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Macrolide antibiotics for cystic fibrosis (Review)

Southern KW, Barker PM, Solis-Moya A, Patel L

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[Intervention Review]

Macrolide antibiotics for cystic fibrosis

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ABSTRACT

Background

Macrolide antibiotics may have a modifying role in diseases which involve airway infection and inflammation, like cystic fibrosis.

Objectives

To test the hypotheses that, in people with cystic fibrosis, macrolide antibiotics:
1. improve clinical status compared to placebo or another antibiotic;
2. do not have unacceptable adverse effects.
If benefit was demonstrated, we aimed to assess the optimal type, dose and duration of macrolide therapy.

Search methods

We searched the Cochrane Cystic Fibrosis and Genetic Disorders Group Trials Register comprising references identified from comprehensive electronic database searches, handsearching relevant journals and abstract books of conference proceedings.

We contacted investigators known to work in the field, previous authors and pharmaceutical companies manufacturing macrolide antibiotics for unpublished or follow-up data (May 2010).

Latest search of the Group's Cystic Fibrosis Trials Register: 29 February 2012.

Selection criteria

Randomised controlled trials of macrolide antibiotics compared to: placebo; another class of antibiotic; another macrolide antibiotic; or the same macrolide antibiotic at a different dose.

Data collection and analysis

Two authors independently extracted data and assessed risk of bias. Seven groups were contacted and provided additional data which were incorporated into the review.

Main results

Ten of 31 studies identified were included (959 patients). Five studies with a low risk of bias examined azithromycin versus placebo and demonstrated consistent improvement in forced expiratory volume in one second over six months (mean difference at six months 3.97% (95% confidence interval 1.74% to 6.19%; n = 549, from four studies)). Patients treated with azithromycin were approximately twice as likely to be free of pulmonary exacerbation at six months, odds ratio 1.96 (95% confidence interval 1.15 to 3.33). With respect to secondary outcomes, there was a significant reduction in need for oral antibiotics and greater weight gain in those taking azithromycin. Adverse

events were uncommon and not obviously associated with azithromycin, although a once-weekly high dose regimen was associated with more frequent gastrointestinal adverse events. Treatment with azithromycin was associated with reduced identification of *Staphylococcus aureus* on respiratory culture, but also a significant increase in macrolide resistance.

Authors' conclusions

This review provides evidence of improved respiratory function after six months of azithromycin. Data beyond six months were less clear, although reduction in pulmonary exacerbation was sustained. Treatment appeared safe over a six-month period; however, emergence of macrolide resistance was a concern. A multi-centre trial examining long-term effects of this antibiotic treatment is needed, especially for infants recognised through newborn screening.

PLAIN LANGUAGE SUMMARY

Treatment with macrolide antibiotics for people with cystic fibrosis and chronic chest infection

People with cystic fibrosis suffer from chest infections, often caused by the bacteria *Pseudomonas aeruginosa.* This bacteria is resistant to nearly all antibiotics that can be taken by mouth. Macrolide antibiotics, e.g. azithromycin, have no direct killing effect on *Pseudomonas aeruginosa*, but they may reduce the activity of these bacteria. We have included ten randomised controlled trials with a total of 959 participants in this review. Eight of these trials compared azithromycin (a macrolide antibiotic) to placebo and two compared different doses of azithromycin. Four trials in children and adults (549 participants) showed significant improvements in lung function after treatment with azithromycin compared to placebo at six months; although data from later time points are not so clear. Patients treated with azithromycin were about twice as likely to be free of pulmonary exacerbation; needed fewer oral antibiotics and had fewer instances of *Staphylococcus aureus* in cultures from their lungs and airways. Adverse events were not common and not obviously associated with azithromycin, although there was an increase in resistance to macrolides. Most studies used a three times a week dosing schedule. Taking a high weekly dose was linked to an increase in mild gastrointestinal adverse events. Further multicentre studies are needed to look at the long-term effects of this antibiotic treatment, especially for infants diagnosed through newborn screening.

BACKGROUND

This review examines the use of macrolide antibiotics for the treatment of cystic fibrosis (CF) chest infection.

Description of the condition

Cystic fibrosis (CF) is caused by mutation of the cystic fibrosis transmembrane conductance regulator (CFTR) gene (Riordan 1989) and is the most common life-shortening inherited disease in the Caucasian population, with reducing prevalence in Hispanic, African and South East Asian populations, respectively. The CFTR protein has an important role in the transport of salt and water across the surface of epithelia (Boucher 1999). In CF, abnormal CFTR function affects a number of organs in the body; however, involvement of the airway has the most dramatic impact on quality of life and survival. The defect in CF salt transport results in abnormal airway secretions, which leads to chronic airway infection and inflammation (Matsui 1998). Chronic bacterial infection in the airway is associated with an intense inflammatory process, which causes lung damage and further infection, eventually leading to respiratory failure.

Characteristic organisms associated with lower airway infection in people with CF are, most notably, *Staphylococcus aureus* (*S. aureus*) in the early course of the disease and *Pseudomonas aeruginosa* (*P. aeruginosa*) at a later stage (Hutchison 1999). Chronic airway infection with *P. aeruginosa* in CF is characterised by the production of alginate which provides the bacteria with a protective mucoid coat. This biofilm may have an important role in the chronic airway infection that characterises CF. This is an unusual chronic airway condition as acute inflammatory cells (neutrophils) are the predominant mediators of the process.

Treatment of chronic *P.aeruginosa* infection in CF airways is challenging because of the limited number of antibiotics with direct killing activity. Quinolones, such as ciprofloxacin, are the only oral antibiotics available with direct killing activity against *P. aeruginosa*. Other classes of anti-pseudomonal antibiotics need to be given intravenously or aerosolised into the lungs. Increasing resistance of *P. aeruginosa* to antibiotics is a significant challenge in the management of chronic airway infection in people with CF.

Description of the intervention

Macrolides are an orally available class of antibiotics that are often prescribed to treat community-acquired pneumonia and skin infections. They have a broad spectrum of action against gram-positive bacteria and some gram-negative bacteria. The oldest and most widely used macrolide (in the United Kingdom) is erythromycin. Newer antibiotics in this class include clarithromycin, roxithromycin and azithromycin (this is quite a distinct molecule, called an azalide). Macrolides work by inhibiting protein synthesis in bacteria, but they can also impact on human cellular functions; care has to be taken when macrolides are prescribed alongside certain other drugs such as statins, theophyliines and the oral contraceptive pill. They have no direct killing activity against *P. aeruginosa*.

How the intervention might work

Although macrolide antibiotics have direct killing properties against a number of characteristic CF pathogens, in particular *S. aureus* and *Haemophilus influenzae* (*H. influenzae*), it is the potential for these agents to have indirect actions against *P. aeruginosa* and possibly other anti-inflammatory actions that has generated the most interest in this class of antibiotic.

In Japan, macrolides have been widely used since 1982 as a treatment for diffuse panbronchiolitis, a rare inflammatory lung condition affecting older Japanese people (Hoiby 1994). Infection with *P. aeruginosa* in these people is associated with a poor outcome. There is some evidence (including one randomised controlled trial) that, even at low doses, the long-term use of macrolides has a beneficial effect on survival for people with this condition (Kobayashi 1993). This has been attributed to a reduction in factors (called virulence factors) that increase the activity of *P. aeruginosa*. These virulence factors, such as the production of the mucoid biofilm, may be important for the pathogenicity of *P. aeruginosa* in diffuse panbronchiolitis and CF. Laboratory studies also suggest that macrolides may have anti-inflammatory properties (Labro 1998; Anderson 1996; Yanagihara 1997).

Azithromycin is reported to show the most significant activity against the virulence factors of *P. aeruginosa* (Ichimiya 1996; Mizukane 1994; Molinari 1993; Retsema 1987). The pharmacokinetics of azithromycin (an azalide) are fairly unique with considerable intracellular uptake and slow excretion (through the liver). The high tissue concentrations and long half-life of azithromycin means that infrequent dosing schedules (for example, three times a week) are possible, making it an attractive oral therapy for people with CF (Ball 1991).

Why it is important to do this review

Macrolide antibiotics are well-tolerated and relatively inexpensive; however, their increasingly widespread use has resulted in the emergence of resistant bacteria (in particular macrolide-resistant *S. aureus*) (Hansen 2009; Phaff 2006; Tramper-Stranders 2007). It is critical therefore that the efficacy and safety of macrolide therapy for CF are examined in a systematic manner.

OBJECTIVES

1. To test the hypothesis that, in people with CF, macrolide antibiotics improve clinical status compared to placebo or another antibiotic
2. and do not have unacceptable adverse effects.

If benefit was demonstrated, we aimed to assess the optimal type, dose and duration of macrolide therapy

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs), published or unpublished. Quasi-randomised (e.g. alternate allocation and stratification) controlled trials were included if there were no significant baseline differences between intervention and control groups. Cross-over trials were included if there was evidence of a sufficient washout period. If the washout period was shorter than three months and if baseline characteristics were not significantly different for intervention and control groups, then data from the first arm were used.

Types of participants

Participants fulfilled criteria for a diagnosis of CF. If two disease-causing genetic mutations were not recognised, participants were required to have a positive sweat test and clinical features consistent with CF.

Types of interventions

Short-term or long-term (greater than 12 months) use of a macrolide antibiotic compared to controls who receive placebo, another antibiotic class, another macrolide or the same macrolide at a different dose.

Types of outcome measures

Primary outcomes

1. Lung function (absolute and per cent predicted values for age, height and gender)
   a. forced expiratory volume in one second (FEV_1)
   b. forced vital capacity (FVC)
   c. non-routine tests (e.g., thoracic gas volume (TGV), airway conductance (Gaw) and lung clearance index (LCI))
2. Pulmonary exacerbation (protocol defined or physician determined)
   a. number of patients free of exacerbation
   b. time to first exacerbation
3. Survival

Secondary outcomes

1. Adverse effects
   a. mild (defined as transient and treatment continued)
   b. moderate (generally treatment discontinued)
   c. severe (life threatening or seriously debilitating)
2. Number of days in hospital
3. Acquisition or eradication of *P. aeruginosa* infection
4. Acquisition or eradication of other significant CF pathogen
   a. *S. aureus* (including MRSA)
   b. *H. influenzae*
   c. Other significant pathogens
5. Additional treatment required (courses or days of treatment)
   a. oral antibiotics
   b. intravenous antibiotics
   c. oral steroids
   d. any other medical CF therapy
6. Development of allergic bronchopulmonary aspergillosis (ABPA)
7. Nutritional markers (for example, weight and body mass index (BMI))
8. Liver disease (as defined by any new clinical, radiographic or biochemical evidence of CF-related liver disease)
9. Quality of life (QoL) (as measured by a valid disease-specific QoL tool)
10. Changes in treatment burden (as measured by a disease-specific tool)
11. Changes in inflammatory markers
    a. broncho-alveolar lavage (BAL) samples
    b. serum samples

Search methods for identification of studies

Electronic searches

Relevant studies were identified from the Group's Cystic Fibrosis Trials Register using the term: macrolide.

The Cystic Fibrosis Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of *The Cochrane Library*), quarterly searches of MEDLINE, a search of EMBASE to 1995 and the prospective handsearching of two journals - *Pediatric Pulmonology* and the *Journal of Cystic Fibrosis*. Unpublished work is identified by searching through the abstract books of three major cystic fibrosis conferences: the International Cystic Fibrosis Conference; the European Cystic Fibrosis Conference and the North American Cystic Fibrosis Conference. For full details of all searching activities for the register, please see the relevant sections of the Cystic Fibrosis and Genetic Disorders Group Module.

Date of the most recent search of the Group's CF Trials Register: 29 February 2012.

Searching other resources

Principal investigators, known to work in the field were contacted for unpublished or follow-up data. Pharmaceutical companies, that manufacture macrolide antibiotics, were also approached (last contacted May 2010).

Data collection and analysis

Selection of studies

Three authors (KWS, PMB and LP (2011 update)) independently selected studies to be included in the review. They resolved any disagreement through discussion with arbitration from the fourth author (AS).

Data extraction and management

Three authors (KWS, PMB and LP (2011 update)) independently extracted data from included studies. For the 2011 update, they entered all data onto data extraction sheets; KWS entered data into the review software (RevMan 2008).

The authors considered outcomes to be short term if they were measured at the end of a treatment period, unless the treatment period was for more than 12 months. They also considered outcomes to be long term if there were more than three months between the end of the treatment and the measure. The authors did not consider long-term outcome measures for cross-over studies.

The authors grouped outcome data into those measured at one, two, three, four, six and twelve months (annually thereafter). They also included outcome data recorded at other time periods.

Study groups sometimes reported the same outcome measure differently. For example, need for additional oral antibiotics could be presented as a dichotomous outcome (number of patients who received additional oral antibiotics) or as a continuous outcome (number of courses or number of days). In these cases, the review authors contacted the primary investigators to request further data for the meta-analysis. One of the primary outcomes was relative change in per cent predicted FEV_1 from the baseline (calculated as (baseline minus post-intervention) divided by baseline multiplied

by 100). If per cent predicted FEV_1 was calculated as absolute change, the authors contacted the primary investigators for further data to include in the meta-analysis.

Assessment of risk of bias in included studies

KWS, PB and LP (2011 update) independently assessed the risk of bias for each included study using the Cochrane risk of bias tool (Higgins 2009). In particular, the authors examined the process of randomisation (allocation and generation), the degree of blinding in the study, whether outcome data were complete (the description of participants lost to follow-up and those excluded from the study), selective outcome reporting and any other potential sources of bias. The authors recorded these factors on a risk of bias table for each study. Risk of bias was assessed as high, low or uncertain.

Measures of treatment effect

For binary outcome measures the authors calculated a pooled estimate of the treatment effect for each outcome across studies using the pooled odds ratio (OR) and 95% confidence intervals (CIs) as a treatment effect estimate.

For continuous outcomes, they recorded either mean change from baseline for each group or mean post-treatment or intervention values and standard deviation (SD) for each group (standard errors were converted to SDs). The authors calculated a pooled estimate of treatment effect by calculating the mean difference (MD) and 95% CIs.

Unit of analysis issues

When outcomes were presented in different forms, the authors have reported both and have approached primary investigators in order to obtain a single outcome. The review authors have reported results at (for continuous data) or after (for dichotomous data) set time periods of the interventions. In this way they have been able to examine for changes over time and for heterogeneity. For adverse events they have combined all data regardless of time period of the study.

