00 L/minute, 95% CI −13.65 to 15.65). Measures of bronchial hyperresponsiveness were too varied to pool, but most studies showed no clear benefit of macrolide over placebo. Two studies with 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 (Peto OR 0.80, 95% CI 0.49 to 1.31; I^2 = 41%; studies = 8, participants = 854), although less than half of the studies reported the outcome which was approaching 10% in each group. Reporting of specific adverse effects was too patchy across studies to be analysed meaningfully. Number of withdrawals from the study was near to equal in both macrolide and placebo groups (OR 1.06, 95% CI 0.76 to 1.48; I^2 = 0%; studies = 10, participants = 984), and quite high in both group (almost 20%). Biomarkers of asthma activity such as sputum and serum ECP, sputum and serum eosinophils were lower in people treated with macrolides, but this was not associated with clinical benefits.

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 people with persistent asthma, but we cannot rule out the possibility of benefit due to several shortcomings in the available studies. The potential benefit of macrolides for the wide range of phenotypes and for clinically relevant groups (e.g. smokers) remains to be confirmed.

The available data from the 25 RCTs included in the present review are difficult to interpret for several reasons. First, four different types of macrolides were used across the studies (roxithromycin, clarithromycin, azithromycin and troleandomycin), often with differences in dosage and frequency of administration. Second, 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 people with aspirin-intolerant asthma (Shoji 1999), one included people with intermittent allergic asthma (Amayasu 2000), and another exclusively recruited smokers with asthma (Cameron 2013); all the other studies enrolled people with mild-to-severe persistent asthma, and we could not properly assess the populations of six Chinese studies. Seven studies tested participants for *C pneumoniae* or *M pneumoniae* infection, but all with different techniques and very different results (Black 2001; Hahn 2006; Kraft 2002; Simpson 2008; Strunk 2008; Sutherland 2010; Wan 2016). The scarcity of data in the primary analyses precluded any meaningful subgroup analyses to assess the possible effect of these factors. Third and perhaps most importantly, the outcomes measured were heterogeneous; reporting of exacerbations and definitions for exacerbations and

their severity 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 recruited people with allergic intermittent asthma (Amayasu 2000), and the other enrolled people whose asthma was aspirin-induced (Shoji 1999).

Only four studies investigated the role of macrolides in children with asthma (Kamada 1993; Piacentini 2007; Strunk 2008; Wan 2016); 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 seemed instead to exclude any role of macrolides used in this way.

Since the last version of this review, two RCTs were published (Gibson 2017; Wan 2016). Wan 2016 explored the effect of macrolides versus placebo on lung function and eosinophil inflammation (measured as exhaled nitric oxide, peripheral blood eosinophil count and ECP). Unfortunately, the quality of reporting of this study did not allow us to include its results in any meta-analysis. Nevertheless, the fact that Wan 2016 included only 58 participants mitigates the impact of the exclusion of its results on the overall conclusions of this review. In contrast, Gibson 2017 was a very well-designed and conducted study, with a large sample-size of well-selected participants, most of them on high-dose ICS and long-acting beta-agonist (LABA)/long-acting muscarinic antagonists (LAMA), falling in the category severe asthma of the current GINA 2021 guidelines. A number of biological drugs such as mepolizumab, reslizumab, benralizumab (Farne 2017) and dupilumab (Castro 2018; Rabe 2018) have entered the market since 2015 and, together with omalizumab (Normansell 2014), are routinely used in clinical practice; their use is now recommended in severe eosinophilic asthma (GINA 2021).

The results of Gibson 2017 and of a subgroup analysis from the same study (Gibson 2019) may indicate that macrolides could be an alternative to biological drugs for severe forms of asthma: that would be valuable especially in low-income countries, although the potential risk of resistance development would remain a serious caveat to their wide use.

Despite all the limitations and considering the heterogeneity, our systematic review and meta-analysis found no benefit of macrolides over placebo on lung function. As discussed, this does not rule out the possibility for significant benefit or harm of macrolides given the shortcomings of the evidence described above. The results of this review might change if further well-designed and appropriately powered RCTs are conducted, but at present, the evidence is not promising enough to support further research for a general use of macrolides, while there is a suggestion that research targeted at specific phenotypes (i.e. severe or non-eosinophilic (or both) asthma) may be warranted.

Overall, the use of macrolides for at least four continuous weeks of treatment proved safe, with similar rates of severe adverse events when macrolides were compared with placebo. There were no reported deaths. Unfortunately, this outcome was not consistently reported across the studies, and internationally approved scales such as the Common Terminology Criteria for Adverse Events were not used (CTCAE 2020). Therefore, the evidence for this outcome was low.

Antibiotic resistance is of increasing concern and only two included studies investigated this (Brusselle 2013; Gibson 2017). Brusselle 2013 reported that 87% of azithromycin-treated participants were colonised with erythromycin-resistant streptococci, a statistically significant increase from baseline and in comparison with the placebo group, while Gibson 2017 reported no significant change on the occurrence of resistant strains.

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; Wan 2016). The number of participants 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 certainty of the evidence is low. We had serious concerns about selective or incomplete reporting, under-reporting or variation of study results; there was uncertainty regarding allocation procedures and blinding of outcome assessment, and all but four trials recruited fewer than 100 people.

Few studies reported clinical data well enough to be included in a 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 people 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 type of events, so it was difficult to reach meaningful conclusions for these outcomes. Several studies excluded people at higher risk of adverse events including prolonged corrected QT interval on electrocardiogram (Brusselle 2013; Cameron 2013; Gibson 2017; Hahn 2012; Sutherland 2010; Wan 2016), abnormal liver function tests (Black 2001; Cameron 2013; Hahn 2012; Sutherland 2010), and hearing impairment (Gibson 2017); the effect of excluding these potential participants is uncertain. 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 two of the studies were conducted in the last five years, and 14 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 that did not appear in our searches (Tong 2015). 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 2015 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 the questions we had about the studies and their outcomes, but these studies could not be assessed as rigorously as the other 19 included studies and we could not be certain that all data relevant to this review were included.

The definitions of severe exacerbation, symptom scales and quality of life were not always consistent across studies. This required a significant post-hoc assessment of which outcomes could be pooled.

For peak flow and blood eosinophils, some of these studies could not be pooled with the others because they used a different unit of analysis. 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 2015 (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 identified 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).

Agreements and disagreements with other studies or reviews

Four other meta-analyses have evaluated the treatment of asthma with long-term macrolides (Hiles 2019; Reiter 2013; Tong 2015; Wang 2019). There are noticeable differences across the systematic reviews and meta-analyses 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 SMD or MD, 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 heterogeneous.

The analysis by Reiter 2013 included 12 RCTs with a minimum treatment duration of three weeks, and reported a positive effect of macrolides on symptoms scores, quality of life, peak flow and bronchial hyperresponsiveness. Tong 2015 included 18 studies, including the six Chinese studies that were not identified by our search, and it reported a positive effect on several measures of lung function (FEV_1, PEF and forced vital capacity (FVC)) and airways hyperresponsiveness, but not on other measures of lung function (percentage predicted FEV_1 and percentage predicted FVC), symptoms, or quality of life. Wang 2019 explored only studies conducted with azithromycin and for at least three weeks of duration. This systematic review and meta-analysis included eight RCTs, reporting a small but statistically significant increase in FEV_1, but no change in exacerbation rate, quality of life measures, PEF or fractional exhaled nitric oxide (FeNO) in the treatment group compared to placebo.

Hiles 2019 performed an individual participant data meta-analysis of three studies comparing azithromycin (treatment duration of at least eight weeks) versus placebo. The studies had to include data on exacerbations for a follow-up of at least six months. Exacerbations were defined as need for at least three days of oral corticosteroids or antibiotic course, or visit to the ED, or admission to hospital. Most of the participants included in this meta-analysis had severe asthma (320/529 participants, 60.5%). The meta-analysis showed a reduction of exacerbations in this population, and in people an eosinophilic or non-eosinophilic phenotype. Azithromycin did not have beneficial effects for secondary outcomes such as quality of life, lung function or biomarkers.

Reiter 2013 and Tong 2015 did not formally assess exacerbations, either because they were not included as an outcome (Tong 2015) or because the data were considered insufficient to do so (Reiter 2013). Wang 2019 explored the exacerbation frequency among the studies they included, but they did not report which definition they used for their analysis. Therefore, the results were difficult to contextualise. The results of Hiles 2019 were limited to people with severe asthma, and seem to confirm the findings of our systematic review and meta-analysis for this specific group of patients.

The lack of hospitalisation and exacerbation data is a major shortcoming of the evidence base, considering that reducing the frequency of these events is the main premise of long-term macrolides treatment.

AUTHORS' CONCLUSIONS

Implications for practice

Existing evidence suggests an effect of macrolides compared with placebo on the rate of exacerbations requiring hospitalisation. Macrolides probably reduce exacerbations requiring emergency department visit/treatment with systemic steroids and may reduce symptoms. Based on one well-designed and powered randomised controlled trial, azithromycin may reduce exacerbation rate and improve symptom scales in people with severe asthma but overall we cannot rule out the possibility of other benefits or harms

because the evidence is of low certainty due to heterogeneity among participants and interventions, imprecision and reporting biases (Gibson 2017).

Implications for research

The review highlights the need for researchers to report clinically relevant outcomes accurately and completely using guideline definitions of exacerbations, validated symptoms and quality of life scales, as well as international scales for adverse effects. The review and meta-analysis showed that macrolides can lead to a reduction of exacerbation rate and future trials could evaluate if this effect is sustained across all the severe asthma phenotypes and in comparison with newer biological drugs, whether effects persist or wane after treatment cessation, and are associated with infection biomarkers. Trials with prespecified subgroup analyses by asthma severity or phenotype would usefully contribute to the literature.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Amayasu 2000

Study characteristics	
Methods	**Design**: randomised controlled, double-blind, 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

Amayasu 2000 *(Continued)*

Participants	**Population**: 17 participants randomised to 2 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, years: 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 ATS. All were in stable condition and had been free of symptoms for respiratory infections for ≥ 6 weeks. **Exclusion criteria**: people using oral or ICSs, theophylline, any anti-leukotriene drug, any other anti-inflammatory agents or clarithromycin
Interventions	**Run-in**: wash-out period ≥ 4 weeks between cross-over **Intervention**: clarithromycin 200 mg twice per 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.
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.

Amayasu 2000 *(Continued)*

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

Study characteristics	
Methods	**Design**: parallel randomised trial (blinding and type of control unclear) **Duration**: 8 weeks Location unclear
Participants	**Population**: 51 adults with chronic stable asthma randomised to azithromycin (n = 28) or 'control' (n = 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.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No mention of blinding.
Incomplete outcome data (attrition bias)	Unclear risk	Number of withdrawals not given.

Belotserkovskaya 2007 *(Continued)*
All outcomes

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

Study characteristics	
Methods	**Design**: parallel randomised, double-blind, placebo-controlled, multicentre, multinational study **Duration**: 6 weeks' treatment with 24 weeks' follow-up Conducted in Australia, New Zealand, Italy and Argentina
Participants	**Population**: 219 participants with asthma randomised to roxithromycin (n = 105) or placebo (n = 114) **Baseline characteristics** % male: roxithromycin, 44.8; placebo, 50.0 Mean age, years: roxithromycin, 40 (SD 11.6); placebo, 42 (SD 11.9) % on maintenance ICS: roxithromycin, 77.1; placebo, 84.2 % on maintenance LABA/ICS: not reported Mean % predicted FEV_1: roxithromycin, 79.0 (SD 19.3); placebo, 75.3 (SD 17.4) Mean daily ICS dose, µg: not reported *Chlamydophila* infection: reported according to serological tests **Inclusion criteria**: aged 18–60 years, physician diagnosis of asthma, FEV_1 ≥ 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 ≥ 2 or night-time symptom score ≥ 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 > 3 weeks in the preceding 4 months; other medicines that were not permitted were ergot alkaloids, terfenadine and astemizole; smoking history > 20 pack-years; bronchiectasis; any other serious systemic diseases; hypersensitivity to macrolides or any significant change in asthma medication in previous month, including a course of OCS; respiratory tract infection during 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 per day **Control**: matching placebo Treatments for asthma other than OCSs were permitted if the dose had not changed in the previous month.
Outcomes	Symptoms, PEF, FEV_1, reliever medication
Notes	**Funding**: not stated

Black 2001 *(Continued)*

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	ITT analysis. This did not include 12 people who withdrew from the study within a few days of randomisation, without recording any diary card data, or a 13th person who was withdrawn because of nausea and vomiting and did not record any diary card data after the first 10 days of treatment. Did not state from which groups but represented < 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

Study characteristics

Methods	**Design**: parallel, randomised, double-blind, placebo-controlled, multicentre study **Duration**: 26 weeks Locations not described in detail; appears to be mostly conducted Belgium
Participants	**Population**: 109 participants randomised to azithromycin (n = 55) or placebo (n = 54) **Baseline characteristics** % male: azithromycin, 47; placebo, 30 Median age, years: azithromycin, 53; placebo, 53 % on maintenance ICS: not reported % on maintenance LABA/ICS: azithromycin, 100; placebo, 100 Mean % predicted FEV_1: azithromycin, 80.1 (SD 21.9); placebo, 84.8 (SD 20.7) Mean daily ICS dose, µg: azithromycin, 2000; placebo, 2000 *Chlamydophila* infection: not reported

Brusselle 2013 *(Continued)*

	Inclusion criteria: aged 18–75 years; diagnosis of persistent asthma; history consistent with GINA step 4 or 5 clinical features; received high doses of ICS (≥ 1000 mg fluticasone or equivalent) plus inhaled LABA for ≥ 6 months prior to screening and had ≥ 2 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 ≤ 10 pack-years; FeNO level below ULN **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 per week **Control**: matching placebo All participants received high-dose combination therapy of ICS and LABA for ≥ 6 months prior to study entry and continued this treatment throughout study
Outcomes	ACQ, AQLQ, rescue medication use, FEV_1, morning and evening PEF, adverse events, withdrawals Severe asthma exacerbations defined as deterioration in asthma leading to ≥ 1 of: hospitalisation, ED visit or need for systemic corticosteroids for ≥ 3 days during the 26-week treatment phase
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.
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% with azithromycin vs 9.3% with placebo). 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 2013

Study characteristics	
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 (n = 39) or placebo (n = 38) **Baseline characteristics** % male: azithromycin, 51.3; placebo, 44.7 Mean age, years: azithromycin, 46.4 (SD 8.8); placebo, 42.8 (SD 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 (prebronchodilator) Mean daily ICS dose, µg: azithromycin, 603 (SD 457); placebo, 709 (SD 564) *Chlamydophila* infection: not reported **Inclusion criteria**: aged 18–70 years, current smokers (≥ 5 pack-years history) with chronic asthma (> 1 year' duration); free of exacerbations and respiratory tract infections for ≥ 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; unstable asthma; current epilepsy, psychosis or history of significant atrial or ventricular tachyarrhythmia; corrected QT interval > 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 times ULN); significant renal disease (creatinine or urea levels ≥ 2 times ULN); any previous severe adverse reactions to macrolides; 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; URTI or LRTI 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); require medications known to interact with azithromycin; on other immunosuppressants or chronic antibiotics; weight < 45 kg; frequent asthma exacerbations (> 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 ICS equivalent to beclomethasone 400 µg ± 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	

Cameron 2013 *(Continued)*

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 (participant, carer, investigator, outcomes assessor).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Masking: double-blind (participant, carer, investigator, outcomes assessor).
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	6 participants 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.

Gibson 2017

Study characteristics	
Methods	**Design**: parallel, randomised, double-blind, placebo-controlled trial **Duration**: 48 weeks Conducted at 8 centres in Australia
Participants	**Population**: 420 participants were randomised to azithromycin (n = 213) or placebo (n = 207) **Baseline characteristics** % male: azithromycin, 37; placebo, 42 Mean age, years: azithromycin, 61.0; placebo, 60.0 % on maintenance ICS: azithromycin, 100; placebo, 99.5 % on maintenance LABA/ICS: azithromycin, 98; placebo, 99 Mean % predicted FEV_1: azithromycin, 72.3; placebo, 73.6 Mean daily ICS dose, µg: not reported, but reported > 85% of participants were on beclomethasone dipropionate ≥ 800 µg equivalent in both groups *Chlamydophila* infection: not reported **Inclusion criteria**: asthma defined as a compatible history and documented objective evidence of variable airflow obstruction from bronchodilator response (with postbronchodilator reversibility of ≥ 12% and FEV_1 > 200 mL, airway hyperresponsiveness, or increased peak flow variability (> 12% of amplitude above the lowest PEF over ≥ 1 week of monitoring); currently symptomatic with at least partial loss of

Gibson 2017 *(Continued)*

	asthma control (ACQ6 ≥ 0.75) despite treatment with maintenance ICSs or long-acting bronchodilators; clinically stable with no recent exacerbations, infections or changes in maintenance medication for ≥ 4 weeks before study entry; non-smokers confirmed by exhaled carbon monoxide < 10 ppm **Exclusion criteria**: substantial parenchymal lung disease, such as emphysema; ex-smokers with > 10 pack-years of smoking if their diffusing capacity for carbon monoxide (gas transfer corrected for effective alveolar volume) was < 70% of the predicted value; hearing impairment; abnormally prolonged QTc interval
Interventions	**Run-in**: 2 weeks after screening visit **Intervention**: azithromycin 500 mg 3 times per week **Control**: matching placebo
Outcomes	Total number of asthma exacerbations (severe and moderate) over 48 weeks (Severe exacerbations defined as need of hospitalisation or ED visit or need for ≥ 3 systemic steroids or increase of a stable oral steroids dose. Moderate exacerbation defined as increase of inhaled steroids or oral antibiotics without systemic steroids, or increased beta-agonists or ED visit without hospitalisation and without systemic steroids) Change in AQLQ and ACQ6, lung function, adverse events, antibiotic courses for respiratory infection, induced sputum cell counts
Notes	**Funding**: Australian Government's National Health and Medical Research Council (NHMRC) and John Hunter Charitable Trust; no commercial input into any aspect of the trial. **Study ID(s)**: ANZCTR 12609000197235

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random allocation from a computer-generated random numbers table with permuted blocks of 4 or 6 and stratification for centre and past smoking.
Allocation concealment (selection bias)	Low risk	Study packs were labelled with the allocated randomisation number and bottle numbers.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All investigators, study research staff and participants' treating doctors were blinded to treatment allocation.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Researchers and treating physicians blinded to the treatment.
Incomplete outcome data (attrition bias) All outcomes	High risk	ITT analysis included participants with no follow-up data as no change.
Selective reporting (reporting bias)	Unclear risk	Exacerbations were grouped (e.g. severe exacerbations = ED + short course steroids + hospitalisation) and separate data were not available. Severe exacerbations were analysed as number per participant-year but were available as events in an associated abstract.
Other bias	Low risk	None noted.

Hahn 2006

Study characteristics	
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 randomised to azithromycin (n = 24) or placebo (n = 21) **Baseline characteristics** % male: azithromycin, 33; placebo, 67 Mean age, years: azithromycin, 50 (SD 14); placebo, 45 (SD 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**: aged ≥ 18 years with diagnosis of current asthma that was persistent, stable and present for > 3 months prior to enrolment, stability assessed during 2–3 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 12% (and > 200 mL) or PEF change 25% (and > 60 L/minute) **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 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, 1 × 600 mg tablet daily for 3 days, followed by 600 mg weekly for an additional 5 weeks **Control**: matching placebo All participants 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**

Hahn 2006 *(Continued)*

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 allocation ratio blocked by site. Block size was 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 (participant, 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 (participant, physician, data collector, data analyst).
Incomplete outcome data (attrition bias) All outcomes	High risk	Used ITT principle. 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

Study characteristics	
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 PBRNs and 1 community-based allergist enrolled patients from their practices
Participants	**Population**: 75 participants randomised to azithromycin (n = 38) or placebo (n = 37) **Baseline characteristics** % male: azithromycin, 29; placebo, 35 Mean age, years: azithromycin, 45.7 (SD 15.5); placebo, 47.4 (SD 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 aged ≥ 18 years with physician-diagnosed asthma (symptomatic > 2 days per week, > 2 nights a month, in exacerbation, or a combination of these characteristics); objective

Hahn 2012 *(Continued)*

	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 ≥ 6 months before enrolment. **Exclusion criteria**: not English literate or had 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 < 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, ciclosporin, hexobarbital, or phenytoin)
Interventions	**Run-in**: unclear **Intervention**: azithromycin 600 mg, 1 tablet per day for 3 days followed by 1 tablet per week for 11 weeks **Control**: matching placebo
Outcomes	Symptoms, ACQ, changes in asthma medications, withdrawals, quality of life, exacerbations Exacerbations 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 participant assignment to the azithromycin or placebo study arms.
Allocation concealment (selection bias)	Low risk	The investigators, participants 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 1–6) in numerical ascending order to eligible consenting study participants.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The investigators, participants, and study site personnel were blinded to treatment allocation.
Incomplete outcome data (attrition bias) All outcomes	High risk	All ITT analyses, and no participants with available data were excluded from any analysis. Withdrawal was high and quite uneven between groups (42% with azithromycin and 30% with placebo).

Hahn 2012 *(Continued)*

Selective reporting (reporting bias)	Low risk	Prospectively registered outcomes reported fully.
Other bias	Unclear risk	More participants in the placebo group were taking regular ICS or ICS/LABA combination.

He 2009

Study characteristics	
Methods	**Design**: randomised controlled trial (assumed parallel assignment; unconfirmed) **Duration**: 12 weeks Conducted in China
Participants	**Population**: 40 participants were randomised to azithromycin (n = 20) or placebo (n = 20) **Baseline characteristics** % male: not reported Mean age, years: azithromycin, 35 (SD 7.3); placebo, 34 (SD 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 unable to detail the specific inclusion and exclusion criteria for this trial because it was included from an existing systematic review (Tong 2015). 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, 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 2015 awarded 2 points for this domain, suggesting well-reported and acceptable methods of random sequence generation.

He 2009 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Information was unavailable.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Tong 2015 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 2015 noted that methods of blinding were not adequately described in the study.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Tong 2015 noted that withdrawals and dropouts were not adequately described in the study.
Selective reporting (reporting bias)	Unclear risk	Information was unavailable.
Other bias	Unclear risk	Information was unavailable.

Kamada 1993

Study characteristics	
Methods	**Design**: parallel, randomised, double-blind, placebo-controlled trial **Duration**: 12 weeks Conducted in Denver, USA
Participants	**Population**: 19 participants randomised to troleandomycin + methylprednisolone (n = 6), troleandomycin + prednisone (n = 8) or placebo + methylprednisolone (n = 5) **Baseline characteristics** % male: troleandomycin + methylprednisolone, 16.7; troleandomycin + prednisone, 100; placebo + methylprednisolone, 60 Mean age, years: troleandomycin + methylprednisolone, 14.3 (SD 2.9); troleandomycin + prednisone, 11.9 (SD 2.6); placebo + methylprednisolone, 11.3 (SD 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**: aged 6–17 years meeting ATS criteria for reversible obstructive airways disease, requiring prednisone in doses of ≥ 20 mg every other day, using inhaled bronchodilators ≥ 4 times per 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**: pregnant, smoker, viral upper respiratory infection within 4 weeks of enrolment

Kamada 1993 *(Continued)*

Interventions	**Run-in**: single-blind run-in period of ≥ 1 week **Intervention 1**: troleandomycin 250 µg + methylprednisolone once daily **Intervention 2**: troleandomycin 250 µg + prednisolone once daily (data not used in this review) **Control**: placebo + methylprednisolone once daily All participants required OCS, given as part of the randomised treatment. The mean daily dose was 34.2 mg in intervention group 1, 21.3 mg in intervention group 2 and 23.5 mg in control group
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 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 participants received identically appearing study medications in the form of 2 blue capsules, which contained either prednisolone or methylprednisolone, and 1 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 participants on the recommendations of investigators who were blinded 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 participants 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

Study characteristics

Methods	**Design**: cross-over, randomised, double-blind, placebo-controlled trial **Duration**: 6 weeks per treatment with 3-week washout

Kapoor 2010 *(Continued)*

	Conducted in India
Participants	**Population**: 40 participants randomised to the 2 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	ACT, 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.
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

Study characteristics

Methods	**Design**: parallel, randomised, double-blind, placebo-controlled trial **Duration**: 8 weeks

Kostadima 2004 *(Continued)*

	Conducted in Greece
Participants	**Population**: 75 participants randomised to clarithromycin twice daily (n = 25), 3 times daily (n = 25) or placebo (n = 25) **Baseline characteristics** % male: clarithromycin twice daily, 72.7; clarithromycin 3 times daily, 40; placebo, 28.6 Mean age, years: clarithromycin twice daily, 48 (SD 16); clarithromycin 3 times daily, 42 (SD 12); placebo, 41 (SD 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: clarithromycin twice daily, 85 (SD 14); clarithromycin 3 times daily, 85 (SD 13); placebo, 86 (SD 14) Mean daily ICS dose, µg: not reported *Chlamydophila* infection: not reported **Inclusion criteria**: aged 18–70 years; 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 ≥ 1 month prior to recruitment; PD_{20} < 2 mg **Exclusion criteria**: history of allergic rhinitis or occupational asthma; history of smoking (past or current); treatment with systemic corticosteroids or history of URTI over the 4 weeks prior to participation in the trial; FEV_1 < 50% of the predicted value or < 1 L at baseline; URTI or asthma exacerbation during the study period; history of systemic diseases (i.e. myocardial infarction or stroke in previous 3 months, uncontrolled hypertension, known aortic aneurysm, epilepsy requiring drug treatment or peptic ulcer disease); treatment with beta-blockers; pregnancy or lactation
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, participants continued their treatment with budesonide and salbutamol. No other medication was allowed. We grouped the results for clarithromycin 250 mg twice daily and clarithromycin 250 mg 3 times daily and compared them with placebo.
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.

Kostadima 2004 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Randomised to 1 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	Participants 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	Participants 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 did not give details of a study protocol to check that all planned 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

Study characteristics	
Methods	**Design**: parallel, randomised, double-blind, placebo-controlled trial **Duration**: 6 weeks Conducted in Denver, USA
Participants	**Population**: 55 participants randomised to clarithromycin (n = 26) or placebo (n = 26); 3 withdrew due to scheduling conflicts (n = 1) and non-compliance (n = 2) (treatment groups unknown) **Baseline characteristics**: reported for the population as a whole, not for each group % male: 49.1 Mean age, years: 33.4 (SD 8.9) % on maintenance ICS: 32.7 % on maintenance LABA/ICS: 100 Mean % predicted FEV_1: 69.3 (SD 15.6) Mean daily ICS dose, µg: not reported *Chlamydophila* infection: 56.4% had evidence of *C pneumoniae* or *M pneumoniae* infection **Inclusion criteria**: fulfilled criteria for asthma, exhibited a provocative concentration of methacholine causing a 20% decline in FEV_1 < 8 mg/mL, and reversibility of lung function by ≥ 12% with bronchodilator **Exclusion criteria**: inpatient status; URTI or LRTI 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

Kraft 2002 *(Continued)*

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 were blinded to treatment status.
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 participants (treatment groups unknown) underwent analysis for *Mycoplasma and Chlamydophila* but were excluded from the treatment analysis due to scheduling difficulties (n = 1) and non-compliance (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

Study characteristics

Methods	**Design**: prospective, parallel, randomised, double-blind, placebo-controlled trial **Duration**: 1–2 years (variable) Conducted in Denver, USA
Participants	**Population**: 75 participants randomised to troleandomycin + methylprednisolone (n = 37) or placebo + methylprednisolone (n = 38) **Baseline characteristics** % male: troleandomycin + methylprednisolone, 36.7; placebo + methylprednisolone, 29.6 Age range, years: troleandomycin + methylprednisolone, 21–75; placebo + methylprednisolone, 22–62

Nelson 1993 *(Continued)*

	% 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**: diagnosis of asthma with demonstrated fluctuation in the FEV_1 ≥ 15% of the predicted value occurring either spontaneously or as a result of therapy. They were required to have received a minimum of prednisone 15 mg per day or an equivalent dose of another corticosteroid over the preceding 3 months with 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 > 10 µg/mL and inhaled β-adrenergic bronchodilator therapy ≥ 4 times daily. People using inhaled sodium cromolyn or ICS were required to discontinue these medications before enrolment. 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 **Exclusion criteria**: receiving anticonvulsant therapy, had significant hepatic disease, current smokers
Interventions	**Run-in**: before entry, each participant's medication was optimally adjusted and often had received a transient increase in corticosteroid dose. Therefore, each participant's asthma was under good control when they were randomised, and steroids were tapered only in a way consistent with maintenance of continued good control **Intervention**: troleandomycin 250 µg once daily + methylprednisolone **Control**: matching placebo + methylprednisolone All participants required OCS, which were given as part of the randomised treatment. Mean daily doses were 30.8 mg for the intervention group and 32.0 mg for the control group.
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 participants and personnel/investigators).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear who performed the evaluations.