The review authors considered data from cross-over studies for this review; although this study design may not be ideal for a condition when the intervention could potentially have a long-standing impact on disease progression. If a washout period is not available, they have considered data from the first arm of the study as for a parallel design study, providing there was no significant differences in the baseline characteristics of both groups. They have included data for dichotomous outcomes (such as adverse events and number of patients free from pulmonary exacerbation) as a direct comparison of the two arms, although this undervalues the power of the cross-over design (Curtin 2002a; Curtin 2002b; Curtin 2002c).

Dealing with missing data

In order to allow an intention-to-treat analysis, the review authors sought data on the number of participants with each outcome event, by allocated treated group, irrespective of compliance and whether or not the participant was later thought to be ineligible or otherwise excluded from treatment or follow-up. If any data were missing or unclear, we contacted the primary investigators for clarification. For one study, the primary outcome was reported at various time points, but only in a figure (Clement 2006). Subsequent individual patient data (IPD) provided by the authors did not contain data from all time points, so these were calculated by measuring the figure (using a formula to convert the CI to SD).

Assessment of heterogeneity

The review authors examined heterogeneity through visual examination of the combined data presented in the Forest plots. Heterogeneity was also assessed by considering the I^2 statistic together with chi-squared (Higgins 2003). They assessed any analysis with an I^2 value above 40% for evidence of heterogeneity with higher values more supportive of significant heterogeneity.

Assessment of reporting biases

Where possible the review authors compared outcomes described in the protocol with those reported in the papers. If protocols were not available, they wrote to the primary investigators requesting the protocol; and if that was not available, they compared the outcomes listed in the 'Methods' section of the full paper to the 'Results' section. If the published papers reported negative findings either only partially or not at all, the review authors have approached the primary investigators for those data.

We have assessed the studies for publication bias (often characterised by presentation at a conference with no subsequent peer-reviewed publication).

Data synthesis

The review authors employed a fixed-effect model to analyse data from studies that were not considered heterogeneous. When significant heterogeneity was present (I^2 greater than 40%), the authors used a random-effects model.

Subgroup analysis and investigation of heterogeneity

When considering the possible mechanism of action of macrolide antibiotics, subgroup analysis may be appropriate, particularly when considering patients with and without chronic airway infection (most commonly with *P. aeruginosa*). A number of authors have reported data independently for these groups, although this is hampered by a clear and consistent definition of chronic airway infection. We are currently undertaking subgroup analysis to examine confounding factors, such as age and chronic airway infection.

Sensitivity analysis

The review authors have examined the impact of bias on the results, by including and excluding studies with concerns over study design from the combined analysis.

RESULTS

Description of studies

The majority of included studies have examined the intervention of azithromycin versus placebo using a parallel study design and some studies have looked at different dosing regimens. Studies examining other macrolides, mostly clarithromycin, have been incompletely reported (*see* Excluded studies). Overall study quality has been good, with complete and thorough reporting (*see* Included studies and Risk of bias in included studies).

Results of the search

A total of 58 publications (abstracts, papers and one thesis) were identified, representing 31 separate studies. In some cases further unpublished data were provided by authors. Only trials examining azithromycin have been published in peer-reviewed journals. Of the 31 studies identified, 10 have been included and 19 excluded; two studies are awaiting classification (Elmasry 2010; Pukhalsky 2008).

Included studies

Trial Design

The ten included studies examined azithromycin as an intervention for CF (Table 1). Two were cross-over studies (Equi 2002; O'Connor 2009) and the rest were of parallel design (Clement 2006; Kabra 2010; McCormack 2007; Rotschild 2005; Saiman 2003; Saiman 2010; Steinkamp 2007; Wolter 2002). Duration of the intervention ranged from 2 to 12 months (Table 1).

Participants

The included studies enrolled people with a confirmed diagnosis of CF. Four studies enrolled children over six years of age (Equi 2002; Kabra 2010; O'Connor 2009; Saiman 2010), one study enrolled adults (Wolter 2002) and the remaining five studies enrolled both adults and children (Table 1). In some studies, *P. aeruginosa* airway infection (presence (Saiman 2003) or absence (Saiman 2010)) was an important entry criteria. The number of participants ranged from 17 to 260. In total, 959 children and adults with CF have been included in these studies.

Interventions

Azithromycin was the intervention in all included studies. In eight studies this was compared to placebo. One study compared high-dose and low-dose regimens (Kabra 2010). Another study compared a once-weekly with a daily dosing regimen (McCormack 2007).

Outcomes

The primary outcome measure in all the trials was a change in FEV_1 over the course of the study (either relative or absolute change). All studies examined for and reported adverse effects. A number of studies have measured and reported pulmonary exacerbations (either total number during study or time to exacerbation). The reporting of this outcome was variable (time to exacerbation, number of exacerbations etc.).

Excluded studies

Twenty studies were excluded. Seven studies examined azithromycin in an open or retrospective manner (Anstead 1999; Anstead 2001; Baumann 2000; Jaffe 1998; Jensen 2005; Pirzada 1999; Rubin 2003). Two studies have provided some important information on the pharmacokinetics of azithromycin in CF (Beringer 2005; Cipolli 2001). In our first review, we included the Cipolli study; however, in the reassessment for this review the authors felt it was not appropriate to include either of these pharmacokinetic studies, given the open label nature.

Six studies examined clarithromycin in an open manner (Dogru 2004; Frederiksen 2001; Kessaris 2003; Ordonez 2001; Pukhalsky 2001; Sriram 2003), and one study compared azithromycin and clarithromycin also in an open manner (Radionovitch 2005). These studies have not been fully reported and have all been presented in abstract form. The number of participants was small and we were not able to adequately assess study design from the abstract reports and subsequent correspondence. Two groups provided protocols that suggested adequate randomisation, but individual patient data provided was not presented in a manner that permitted analysis (Frederiksen 2001; Sriram 2003).

One study compared clarithromycin to nimesulide not to placebo, another antibiotic class, another macrolide or the same macrolide at a different dose (Shmarina 2004).

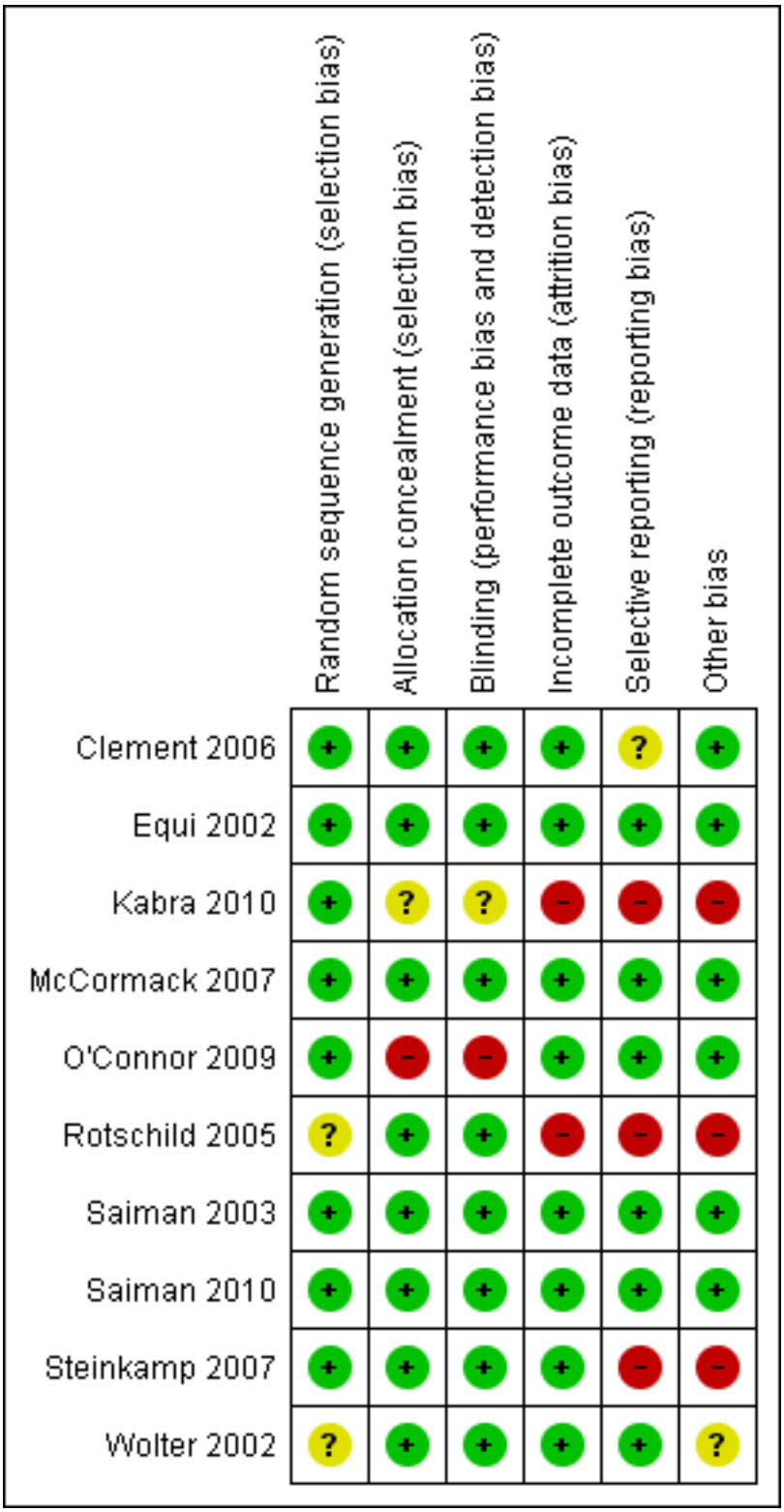
One study examined roxithromycin. This was presented in abstract form and not with sufficient detail to assess the study design and outcomes (Dionyssopoulou 2005).

One study did not examine macrolides as an intervention *per se*, rather the use of multiple antibiotic sensitivity testing (Aaron 2005).

Risk of bias in included studies

In four of the ten included studies, there was no apparent risk of bias (Equi 2002; McCormack 2007; Saiman 2003; Saiman 2010). For two studies there were minor concerns over reporting and baseline characteristics (Clement 2006; Wolter 2002). These six studies enrolled the majority of patients included in this review (836 of 959 total patients). In four studies there were significant concerns over the risk of bias (Kabra 2010; O'Connor 2009; Rotschild 2005; Steinkamp 2007) (see Figure 1).

Figure 1. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

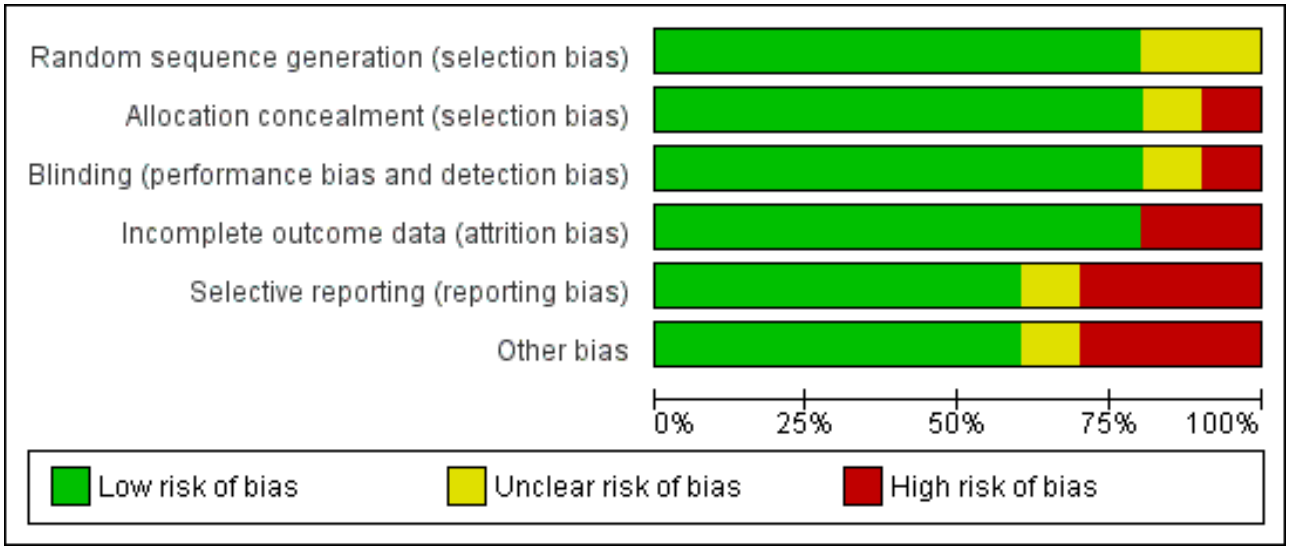


Allocation

For the majority of studies, the generation and concealment of allocation was undertaken in a correct and rigorous manner leading to a low risk of bias (Figure 1; Figure 2). In some studies, this was not clear in the trial reports, but subsequent correspondence has clarified the situation. Two studies caused concern (Kabra 2010; O'Connor 2009). Details of allocation were unclear in the Indian study and we judged this to have an unclear risk of bias (Kabra 2010). In the Northern Irish study, the placebo and active

interventions were different colour capsules, permitting some conjecture by the participants and investigators as to the active and placebo arms and we judged this study to have a risk of bias (O'Connor 2009).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Blinding

Aside from the Northern Irish study, which we judged to have a high risk of bias from blinding (O'Connor 2009), the interventions were identical in the placebo-controlled studies. Investigators, clinicians and participants were blinded adequately leading to a low risk of bias.

For the studies examining different dosing regimens, in the Indian study (Kabra 2010), it was not clear if treatment allocation was blinded (high or low dose) and so this needs to be considered an unclear risk of bias. The second Australian study comparing two dosing regimens was adequately blinded and had a low risk of bias (McCormack 2007).

Incomplete outcome data

For the French study, the primary outcome was reported at various time points, but only in a figure (Clement 2006). Subsequent IPD provided by the authors did not contain data from all time points, so these were calculated by measuring the figure (using a formula to convert the CI to SD). These were the only data beyond six months available for this review from placebo-controlled trials. Overall outcome data were well reported leading to a low risk of bias.