Nelson 1993 *(Continued)*

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 were reported; study predated requirement to register a protocol.
Other bias	Low risk	None noted.

Piacentini 2007

Study characteristics	
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 randomised to azithromycin (n = 8) or placebo (n = 8) **Baseline characteristics** % male: azithromycin, 75; placebo, 75 Mean age, years: azithromycin, 13.9 (SD 2.4); placebo, 12.9 (SD 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 per day for 3 consecutive days every week, at 10 mg/kg bodyweight **Control**: matching placebo All participants continued their long-term treatment for asthma with low-dose ICS: either fluticasone 100–200 µg/day, or beclomethasone dipropionate 200–400 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	

Piacentini 2007 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Active or placebo treatment 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; could not check if outcomes were missing.
Other bias	Low risk	None noted.

Shoji 1999

Study characteristics	
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 1 centre in Japan
Participants	**Population**: 14 participants randomised to the 2 treatment sequences (roxithromycin-placebo and placebo-roxithromycin) **Baseline characteristics:** presented for the whole population due to the cross-over design % male: 42.9 Mean age, years: 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**: adults 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

Shoji 1999 *(Continued)*

	criteria. The participants were in a stable condition and had been free of symptoms of respiratory infection for at least 6 weeks. **Exclusion criteria**: people using OCS or ICSs, theophylline, any anti-leukotriene drug, such as pranlukast, or any other anti-allergic agents as well as roxithromycin
Interventions	**Run-in**: washout period ≥ 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 participants and personnel); matching placebo.
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

Study characteristics

Methods	**Design**: parallel, randomised, double-blind, placebo-controlled trial **Duration**: 8 weeks Participants recruited from the Ambulatory Care Service of the Department of Respiratory and Sleep Medicine at the John Hunter Hospital, New Lambton, Australia

Simpson 2008 *(Continued)*

Participants	**Population**: 45 participants randomised to clarithromycin (n = 23) or placebo (n = 22) **Baseline characteristics** % male: clarithromycin, 43.5; placebo, 54.5 Mean age, years: clarithromycin, 60; placebo, 55 % on maintenance ICS: not reported % on maintenance LABA/ICS: clarithromycin, 83; placebo, 82 Mean % predicted FEV_1: clarithromycin, 73.6 (SD 15.8); placebo, 67.6 (SD 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. Antihistamine therapies were ceased for the duration of the study **Exclusion criteria**: smoked > 5 pack-years or if they had any known sensitivity to macrolide antibiotics
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 metalloprotein-9, lung function, airway hyperresponsiveness to hypertonic saline, asthma control, quality of life, symptoms
Notes	**Funding**: not stated **Study ID(s)**: ACTR12605000318684

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	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 participants 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	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.

Simpson 2008 *(Continued)*

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	Low risk	None noted.

Strunk 2008

Study characteristics	
Methods	**Design**: parallel, randomised, double-blind, placebo-controlled multicentre trial **Duration**: 30 weeks, depending on asthma control Recruited from 5 CARE Network centres in the USA
Participants	**Population**: 55 participants randomised to azithromycin (n = 17), placebo (n = 19), or montelukast (n = 19; not relevant to this review) **Baseline characteristics:** presented for the whole population % male: 58.2 Mean age, years: 11.2 (SD 2.6) % on maintenance ICS: not reported % on maintenance LABA/ICS: 100 Mean % predicted FEV_1: 101.9 (SD 13.7) Mean daily ICS dose, µg: 60% were taking budesonide 800 µg per 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 6–17 years, and demonstration of moderate-to-severe persistent asthma; pre-bronchodilator values of FEV_1 ≥ 80% predicted for consideration of step-down at enrolment, or ≥ 50% predicted if inadequately controlled and step-up planned; children demonstrated ability to perform reproducible spirometry and had airway lability demonstrated either by an improvement in FEV_1 ≥ 12% after 4 puffs of albuterol or airway hyperresponsiveness, reflected by ≥ 20% fall in FEV_1 after a methacholine dose of ≤ 12.5 mg/mL **Exclusion criteria**: very severe asthma, as indicated by > 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, ciclosporin, 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 + salmeterol, with subsequent documentation that step-up to a higher dose of ICS (to a maximum of 1600 µg daily, with salmeterol) established control. Participants were excluded if they were unable to use the study drug delivery systems or to adhere

Strunk 2008 *(Continued)*

	to ≥ 80% of days with use of salmeterol Diskus and oral capsules and of diary card completion during the run-in (prerandomisation) period. **Intervention**: azithromycin 250 mg (25–40 kg bodyweight) or 500 mg (> 40 kg bodyweight) once daily + placebo montelukast tablet **Control**: 1 or 2 placebo capsules once daily plus 1 placebo 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 OCSs, 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 stratified according to clinical centre and dose of budesonide (800 µg/day vs 1600 µg/day) that achieved asthma control during run-in. Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Double-blind. 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-blind. 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.
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

Study characteristics

Methods	**Design**: parallel, randomised, double-blind, placebo-controlled trial **Duration**: 16 weeks

Sutherland 2010 *(Continued)*

	Recruited from 10 hospitals and medical centres in the USA
Participants	**Population**: 92 participants randomised to clarithromycin (n = 47) or placebo (n = 45) **Baseline characteristics** % male: clarithromycin, 42.6; placebo, 44.4 Mean age, years: clarithromycin, 41.3 (SD 12.5); placebo, 37.5 (SD 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 participants in each group were PCR positive for *M pneumoniae* or *C pneumoniae* **Inclusion criteria**: history of physician-diagnosed asthma; methacholine PC_{20} ≤ 16 mg/mL, FEV_1 improvement ≥ 12% in response to albuterol 180 µg, or both; stable asthma for ≥ 6 weeks prior to study entry; FEV_1 ≥ 60% of predicted result following albuterol 180 µg; Juniper ACQ score ≥ 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 tablet trial (monitored electronically with electronic Drug Exposure Monitor (eDEM) tablet 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 < 5 µg/dL (if adrenal suppression occurs, ACTH 250 µg stimulation test was performed. Plasma cortisol levels were collected at baseline, and 30 and 60 minutes after the ACTH stimulation test. Participants must have had a cortisol concentration > 20 µg/dL on ≥ 1 of the post-ACTH time points); absence of bronchoscopy-induced exacerbation (if bronchoscopy-induced exacerbation had occurred, prednisone therapy must have stopped ≥ 6 weeks prior to study entry); absence of respiratory tract infection (if infection had occurred, infection-related symptoms must have stopped ≥ 6 weeks prior to study entry); had experienced ≤ 2 exacerbations or respiratory tract infections prior to study entry; if female and able to conceive, willing to utilise 2 medically acceptable forms of contraception (1 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 co-ordinate use of dry powder or MDI or to comply with medication regimens; inability or unwillingness to perform required study procedures; prolonged heart rate corrected QT interval (> 450 ms in women and > 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 or partial thromboplastin time 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 sulphate 180 µg as needed every 4–6 hours for relief of acute symptoms. If, at the end of the 4-week run-in, participants demonstrated an ACQ score ≥ 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.*

Sutherland 2010 *(Continued)*

	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 2 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 2 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	Double-blind (participant, carer, investigator, outcomes assessor)
Incomplete outcome data (attrition bias) All outcomes	High risk	All analyses invoked the ITT paradigm, with truncation at the time of exacerbation or treatment failure in relevant analyses. Dropout was 17% in clarithromycin group and 11% in placebo group, 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 were uploaded to ClinicalTrials.gov.
Other bias	Low risk	None noted.

Wan 2016

Study characteristics

Methods	**Design**: randomised, placebo-controlled trial (assumed parallel assignment; unconfirmed) **Duration**: 4 weeks Conducted in Taipei

Wan 2016 *(Continued)*

Participants	**Population**: 58 children randomised to clarithromycin (n = 36) or placebo (n = 22) **Baseline characteristics** % male: clarithromycin, 66.6; placebo, 50 Mean age, years: clarithromycin, 10.1 (SD 3.1); placebo, 10.2 (SD 3.1) % on maintenance ICS: 100% according to protocol % on maintenance LABA/ICS: 0 in both groups Mean % predicted FEV_1: clarithromycin, 79.4; placebo, 80.1 Mean daily ICS dose, µg: budesonide dipropionate 200 *Chlamydophila* infection: clarithromycin, 58% IgG, 41.7% IgM; placebo, 65% IgG, 35% IgM **Inclusion criteria**: persistent asthma according to GINA guidelines; positivity to ≥ 2 common inhaled allergens; consent given by parents **Exclusion criteria**: < 2 antigens; no consent obtained; congenital long QT-syndrome or prolonged QT
Interventions	**Run-in**: 1-week washout systemic steroids and montelukast **Intervention**: clarithromycin orally 5 mg/kg daily for 4 weeks **Control**: placebo matching orally for 4 weekly
Outcomes	Childhood ACT, FEV_1%, forced expiratory flow at 25–75% of the pulmonary volume, FeNO, total IgE, absolute eosinophil count, ECP
Notes	**Funding**: unknown **Study ID(s)**: unknown

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers.
Allocation concealment (selection bias)	Low risk	Sealed envelope for allocation.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported, but placebo used.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Reported 2 withdrawals in the control group, but rate of completion of investigations not reported.
Selective reporting (reporting bias)	Unclear risk	Childhood ACT not reported at end of study. Rate of completion of investigations not reported.

Wan 2016 *(Continued)*

Other bias	Low risk	None noted.

Wang 2012

Study characteristics	
Methods	**Design**: randomised controlled trial (assumed parallel assignment; unconfirmed) **Duration**: 8 weeks Conducted in China
Participants	**Population**: 45 participants randomised to clarithromycin (n = 23) or placebo (n = 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 unable to detail the specific inclusion and exclusion criteria for this trial because it was included from an existing systematic review (Tong 2015). 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 2015 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.

Wang 2012 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Tong 2015 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 2015 noted that methods of blinding were not adequately described in the study.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Tong 2015 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

Study characteristics	
Methods	**Design**: randomised controlled trial (assumed parallel assignment; unconfirmed) **Duration**: 52 weeks Conducted in China
Participants	**Population**: 58 participants randomised to azithromycin (n = 29) or placebo (n = 29) **Baseline characteristics** % male: not reported Mean age, years: azithromycin, 28.4 (SD 16.0); placebo, 29.6 (SD 14.2) % 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 unable to detail the specific inclusion and exclusion criteria for this trial because it was included from an existing systematic review (Tong 2015). 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

Wang 2014 *(Continued)*

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 2015 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 2015 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 2015 noted that methods of blinding were not adequately described in the study.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Tong 2015 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

Study characteristics

Methods	**Design**: randomised controlled trial (assumed parallel assignment; unconfirmed) **Duration**: 12 weeks Conducted in China
Participants	**Population**: 210 participants randomised to roxithromycin (n = 106) or placebo (n = 104) **Baseline characteristics** % male: not reported Mean age, years: roxithromycin, 34.5 (SD 7.2); placebo, 33.7 (SD 8.3) % on maintenance ICS: not reported % on maintenance LABA/ICS: not reported Mean % predicted FEV_1: not reported

Xiao 2013 *(Continued)*

	Mean daily ICS dose, µg: not reported *Chlamydophila* infection: not reported **Inclusion criteria**: we were unable to detail the specific inclusion and exclusion criteria for this trial because it was included from an existing systematic review (Tong 2015). 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

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Tong 2015 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 2015 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 2015 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

Study characteristics

Methods	**Design**: randomised controlled trial (assumed parallel assignment; unconfirmed) **Duration**: 4 weeks

Yan 2008 *(Continued)*

	Conducted in China
Participants	**Population**: 40 participants randomised to roxithromycin (n = 20) or placebo (n = 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 unable to detail the specific inclusion and exclusion criteria for this trial because it was included from an existing systematic review (Tong 2015). 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	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 2015 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 2015 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 2015 noted that methods of blinding were not adequately described in the study.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Tong 2015 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.

Yan 2008 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Information was not available.
Other bias	Unclear risk	Information was not available.

Zhang 2013

Study characteristics	
Methods	**Design**: randomised controlled trial (assumed parallel assignment; unconfirmed) **Duration**: 60 days (8.7 weeks) Conducted in China
Participants	**Population**: 60 participants randomised to azithromycin (n = 30) or placebo (n = 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 unable to detail the specific inclusion and exclusion criteria for this trial because it was included from an existing systematic review (Tong 2015). 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 2015 awarded 2 points for this domain, suggesting well-reported and acceptable methods of random sequence generation.

Zhang 2013 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Information was not available.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Tong 2015 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 2015 noted that methods of blinding were not adequately described in the study.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Tong 2015 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**: chlorofluorocarbon; **CPAP**: continuous positive airway pressure; **DRS**: dose–response slope; **ECG**: electrocardiography;**ECP**: eosinophil cationic protein; **ED**: emergency department; **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 corticosteroid;**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; **n**: number of participants; **NIH**: National Institutes of Health (USA) **MCID**: minimal clinically important difference; **MDI**: metred dose inhaler; **OCS**: oral corticosteroid; **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 infection.

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.
Bacharier 2015	Participants not affected by asthma.
Baigelman 2015	Participants not affected by asthma.
Ball 1990	Study period too short (2 weeks).
Cogo 1994	Study of inadequate duration.
D'Azevedo Silveira 2016	Participants not affected by asthma.
Ebling 1984	Basic science study.
Feldman 1997	Basic science in vitro study.

Study	Reason for exclusion
Gong 2016	Missing a control group without macrolides. Classification of the participants unclear.
Gotfried 2004	Study was suspended because the slow enrolment of participants. 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 participants. Therefore, the study was excluded because there were no between-study comparisons.
Hodgson 2016	Participants affected by chronic cough, not asthma.
Hueston 1991	Participants not affected by asthma.
Itkin 1970	Treatment duration < 4 weeks.
Johnston 2016	Treatment duration < 4 weeks.
Kaplan 1958	Not an RCT.
Koh 1997	Participants were children with bronchiectasis; 7 children had asthma and insufficient data were reported for these children separately.
Koutsoubari 2012	Acute exacerbations in children, trial < 4 weeks.
Lee 1998	Study on the pharmacokinetics of theophylline during macrolides administration.
Mandhane 2017	Treatment duration < 4 weeks.
Oldach 2015	Target condition not asthma.
Ram 2016	Target condition not asthma. Intervention not a macrolide.
Spector 1974	Not an RCT.
Stokholm 2016	Treatment duration < 4 weeks.
Szefler 1980	Not an RCT.
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 ongoing studies *[ordered by study ID]*

NCT02517099

Study name	Preschool Wheeze: Inflammation/Infection Guided Management (PrIGMa)

NCT02517099 *(Continued)*

Methods	Randomised controlled trial
Participants	Children aged 1–5 years
Interventions	Regular inhaled steroids (beclometasone dipropionate 200 µg twice for 4 months) or antibiotic therapy (co-amoxiclav 0.3 mL/kg twice daily or azithromycin 10 mg/kg once daily for 4 weeks).
Outcomes	Number of unscheduled healthcare visits at 4 months Health-related quality of life at 4 months and up to 1 year later Number of hospital admissions at 4 months and up to 1 year later Number of days of oral steroids at 4 months and up to 1 year later
Starting date	5 June 2015
Contact information	Imperial College London, UK
Notes	

DATA AND ANALYSES

Comparison 1. Macrolide versus placebo

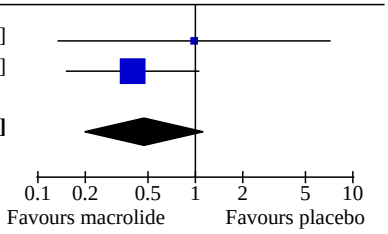
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Exacerbation requiring hospitalisation	2	529	Odds Ratio (M-H, Fixed, 95% CI)	0.47 [0.20, 1.12]
1.2 Severe exacerbations: exacerbations requiring emergency department visits/systemic steroids	4	640	Rate Ratio (IV, Fixed, 95% CI)	0.65 [0.53, 0.80]
1.3 Asthma symptom scales	4	136	Std. Mean Difference (IV, Fixed, 95% CI)	-0.46 [-0.81, -0.11]
1.4 Asthma control	5	773	Std. Mean Difference (IV, Fixed, 95% CI)	-0.17 [-0.31, -0.03]
1.5 Asthma Quality of Life Questionnaire (AQLQ)	6	802	Mean Difference (IV, Fixed, 95% CI)	0.24 [0.12, 0.35]
1.6 Need for rescue medication puffs/day	4	314	Mean Difference (IV, Fixed, 95% CI)	-0.43 [-0.81, -0.04]
1.7 Morning PEF (L/minute)	4	289	Mean Difference (IV, Fixed, 95% CI)	1.60 [-10.35, 13.56]
1.8 Evening PEF (L/minute)	3	212	Mean Difference (IV, Fixed, 95% CI)	1.00 [-13.65, 15.65]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.9 Forced expiratory volume in 1 second (FEV_1; L)	10	1046	Mean Difference (IV, Fixed, 95% CI)	0.04 [0.00, 0.08]
1.10 Bronchial hyperresponsiveness (BHR)	9		Other data	No numeric data
1.11 Oral corticosteroid dose	2		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.12 Serious adverse events (including mortality)	8	854	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.80 [0.49, 1.31]
1.13 Withdrawal	10	984	Odds Ratio (M-H, Fixed, 95% CI)	1.06 [0.76, 1.48]
1.14 Blood eosinophils	2	62	Mean Difference (IV, Fixed, 95% CI)	-32.16 [-34.77, -29.56]
1.15 Sputum eosinophils	3		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.16 Eosinophil cationic protein (ECP) in serum	2	62	Mean Difference (IV, Fixed, 95% CI)	-12.07 [-14.90, -9.24]
1.17 ECP in sputum	2	62	Mean Difference (IV, Fixed, 95% CI)	-1.35 [-1.69, -1.01]

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

Study or Subgroup	Macrolide Events	Macrolide Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Brusselle 2013	2	55	2	54	12.4%	0.98 [0.13 , 7.23]
Gibson 2017	6	213	14	207	87.6%	0.40 [0.15 , 1.06]
Total (95% CI)		**268**		**261**	**100.0%**	**0.47 [0.20 , 1.12]**
Total events:	8		16			

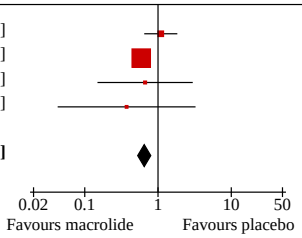
Heterogeneity: Chi² = 0.63, df = 1 (P = 0.43); I² = 0%
Test for overall effect: Z = 1.70 (P = 0.09)
Test for subgroup differences: Not applicable



Analysis 1.2. Comparison 1: Macrolide versus placebo, Outcome 2: Severe exacerbations: exacerbations requiring emergency department visits/systemic steroids

Study or Subgroup	log[Rate Ratio]	SE	macrolide Total	placebo Total	Weight	Rate Ratio IV, Fixed, 95% CI
Brusselle 2013	0.0871	0.2653	55	54	15.6%	1.09 [0.65 , 1.84]
Gibson 2017	-0.5276	0.116	213	207	81.6%	0.59 [0.47 , 0.74]
Kostadima 2004	-0.4055	0.7638	50	25	1.9%	0.67 [0.15 , 2.98]
Strunk 2008	-0.9874	1.1054	17	19	0.9%	0.37 [0.04 , 3.25]
Total (95% CI)			**335**	**305**	**100.0%**	**0.65 [0.53 , 0.80]**

Heterogeneity: Chi² = 4.76, df = 3 (P = 0.19); I² = 37%
Test for overall effect: Z = 4.14 (P < 0.0001)
Test for subgroup differences: Not applicable

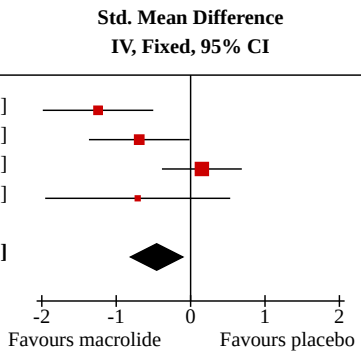


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Analysis 1.3. Comparison 1: Macrolide versus placebo, Outcome 3: Asthma symptom scales

Study or Subgroup	SMD	SE	Macrolide Total	Placebo Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Amayasu 2000 (1)	-1.2444	0.3787	17	17	22.3%	-1.24 [-1.99 , -0.50]
Hahn 2006	-0.6906	0.3448	19	17	27.0%	-0.69 [-1.37 , -0.01]
Hahn 2012	0.1515	0.2738	32	23	42.7%	0.15 [-0.39 , 0.69]
Kamada 1993	-0.7111	0.6344	6	5	8.0%	-0.71 [-1.95 , 0.53]
Total (95% CI)			**74**	**62**	**100.0%**	**-0.46 [-0.81 , -0.11]**

Heterogeneity: Chi² = 9.88, df = 3 (P = 0.02); I² = 70%
Test for overall effect: Z = 2.55 (P = 0.01)
Test for subgroup differences: Not applicable

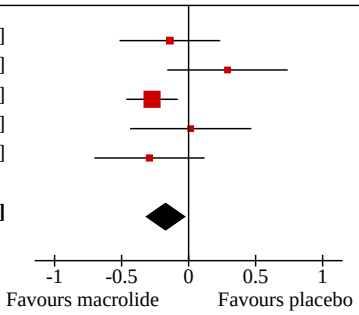


Footnotes
(1) Cross-over study including 17 participants who received macrolide and placebo in random order.

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

Study or Subgroup	SMD	SE	Macrolide Total	Placebo Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Brusselle 2013 (1)	-0.1398	0.1918	55	54	14.2%	-0.14 [-0.52 , 0.24]
Cameron 2013 (2)	0.2902	0.2292	39	38	9.9%	0.29 [-0.16 , 0.74]
Gibson 2017 (3)	-0.2728	0.0981	213	207	54.2%	-0.27 [-0.47 , -0.08]
Hahn 2012 (4)	0.0156	0.231	38	37	9.8%	0.02 [-0.44 , 0.47]
Sutherland 2010	-0.2923	0.2097	47	45	11.9%	-0.29 [-0.70 , 0.12]
Total (95% CI)			**392**	**381**	**100.0%**	**-0.17 [-0.31 , -0.03]**

Heterogeneity: Chi² = 6.14, df = 4 (P = 0.19); I² = 35%
Test for overall effect: Z = 2.38 (P = 0.02)
Test for subgroup differences: Not applicable

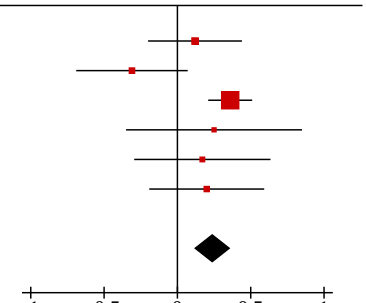


Footnotes
(1) Adjusted change in Asthma Control Questionnaire (ACQ) score, baseline to week 26.
(2) Adjusted change in 7-point ACQ score, baseline to week 12.
(3) Adjusted ACQ6 score end of treatment difference vs placebo.
(4) Adjusted change in asthma control, from baseline to week 12.

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

Study or Subgroup	MD	SE	Macrolide Total	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Brusselle 2013	0.12	0.1633	55	54	13.0%	0.12 [-0.20 , 0.44]
Cameron 2013	-0.31	0.1939	39	38	9.2%	-0.31 [-0.69 , 0.07]
Gibson 2017	0.36	0.0765	209	204	59.2%	0.36 [0.21 , 0.51]
Hahn 2006	0.25	0.3061	19	17	3.7%	0.25 [-0.35 , 0.85]
Hahn 2012	0.17	0.2371	38	37	6.2%	0.17 [-0.29 , 0.63]
Sutherland 2010	0.2	0.2	47	45	8.7%	0.20 [-0.19 , 0.59]
Total (95% CI)			**407**	**395**	**100.0%**	**0.24 [0.12 , 0.35]**

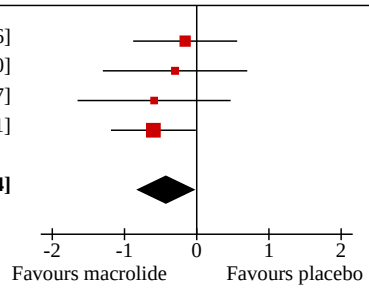
Heterogeneity: Chi² = 11.17, df = 5 (P = 0.05); I² = 55%
Test for overall effect: Z = 4.03 (P < 0.0001)
Test for subgroup differences: Not applicable



Analysis 1.6. Comparison 1: Macrolide versus placebo, Outcome 6: Need for rescue medication puffs/day

Study or Subgroup	MD	SE	Macrolide Total	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Brusselle 2013	-0.16	0.3674	55	54	28.7%	-0.16 [-0.88 , 0.56]
Cameron 2013	-0.3	0.5102	39	38	14.9%	-0.30 [-1.30 , 0.70]
Hahn 2006	-0.59	0.5408	19	17	13.3%	-0.59 [-1.65 , 0.47]
Sutherland 2010	-0.6	0.3	47	45	43.1%	-0.60 [-1.19 , -0.01]
Total (95% CI)			**160**	**154**	**100.0%**	**-0.43 [-0.81 , -0.04]**

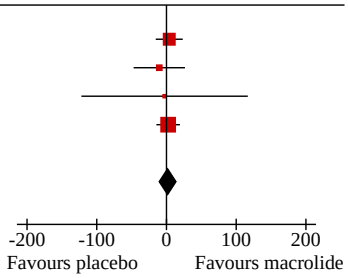
Heterogeneity: Chi² = 1.01, df = 3 (P = 0.80); I² = 0%
Test for overall effect: Z = 2.17 (P = 0.03)
Test for subgroup differences: Not applicable



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

Study or Subgroup	MD	SE	Macrolide Total	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Brusselle 2013	3.96	9.8777	55	54	38.1%	3.96 [-15.40 , 23.32]
Cameron 2013	-10.3	18.7759	39	38	10.6%	-10.30 [-47.10 , 26.50]
Kamada 1993 (1)	-2.7	60.883	6	5	1.0%	-2.70 [-122.03 , 116.63]
Sutherland 2010	2.4	8.6	47	45	50.3%	2.40 [-14.46 , 19.26]
Total (95% CI)			**147**	**142**	**100.0%**	**1.60 [-10.35 , 13.56]**

Heterogeneity: Chi² = 0.47, df = 3 (P = 0.92); I² = 0%
Test for overall effect: Z = 0.26 (P = 0.79)
Test for subgroup differences: Not applicable

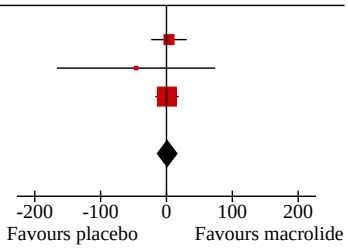


Footnotes
(1) PEF predose.