Selective reporting

Protocols were not available for the included studies, but overall there was a good level of reporting of outcomes and aggregate data were included in this review. On some occasions, data were not fully reported. We contacted all authors and have subsequently been able to obtain most data, sometimes in the form of individual patient data (IPD). Overall, there were no major issues with selective reporting (low risk of bias), although again two studies were assessed as having a high risk of bias (Kabra 2010; Rotschild 2005). In one study, data were only reported for eight weeks although were collected for longer on some participants (Steinkamp 2010). Six studies measured QoL and the reporting of these results was incomplete with a lack of negative data (Clement 2006; McCormack 2007; O'Connor 2009; Saiman 2003; Steinkamp 2007; Wolter 2002). One author has consequently provided a full aggregate data set (Steinkamp 2007). Similarly, nutritional outcomes were reported as summary outcomes, rather than complete data sets (Wolter 2002; Clement 2006; Saiman 2003; Saiman 2010).

Other potential sources of bias

Two studies employed a cross-over design, which may not be the ideal design for an intervention that potentially could have a significant impact on longer-term disease progression (Equi 2002; O'Connor 2009). However, both studies employed two-month washout periods and there did not appear to be any carry-over effects. Data have been included in the meta-analysis from the first arm of the Equi study, as the baseline characteristics of both groups were similar, although we appreciate this loses some of the power of the cross-over design (Equi 2002). Other concerns over potential bias from the O'Connor study precluded inclusion of these data (see above) and data from individual arms were not provided (O'Connor 2009).

There was a potential source of bias in the Wolter study, which reported different baseline characteristics of the two treatment groups, with the placebo group having significantly more males with better respiratory function and nutritional status (Wolter 2002). The investigators adjusted for the differences between sex, BMI and FEV_1 in the analysis of their data.

Only studies examining azithromycin have been published in peer-reviewed journals. Studies examining clarithromycin and roxithromyicn have only been presented at conference and published in abstract form. All these studies were reported as "negative" and this lack of publication in a peer-reviewed journal represents positive publication bias.

Effects of interventions

This review has identified six studies with a low risk of bias (Figure 1). These studies enrolled 836 of the total 959 recruited patients. Data from the four studies with methodological concerns have not had any significant impact on the overall conclusions from the meta-analysis of efficacy outcomes, although numbers were too small for a formal sensitivity analysis (O'Connor 2009; Kabra 2010; Rotschild 2005; Steinkamp 2007).

Primary outcomes

1. Lung function

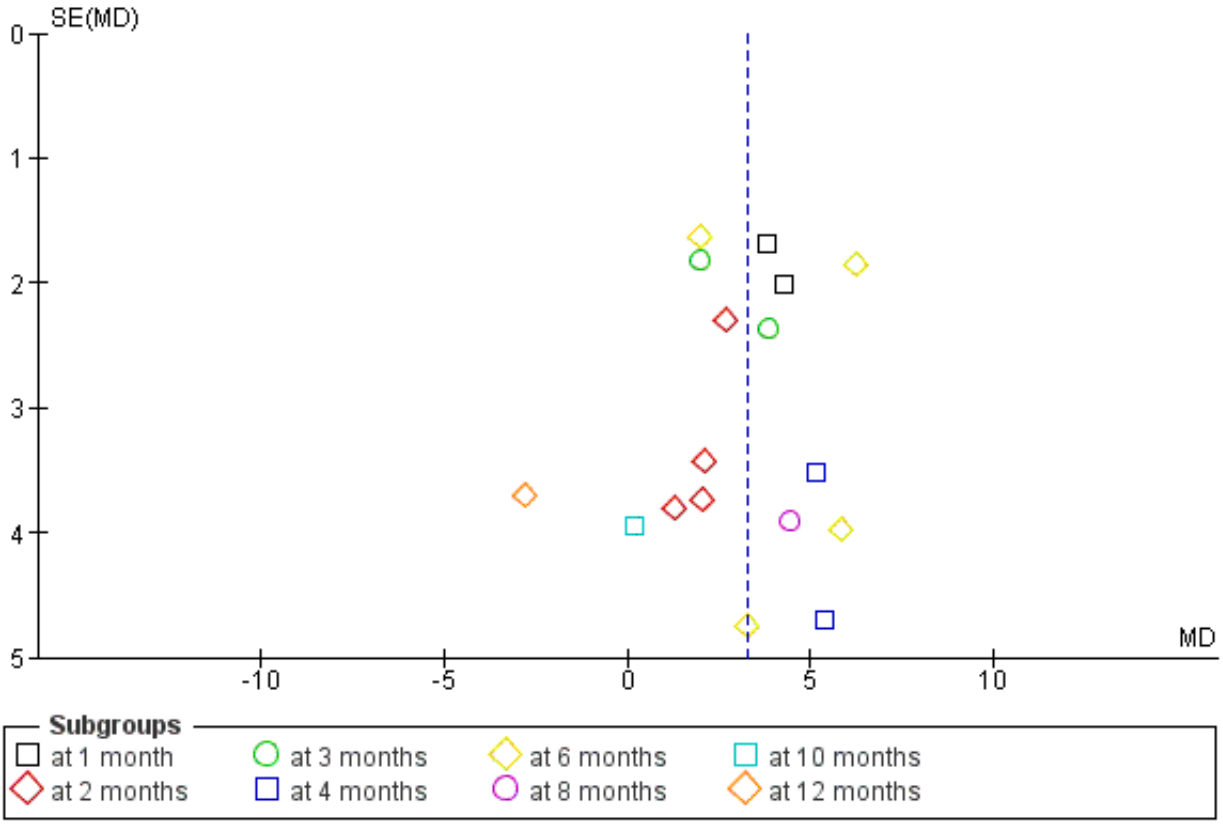
a. FEV_1

The first three studies examining azithromycin versus placebo reported a significant difference in favour of azithromycin with respect to their primary outcome measure, change in FEV_1 from baseline (Equi 2002; Saiman 2003; Wolter 2002). The meta-analysis of these trials in an earlier version of this review supported this finding, particularly with respect to data at six months (azithromycin (n = 104) versus placebo (n = 114); MD 5.82% (95% CI 2.45% to 9.20%)) (Southern 2004).

Subsequent studies have not reported a difference in this outcome, including two studies with sizeable recruitment comparing azithromycin to placebo (Clement 2006; Saiman 2010). The French study recruited adults and children (n = 82), both with and without chronic *P. aeruginosa* airway infection, over a twelve-month period (Clement 2006). The North American study was over six months and recruited 260 children aged 6 to 18 years without chronic *P. aeruginosa* airway infection (Saiman 2010).

When data from these two studies were included in the most recent meta-analysis, the improvement in FEV_1 remained consistent at six months (azithromycin (n = 269) versus placebo (n = 280); MD 3.97% (95% CI 1.74% to 6.19%) (Analysis 1.1). The validity of this result was supported by the lack of heterogeneity as demonstrated by the I^2 value and the funnel plot (Figure 3).

Figure 3. Funnel plot of comparison: 1 Azithromycin versus placebo, outcome: 1.1 Relative change in FEV_1 (% predicted).



Studies have examined this outcome at different time points; however, the overall pattern of the meta-analysis was consistent before six months, again supporting the validity of this as a true finding (Analysis 1.1). The French study provides data beyond six months and demonstrates no difference in this outcome at 8, 10 and 12 months (Analysis 1.1). From the graph it can be seen that this represents a gradual reduction in the difference in FEV_1 over this time period (Analysis 1.1).

One smaller study with 38 participants reported absolute change in FEV_1 and did not demonstrate a difference between azithromycin and placebo after two months (Steinkamp 2007) (Analysis 1.2).

A large Australian study with 208 participants compared daily versus weekly dosing regimens and showed clinical equivalence with respect to the relative change in FEV_1 (McCormack 2007) (Analysis 2.1).

In contrast to the first North American study, which recruited older patients with chronic *Pseudomonas aeruginosa* airway infection (Saiman 2003), the second North American study did not demonstrate a difference in relative change in FEV_1 between the azithromycin and placebo groups (Saiman 2010). Other studies enrolled patients with and without pseudomonas infection. Further analysis with individual patient data is required to examine the impact of *P. aeruginosa* infection on outcomes, particularly FEV_1; however, the consistent pattern of response in favour of azithromycin seen in the meta-analysis suggests that this is not a significant confounding factor (Analysis 1.1).

b. FVC

The results for relative change in FVC track those of FEV_1 and demonstrate significance differences at two and six months, MD 5.42 (95% CI 1.79 to 9.05) and MD 4.57% (95% CI 1.71 to 7.42) respectively. The confidence intervals are wider for this outcome, reflecting the variability of this outcome measure (Analysis 1.3).

c. Non-routine tests

Non-routine tests such as TGV, Gaw and LCI were not reported in any of the included studies.

2. Respiratory exacerbations

Respiratory exacerbations (either protocol defined or physician determined) were recorded in a number of ways (including time to exacerbation and total number). With data from five studies, it was possible to calculate the number of patients free of exacerbation at reported time points (Equi 2002; Clement 2006; Rotschild 2005; Saiman 2003; Saiman 2010). A meta-analysis of these data demonstrated that patients on azithromycin are more likely to be free of exacerbation at all time points reported (Analysis 1.4). At six months, data were available from 609 patients and demonstrated an OR in favour of azithromycin; OR 1.96 (95% CI 1.15 to 3.33). Both the French and North American studies report in favour of azithromycin with respect to being free of exacerbation, in contrast to the negative result for the primary outcome in those studies, relative change in FEV_1 (Clement 2006; Saiman 2010). The French study reported in favour of azithromycin at 12 months for being free of exacerbation; OR 10.77 (95% CI 2.26 to 51.34) (Clement 2006) (Analysis 1.4).

The Australian study comparing daily to weekly dosing demonstrated significantly more days to first respiratory exacerbation in the weekly dose group, MD 17.30 days (95% CI 4.32 days to 30.28 days) (Analysis 2.2). However, this analysis is not consistent with the authors report, which suggests the difference is not significant (P = 0.17). The authors have been contacted for clarification.

3. Survival

There were no deaths reported in any of the included studies.

Secondary

1. Adverse effects

The included studies have recruited 959 children and adults, of whom 632 received azithromycin as described in the additional tables (Table 1). This provides a useful data set for assessing safety. All studies report standard clinical and laboratory monitoring for adverse events, including liver function tests. Hearing was assessed in the English study (Equi 2002) and in 11 out of 23 centres recruiting for the first North American study (Saiman 2003). Overall, adverse events were not reported more frequently in the azithromycin group compared to placebo (Analysis 1.5).

a. Mild

We defined mild adverse events as transient and which did not necessitate discontinuation of treatment. In the first North American study, treatment with azithromycin was associated with a significant increased risk of nausea, diarrhoea and wheeze (Saiman 2003). In the second North American study of children without *P. aeruginosa* infection, these findings were not replicated (Saiman 2010); although children receiving azithromycin had a decreased risk of cough, OR 0.39 (95% CI 0.23 to 0.64) (Analysis 1.5).

Although data from individual trials were not significantly different combined data from three studies (North American and French studies) suggest that patients treated with azithromycin were less likely to have a fever, OR 0.65 (95% CI 0.43 to 0.97) (Analysis 1.5).

In the second Australian study comparing weekly to daily dosing regimens, patients taking azithromycin weekly were more likely to have gastrointestinal adverse events (27 out of 105 versus 9 out of 103; P < 0.02, OR 3.62 (95% CI 1.61 to 8.14)) (McCormack 2007) (Analysis 2.3).

b. Moderate

We defined moderate adverse events as those which generally resulted in treatment being discontinued or which resulted in hospitalisation. In studies comparing azithromycin versus placebo, study withdrawals were rare and did not increase in the azithromycin group. In the first Australian study, one patient receiving azithromycin discontinued treatment following an urticarial reaction (Wolter 2002). In the French study, one patient treated with azithromycin developed ABPA and was withdrawn (Clement 2006).

In the second Australian study, 12 out of 105 of the weekly treatment arm discontinued treatment compared to 5 out of 103 from the daily regimen (McCormack 2007) (Analysis 2.3).

c. Severe

We defined severe adverse events as those which are life-threatening or seriously debilitating. There were no serious adverse events reported in the included studies.

2. Number of days in hospital

Only three studies reported on this outcome (Saiman 2003; Saiman 2010; Wolter 2002). The first North American study reports a significant reduced risk of hospitalisation with azithromycin, 29 out of 98 patients on placebo versus 14 out of 87 who received azithromycin, OR 0.46 (95% CI 0.22 to 0.94) (Saiman 2003), but this was not found in the second study on children (Saiman 2010).

When these data were combined there was no significant difference between the azithromycin and placebo groups (Analysis 1.6).

The first Australian study did not demonstrate a significant reduction in hospital inpatient days over three months (placebo median 5.2 days (range 0 days to 36 days), azithromycin median 2.1 days (range 0 days to 15 days), P = 0.056) (Wolter 2002).

The second Australian study did not demonstrate a difference between weekly and daily dosing with respect for need for hospitalisation and number of hospital days (McCormack 2007) (Analysis 2.4; Analysis 2.5).

3. Acquisition or eradication of P. aeruginosa infection

The North American and French studies reported acquisition of *P. aeruginosa*, but the number of events were very low (no new growths in the French study) (Clement 2006; Saiman 2003; Saiman 2010) (Analysis 1.7). In the first North American study, three participants in the azithromycin group (one multi-resistant) and five in the placebo group had newly detected *P. aeruginosa* at the end of the study (Saiman 2003).

4. Acquisition or eradication of other significant CF pathogens

a. *S. aureus* (including MRSA)

In the four studies reporting acquisition of *S. aureus,* treatment with azithromycin was associated with a reduced risk of *S. aureus* acquisition, OR 0.25 (95% CI 0.12 to 0.51) (Clement 2006; Saiman 2003; Saiman 2010; Steinkamp 2007) (Analysis 1.8).

Two of these studies also looked at the number of patients with *S. aureus* who had eradication of this bacteria at the end of the study (Clement 2006; Saiman 2003). Treatment with azithromycin was not associated with increased eradication (Analysis 1.9).

The second North American study reported an increased risk of acquiring macrolide-resistant *S. aureus* for those patients on azithromycin, OR 5.01 (95% CI 2.14 to 11.71) (Saiman 2010) (Analysis 1.10).

The second Australian study reported a number of patients acquiring azithromycin resistant *S. aureus* (2 out of 105 weekly patients and 3 out of 103 daily patients) (Analysis 2.6).