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

Study or Subgroup	MD	SE	Macrolide Total	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Brusselle 2013	3.84	13.7452	55	54	29.6%	3.84 [-23.10 , 30.78]
Kamada 1993 (1)	-46.1	61.2868	6	5	1.5%	-46.10 [-166.22 , 74.02]
Sutherland 2010	0.8	9	47	45	69.0%	0.80 [-16.84 , 18.44]
Total (95% CI)			**108**	**104**	**100.0%**	**1.00 [-13.65 , 15.65]**

Heterogeneity: Chi² = 0.63, df = 2 (P = 0.73); I² = 0%
Test for overall effect: Z = 0.13 (P = 0.89)
Test for subgroup differences: Not applicable

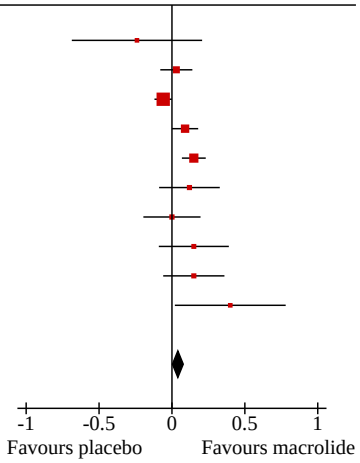


Footnotes
(1) PEF postdose.

Analysis 1.9. Comparison 1: Macrolide versus placebo, Outcome 9: Forced expiratory volume in 1 second (FEV $_1$; L)

Study or Subgroup	MD	SE	Macrolide Total	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Amayasu 2000 (1)	-0.24	0.228	17	17	0.7%	-0.24 [-0.69 , 0.21]
Cameron 2013	0.03	0.0561	39	38	11.3%	0.03 [-0.08 , 0.14]
Gibson 2017	-0.06	0.0306	210	205	37.8%	-0.06 [-0.12 , -0.00]
He 2009	0.09	0.0459	20	20	16.8%	0.09 [0.00 , 0.18]
Kraft 2002	0.15	0.0417	26	26	20.4%	0.15 [0.07 , 0.23]
Shoji 1999 (2)	0.12	0.1061	14	14	3.1%	0.12 [-0.09 , 0.33]
Sutherland 2010 (3)	0	0.1	47	45	3.5%	0.00 [-0.20 , 0.20]
Wang 2014	0.15	0.1225	29	29	2.4%	0.15 [-0.09 , 0.39]
Xiao 2013	0.15	0.1071	106	104	3.1%	0.15 [-0.06 , 0.36]
Yan 2008	0.4	0.1939	20	20	0.9%	0.40 [0.02 , 0.78]
Total (95% CI)			**528**	**518**	**100.0%**	**0.04 [0.00 , 0.08]**

Heterogeneity: Chi² = 26.40, df = 9 (P = 0.002); I² = 66%
Test for overall effect: Z = 2.15 (P = 0.03)
Test for subgroup differences: Not applicable



Footnotes

(1) Cross-over study including 17 participants who received macrolide and placebo in random order.
(2) Cross-over study with 14 participants who received both treatments.
(3) Prebronchodilator.

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

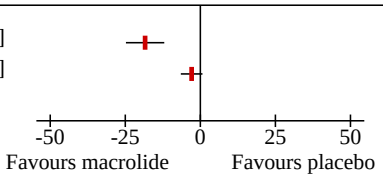
Bronchial hyperresponsiveness (BHR)

Study	Measure of BHR (units)	Results	Conclusions
Amayasu 2000	Methacholine challenge test (log PC_{20})	Clarithromycin: 2.96, standard deviation (SD) 0.57 Placebo: 2.60, SD 0.51 (P < 0.01)	Clarithromycin significantly reduced BHR in people with allergic intermittent asthma.
Cameron 2013	Methacholine challenge test (log PC_{20})	Azithromycin: 0.20, SD 1.52 Placebo: 0.19, SD 1.29 (P < 0.93)	No effect of azithromycin in smokers with persistent asthma.
Kamada 1993	Methacholine challenge test (PC_{20})	16/19 participants completed the test at the beginning and end of the analysis. Data were 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	Methacholine challenge test (PC_{20})	Median before and after the treatment: Clarithromycin 250 mg twice daily: 0.3 mg (interquartile range (IQR) 0.1 to 1) and 1.3 mg (IQR 0.6 to 2) mg (P < 0.001) Clarithromycin 250 mg 3 times daily: 0.4 mg (IQR 0.1 to 0.9) and 2.0 mg (IQR 2.0 to 2.0) (P < 0.001) Placebo: 0.4 mg (IQR 0.1 to 0.9) and 0.3 mg (IQR 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	Methacholine challenge test (PC_{20})	11/27 participants in placebo group and 13/30 participants in troleandomycin group completed 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, SD 2.12 to 1.42, SD 1.54 (P < 0.02) Placebo: 1.48, SD 1.75 to 1.01, SD 1.38 (P = 0.21)	The reduction of BHR in the treatment group was driven by the change from the baseline in 3/9 participants. No significant difference observed in a comparison between the groups. Study in children.
Shoji 1999	Sulpyrine inhalation testing (log PC_{20}-sulpyrine)	Roxithromycin: 1.18, SD 0.40 Placebo: 1.15, SD 0.43	No significant improvement of BHR recorded within and between group comparisons.

Simpson 2008	Hypertonic saline challenge (dose–response slope; DSR)	DSR before: 1.8 (IQR 0.6 to 6.4) and after clarithromycin: 1 (IQR 0.5 to 4.2) DSR before: 1 (IQR 0.6 to 3.2) and after placebo: 1 (IQR 0.5 to 3.3)	No significant improvement of BHR within and between group comparisons.
Sutherland 2010	Methacholine 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, SD 0.5 (P = 0.01) In participants with positive PCR status: +0.9, SD 1.8 (P = 0.6) In participants with negative PCR status: +1.2, SD 0.5 (P = 0.02)	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 participants.

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

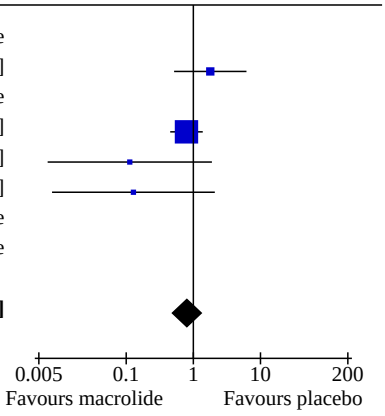
Study or Subgroup	MD	SE	Macrolide Total	Placebo Total	Mean Difference IV, Fixed, 95% CI
Kamada 1993	-18.4	3.2573	6	5	-18.40 [-24.78 , -12.02]
Nelson 1993	-2.9	1.8385	29	27	-2.90 [-6.50 , 0.70]



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

Study or Subgroup	Macrolide Events	Macrolide Total	Placebo Events	Placebo Total	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Amayasu 2000 (1)	0	17	0	17		Not estimable
Brusselle 2013	7	55	4	54	15.8%	1.79 [0.52 , 6.18]
Cameron 2013	0	39	0	38		Not estimable
Gibson 2017	26	213	31	207	78.0%	0.79 [0.45 , 1.38]
Hahn 2006	0	19	2	17	3.1%	0.11 [0.01 , 1.89]
Hahn 2012	0	38	2	37	3.1%	0.13 [0.01 , 2.09]
Kamada 1993	0	6	0	5		Not estimable
Sutherland 2010	0	47	0	45		Not estimable
Total (95% CI)		**434**		**420**	**100.0%**	**0.80 [0.49 , 1.31]**
Total events:	33		39			

Heterogeneity: Chi² = 5.12, df = 3 (P = 0.16); I² = 41%
Test for overall effect: Z = 0.89 (P = 0.38)
Test for subgroup differences: Not applicable



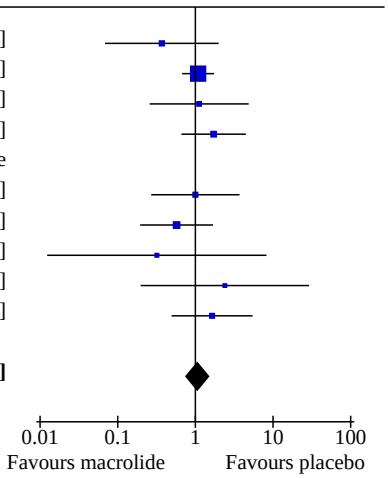
Footnotes

(1) Cross-over trial; no events in either phase. Participants not split to avoid double-counting as study did not contribute to effect estimate.

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

Study or Subgroup	Macrolide Events	Macrolide Total	Placebo Events	Placebo Total	Weight	Odds Ratio M-H, Fixed, 95% CI
Brusselle 2013	2	55	5	54	7.2%	0.37 [0.07 , 1.99]
Gibson 2017	45	213	41	207	48.7%	1.08 [0.67 , 1.74]
Hahn 2006	5	24	4	21	5.0%	1.12 [0.26 , 4.86]
Hahn 2012	16	38	11	37	9.6%	1.72 [0.66 , 4.47]
Kamada 1993	0	6	0	5		Not estimable
Kostadima 2004 (1)	8	50	4	25	6.7%	1.00 [0.27 , 3.70]
Nelson 1993	7	37	11	38	13.1%	0.57 [0.19 , 1.69]
Simpson 2008	0	23	1	23	2.2%	0.32 [0.01 , 8.25]
Strunk 2008	2	17	1	19	1.2%	2.40 [0.20 , 29.13]
Sutherland 2010	8	47	5	45	6.3%	1.64 [0.49 , 5.46]
Total (95% CI)		**510**		**474**	**100.0%**	**1.06 [0.76 , 1.48]**
Total events:	93		83			

Heterogeneity: Chi² = 5.20, df = 8 (P = 0.74); I² = 0%
Test for overall effect: Z = 0.33 (P = 0.74)
Test for subgroup differences: Not applicable

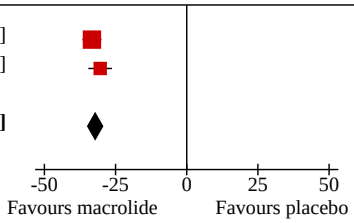


Footnotes
(1) 2 dose groups merged.

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

Study or Subgroup	MD	SE	Macrolide Total	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Amayasu 2000 (1)	-33.3	1.7033	17	17	60.8%	-33.30 [-36.64 , -29.96]
Shoji 1999	-30.4	2.1222	14	14	39.2%	-30.40 [-34.56 , -26.24]
Total (95% CI)			**31**	**31**	**100.0%**	**-32.16 [-34.77 , -29.56]**

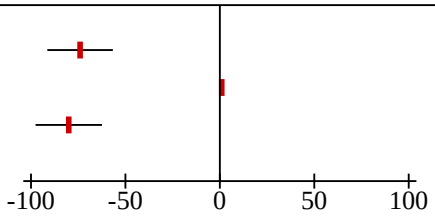
Heterogeneity: Chi² = 1.14, df = 1 (P = 0.29); I² = 12%
Test for overall effect: Z = 24.21 (P < 0.00001)
Test for subgroup differences: Not applicable



Footnotes
(1) Amayasu 2000 and Shoji 1999 are cross-over studies (macrolide and placebo received in random order).

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

Study or Subgroup	MD	SE	Mean Difference IV, Fixed, 95% CI
Amayasu 2000 (1)	-74	8.8517	-74.00 [-91.35 , -56.65]
Cameron 2013	1	0.2551	1.00 [0.50 , 1.50]
Shoji 1999	-80	8.9642	-80.00 [-97.57 , -62.43]



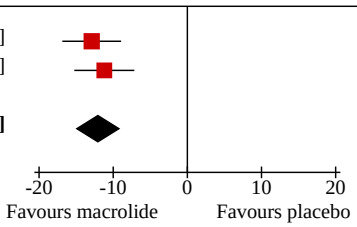
Footnotes

(1) Amayasu 2000 and Shoji 1999 are cross-over studies (macrolide and placebo received in random order).

Analysis 1.16. Comparison 1: Macrolide versus placebo, Outcome 16: Eosinophil cationic protein (ECP) in serum

Study or Subgroup	MD	SE	Macrolide Total	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Amayasu 2000 (1)	-12.9	2.0218	17	17	51.1%	-12.90 [-16.86 , -8.94]
Shoji 1999	-11.2	2.0654	14	14	48.9%	-11.20 [-15.25 , -7.15]
Total (95% CI)			**31**	**31**	**100.0%**	**-12.07 [-14.90 , -9.24]**

Heterogeneity: Chi² = 0.35, df = 1 (P = 0.56); I² = 0%
Test for overall effect: Z = 8.35 (P < 0.00001)
Test for subgroup differences: Not applicable



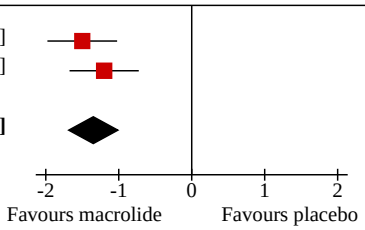
Footnotes

(1) Amayasu 2000 and Shoji 1999 are cross-over studies (macrolide and placebo received in random order).

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

Study or Subgroup	MD	SE	Macrolide Total	Placebo Total	Weight	Mean Difference IV, Fixed, 95% CI
Amayasu 2000 (1)	-1.5	0.2437	17	17	49.6%	-1.50 [-1.98 , -1.02]
Shoji 1999	-1.2	0.242	14	14	50.4%	-1.20 [-1.67 , -0.73]
Total (95% CI)			**31**	**31**	**100.0%**	**-1.35 [-1.69 , -1.01]**

Heterogeneity: Chi² = 0.76, df = 1 (P = 0.38); I² = 0%
Test for overall effect: Z = 7.86 (P < 0.00001)
Test for subgroup differences: Not applicable



Footnotes

(1) Amayasu 2000 and Shoji 1999 are cross-over studies (macrolide and placebo received in random order).

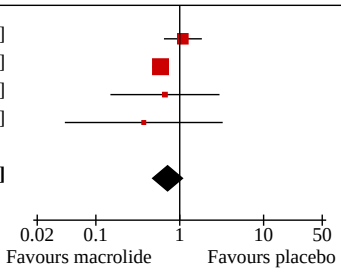
Comparison 2. Sensitivity analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Severe exacerbations: exacerbations requiring emergency department visits/systemic steroids	4	640	Rate Ratio (IV, Random, 95% CI)	0.72 [0.48, 1.08]
2.2 Symptom scales	4	156	Std. Mean Difference (IV, Random, 95% CI)	-0.58 [-1.27, 0.11]
2.3 Asthma control	5	773	Std. Mean Difference (IV, Random, 95% CI)	-0.13 [-0.33, 0.06]
2.4 Asthma Quality of Life Questionnaire (AQLQ)	6	802	Mean Difference (IV, Random, 95% CI)	0.15 [-0.06, 0.36]
2.5 Forced expiratory volume in 1 second (FEV $_1$; L)	10		Mean Difference (IV, Random, 95% CI)	0.07 [-0.01, 0.15]

Analysis 2.1. Comparison 2: Sensitivity analysis, Outcome 1: Severe exacerbations: exacerbations requiring emergency department visits/systemic steroids

Study or Subgroup	log[Rate Ratio]	SE	macrolide Total	placebo Total	Weight	Rate Ratio IV, Random, 95% CI
Brusselle 2013	0.0871	0.2653	55	54	32.7%	1.09 [0.65 , 1.84]
Gibson 2017	-0.5276	0.116	213	207	57.2%	0.59 [0.47 , 0.74]
Kostadima 2004	-0.4055	0.7638	50	25	6.7%	0.67 [0.15 , 2.98]
Strunk 2008	-0.9874	1.1054	17	19	3.4%	0.37 [0.04 , 3.25]
Total (95% CI)			**335**	**305**	**100.0%**	**0.72 [0.48 , 1.08]**

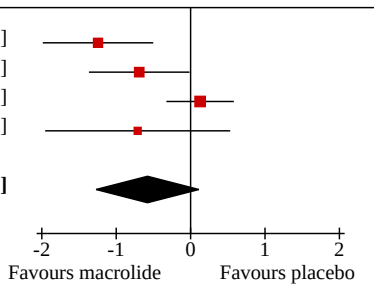
Heterogeneity: Tau² = 0.06; Chi² = 4.76, df = 3 (P = 0.19); I² = 37%
Test for overall effect: Z = 1.60 (P = 0.11)
Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2: Sensitivity analysis, Outcome 2: Symptom scales

Study or Subgroup	SMD	SE	Macrolide Total	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Amayasu 2000 (1)	-1.2444	0.3787	17	17	25.4%	-1.24 [-1.99 , -0.50]
Hahn 2006	-0.6906	0.3448	19	17	26.8%	-0.69 [-1.37 , -0.01]
Hahn 2012	0.1279	0.2312	38	37	31.2%	0.13 [-0.33 , 0.58]
Kamada 1993	-0.7111	0.6344	6	5	16.6%	-0.71 [-1.95 , 0.53]
Total (95% CI)			**80**	**76**	**100.0%**	**-0.58 [-1.27 , 0.11]**

Heterogeneity: Tau² = 0.34; Chi² = 11.12, df = 3 (P = 0.01); I² = 73%
Test for overall effect: Z = 1.65 (P = 0.10)
Test for subgroup differences: Not applicable



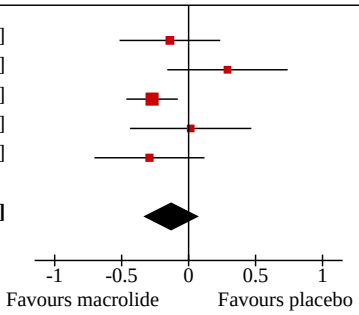
Footnotes

(1) Cross-over study including 17 participants who received macrolide and placebo in random order.

Analysis 2.3. Comparison 2: Sensitivity analysis, Outcome 3: Asthma control

Study or Subgroup	SMD	SE	Macrolide Total	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Brusselle 2013 (1)	-0.1398	0.1918	55	54	18.4%	-0.14 [-0.52 , 0.24]
Cameron 2013 (2)	0.2902	0.2292	39	38	14.2%	0.29 [-0.16 , 0.74]
Gibson 2017 (3)	-0.2728	0.0981	213	207	37.1%	-0.27 [-0.47 , -0.08]
Hahn 2012 (4)	0.0156	0.231	38	37	14.1%	0.02 [-0.44 , 0.47]
Sutherland 2010	-0.2923	0.2097	47	45	16.2%	-0.29 [-0.70 , 0.12]
Total (95% CI)			**392**	**381**	**100.0%**	**-0.13 [-0.33 , 0.06]**

Heterogeneity: Tau² = 0.02; Chi² = 6.14, df = 4 (P = 0.19); I² = 35%
Test for overall effect: Z = 1.31 (P = 0.19)
Test for subgroup differences: Not applicable



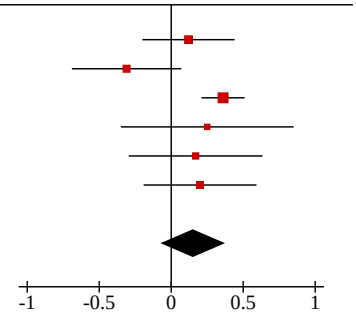
Footnotes

(1) Adjusted change in Asthma Control Questionnaire (ACQ) score, baseline to week 26
(2) Adjusted change in 7-point ACQ score, baseline to week 12
(3) Adjusted ACQ6 score end of treatment difference vs placebo
(4) Adjusted change in asthma control, from baseline to week 12.

Analysis 2.4. Comparison 2: Sensitivity analysis, Outcome 4: Asthma Quality of Life Questionnaire (AQLQ)

Study or Subgroup	MD	SE	Macrolide Total	Placebo Total	Weight	Mean Difference IV, Random, 95% CI
Brusselle 2013	0.12	0.1633	55	54	18.7%	0.12 [-0.20 , 0.44]
Cameron 2013	-0.31	0.1939	39	38	15.9%	-0.31 [-0.69 , 0.07]
Gibson 2017	0.36	0.0765	209	204	28.3%	0.36 [0.21 , 0.51]
Hahn 2006	0.25	0.3061	19	17	9.0%	0.25 [-0.35 , 0.85]
Hahn 2012	0.17	0.2371	38	37	12.7%	0.17 [-0.29 , 0.63]
Sutherland 2010	0.2	0.2	47	45	15.4%	0.20 [-0.19 , 0.59]
Total (95% CI)			**407**	**395**	**100.0%**	**0.15 [-0.06 , 0.36]**

Heterogeneity: Tau² = 0.04; Chi² = 11.17, df = 5 (P = 0.05); I² = 55%
Test for overall effect: Z = 1.39 (P = 0.16)
Test for subgroup differences: Not applicable



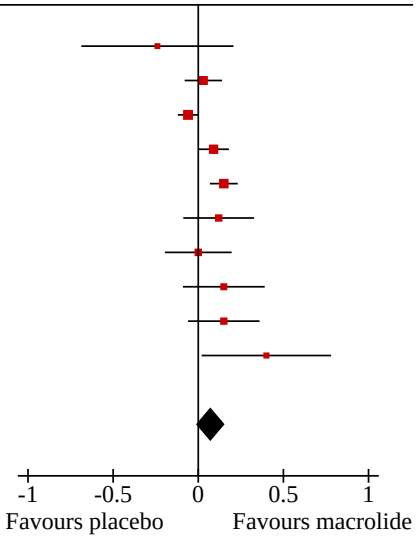
Analysis 2.5. Comparison 2: Sensitivity analysis, Outcome 5: Forced expiratory volume in 1 second (FEV $_1$; L)

Study or Subgroup	MD	SE	Weight	Mean Difference IV, Random, 95% CI
Amayasu 2000 (1)	-0.24	0.228	2.6%	-0.24 [-0.69 , 0.21]
Cameron 2013	0.03	0.0561	13.9%	0.03 [-0.08 , 0.14]
Gibson 2017	-0.06	0.0306	17.4%	-0.06 [-0.12 , -0.00]
He 2009	0.09	0.0459	15.4%	0.09 [0.00 , 0.18]
Kraft 2002	0.15	0.0417	15.9%	0.15 [0.07 , 0.23]
Shoji 1999 (2)	0.12	0.1061	8.1%	0.12 [-0.09 , 0.33]
Sutherland 2010 (3)	0	0.1	8.6%	0.00 [-0.20 , 0.20]
Wang 2014	0.15	0.1225	6.7%	0.15 [-0.09 , 0.39]
Xiao 2013	0.15	0.1071	8.0%	0.15 [-0.06 , 0.36]
Yan 2008	0.4	0.1939	3.4%	0.40 [0.02 , 0.78]
Total (95% CI)			**100.0%**	**0.07 [-0.01 , 0.15]**

Heterogeneity: Tau² = 0.01; Chi² = 26.40, df = 9 (P = 0.002); I² = 66%

Test for overall effect: Z = 1.79 (P = 0.07)

Test for subgroup differences: Not applicable



Footnotes

(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) Prebronchodilator.

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 (years)	% 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 3 times per week	53.0 (median)	38.5	100[a]	82.5
Cameron 2013	UK	77	P, R, DB, PC	12	Azithromycin 250 mg once daily	44.6	48.1	85.7	78.3
Gibson 2017	Australia	420	P, R, DB, PC	48	Azithromycin 500 mg 3 times per week	60.5	39.3	99.8	72.9
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
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 3 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

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

Piacentini 2007	Italy	16	P, R, DB, PC	8	Azithromycin 10 mg/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 500 mg twice daily	57.6	48.9	NR[b]	70.7
Strunk 2008	USA	55[c]	P, R, DB, PC	30	Azithromycin 250 mg 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
Wan 2016	Taiwan	58	P, R, PC	4	Clarithromycin 5 mg/kg daily	10.1	60.3	100	79.7
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; **FEV_1**: forced expiratory volume in one second; **ICS**: inhaled corticosteroid; **NR**: not reported; **OCS**: oral corticosteroids; **P**: parallel; **PC**: placebo-controlled; **R**: randomised.

[a]All participants were taking long-acting $beta_2$-agonist + ICS combination.

[b]82.2% were taking long-acting $beta_2$-agonist + ICS combination.

[c]19 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 April 2015

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 randomised controlled trials.

Appendix 2. Sources and search methods for the Cochrane Airways Trials Register

Electronic searches: core databases

Database	Dates searched	Frequency of search
CENTRAL (via the Cochrane Register of Studies)	From inception	Monthly
MEDLINE (Ovid)	1946 onwards	Weekly
Embase (Ovid)	1974 onwards	Weekly
PsycINFO (Ovid)	1967 onwards	Monthly
CINAHL (EBSCO)	1937 onwards	Monthly
AMED (EBSCO)	From inception	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

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 randomised controlled trials

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 were adapted to identify trials in other electronic databases.

Appendix 3. Search strategies for the Cochrane Airways Trials Register, ClinicalTrials.gov, and the WHO ICTRP portal

Cochrane Airways Trials Register (via Cochrane Register of Studies)

#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]

ClinicalTrials.gov

Condition: asthma
Study type: interventional
Intervention: azithromycin OR clarithromycin OR erythromycin OR roxithromycin OR spiramycin OR telithromycin OR troleandomycin

World Health Organization International Clinical Trials Registry Platform

Condition: asthma
Intervention: azithromycin OR clarithromycin OR erythromycin OR roxithromycin OR spiramycin OR telithromycin OR troleandomycin

Appendix 4. Narrative of individual study results

Study ID	Detail of results
Amayasu 2000	• Clarithromycin vs placebo in cross-over trial. • 15/17 participants improved their symptom score; 2 reported no improvement. Mean symptom score decreased significantly after treatment with clarithromycin (1.64 SD 0.48 vs 0.88 SD 0.72; P < 0.05). • No change in FVC and FEV_1 during clarithromycin therapy. No bronchodilating effect of the macrolide. Blood eosinophil count and 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 participants independently of 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 between increased PC_{20} methacholine and ECP levels. No adverse reactions during treatment with clarithromycin. • Authors concluded that clarithromycin has not only antibacterial, but also an anti-inflammatory activity, associated with a reduction of the eosinophilic infiltration in people with asthma. It is able to improve symptoms and bronchial hyperresponsiveness, but further trials are needed to investigate its clinical utility.