There was no evidence of increased risk of acquiring MRSA at either 6 or 12 months following treatment with azithromycin compared to placebo (Analysis 1.11).

b. *H. influenzae*

There was no difference between placebo and azithromycin in the studies that reported this outcome at 6 months (Saiman 2010) or at 12 months (Clement 2006) (Analysis 1.12). The second North American study reported acquisition of macrolide-resistant *H. influenzae* in 10 patients in the azithromycin group compared to 1 in the placebo group, OR 10.09 (95% CI 1.27 to 80.09) (Saiman 2010) (Analysis 1.13).

c. Other significant pathogens

There was no evidence of emergence of gram-negative bacteria or other significant CF pathogens. Five studies reported that culture for non-tuberculous mycobacterium (NTM) was undertaken on sputum samples and there was no evidence of emergence of this bacteria in azithromycin-treated patients (Clement 2006; Equi 2002; Saiman 2003; Saiman 2010; Wolter 2002). The first North American study was the only trial that recognised treatment-emergent NTM in 4 out of 92 patients on placebo versus 1 out of 84 on azithromycin (Saiman 2003) (Analysis 1.14). In the second North American study, NTM was cultured on screening for one patient, who was subsequently discontinued from study drug (placebo) but included in the analysis (Saiman 2010).

5. Additional treatment required (courses or days of treatment)

a. oral antibiotics

This outcome was reported as need for extra oral antibiotics by three studies (Equi 2002; Saiman 2003; Saiman 2010). Treatment with azithromycin was associated with a significant reduced risk, OR 0.28 (95% CI 0.19 to 0.42) (Analysis 1.15). The French study confirmed this finding over 12 months with a reduction in both the number of courses, MD -1.70 (95% CI -1.90 to -1.50), and days of treatment, MD -12.00 (95% CI -17.63 to -6.37) (Clement 2006) (Analysis 1.16; Analysis 1.17).

b. intravenous antibiotics

Three studies reported need for intravenous antibiotic treatment and did not demonstrate a difference between azithromycin or placebo (Equi 2002; Saiman 2003; Saiman 2010) (Analysis 1.18).

The first Australian study reported significant reductions in the number of courses of intravenous antibiotic treatment (mean number of courses with azithromycin 0.4 (range zero to two courses) versus mean number of courses with placebo 1.1 (range zero to seven courses), P < 0.016) and number of days of intravenous antibiotic treatment (mean number of days with azithromycin 2.0 (range 0 to 14 days) versus mean number of days with placebo 7.1 (range 0 to 44 days)) (Wolter 2002).

The French study reported a reduction in both the number of courses, MD -0.80 (95% CI -0.94 to -0.66), and days of intravenous antibiotics, MD -12.00 (95% CI -13.96 to -10.04) over 12 months (Clement 2006) (Analysis 1.19; Analysis 1.20).

c. oral steroids

This outcome was not reported in any of the included studies.

d. any other CF therapy

This outcome was not reported in any of the included studies.

6. Development of ABPA

The first North American study reported an increase incidence of wheeze in the azithromycin group but no other evidence of ABPA (Saiman 2003). One patient treated with azithromycin in the French study was diagnosed with ABPA and withdrawn from the study (Clement 2006) (Analysis 1.21).

7. Nutritional markers

Overall, the reporting of nutritional parameters was limited. The French study reported change in BMI z score after 12 months (Clement 2006). There was no difference between patients treated with azithromycin and placebo (Analysis 1.22).

Full aggregate data from other groups were not available; however, summary findings were reported in some cases.

The first Australian study reported no significant change in BMI (Wolter 2002). Both of the North American studies, which recruited a total of 445 children and adults, reported more weight gain in patients receiving azithromycin (Saiman 2003; Saiman 2010). In the first study, the MD was 0.7 kg (95% CI 0.1 kg to 1.4 kg) (P = 0.02) (Saiman 2003). In the second paediatric study, the MD was 0.58 kg (95% CI 0.14 kg to 1.02 kg) (P = 0.01) (Saiman 2010). When combined, these data demonstrated a significant weight gain in the patients treated with azithromycin, MD 0.62 kg (95% CI 0.26 to 0.98) (Analysis 1.23).

8. Liver disease

There were no reports of significant liver involvement from any study.

Transient increases in liver transaminases were reported in some studies, but infrequently and not at an increased risk in patients treated with azithromycin (Equi 2002; Saiman 2003).

9. QoL

Six studies undertook questionnaire assessment of QoL (Clement 2006; McCormack 2007; O'Connor 2009; Saiman 2003; Steinkamp 2007; Wolter 2002). One used the Chronic Respiratory Disease Questionnaire, which is not validated in CF (Wolter 2002). The others used language appropriate versions of the Cystic Fibrosis Questionnaire (CFQ).

The first North American study reported no difference between groups in the change in total QoL score (Analysis 1.23), an improvement from baseline in the 'physical functioning' component in the azithromycin group, MD 2.70 (95% CI 0.09 to 5.31) (P = 0.05) (Analysis 1.25), and no difference in other aspects of the questionnaire, including psychosocial functioning and body image (Analysis 1.26; Analysis 1.27) (Saiman 2003). In the German study, significant improvement was described in three domains in azithromycin-treated patients compared to placebo after two months: respiratory symptoms, MD 15.40 (95% CI 2.16 to 28.64); eating disorder, MD 13.70 (95% CI 0.79 to 26.61); and problems with body weight, MD 35.20 (95% CI 14.82 to 55.58) (Steinkamp 2007) (Analysis 1.28; Analysis 1.29; Analysis 1.30), but not in the domain of body image (Analysis 1.26). The French study reported no significant difference in any domain at 12 months (Clement 2006). The Northern Irish study reported significant improvement in two domains (vitality and physical functioning) comparing the azithromycin arm to the placebo arm of the cross-over study (O'Connor 2009). In the second Australian study comparing weekly and daily regimens, there was a significant improvement in the physical domain in the weekly group (+8.2 points, P = 0.02) and parents of patients aged less than 14 years reported higher scores for the health domain in the daily group (McCormack 2007).

One study used a non-validated visual analogue scale for well-being (Equi 2002).

10. Changes in treatment burden

This outcome was not reported in the included studies.

11. Changes in inflammatory markers

a. BAL or sputum

There were no differences in IL8 or neutrophil elastase in the first North American study (Saiman 2003).

b. Blood

The first Australian study reported that treatment with azithromycin had a significant effect on the time trend of the inflammatory marker C-reactive protein (CRP) (P < 0.001) (Wolter 2002). Median values for CRP were stated to have fallen in the azithromycin group but to have remained stable in the placebo group (Wolter 2002). The second Australian study demonstrated a greater fall in CRP (though not clinically relevant) in the daily compared to the weekly treatment group at one, three and six months (McCormack 2007) (Analysis 2.7).

In the German study patients were randomised following a two-week course of intravenous antibiotics (Steinkamp 2007). Over the eight-week study period, CRP increased in both treatment arms; while this is not significantly more in the placebo group in our analysis (Analysis 1.31), this was reported as a significant difference in favour of azithromycin in the original published paper.

The Israeli study examined antibodies against bactericidal or permeability-increasing protein (BPI-ANCA) and found no difference following treatment with placebo or azithromycin (Rotschild 2005).

The second North American study measured serum inflammatory markers at baseline, day 28 and day 168 of the study (Saiman 2010). They report small but significant reductions in serum myeloperoxidase, absolute neutrophil count and CRP in children treated with azithromycin at day 28, but not at day 168 (Ratjen 2012). Due to the skewed distribution of the inflammatory markers, logarithmically transformed values were presented in the paper; for this reason these data have not been included in this review. We have contacted the authors and are awaiting non-transformed data from them.

DISCUSSION

A number of studies have examined azithromycin as a treatment for CF and analysis of combined data from these studies can guide the use of this intervention. For other macrolide antibiotics data were not so useful. Clarithromycin, in particular, has been the intervention investigated in a number of underpowered or aborted studies, which have been reported only in abstract form. Despite provision of some IPD, it has not been possible to adequately assess and meta-analyse these studies.

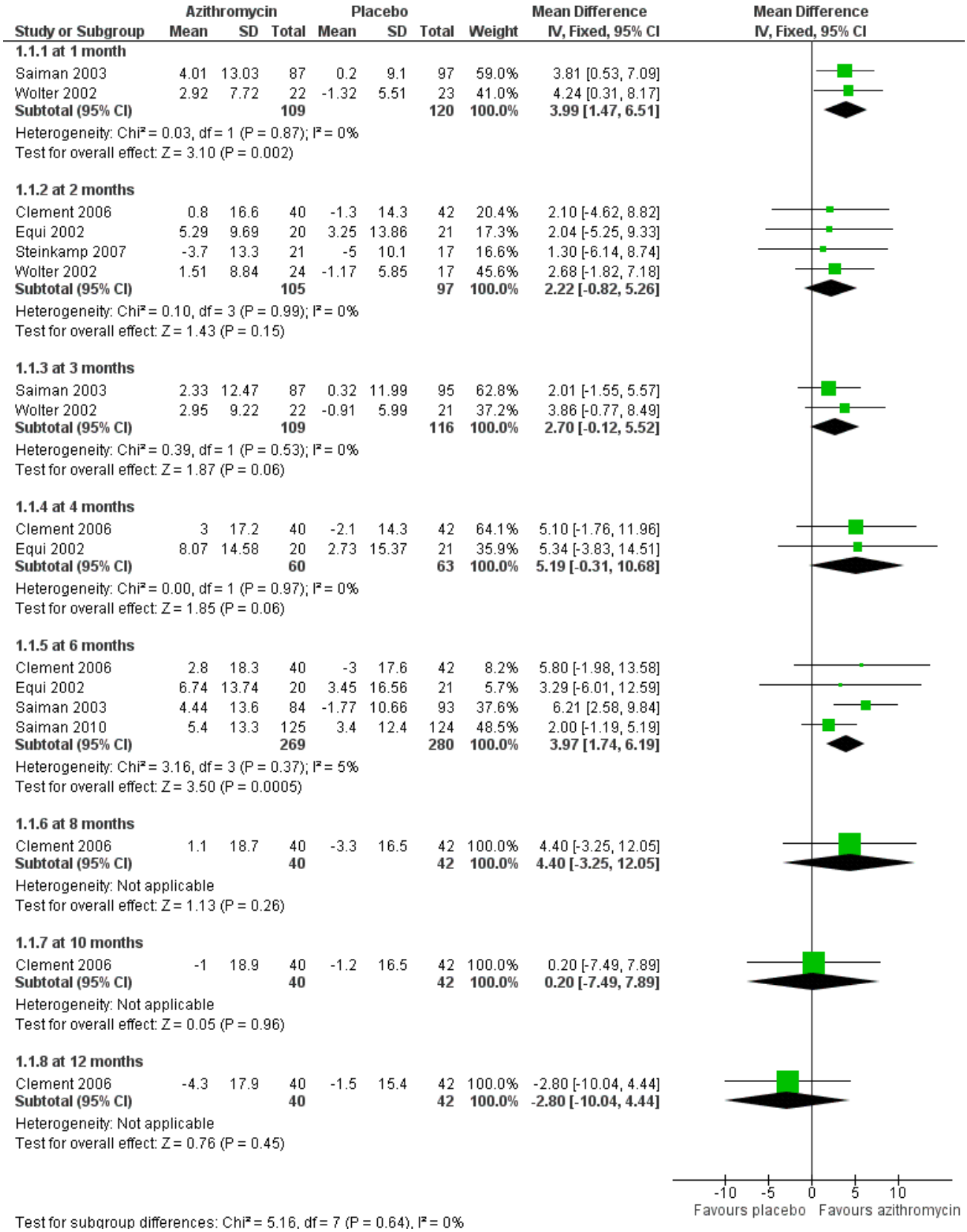
In contrast, study design and reporting has been good in six out of ten selected studies of azithromycin (Figure 1). Five of these studies examined placebo versus azithromycin (Clement 2006; Equi 2002; Saiman 2003; Saiman 2010; Wolter 2002) and one compared two dosing regimens (McCormack 2007). Despite some variation in study design and the length of intervention, meta-analysis of data has been possible.

Summary of main results

Treatment with azithromycin for six months resulted in a consistent improvement in respiratory function (relative change in FEV_1) compared to placebo (Figure 4). This improvement is small but of clinical significance in a condition that reports minimal reduction in respiratory function over time in stable patients. Two large studies published since the last update of this review did not report a significant difference in their primary outcome measure, relative change in FEV_1 (Clement 2006; Saiman 2010). The baseline

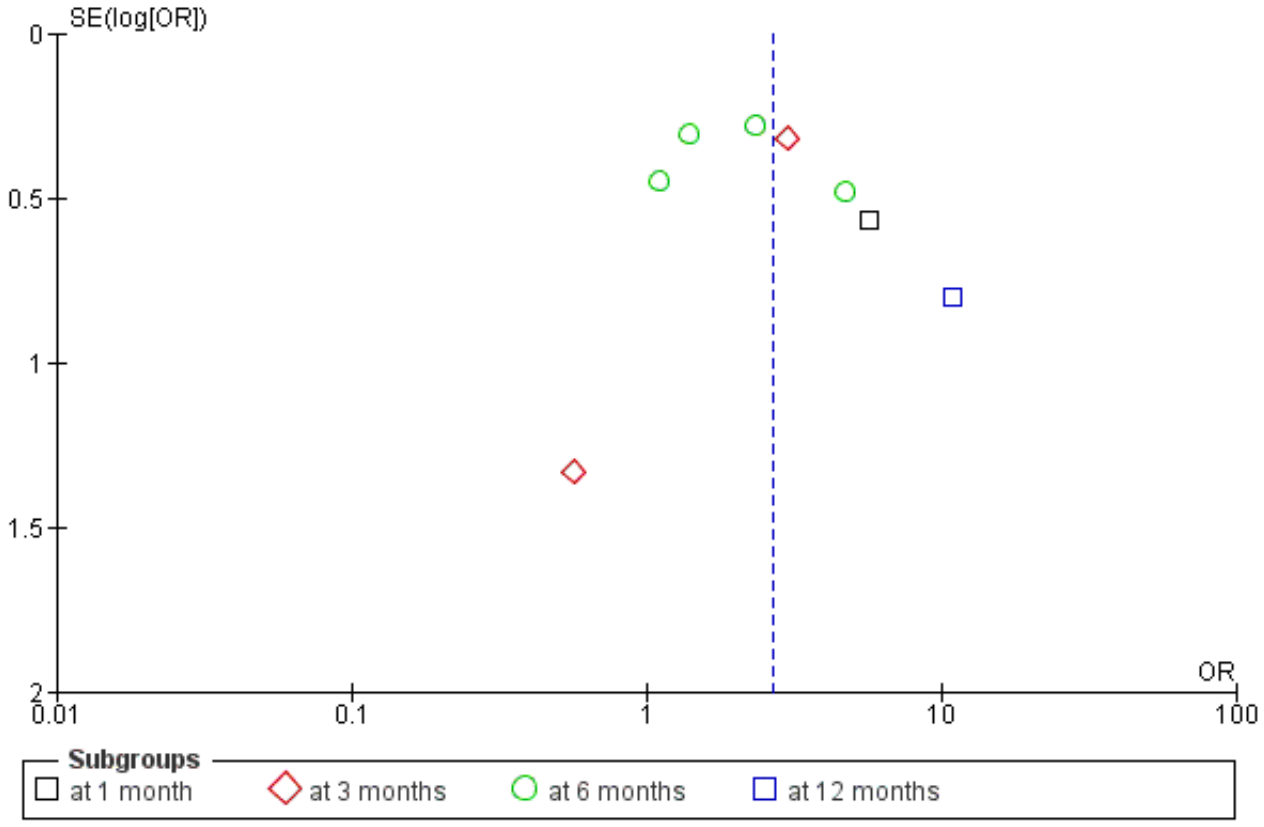
characteristics of these studies suggest that the patients had better respiratory condition than those enrolled in previous studies and this may have been a factor when considering the lack of improvement in the primary outcome. However, when aggregate data from these studies were included in the meta-analysis, the difference between interventions remained significant in favour of azithromycin (Figure 4). The magnitude of difference (4%) was less than that reported in our first meta-analysis (5.3%), but the confidence intervals were narrower reflecting the increased number of participants included (Figure 4). Homogeneity of the data up to six months further supports the validity of this finding (Figure 3). After six months, data were limited to one study (Clement 2006) and demonstrated a drift towards equivalence between placebo and azithromycin (Figure 4).

Figure 4. Forest plot of comparison: 1 Azithromycin versus placebo, outcome: 1.1 Relative change in FEV_1 (% predicted).



Patients treated with azithromycin for six months were approximately twice as likely to be free of respiratory exacerbation compared to placebo and, in contrast to relative change in FEV_1, this difference remained consistent beyond six months in the French study (Analysis 1.4). When examining respiratory exacerbation data from individual trials, it is evident that there is a degree of heterogeneity (in contrast to FEV_1 data). This is well illustrated in the funnel plot (Figure 5). Therefore caution needs to be exercised in the assessment of these results and further trials are required to confirm these findings. In an improving population, it may be that outcomes such as exacerbation have an increasing role in determining efficacy, it is important therefore that these outcomes are assessed and analysed in a robust and consistent manner. For this review a degree of manipulation of the available data was required in order to include all data in the meta-analysis.

Figure 5. Funnel plot of comparison: 1 Azithromycin versus placebo, outcome: 1.5 Free of pulmonary exacerbation.



Treatment with azithromycin was associated with a significant reduction in the need for additional oral antibiotic treatment (Analysis 1.15). The data were less conclusive with respect to a reduction in the need for intravenous antibiotic treatment (Analysis 1.19). Two studies reported significantly fewer courses and days on intravenous antibiotics (Clement 2006; Wolter 2002); however, combined data from the three studies that reported this as a dichotomous outcome did not support this finding (Equi 2002; Saiman 2003; Saiman 2010) (Analysis 1.18).

Reduction in treatment and fewer respiratory exacerbations are outcomes that have a direct positive impact on patients. It is disappointing therefore that the only patient-reported outcome, QoL, did not demonstrate any clear patterns with respect to azithromycin treatment (Effects of interventions, secondary outcome 9).

Other pragmatic outcomes, such as need for hospitalisation and eradication of *P. aeruginosa* have less consistent or negative results.

Over 600 children and adults have received azithromycin under the controlled environment of these clinical trials. Whilst an RCT is not the ideal mechanism to determine long-term safety, we can take some confidence from the small number of adverse events reported in these studies (Effects of interventions, secondary outcome 1). Initial concerns raised in the first North American study (Saiman 2003) were not reproduced in the second study on children (Saiman 2010) or in the French study (Clement 2006) (Effects of interventions, secondary outcome 1). In the second Australian study patients receiving the higher weekly dose of azithromycin had significantly more gastrointestinal adverse events compared to those on the daily regimen (McCormack 2007) (Analysis 2.3). Given the similar efficacy of these regimens, this represents a significant disadvantage of weekly dosing.

Microbiological data may give us some insight into the mechanism of action of azithromycin. Combined data from four studies, demonstrated that patients treated with azithromycin were less likely to have *S. aureus* identified on the respiratory cultures during the study (Analysis 1.8). Significant eradication of this

bacteria was not demonstrated (Effects of interventions, secondary outcome 4a). The second North American study demonstrated a significant increase in macrolide resistance in patients treated with azithromycin (Saiman 2010), which is consistent with other epidemiological studies that have highlighted the swift emergence of macrolide resistance in clinics that have prescribed azithromycin for all their patients (Hansen 2009; Phaff 2006; Tramper-Stranders 2007). The impact of this increase in macrolide resistance on efficacy is not clear. There was no evidence of emergence of other resistant bacteria during azithromycin treatment, such as NTM and *Burkholderia cepacia* complex.

Overall completeness and applicability of evidence

The combined data from these studies can provide us with confidence concerning the impact of azithromycin on respiratory function and other more pragmatic outcomes, such as need for oral antibiotics and risk of respiratory exacerbation. The studies have enrolled a broad range of patients over the age of six years, with and without chronic *P. aeruginosa* airway infection. To date, 959 children and adults have been enrolled in RCTs examining azithromycin for CF, of whom 632 have received azithromycin. No children below the age of six years have been recruited to these studies. This reflects the use of respiratory function as a primary outcome measure in all the studies and the difficulty in assessing this outcome in young children and infants. It is not possible, therefore, to comment on the applicability of this intervention in this younger age group. This is particularly pertinent following the expansion of newborn screening for CF and discrepancy in the advice regarding the need for long-term antibiotic prophylaxis in these infants (Smyth 2003).

The second confounding variable that needs to be considered is chronic infection of the airways with *P. aeruginosa*. The North American studies enrolled patients with chronic *P. aeruginosa* infection (Saiman 2003) and without (Saiman 2010). Others have enrolled both populations. The second North American study did not demonstrate a significant improvement in the primary outcome of relative change in FEV_1; however, when these data were included in the meta-analysis they did not change the overall result after six months and were consistent with other study results. In the French study sub-group analysis of patients with and without chronic *P. aeruginosa* infection did not alter the overall results, although data at six months were not presented.

The French study is the only one to examine outcomes beyond six months (Clement 2006) and further data are required to determine the impact of azithromycin on long-term outcomes.

Overall there is not sufficient evidence to advocate azithromycin therapy in any particular subgroup of patients (for example, children over six years of age or patients with chronic pseudomonas airway infection)

Quality of the evidence

This review has identified six studies with a low risk of bias (Figure 1). These studies enrolled 836 of the total 959 recruited patients. Data from the four studies with methodological concerns have not had any significant impact on the overall conclusions from the meta-analysis of efficacy outcomes, although numbers were too small for a formal sensitivity analysis (O'Connor 2009; Kabra 2010; Rotschild 2005; Steinkamp 2007). These studies have contributed to the overall safety data by reporting adverse events.

Potential biases in the review process

The mean and SD of the difference in relative change in FEV_1 was estimated at time points other than 12 months in the French study by measurements from a figure in the final publication (Clement 2006). Our previous experience with data from the Equi study suggests this is a valid technique, as subsequent IPD provided by those authors confirmed the accuracy of the process. The data from the French study represented the only results of this outcome measure beyond six months and we felt it important to include these data.

Agreements and disagreements with other studies or reviews

A previous meta-analysis by Florescu examined azithromycin for CF (Florescu 2009) and included data from four studies (Clement 2006; Equi 2002; Saiman 2003; Wolter 2002). Only data from the first arm of the English cross-over study were included (Equi 2002). The authors demonstrated a significant increase in FEV_1 with azithromycin compared to placebo, MD 3.53% (95% CI 0.0 to 7.1%) (P = 0.05). They reported significant heterogeneity, which is improved when data from patients chronically infected with *P. aeruginosa* were analysed separately. Whilst we have demonstrated a similar small but significant improvement in relative change in FEV_1, we do not agree with the conclusion that heterogeneity relates to *P. aeruginosa* infection. The reasons for this are:

1. we have included data from all time points reported in the French study (Clement 2006);
2. we do not feel it is appropriate to combine data from 6 and 12 months (we have reported data from each time point separately); and
3. we have included data from the most recent North American study (and other smaller studies).

With these factors, our data were more homogeneous and the impact of chronic *P. aeruginosa* infection was not apparent.

AUTHORS' CONCLUSIONS

Implications for practice

From the efficacy data presented in this review, there may be an argument that all adults and children over six years of age with CF should be offered therapy with azithromycin. Azithromycin therapy is associated with a small but consistent improvement in respiratory function at six months and appears to have a good safety profile. The three-times a week dosing regimen used by most studies represents a minimal treatment burden for patients and azithromycin is relatively inexpensive.

The evidence for treatment efficacy beyond six months is limited. One trial examined outcomes beyond six months and did not demonstrate a significant improvement in relative change in FEV_1; however, other more pragmatic outcomes (need for oral antibiotics and remaining free of respiratory exacerbation) were in favour of azithromycin.

A wider concern may relate to the emergence of macrolide resistance reported in the most recent study and the reports from other epidemiological studies of the emergence of macrolide resistance in clinics prescribing azithromycin for all their patients. Early reports suggest that this phenomenon does not have a negative impact on clinical well-being; however, it is a concern. If the mechanism of action of azithromycin relates to its anti-staphylococcal activity, then there may be agents with better potency and a narrower spectrum of action against *S. aureus* that are more appropriate to employ.

Two recent studies enrolled patients without chronic *P. aeruginosa* airway infection (Clement 2006; Saiman 2010). The fact that neither study demonstrated a statistically significant change in their primary outcome measure (relative change in FEV_1) supports the argument that azithromycin therapy is not appropriate in this patient group. However, when data from these studies were incorporated into our meta-analysis, they were consistent with previous studies and strengthened the finding of a small but significant improvement in FEV_1 after six months. We will continue to explore the impact of chronic *Pseudomonas* infection in an IPD analysis, but at present we do not feel there is sufficient evidence to preclude the use of azithromycin in this group of patients.

In view of the lack of long-term data and concerns over the emergence of macrolide-resistant strains of *S. aureus,* NTM and other bacteria, we do not feel that the current evidence is strong enough to support azithromycin therapy for all patients with CF. Given the consistent finding of a short-term improvement in FEV_1 in stable patients, there may be an argument for use in patients with poor respiratory condition despite maximal therapy or patients who have problems adhering to therapies (given the relatively infrequent dosing regimen). However, the intervention has not been formally evaluated in either of these circumstances.

A three-times a week dose of 500 mg (250 mg if weight less than 40 kg) has been employed in the North American studies and the French study, which together enrolled 547 patients (Table 1). All these studies have contributed to the positive efficacy data reported in this review and the drug appeared to be well-tolerated with this dosing regimen. A larger once-a-week dose was associated with significantly more gastrointestinal side effects, which probably precludes it as a dosing strategy for a long-term therapy.

Implications for research

1. There is an urgent need for a multi-centre RCT examining long-term antibiotic treatment for infants recognised through newborn screening. The findings of this review suggest that azithromycin should be considered as an intervention for such a trial; although given the relative lack of potency of azithromycin versus *S. aureus*, a comparison with another agent would be appropriate. The expansion of newborn screening and the international discrepancy in consensus statements highlights the need for a trial with pragmatic outcomes that are of relevance to families. The design and implementation of a trial that provides relevant long-term data and reassurance over safety will be challenging.
2. Clinics that currently employ azithromycin therapy should continue to monitor for and report adverse events, in particular relating to theoretical concerns over liver function and hearing. The emergence of macrolide resistance should also be recorded.
3. Data are required on the long-term efficacy of azithromycin, but in the current climate it seems unlikely that such studies will be organised.
4. Further studies are needed examining the dosing schedule (for example, a lower weekly dose).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Clement 2006

Methods	Randomised, multicentre, double-blind, placebo-controlled trial.
Participants	82 young people with CF (6-21 years, mean age 11.0 years, SD 3.3 years), 40 in azithromycin group, 42 in placebo group. 35 in treatment group and 37 in placebo group completed trial. FEV_1 >40% predicted.
Interventions	Azithromycin 250 mg tablet 3 times per week (>40 kg, 500 mg) versus placebo.
Outcomes	Relative change in FEV_1 & FVC % predicted, number of pulmonary exacerbations, additional antibiotic treatment (oral and IV), lung microbiology and adverse events.
Notes	French study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Centralised secure randomisation department".
Allocation concealment (selection bias)	Low risk	Centralised, study number assigned by interactive voice response system, study kits distributed by chief pharmacist in each centre.

Clement 2006 *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Identically packaged, all participants and investigators blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	A complete ITT analysis undertaken on primary outcome and pulmonary exacerbation data. Some per protocol analysis on other outcomes.
Selective reporting (reporting bias)	Unclear risk	Some data at intermediate time points not reported (requested from authors, who kindly provided some IPD, although intermediate time points not available).
Other bias	Low risk	None identified.

Equi 2002

Methods	Randomised placebo controlled cross-over trial.
Participants	41 children (8 to 18 years).
Interventions	Azithromycin, 250 mg (500 mg if weight > 40 kg) once a day for 6 months versus placebo.
Outcomes	% change in FEV_1 (average of 4 and 6 month values, also for FVC and MEF), hearing, sputum bacterial densities, inflammatory markers, exercise tolerance, subjective well-being.
Notes	Treatment arms not reported individually, these have subsequently been calculated for the first arm from figures provided in the paper and IPD kindly provided by the authors.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Provided by Statistics Dept at Pfizer, USA.
Allocation concealment (selection bias)	Low risk	Hospital Pharmacy department, described in detail.
Blinding (performance bias and detection bias) All outcomes	Low risk	All parties involved, identical packaging for intervention and placebo.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete ITT analysis undertaken on primary outcome. Not clear from paper whether primary outcome was a *post hoc* protocol change, but subsequent correspondence has confirmed that this was determined *a priori.*
Selective reporting (reporting bias)	Low risk	Not clear if primary outcome calculation (months 4 and 6 averaged for relative change) was an *a priori* decision.
Other bias	Low risk	Adequate washout, authors have provided IPD.