(Continued)

Belotserkovskaya 2007	• Azithromycin vs control (no details) • Only in abstract form from the ERS congress 2007. Data only partially reported. • No significant difference for FEV_1, PEF, rescue medications and symptoms between the azithromycin and placebo groups. • Subgroup analysis for participants treated with azithromycin and with serological positivity for *C pneumoniae* showed a statistically significant improvement from the baseline for FEV_1 (from 1.99 L to 2.25 L; P = 0.01) and PEF (from 305.1 L/minute to 348 L/minute; P = 0.03).
Black 2001	• Roxithromycin vs placebo • At end of 6 weeks' treatment, increase in mean values of morning PEF were significantly higher with roxithromycin (14 L/minute) compared to placebo (8 L/minute). There was a subsequent increase of morning PEF values in both groups over the following 6 months after the end of treatment, where the improvement over baseline was 18 L/minute with roxithromycin compared to 12 L/minute with placebo (P = not significant). For evening PEF values, roxithromycin significantly improved PEF values (15 L/minute vs 3 L/minute in the placebo group) at the end of the treatment (P = 0.02), but not at later time points. • Both daytime and night-time symptom scores showed a non-significant improvement with roxithromycin compared to with placebo over the 6-month study period. • Non-significant trend for improved AQLQ score with treatment. No statistically significant difference for daytime and night-time symptoms scores. • No difference for rescue medications or for *Chlamydophila* antibody titres measured during the study. No difference for adverse effects between groups. Only mild and reversible liver function test alterations were recorded in 2 participants treated with roxithromycin. • Authors concluded that the (not statistically significant) trend of improvement of pulmonary function test as seen in the 3 months following end of treatment with roxithromycin compared to with placebo suggest that the effect of macrolide therapy on PEF values could be due more to the antimicrobial effect than to the anti-inflammatory 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	• Azithromycin vs placebo • No difference between groups in rate of severe asthma exacerbations (defined as need for hospitalisation, need for systemic steroids for ≥ 3 days or ED visits) or lower respiratory tract infections requiring antibiotics. • No effect of azithromycin compared with placebo after 26 weeks for lung function (FEV_1 and morning and evening PEF), or for ACQ. AQLQ score was significantly improved after 26 weeks from baseline with azithromycin, but with placebo. No significant difference between groups in AQLQ score after 26 weeks of treatment. • No differences in rate of adverse events with azithromycin or placebo. A significantly higher proportion of participants with azithromycin compared with placebo had macrolide-resistant strains of streptococci at end of study (87% with azithromycin vs 35% with placebo; P < 0.001). • A predefined subgroup analysis for the main outcome showed a statistically significant reduction in rate of exacerbations in participants with non-eosinophilic severe asthma (defined as blood eosinophils ≤ 200/µL) treated with macrolides vs placebo (0.44 primary endpoint rate, 95% CI 0.25 to 0.78 with azithromycin vs 1.03 primary endpoint rate, 95% CI 0.72 to 1.48 with placebo; P = 0.01). Conversely, there was a higher primary endpoint rate with azithromycin (0.96, 95% CI 0.66 to 1.41) compared with placebo (0.50, 95% CI 0.28 to 0.88) among the participants with severe asthma and blood eosinophils > 200/µL.
Cameron 2013	• Azithromycin vs placebo • No significant differences between the azithromycin and placebo groups. • Change from the baseline of the morning PEF (primary outcome): mean difference −10.3 L/minute, 95% CI −47.1 to 26.5 (P = 0.58); FEV_1 at 12 weeks (pre-albuterol): 2.41, SD 0.77 L/second with azithromycin vs 2.46, SD 0.75 L/second with placebo (P = NS); bronchial hyperreactivity: 0.20, SD 1.52 Log PC_{20} mg/mL with azithromycin vs 0.19, SD 1.29 Log PC_{20} mg/mL with placebo (P = NS).

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	• After 12-week study period: use of rescue medications: 2.7, SD 2.5 times/day with azithromycin vs 3.0, SD 4.0 times/day with placebo; P = NS); ACQ score: 1.75, SD 0.83 with azithromycin vs 1.58, SD 0.96 with placebo (P = NS); AQLQ score: 5.2, SD 1.06 with azithromycin vs 5.42, SD 1.31 with placebo (P = NS); eosinophil count in induced sputum: 10.3, SD 20.1 × 10^4 with azithromycin vs 6.8, SD 13.9 × 10^4 with placebo (P = NS). • No adverse events in either groups.
Gibson 2017	• Azithromycin vs placebo • Participants had a median age of 60 years (IQR 50–68), with history of atopic asthma (76%) for a median of 32 years (IQR 14–48). Ex-smokers (38% of the total) were also included. Most participants entering this trial were receiving high-dose ICS, and all had prescribed long-acting bronchodilators such as LABA, LAMA or theophylline. Their asthma was uncontrolled (ACQ6 1.55, SD 0.79; FEV_1 73% predicted). All these characteristics were similar in the 2 groups. • Withdrawals: 45 with azithromycin vs 41 with placebo. • Azithromycin reduced frequency of total asthma exacerbations (1.07 exacerbations per year per person, 95% CI 0.85 to 1.29) compared to placebo (1.86 exacerbations per person per year, 95% CI 1.54 to 2.18) (IRR 0.59, 95% CI 0.47 to 0.74; P < 0.0001). Azithromycin reduced time to exacerbation (HR 0.65, 95% CI 0.50 to 0.85; P = 0.001). • Severe exacerbations (defined as worsening of symptoms causing a cure with oral steroids (or variation of their dosage), a hospitalisation or an ED visit) were significantly fewer with azithromycin (IRR 0.59, 95% CI 0.42 to 0.83; P = 0.002). • Reduction of exacerbations was consistent in participants with both eosinophilic and non-eosinophilic asthma. • FEV_1 at end of the treatment was lower with azithromycin compared to placebo, but this difference was not clinically relevant (adjusted mean −0.06 L, 95% CI −0.12 to −0.001). • Azithromycin improved quality of life (AQLQ adjusted mean difference 0.36, 95% CI 0.21 to 0.52; P = 0.001) and asthma control (ACQ6 adjusted mean difference −0.20, 95% CI −0.34 to −0.05). • No significant difference in incidence of adverse events, except for diarrhoea, which was more frequent among participants treated with azithromycin (n = 72, 34%) than in the placebo group (n = 39, 19%) (P = 0.001). • No difference in isolation of resistant strains detected in sputum cultures at end of treatment between groups.
Hahn 2006	• Azithromycin vs placebo • No significant difference at 3 months after completion of 6-week treatment for Juniper AQLQ (0.59, SD 0.8 with azithromycin vs 0.34, SD 1.0 with placebo; P = NS) and rescue medications (0.43, SD 1.8 times per day with azithromycin vs −0.16, SD 1.3 times per day with placebo; P = NS). Symptoms and daily activities, recorded with a homemade scale from 0 = no symptoms to 4 = worse than ever, were significantly improved with azithromycin (0.55, SD 0.7 with azithromycin vs −0.13, SD 0.9 with placebo; P = 0.04). • 3 participants per group withdrew consent during study, while 1 participant in azithromycin group discontinued the study. • No adverse events with azithromycin vs 1 serious adverse event with placebo (death from asthma-related causes).
Hahn 2012	• Azithromycin vs placebo • Only data from randomised treatment group and the placebo group were considered in our review/meta-analysis; the open-label group was excluded. Of 304 screened patients, 97 (32%) were enrolled: 38 to azithromycin, 37 to placebo and 22 to open-label group. • No significant difference for severe exacerbations across groups, but rates were not reported. • 1 year after randomisation, no significant differences for symptoms with a home scale from 0 = no symptoms to 4 = worse than ever (−0.31, SD 0.74 with azithromycin vs −0.48, SD 1.16 with placebo; P = NS), ACQ score (−0.40, SD 0.8 with azithromycin vs −0.41, SD 1.1 with placebo; P = NS) and Juniper AQLQ (0.67, SD 1.10 with azithromycin vs 0.50, SD 0.95 with placebo). • Withdrawal was high and uneven between groups (19 (50%) participants with azithromycin and 12 (32.4%) participants with placebo at 12-month-follow-up).

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	• 1 participant discontinued study with placebo because of acute coronary syndrome; 1 participant discontinued study with placebo because of adverse effects. Mild adverse effects were common with azithromycin (nausea: 33% with azithromycin vs 9% with placebo; stomach pain: 42% with azithromycin vs 12% with placebo; diarrhoea: 42% with azithromycin vs 15% with placebo), but no-one discontinued medications because of the adverse effects.
Kamada 1993	• Troleandomycin + methylprednisolone (n = 6) vs troleandomycin + prednisone (n = 8) vs placebo + methylprednisolone (n = 5) • Significant glucocorticoid dosage reduction in all 3 groups. The maximum tolerated percentage dosage reductions were 80%, SD 6% with troleandomycin + methyl prednisone (P < 0.001), 55%, SD 8% (P < 0.001) with troleandomycin + prednisone and 44%, SD 14% (P = 0.04) with placebo + methylprednisolone. Significant difference only between the troleandomycin + methylprednisolone and placebo + methylprednisolone groups. • No statistically significant difference for days of supplemental prednisone for exacerbations. Symptom score was reduced by nearly 50% with troleandomycin + methylprednisolone (P = 0.03). No significant differences in other groups. Pulmonary function tests were slightly reduced in all groups, with a significant reduction of prebronchodilator FEV_1 and $FEF_{25–75}$ in the troleandomycin + prednisone group (FEV_1: P = 0.03; $FEF_{25–75}$: P = 0.01). Methacholine PC_{20} was significantly reduced only in the troleandomycin + methylprednisolone group and slightly increased in the troleandomycin + prednisone group, but the difference may reflect glucocorticoid dosage taper and supplemental prednisone before the final evaluation. • Safety aspects: 13 participants received troleandomycin. 1 participant in the troleandomycin + prednisone group experienced an elevation of liver enzymes that was resolved by the discontinuation of troleandomycin. 1 participant in the troleandomycin + methylprednisolone group reported a mild elevation of liver enzymes, which resolved spontaneously without discontinuation of the treatment. No significant alterations of serum and urine cortisol concentrations, whereas there was an increase in the methylprednisolone group. Bone density was unchanged in all groups. There was a slight decrease (NS) in bone density in the 2 groups receiving troleandomycin. 1 participant in the troleandomycin + prednisone group had severe osteopenia before the start of the study and experienced a vertebral compression fracture that was attributed to her previous glucocorticoid exposure. 1 participant in the troleandomycin + prednisone group developed marked striae on the arms and trunk. She was also affected by Marfan's syndrome. • Authors concluded that, despite the absence of a control group with only prednisone and the low numbers of participants for each group, some conclusions could be drawn from this study: it was not possible to improve lung function by tapering the steroid dose; the only goal reached was to keep the same level of lung function when reducing the dose of steroids, without severe adverse effect.
Kapoor 2010	• Roxithromycin vs placebo • Presented in abstract at the ERS Congress 2010 in Barcelona. • Significant improvement from baseline for the ACT score in both groups, but no difference when comparing the improvements between the 2 groups after the 6 weeks of treatment (2.68, SD 3.17 with roxithromycin vs 1.80, SD 2.83 with placebo; P = NS). No significant difference between groups for FEV_1 at end of study. • There was only very limited information on participants' characteristics and randomisation available. There were no data for withdrawal or adverse events, and data on lung function and impulse oscillometry were described only as not significantly different in the 2 groups.
Kostadima 2004	• Clarithromycin twice daily vs clarithromycin 3 times daily vs placebo • Significant increase in FEV_1% only with clarithromycin 250 mg 3 times daily (from 85, SD 13 at baseline to 88, SD 12 at end of study; P < 0.05). No difference in other groups (from 85, SD 14 at baseline to 86, SD 14 at end of study with clarithromycin 250 mg twice daily; from 85, SD 12 at baseline to 88, SD 15 at end of study with placebo). • Compared to baseline, there was a significant increase in the median PD_{20} with clarithromycin 250 mg twice daily and clarithromycin 250 mg 3 times daily but not with placebo. Median (IQR) in the 3 groups were before and after the treatment were: clarithromycin 250 mg twice daily: 0.3 (IQR 0.1 to 1) and 1.3 (IQR 0.6 to 2) mg (P < 0.001); clarithromycin 250 mg 3 times daily: 0.4 (IQR

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	0.1 tp 0.9) and 2.0 (IQR 2.0 to 2.0) mg (P < 0.001); and placebo: 0.4 (IQR 0.1 to 0.9) and 0.3 (IQR 0.1 to 0.6) mg (P = NS). • No adverse effects were clearly reported, but 1 participant in the clarithromycin 250 mg 3 times daily group withdrew for a gastrointestinal disorder (no further details reported). Cortisol levels were measured in 40 participants, and there were no differences at the baseline and after the treatment with the macrolide.
Kraft 2002	• Clarithromycin vs placebo • Of 55 participants included in the study, 3 were not randomised due to scheduling difficulties (n = 1) and non-compliance (n = 2). Clarithromycin n = 26, control n = 26. 14 participants in the clarithromycin group and 13 participants 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 FEV_1 mean values between clarithromycin and placebo at end of treatment (2.64, SD 0.14 L with clarithromycin vs 2.69, SD 0.16 with placebo; P = 0.75). A subanalysis for PCR status found participants with a positive PCR for *M pneumoniae* or *C pneumoniae* showed a significant increase after clarithromycin (FEV_1 mean value 2.50, SD 0.16 at baseline to 2.69, SD 0.16 after treatment; P = 0.05; n = 14), while there was no change in participants with a positive or negative PCR who received placebo (data not reported in the paper) or with a negative PCR who received the macrolide (FEV_1 mean value from 2.59, SD 0.24 L at baseline to 2.54, SD 0.18 L after treatment; P = 0.85; n = 12). • Study was also designed to investigate the modulation of inflammatory cytokines in BAL and bronchial biopsies during the treatment with clarithromycin. 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 participants treated with macrolides and the PCR-negative participants receiving clarithromycin showed a significant reduction in the expression of TNF-alpha and IL-12 mRNA in BAL and TNF-alpha in airways tissue. There was no significant difference in cytokine expression among participants receiving placebo. • Unclear why the participants underwent a sinus computer tomography evaluation if they were not affected by chronic sinusitis and if 1 of the exclusion criteria was a history of upper airways infection in the last 3 months before the study. • No data on adverse events.
Nelson 1993	• Troleandomycin + methylprednisolone (n = 37) vs placebo + methylprednisolone (n = 38) • Significant reduction in the requirement for hospitalisation and steroid boost relative to the year before the study in both groups. Similar results during the 2 years of follow-up. Data were expressed as rate per 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: mean steroid dose at enrolment was not significantly different between groups. Mean dose reported in the placebo group during the year preceding the study entry was significantly higher with troleandomycin + methylprednisolone (22.8, SD 1.9 mg/day with troleandomycin + methylprednisolone vs 17.6, SD 1.5 mg/day with placebo + methylprednisolone; P = 0.02). Significant reduction from the previous corticosteroid usage for the lowest stable dose in both groups, with troleandomycin-treated participants reaching a lower dose (10.4, SD 1.3 mg/day with troleandomycin + methylprednisolone vs 6.3, SD 1.3 mg/day with placebo + methylprednisolone; 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 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 + methylprednisolone group (1 year: P = 0.01; 2 years: P = 0.001). Significant differences between groups for mean IgG level decreased with troleandomycin + methylprednisolone, and this change was not observed with placebo + methylprednisolone (2 years: P = 0.03); fasting blood sugar increased with troleandomycin + methylprednisolone and decreased with placebo + methylprednisolone (2 years: P = 0.02); mean cholesterol level increased with troleandomycin + methylprednisolone, although not significantly; it was low-