Kabra 2010

Methods	Randomised study comparing 2 doses of azithromycin.
Participants	Children with CF (5-18 years). 56/105 children screened were randomised, 47 completed 12 months follow-up.
Interventions	High (15 mg/kg/day) versus low (5 mg/kg/day) dose of azithromycin for 12 months.
Outcomes	Change in FEV_1 (% predicted), pulmonary exacerbation (hospitalisation), microbiology, antibiotic use.
Notes	Children admitted if breathlessness or hypoxia occurred with exacerbation (suggests severe respiratory compromise).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated blocks of 4.
Allocation concealment (selection bias)	Unclear risk	Not clear if patients or physicians knew of allocation to high or low dose.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	As above.
Incomplete outcome data (attrition bias) All outcomes	High risk	Primary outcome assessed on per protocol basis not ITT.
Selective reporting (reporting bias)	High risk	Only limited time points reported, patients seen monthly. All outcomes measured were reported, but not completely.
Other bias	High risk	More boys in the high-dose group.

McCormack 2007

Methods	Multicentre parallel RCT comparing 2 dosing regimens (daily versus weekly) of azithromycin.
Participants	208 CF patients (6-58 years).
Interventions	250 mg daily versus 1200 mg weekly doses of azithromycin.
Outcomes	Change in FEV_1 (%) at 1,3 and 6 months from baseline. Also time to PEx, adverse effects, days in hospital, QoL, changes in inflammatory markers, acquisition of azithromycin resistant *S. aureus*.
Notes	Australian study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Microsoft Excel program used by Mater Hospital Pharmacy to generate randomisation schedule.

McCormack 2007 *(Continued)*

Allocation concealment (selection bias)	Low risk	By hospital pharmacy staff (code A or B seen by them and then removed prior to allocation).
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical capsules, all parties involved were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	A clear ITT analysis of the primary outcome and time to first exacerbation.
Selective reporting (reporting bias)	Low risk	Some data requested from authors (QoL, relative change in FEV_1 and weight z scores).
Other bias	Low risk	None identified.

O'Connor 2009

Methods	Single centre randomised double blind cross-over study.
Participants	CF patients, aged 6-20 years (mean, 11.7 years).
Interventions	Azithromycin, 250 mg (or 500 if weight >40 kg) 3 times a week or placebo for 4 months, then following 2-month washout period cross-over to other arm for 4 months.
Outcomes	Primary: comparative change in FEV_1. Also QoL and nutritional parameters. Adverse events.
Notes	Northern Ireland study.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated random numbers in pharmacy.
Allocation concealment (selection bias)	High risk	Placebo were coloured red and the intervention brown (known by pharmacy but not investigators, CF team or participants, but resulted in speculation).
Blinding (performance bias and detection bias) All outcomes	High risk	See above, a concern.
Incomplete outcome data (attrition bias) All outcomes	Low risk	21 randomised and completed first arm. 4 dropped out for second arm and not included in comparative analysis.
Selective reporting (reporting bias)	Low risk	All outcomes measured were reported.
Other bias	Low risk	None identified.

Rotschild 2005

Methods	Single centre randomised placebo controlled study.
Participants	18 CF patients (5.5-36.3 years, median 15.1). Diagnosis not clear, mean sweat chloride, 74.5 mg/L. One patient had 5T mutation (associated with a milder phenotype).
Interventions	Azithromycin (10 patients) 250 mg twice a week for 12 weeks versus placebo (8 patients).
Outcomes	BPI-ANCA levels in the blood (a possible marker of inflammation). Also respiratory function. Also secondary outcomes not fully reported (authors contacted). Overall weight gain in both groups, but wide range and differences not reported.
Notes	Israeli study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not described.
Allocation concealment (selection bias)	Low risk	By hospital pharmacy staff independent of trial staff
Blinding (performance bias and detection bias) All outcomes	Low risk	Tablets identical in colour and shape.
Incomplete outcome data (attrition bias) All outcomes	High risk	3 patients dropped out and were not included in analysis.
Selective reporting (reporting bias)	High risk	Patients seen at 4, 8 and 12 weeks, but data only reported for week 12.
Other bias	High risk	Visual analogue scale not validated.

Saiman 2003

Methods	Multicentre randomised placebo-controlled trial.
Participants	185 participants: adults and children with CF (> 6 years) with chronic *P. aeruginosa* chest infection (> 1 year) and an FEV_1 >30% predicted.
Interventions	Azithromycin, 500 mg (250 mg if weight <40 kg) 3 days a week versus placebo.
Outcomes	Primary: relative change in FEV_1 (% predicted). Secondary: adverse events, self-reported symptoms, audiology and laboratory tests, respiratory cultures, relative change in FVC (% predicted), body weight, PEx (number and time to), hospitalisation rate, use of non-quinolone antibiotics, inflammatory markers, and QoL.
Notes	First North American Study.

Risk of bias

Saiman 2003 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	By CF TDN Co-ordinating Centre. Randomisation included a valid allocation strategy to ensure equivalence between placebo and intervention with respect to weight, respiratory function and site of study.
Allocation concealment (selection bias)	Low risk	Centralised secure randomisation system at the co-ordinating centre.
Blinding (performance bias and detection bias) All outcomes	Low risk	All study personnel and participants.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Clear ITT analysis of primary outcome.
Selective reporting (reporting bias)	Low risk	Outcomes clearly reported. Subsequent subgroup analysis published separately.
Other bias	Low risk	None identified.

Saiman 2010

Methods	Multi-centre placebo-controlled parallel design.
Participants	Young CF patients (6-18 years) without chronic *P. aeruginosa* airway infection (clear (2 or more cultures) for > 12 months)
Interventions	Azithromycin (250 mg 3 times a week, increased to 500, if weight >36 kg) versus placebo; for 6 months.
Outcomes	Primary: relative change in FEV_1 from baseline. Secondary: respiratory exacerbations; treatment requirements; and adverse events. Acquisition of resistant bacteria in respiratory culture. Authors contacted for full data on nutritional outcomes.
Notes	Second North American study.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	University of South Florida generated assignments via secure centralized randomisation system.
Allocation concealment (selection bias)	Low risk	Data co-ordinating centre distributed blinded study drug kits.
Blinding (performance bias and detection bias) All outcomes	Low risk	Identically packaged tablets.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Modified ITT analysis (3 patients in placebo arm did not receive study drug and were removed) of primary outcome and most others.

Saiman 2010 *(Continued)*

Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Low risk	Very clearly reported study.

Steinkamp 2007

Methods	Double-blind placebo-controlled study from 10 German and 1 Swiss centre.
Participants	38/40 screened patients were randomised. Mean age (SD), 24.8 years (10.0).
Interventions	Azithromycin (once a week, dose from 500-1250 mg depending on weight) versus placebo for 8 weeks, following a course of IV antibiotic treatment.
Outcomes	Change in pulmonary function tests from baseline, adverse events, change in QoL domains, inflammatory markers in sputum.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Allocation was undertaken centrally using a computer-generated sequence.
Allocation concealment (selection bias)	Low risk	Allocation was organised centrally with support from the Clinical Trials Officer.
Blinding (performance bias and detection bias) All outcomes	Low risk	Indentical look and taste of tablets.
Incomplete outcome data (attrition bias) All outcomes	Low risk	A clear ITT analysis of the primary outcome. Some secondary outcomes analysed per protocol.
Selective reporting (reporting bias)	High risk	All measured outcomes reported, some provided by authors directly (QoL). Data from outcomes beyond 8 weeks not reported.
Other bias	High risk	Duration of study was shortened after commencement of study and data only reported for 8 weeks (correspondence with Prof Steinkamp).

Wolter 2002

Methods	Randomised placebo-controlled trial.
Participants	60 adult participants. Mean age 27.9 (SD, 6.5). The placebo group contained more men (20/30 versus 9/30), was taller, heavier and had better lung function (FEV_1 mean (SD), 62.3 (24.8) versus 50.9 (18.3)).
Interventions	Azithromycin, 250 mg once a day for 3 months versus placebo.

Wolter 2002 *(Continued)*

Outcomes	% change in FEV_1 (FVC), weight, QoL, inflammatory markers, microbiology, respiratory exacerbations.
Notes	Patients recruited from two adult clinics in Brisbane (first Australian study).

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Hospital pharmacy staff, exact method not stated ("randomised prior to commencement of study").
Allocation concealment (selection bias)	Low risk	By hospital pharmacy.
Blinding (performance bias and detection bias) All outcomes	Low risk	Identical capsules and number, all parties blind.
Incomplete outcome data (attrition bias) All outcomes	Low risk	ITT analysis performed on primary outcome, others reported per protocol.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Unclear risk	Baseline characteristics significantly different between interventions, see above "Participants".

AB: antibiotic
BPI-ANCA: bactericidal or permeability-increasing protein
CF: cystic fibrosis
FEV_1: forced expiratory volume at one second
FVC: forced vital capacity
IPD: individual patient data
ITT: intention to treat
IV: intravenous
MEF: maximum expiratory flow
P. aeruginosa: *Pseudomonas aeruginosa*
PEx: pulmonary exacerbation
QoL: quality of life
Relative change in FEV_1: ((Intervention value - Baseline value)*100)/Baseline value
S. aureus: *Staphylococcal aureus*
SD: standard deviation
TDN: therapeutics development network

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

Study	Reason for exclusion
Aaron 2005	Intervention is not a macrolide antibiotic.
Anstead 1999	Not a randomised controlled trial. An open study.
Anstead 2001	Small RCT presented in abstract form only. Not able to assess study design, randomisation process or results. Authors contacted for more details (2002).

Study	Reason for exclusion
Baumann 2000	Not a randomised controlled trial. An open prospective study.
Beringer 2005	Open label pharmacokinetic study on adults, results suggest considerable intracellular accumulation of azithromycin and no dose adjustment required for CF patients who are pancreatic insufficient.
Cipolli 2001	Randomised but open label short-term (5 days) pharmacokinetic study of 2 dosing regimens (500 versus 1000 mg azithromycin a day) on adult patients.
Dionyssopoulou 2005	Authors report randomised trial of roxithromycin in CF patients in abstract form. No details of study design, randomisation process or whether placebo used. Authors contacted for further details in 2005.
Dogru 2004	Small randomised cross-over study of clarithromycin versus placebo. Results presented in abstract form; not able to assess study design design, randomisation process or results. Authors contacted for further details (2004 and 2006).
Frederiksen 2001	Authors report a randomised cross-over study of clarithromycin (500 bd) versus placebo in abstract form. Not able to assess study design, randomisation process or results from abstract. Large number of drop outs from study (20/41) and lack of positive findings probably influenced the decision not to submit for publication. Authors contacted and kindly provided protocol, suggesting adequate sequence generation, allocation and blinding, however it was not possible to analyse the data provided as it was not in a manner that permits analysis (2001).
Jaffe 1998	Not a randomised controlled trial. Open study.
Jensen 2005	Not a randomised controlled trial.
Kessaris 2003	Authors present results in abstract form only, describing small (n = 12) RCT of clarithromycin versus placebo for six months. Not able to assess randomisation process or results from the abstract. Authors contacted for further information and results (2006).
Ordonez 2001	Not randomised controlled trial. A single-blinded prospective pilot study.
Pirzada 1999	Retrospective case control study, no randomisation.
Pukhalsky 2001	Not a randomised controlled trial.
Radionovitch 2005	Authors confirm not randomised. Treatments allocated in open manner.
Rubin 2003	Study described as an RCT, examining the impact of clarithromycin on airway ion transport. Nasal PD data published, suggesting no impact of clarithromycin on airway ion transport.
Shmarina 2004	Study comparing clarithromycin to nimesulide not to placebo, another antibiotic class, another macrolide or the same macrolide at a different dose.
Sriram 2003	Study presented in abstract form. Authors approached and have kindly provided protocol which suggests adequate randomisation processes. No aggregate data available, it has not been possible to analyse the limited IPD provided due to format.

bd: twice daily
CF: cystic fibrosis
IPD: individual patient data
PD: potential difference
RCT: randomised controlled trial

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

Elmasry 2010

Methods	Randomised (no details of method given) parallel study. Duration 24 weeks.
Participants	49 participants with CF. Mean (SD) age 33.4 (8) years. Mean (SD) baseline FEV_1 % predicted 59.9 (21.5)%
Interventions	Azithromycin either 1 g weekly (n=22) or 1.5 g 3x per week (n=27).
Outcomes	Total adherence (total medication taken / total medication prescribed), total number of days adhered (number of days prescribed doses taken / number of days monitored), pill counts, pharmacy pick-up, self-reports using a Morisky and a Beliefs and Behaviour Questionnaire, FEV_1 % predicted.
Notes	Supported by ARC Linkage grant, Roche Australia Pty. Ltd

Pukhalsky 2008

Methods	Parallel study, not clear if randomised.
Participants	160 participants with CF, 100 healthy controls (children). Of CF participants, 90 received no anti-inflammatory treatment, 70 received anti-inflammatory treatment.
Interventions	Anti-inflammatory treatment (either azithromycin at a dose of 500 mg orally 3x per week (n=48) or alternated course of prednisolone at a dose of 0.3 mg/kg body weight every other day (n=22) versus no treatment.
Outcomes	Plasma cytokines, hepatobiliary abnormalities (portal hypertension, cirrhosis).
Notes	

ARC: Australian Research Council
CF: cystic fibrosis
FEV_1: forced expiratory volume at one second
SD: standard deviation

DATA AND ANALYSES

Comparison 1. Azithromycin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Relative change in FEV_1 (% predicted)	6		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1 at 1 month	2	229	Mean Difference (IV, Fixed, 95% CI)	3.99 [1.47, 6.51]
1.2 at 2 months	4	202	Mean Difference (IV, Fixed, 95% CI)	2.22 [-0.82, 5.26]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.3 at 3 months	2	225	Mean Difference (IV, Fixed, 95% CI)	2.70 [-0.12, 5.52]
1.4 at 4 months	2	123	Mean Difference (IV, Fixed, 95% CI)	5.19 [-0.31, 10.68]
1.5 at 6 months	4	549	Mean Difference (IV, Fixed, 95% CI)	3.97 [1.74, 6.19]
1.6 at 8 months	1	82	Mean Difference (IV, Fixed, 95% CI)	4.4 [-3.25, 12.05]
1.7 at 10 months	1	82	Mean Difference (IV, Fixed, 95% CI)	0.20 [-7.49, 7.89]
1.8 at 12 months	1	82	Mean Difference (IV, Fixed, 95% CI)	-2.8 [-10.04, 4.44]
2 Absolute change in FEV_1 (% predicted)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 At 2 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Percentage change in FVC	4		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 at 1 month	2	225	Mean Difference (IV, Fixed, 95% CI)	1.89 [-0.42, 4.19]
3.2 at 2 months	2	76	Mean Difference (IV, Fixed, 95% CI)	5.42 [1.79, 9.05]
3.3 at 3 months	2	220	Mean Difference (IV, Fixed, 95% CI)	1.95 [-0.35, 4.26]
3.4 at 4 months	1	41	Mean Difference (IV, Fixed, 95% CI)	2.55 [-5.37, 10.47]
3.5 at 6 months	2	218	Mean Difference (IV, Fixed, 95% CI)	4.57 [1.71, 7.42]
3.6 at 12 months	1	82	Mean Difference (IV, Fixed, 95% CI)	2.7 [-2.88, 8.28]
4 Free of pulmonary exacerbation	5		Odds Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 at 1 month	1	185	Odds Ratio (M-H, Random, 95% CI)	5.66 [1.86, 17.23]
4.2 at 3 months	2	203	Odds Ratio (M-H, Random, 95% CI)	2.16 [0.59, 7.97]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.3 at 6 months	4	609	Odds Ratio (M-H, Random, 95% CI)	1.96 [1.15, 3.33]
4.4 at 12 months	1	82	Odds Ratio (M-H, Random, 95% CI)	10.77 [2.26, 51.34]
5 Mild adverse effects of antibiotic treatment	4		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
5.1 Nausea	2	445	Odds Ratio (M-H, Fixed, 95% CI)	1.69 [0.99, 2.87]
5.2 Diarrhoea	3	527	Odds Ratio (M-H, Fixed, 95% CI)	1.39 [0.78, 2.45]
5.3 Wheezing	2	445	Odds Ratio (M-H, Fixed, 95% CI)	2.13 [1.07, 4.25]
5.4 Cough	2	445	Odds Ratio (M-H, Fixed, 95% CI)	0.46 [0.30, 0.69]
5.5 Productive cough	1	260	Odds Ratio (M-H, Fixed, 95% CI)	0.36 [0.17, 0.79]
5.6 Sore throat	2	445	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.57, 1.26]
5.7 Increased sputum	1	185	Odds Ratio (M-H, Fixed, 95% CI)	0.67 [0.37, 1.20]
5.8 Rhinorrhea	2	445	Odds Ratio (M-H, Fixed, 95% CI)	0.91 [0.59, 1.38]
5.9 Headache	3	527	Odds Ratio (M-H, Fixed, 95% CI)	0.84 [0.56, 1.27]
5.10 Abdominal pain	3	527	Odds Ratio (M-H, Fixed, 95% CI)	0.90 [0.59, 1.38]
5.11 Fever	3	527	Odds Ratio (M-H, Fixed, 95% CI)	0.65 [0.43, 0.97]
5.12 Fatigue	2	445	Odds Ratio (M-H, Fixed, 95% CI)	0.66 [0.39, 1.09]
5.13 Dyspnea	1	185	Odds Ratio (M-H, Fixed, 95% CI)	1.11 [0.57, 2.15]
5.14 Nasal congestion	2	445	Odds Ratio (M-H, Fixed, 95% CI)	1.07 [0.72, 1.58]
5.15 Hemoptysis	2	267	Odds Ratio (M-H, Fixed, 95% CI)	0.65 [0.33, 1.28]
5.16 Dizziness (except vertigo)	1	185	Odds Ratio (M-H, Fixed, 95% CI)	1.90 [0.78, 4.63]
5.17 Vomiting	3	527	Odds Ratio (M-H, Fixed, 95% CI)	0.83 [0.52, 1.32]
5.18 Decreased lung function	2	445	Odds Ratio (M-H, Fixed, 95% CI)	0.95 [0.51, 1.76]
5.19 Decreased appetite	1	185	Odds Ratio (M-H, Fixed, 95% CI)	0.97 [0.43, 2.18]
5.20 Hearing impairment	1	185	Odds Ratio (M-H, Fixed, 95% CI)	1.13 [0.07, 18.31]
5.21 Tinnitus	1	185	Odds Ratio (M-H, Fixed, 95% CI)	1.13 [0.07, 18.31]
5.22 Pulmonary congestion	1	185	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.53, 2.23]

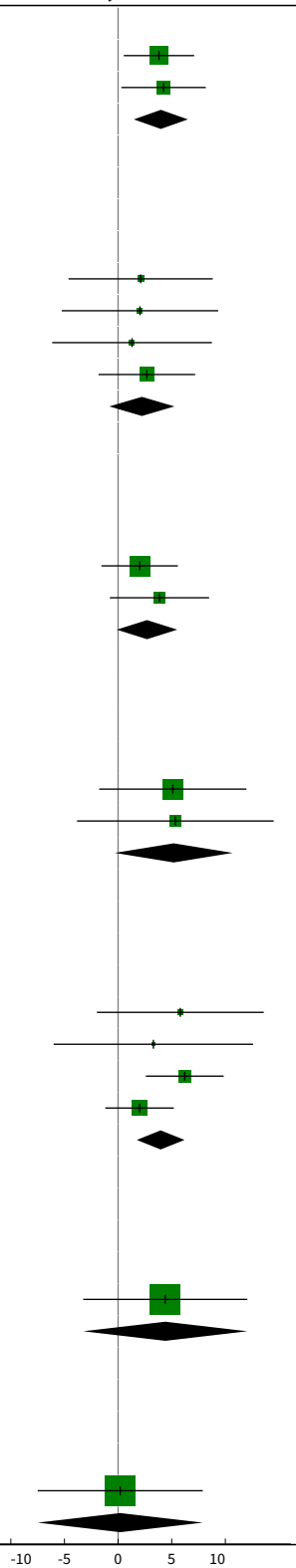
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.23 Rash	1	82	Odds Ratio (M-H, Fixed, 95% CI)	0.2 [0.01, 4.30]
5.24 Total	1	38	Odds Ratio (M-H, Fixed, 95% CI)	1.14 [0.31, 4.20]
6 Admission to hospital	2		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
6.1 After 6 months	2	445	Odds Ratio (M-H, Fixed, 95% CI)	0.61 [0.36, 1.04]
7 Acquisition of *Pseudomonas aeruginosa*	2	258	Odds Ratio (M-H, Fixed, 95% CI)	0.64 [0.15, 2.78]
7.1 after 6 months	1	176	Odds Ratio (M-H, Fixed, 95% CI)	0.64 [0.15, 2.78]
7.2 after 12 months	1	82	Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Acquisition of *Staphylococcal aureus*	4	353	Odds Ratio (M-H, Fixed, 95% CI)	0.25 [0.12, 0.51]
8.1 after 2 months	1	31	Odds Ratio (M-H, Fixed, 95% CI)	0.05 [0.00, 0.99]
8.2 after 6 months	2	240	Odds Ratio (M-H, Fixed, 95% CI)	0.31 [0.14, 0.71]
8.3 after 12 months	1	82	Odds Ratio (M-H, Fixed, 95% CI)	0.19 [0.02, 1.70]
9 Eradication of *Staphylococcal aureus* present at baseline	2	220	Odds Ratio (M-H, Fixed, 95% CI)	1.94 [0.92, 4.10]
9.1 after 6 months	1	181	Odds Ratio (M-H, Fixed, 95% CI)	1.56 [0.70, 3.46]
9.2 after 12 months	1	39	Odds Ratio (M-H, Fixed, 95% CI)	11.90 [0.60, 237.96]
10 Acquisition of macrolide-resistant *Staphylococcal aureus*	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
10.1 after 6 months	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Acquisition of MRSA	3	477	Odds Ratio (M-H, Fixed, 95% CI)	1.33 [0.60, 2.98]
11.1 after 6 months	2	395	Odds Ratio (M-H, Fixed, 95% CI)	1.43 [0.57, 3.60]
11.2 after 12 months	1	82	Odds Ratio (M-H, Fixed, 95% CI)	1.05 [0.20, 5.56]
12 Acquisition of *Haemophilus influenzae*	2	320	Odds Ratio (M-H, Fixed, 95% CI)	1.12 [0.44, 2.88]
12.1 after 6 months	1	238	Odds Ratio (M-H, Fixed, 95% CI)	1.20 [0.31, 4.57]
12.2 after 12 months	1	82	Odds Ratio (M-H, Fixed, 95% CI)	1.06 [0.28, 3.97]
13 Acquisition of macrolide-resistant *Haemophilus influenzae*	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
13.1 after 6 months	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

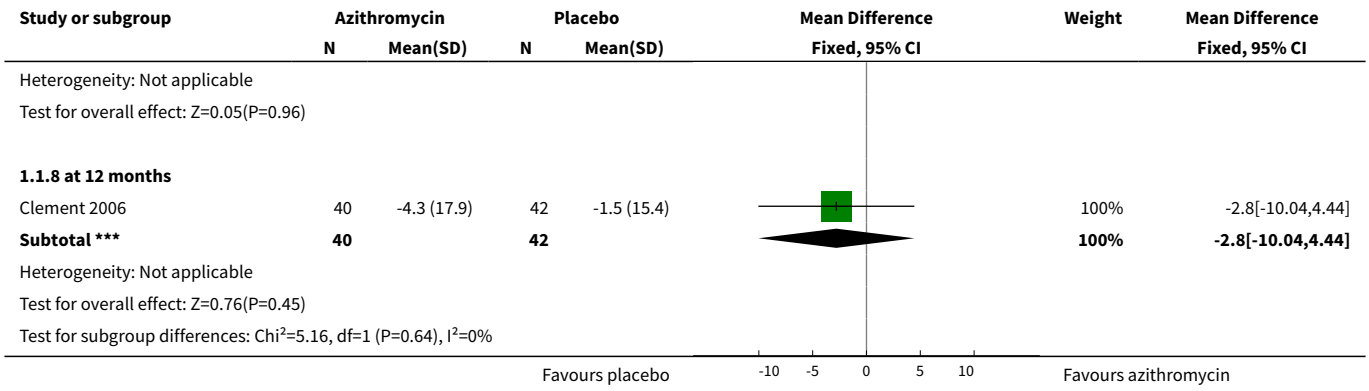
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14 Acquisition of non-tuberculous mycobacterium	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
14.1 After 6 months	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15 Need for additional oral antibiotics	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 After 6 months	3	527	Odds Ratio (M-H, Fixed, 95% CI)	0.28 [0.19, 0.42]
16 Number of courses of oral antibiotics	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
16.1 after 12 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
17 Number of days of additional oral antibiotics	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
17.1 after 12 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
18 Need for intravenous antibiotics	3		Odds Ratio (M-H, Fixed, 95% CI)	Subtotals only
18.1 After 6 months	3	527	Odds Ratio (M-H, Fixed, 95% CI)	0.78 [0.49, 1.23]
19 Number of courses of intravenous antibiotics	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
19.1 After 12 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
20 Number of days of intravenous antibiotics	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
20.1 after 12 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
21 Development of allergic bronchopulmonary aspergillosis	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
21.1 after 12 months	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
22 Change in BMI z score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
22.1 at 12 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
23 Change in weight	2		Mean Difference (Fixed, 95% CI)	0.62 [0.26, 0.98]
24 Change in total quality of life score (CFQ-R)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
24.1 at 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
25 Change in physical domain of CFQ-R QoL score	2	205	Mean Difference (IV, Fixed, 95% CI)	2.84 [0.26, 5.42]
25.1 at 2 months	1	28	Mean Difference (IV, Fixed, 95% CI)	8.4 [-8.25, 25.05]
25.2 at 6 months	1	177	Mean Difference (IV, Fixed, 95% CI)	2.7 [0.09, 5.31]
26 Change in psychosocial domain of CFQ-R QoL score	2	204	Mean Difference (IV, Fixed, 95% CI)	0.08 [-3.14, 3.30]
26.1 at 2 months	1	27	Mean Difference (IV, Fixed, 95% CI)	-2.70 [-12.74, 7.34]
26.2 at 6 months	1	177	Mean Difference (IV, Fixed, 95% CI)	0.40 [-3.00, 3.80]
27 Change in body image domain of CFQ-R QoL score	2	205	Mean Difference (IV, Fixed, 95% CI)	2.73 [-0.54, 6.01]
27.1 at 2 months	1	28	Mean Difference (IV, Fixed, 95% CI)	-1.80 [-12.54, 8.94]
27.2 at 6 months	1	177	Mean Difference (IV, Fixed, 95% CI)	3.2 [-0.24, 6.64]
28 Change in respiratory symptom domain of CFQ-R QoL score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
28.1 at 2 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
29 Change in eating disorder domain of CFQ-R QoL score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
29.1 at 2 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
30 Change in problems with body weight domain of the CFQ-R QoL score	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
30.1 at 2 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
31 Change in CRP	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
31.1 After 2 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

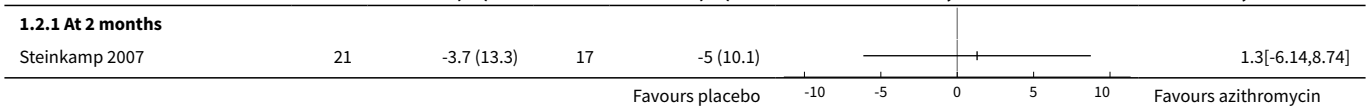
Analysis 1.1. Comparison 1 Azithromycin versus placebo, Outcome 1 Relative change in FEV_1 (% predicted).