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	er with placebo + methylprednisolone after 1 (P = 0.03) and 2 years (P = 0.01), with a significant difference between groups (1 year: P = 0.02; 2 years: P = 0.03). Methacholine challenge was performed in only 13 with troleandomycin + methylprednisolone and 11 participants with placebo + methylprednisolone. The dose producing a 20% fall in FEV_1 rose with 13 with troleandomycin + methylprednisolone, indicating less airway responsiveness (1.86 mg/mL with troleandomycin + methylprednisolone vs 0.55 mg/mL with placebo + methylprednisolone; P = 0.08). • 3 participants died during study (2 with troleandomycin + methylprednisolone vs 1 with placebo + methylprednisolone; 0 related to asthma). • Number of dropouts at 1 year of the study were higher with placebo + methylprednisolone (n = 11, 28.9%) than with troleandomycin + methylprednisolone (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 with troleandomycin + methylprednisolone, the increase in indicators of adverse effects such as cholesterol and fasting blood sugar, and a less significant reduction in 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	• Azithromycin (n = 8) vs placebo (n = 8). • No statistically significant variation for FEV_1 within and between groups (azithromycin FEV_1 % of reference value: 73.5, 12.90 at time point 0 and 74.62, SD 9.76 after treatment; P = NS; placebo FEV_1 % of reference value: 84.25, SD 9.58 at time point 0 and 86.00, SD 9.85 after treatment; P = NS). Comparison between azithromycin and placebo group at end of study not statistically significant. • Bronchial hyperresponsiveness was assessed with a hypertonic saline challenge and expressed as dose–response slope rather than PD_{15}, reflecting the fall of FEV_1 per unit of substance inhaled. Significant reduction from baseline in dose–response slope observed with azithromycin at the end of the study (from 2.75, SD 2.12 to 1.42, SD 1.54; P = 0.02), but not with placebo (from 1.48, SD 1.75 to 1.01, SD 1.38; P = NS). No between-group differences. • Sputum analysis was conducted in 6 participants in the azithromycin group and in 7 participants in the placebo group. Percentage of neutrophils in the sputum was significantly decreased from baseline with azithromycin (from 10%, SD 5% to 2.2%, SD 2.4%; P < 0.01), but with placebo (from 7.2%, SD 4.2% to 3.2%, SD 3.6%; P = NS). There were no between-group differences. • Dropouts and adverse events not reported.
Shoji 1999	• Roxithromycin vs placebo in cross-over trial • Symptom score significantly decreased after roxithromycin treatment (1.63, SD 0.48 vs 0.87, SD 0.70; P < 0.05). • No statistically significant differences in FEV_1 between roxithromycin and placebo groups after 8 weeks (2.37, SD 0.30 with roxithromycin vs 2.25, SD 0.26 with placebo; P = NS) or for the provocation test with sulpyrine (PC_{20} sulpyrine 1.18, SD 0.40 with roxithromycin vs 1.15, SD 0.43 with placebo at end of study; P = NS). No difference in 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 8-week treatment with the antibiotic (blood eosinophils: from 43.36, SD 7.3 × 10^4/mL to 12.4, SD 2.3 × 10^4/mL; P < 0.01; sputum eosinophils: from 94, SD 28 × 10^4/mL to 10, SD 6 × 10^4/mL; serum ECP: 15.8, SD 6.3 mg/L to 3.6, SD 1.4 mg/L; P < 0.05; sputum ECP: 1.8, SD 0.4 mg/L to 0.4, SD 0.1 mg/L; P < 0.05). • Dropouts were not reported. None of the participants reported any adverse effects.
Simpson 2008	• Clarithromycin vs placebo • Study designed and powered primarily to detect a difference in the IL-8 expression in sputum supernatants of people with refractory asthma after treatment with macrolides. Results reported as median and IQR for most of the descriptive statistics. • Levels of IL-8 were significantly reduced from the baseline with clarithromycin, with 6.6 ng/mL (IQR 2.7–11.9) before and 3.9 ng/mL (IQR 1.8–5.4) after treatment (P = 0.001). Statistically significant difference (with a cut-off point of 0.05 used to determine significance) in IL-8 levels with clarithromycin at the end of the study vs with placebo (6.3 ng/mL, IQR 3.1–17.3 at beginning and 6.4 ng/mL, IQR 3.711.3 at end).

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	• Number of neutrophils in the sputum significantly reduced with clarithromycin from the baseline at end of treatment (from 142.9 × 10^4/mL to 66.7 × 10^4/mL; P < 0.04), but no difference with placebo. • No effect of clarithromycin on FEV_1 % within the treatment arm (73.6, SD 15.8 at time point 0 and 74.6, SD 17.1 at end of treatment; P = NS) or with placebo group (P = NS). • No effect of clarithromycin on bronchial hyperresponsiveness within the treatment group, with a dose-related slope in the hypertonic saline challenge (median 1.8, IQR 0.6–6.4 at time points 0 vs 1, IQR 0.5–4.2 at end of treatment; P = NS), or compared with placebo (P = NS). • Total score for the AQLQ was significantly improved with clarithromycin from baseline (score 5.5, IQR 4.8–6.4) after the treatment period (score 6.2, IQR 5.4–6.6, P = 0.014), but not compared with placebo (score 6.4, IQR 5.2–6.7 at time point 0 and score 6.4, IQR 5.7–6.8, P = NS) both within the placebo group and compared with the treatment arm). • Total asthma control score was not significantly improved in the clarithromycin group from the baseline (score 1.6, SD 0.6) after the treatment period (score 1.3, SD 0.7, P = NS); no difference in the comparison with and within the placebo group (score 1.3, 1.0 at time point 0 and 1.2, SD 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 participants with non-eosinophilic asthma defined as proportion of neutrophils in induced sputum ≥ 61%.
Strunk 2008	• Study was designed to test a potential inhaled steroid-sparing effect of azithromycin compared with montelukast and placebo, in children with persistent-to-severe asthma. After a 6-week run-in period, when participants were treated with salmeterol and an increasing dose of inhaled budesonide to obtain good control of asthma, participants 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 55/292 (19%) participants enrolled for inclusion in the study reached the randomisation. Of the 55 participants randomised, 35 (63.6%) reached inadequately controlled status of asthma within a median of 5.1 weeks (range 2.4–23.4) after randomisation. The study was prematurely terminated by the Data Safety Monitoring Board. • No difference in time regarding inadequate control among the 3 groups (median: azithromycin: 8.4 weeks, 95% CI 4.3 to 17.3; montelukast: 13.9 weeks, 95% CI 4.7 to 20.6; placebo: 19.1 weeks, 95% CI 11.7 to 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 participants randomised to the treatment groups.

Sutherland 2010	• Clarithromycin vs placebo
	• Study investigated 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 ≥ 72 participants for PCR status was required to achieve a 90% power to detect a difference of 0.5 in ACQ score.
	• Of 253 people meeting the criteria for inclusion, only 92 were randomised in the 2 treatment groups due to suboptimal asthma control during the 4-week run-in period. Among them, 12 (13%) had a positive PCR for *M pneumoniae* or *C pneumoniae*, while 80 (87%) had a negative PCR. The original purpose to reach 72 participants with evidence of infection was judged as not feasible, and further enrolment stopped.
	• 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 groups irrespective of PCR status (0.2, SD 0.2; P = 0.2; n = 92);
	  ◦ difference in ACQ score between groups in participants with a positive PCR status (0.3, SD 0.5; P = 0.6; n = 12);
	  ◦ difference in ACQ score between groups in participants with a negative PCR status (0.2, SD 0.2; P = 0.3; n = 80).
	• FEV_1 (pre-albuterol) was not significantly improved in any comparison at the end of the study period:
	  ◦ difference in FEV_1 (L) between groups irrespective of PCR status (0, SD 0.1; P = 0.8; n = 92);

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	○ difference in FEV_1 (L) between groups in participants with a positive PCR status (0.4, SD 0.2; P = 0.9; n = 12); ○ difference in FEV_1 (L) between groups in participants with a negative PCR status (−0.2, SD 0.1; P = 0.8; n = 80). • There were similar results for FEV_1 %, morning and evening PEF, and rescue medications, with no statistically significant differences 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 participants: ○ difference in PC_{20} doubling dose between groups irrespective of PCR status (1.2, SD 0.5; P = 0.01; n = 92); ○ difference in PC_{20} doubling dose between groups in participants with a positive PCR status (+0.9, SD 1.8; P = 0.6; n = 12); ○ difference in PC_{20} doubling dose between groups in participants with a negative PCR status (+1.2, SD 0.5; P = 0.02; n = 80). • Incidence of adverse events was not different between groups; there were no severe adverse events.
Wan 2016	• Clarithromycin vs placebo • Study, performed in Taiwan, enrolled 58 children (aged 5–16 years, 32 boys) with newly diagnosed mild persistent asthma. All participants had atopic asthma and were sensitive to ≥ 2 inhaled antigens. • Children were randomised to clarithromycin 5 mg/kg daily (n = 36) or placebo (n = 22) for 4 weeks. 2 participants withdrew from placebo group, all the others completed the study. • Increase of FEV_1 (% of predicted) and of $FEF_{25–75}$; and a decrease in blood eosinophil count, ECP and FeNO in the treatment group before and after the treatment with clarithromycin. However, the reporting of data/results was scanty, and no statistics, no comparisons with the control group were presented in the manuscript.

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; **ED**: emergency department; **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; **HR:** hazard ratio; **ICS:** inhaled corticosteroid: **IgG**: immunoglobulin G; **IL**: interleukin; **IQR**: interquartile range; **IRR:** incidence rate ratio: **LABA:** long-acting beta-agonists; **LAMA**: long-acting muscarinic antagonists; **MMP**: matrix metallopeptidase; **mRNA**: messenger ribonucleic acid; **n**: number of participants; **NS**: not significant; **PCR**: polymerase chain reaction; **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); **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 Review Manager 2014. 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.

Contributors

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WHAT'S NEW

Date	Event	Description
31 March 2021	New search has been performed	New literature search run.
31 March 2021	New citation required but conclusions have not changed	Main conclusions not changed from the previous version. Based on a single, high-quality RCT, there is a potential benefit of macrolides in the treatment of people with severe asthma.

HISTORY

Protocol first published: Issue 1, 2000
Review first published: Issue 3, 2001

Date	Event	Description
5 November 2019	New search has been performed	New literature search run
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.

Date	Event	Description
15 April 2015	New search has been performed	New literature search run
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.
7 August 2008	Amended	Converted to new review format.
6 June 2005	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

KU: data extraction, entry and analysis, interpretation, drafting of the review.

LG: entry and data analysis, interpretation, revision of the review.

KK: data extraction, entry and analysis.

GF: data extraction, entry, interpretation, drafting of the review.

Contributions of editorial team

Rebecca Fortescue (Co-ordinating Editor) edited the protocol; advised on methodology; approved the protocol prior to publication.

Christian Osadnik (Contact Editor): edited the review; advised on methodology, interpretation and content.

Emma Dennett (Managing Editor): co-ordinated the editorial process; advised on interpretation and content; edited the review.

Emma Jackson (Assistant Managing Editor): conducted peer review and edited the references and other sections of the protocol and review.

Elizabeth Stovold (Information Specialist): designed the search strategy; ran the searches; edited the search methods section.

DECLARATIONS OF INTEREST

KU: none.

LG: I was the statistical Editor at Cochrane Airways Group and checked the data and then joined the team after providing extensive help.

KK: I was a paid researcher on a National Institute for Health Research (NIHR) Cochrane Programme Grant until December 2016, during which time I contributed to the first version of this review. The grant was awarded to the Cochrane Airways review group at St George's, University of London, where I continued as an honorary research assistant until April 2017. I am currently an employee of the Cochrane Central Executive Team and my contribution to the update for this review is not subject to any funding.

GF: I received fees for lectures (AstraZeneca) and advisory boards/lectures (Boehringer Ingelheim and Roche) for topics not related to and outside the work of this systematic review and meta-analysis.

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Internal sources

- All, Other

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

External sources

- All, Other

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

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We updated the review to conform with current methodology and reporting. We used GRADE to assess the certainty of the evidence for the primary outcomes, and modified the summary of findings table to the current standard format. We explained methods for data synthesis in more detail. There are no major changes in methodology in this updated version of the review.

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [adverse effects]; *Asthma [drug therapy]; Disease Progression; Macrolides [therapeutic use]; *Quality of Life

MeSH check words

Adult; Humans; Middle Aged; Young Adult