Study or subgroup	Azithromycin N	Azithromycin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
1.1.1 at 1 month							
Saiman 2003	87	4 (13)	97	0.2 (9.1)		58.95%	3.81[0.53,7.09]
Wolter 2002	22	2.9 (7.7)	23	-1.3 (5.5)		41.05%	4.24[0.31,8.17]
Subtotal ***	**109**		**120**			**100%**	**3.99[1.47,6.51]**
Heterogeneity: Tau^2=0; Chi^2=0.03, df=1(P=0.87); I^2=0%							
Test for overall effect: Z=3.1(P=0)							
1.1.2 at 2 months							
Clement 2006	40	0.8 (16.6)	42	-1.3 (14.3)		20.42%	2.1[-4.62,8.82]
Equi 2002	20	5.3 (9.7)	21	3.3 (13.9)		17.35%	2.04[-5.25,9.33]
Steinkamp 2007	21	-3.7 (13.3)	17	-5 (10.1)		16.65%	1.3[-6.14,8.74]
Wolter 2002	24	1.5 (8.8)	17	-1.2 (5.9)		45.58%	2.68[-1.82,7.18]
Subtotal ***	**105**		**97**			**100%**	**2.22[-0.82,5.26]**
Heterogeneity: Tau^2=0; Chi^2=0.1, df=3(P=0.99); I^2=0%							
Test for overall effect: Z=1.43(P=0.15)							
1.1.3 at 3 months							
Saiman 2003	87	2.3 (12.5)	95	0.3 (12)		62.8%	2.01[-1.55,5.57]
Wolter 2002	22	3 (9.2)	21	-0.9 (6)		37.2%	3.86[-0.77,8.49]
Subtotal ***	**109**		**116**			**100%**	**2.7[-0.12,5.52]**
Heterogeneity: Tau^2=0; Chi^2=0.39, df=1(P=0.53); I^2=0%							
Test for overall effect: Z=1.87(P=0.06)							
1.1.4 at 4 months							
Clement 2006	40	3 (17.2)	42	-2.1 (14.3)		64.08%	5.1[-1.76,11.96]
Equi 2002	20	8.1 (14.6)	21	2.7 (15.4)		35.92%	5.34[-3.83,14.51]
Subtotal ***	**60**		**63**			**100%**	**5.19[-0.31,10.68]**
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.97); I^2=0%							
Test for overall effect: Z=1.85(P=0.06)							
1.1.5 at 6 months							
Clement 2006	40	2.8 (18.3)	42	-3 (17.6)		8.18%	5.8[-1.98,13.58]
Equi 2002	20	6.7 (13.7)	21	3.5 (16.6)		5.72%	3.29[-6.01,12.59]
Saiman 2003	84	4.4 (13.6)	93	-1.8 (10.7)		37.61%	6.21[2.58,9.84]
Saiman 2010	125	5.4 (13.3)	124	3.4 (12.4)		48.49%	2[-1.19,5.19]
Subtotal ***	**269**		**280**			**100%**	**3.97[1.74,6.19]**
Heterogeneity: Tau^2=0; Chi^2=3.16, df=3(P=0.37); I^2=5.07%							
Test for overall effect: Z=3.5(P=0)							
1.1.6 at 8 months							
Clement 2006	40	1.1 (18.7)	42	-3.3 (16.5)		100%	4.4[-3.25,12.05]
Subtotal ***	**40**		**42**			**100%**	**4.4[-3.25,12.05]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.13(P=0.26)							
1.1.7 at 10 months							
Clement 2006	40	-1 (18.9)	42	-1.2 (16.5)		100%	0.2[-7.49,7.89]
Subtotal ***	**40**		**42**			**100%**	**0.2[-7.49,7.89]**

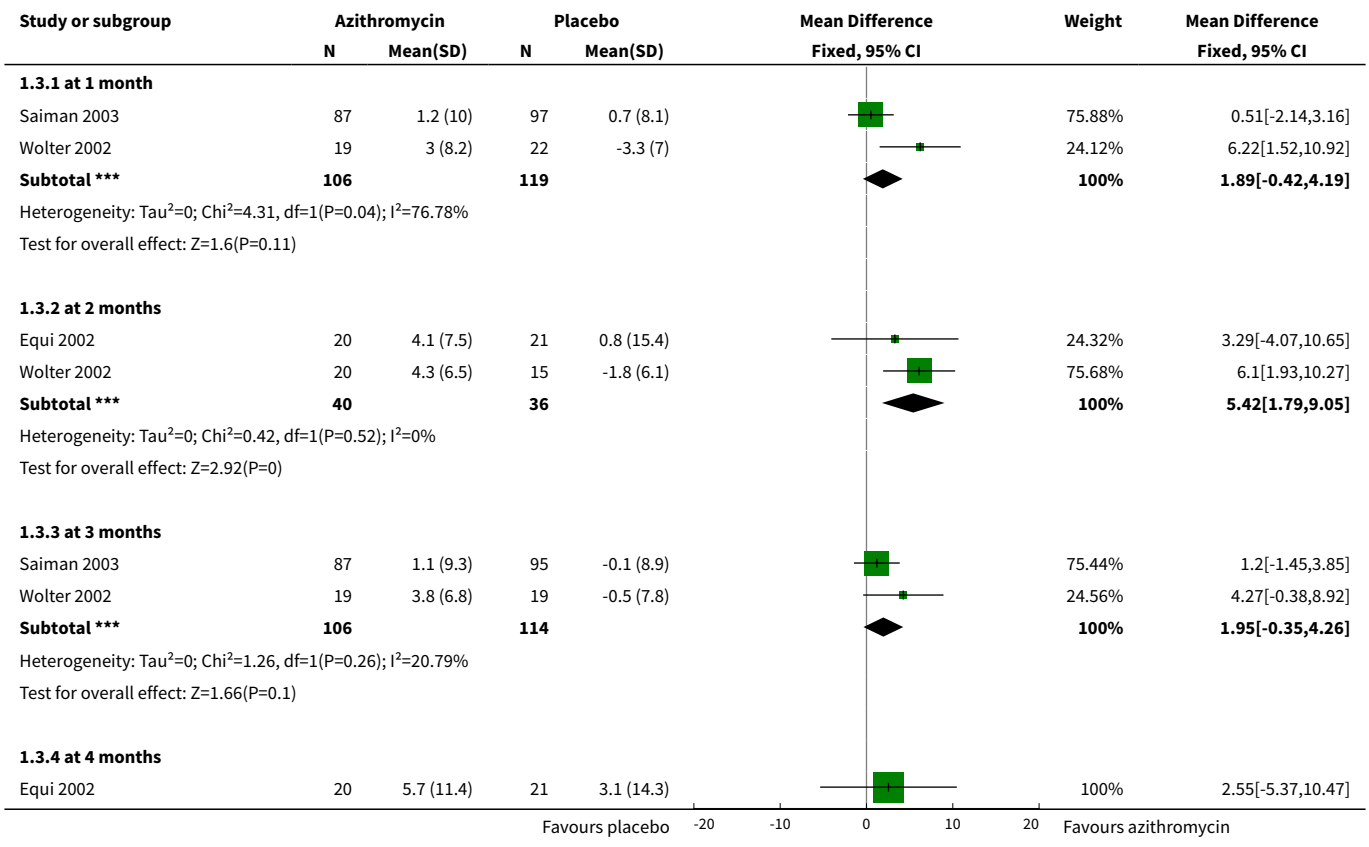


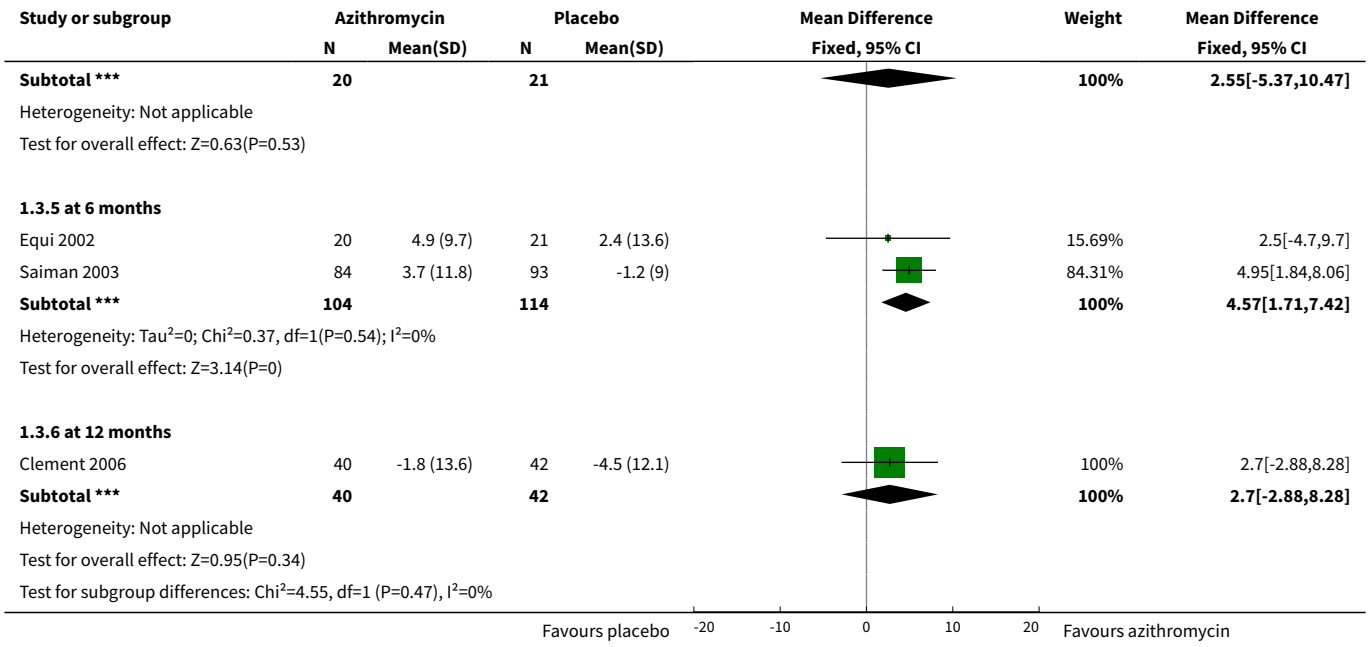


Analysis 1.2. Comparison 1 Azithromycin versus placebo, Outcome 2 Absolute change in FEV_1 (% predicted).

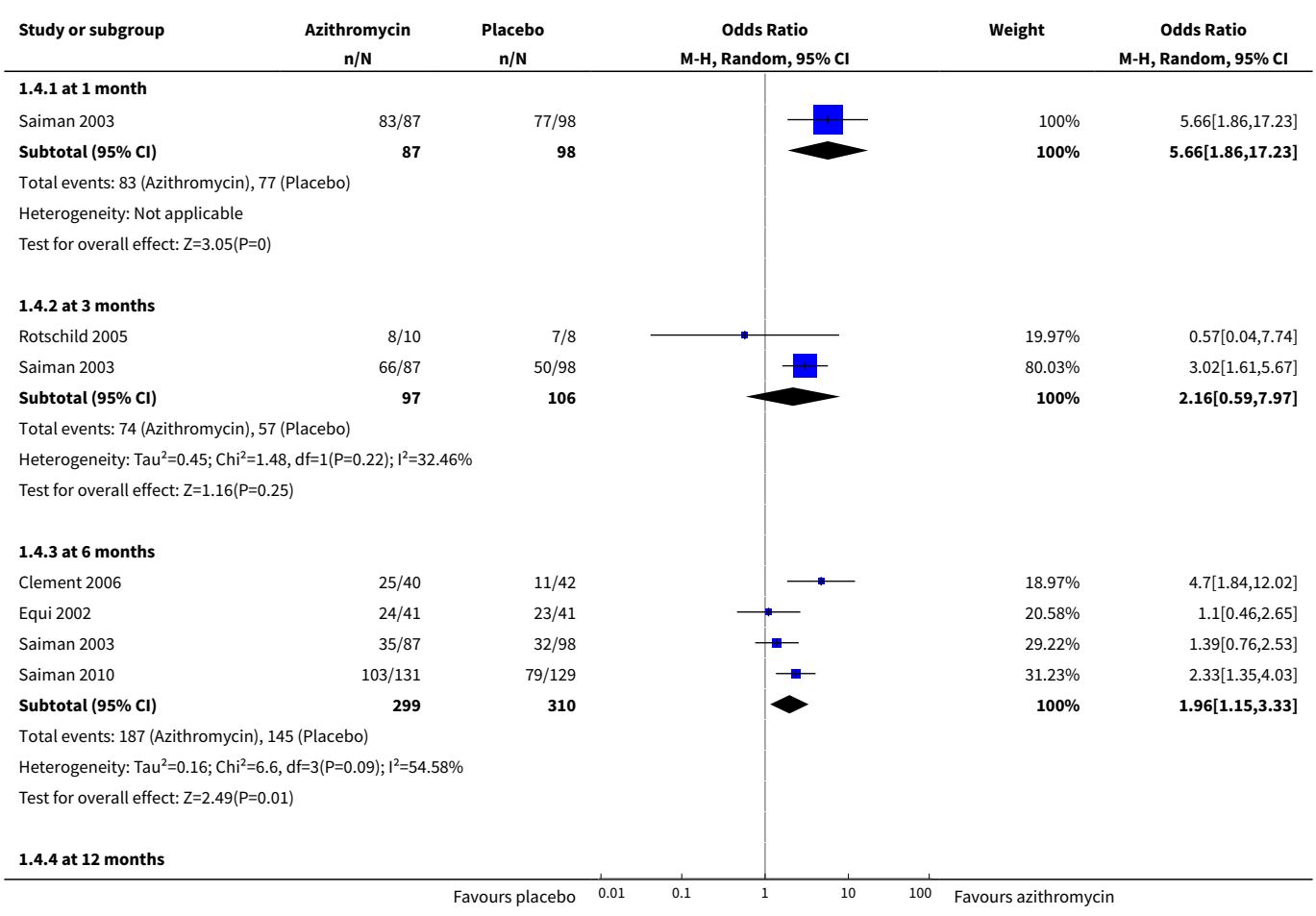


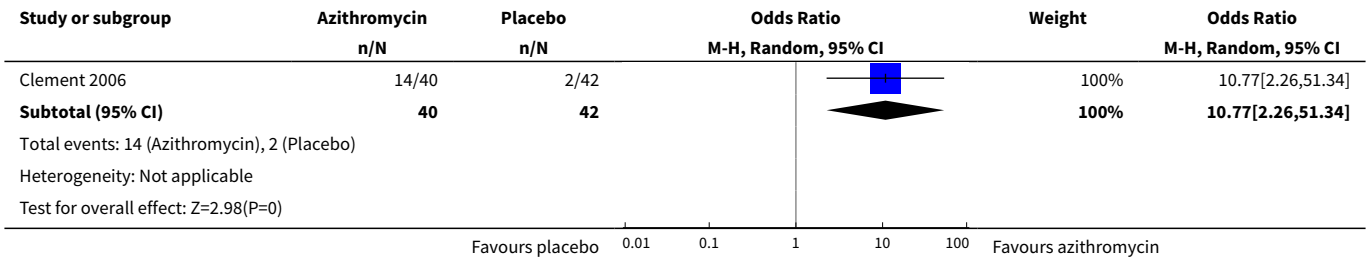
Analysis 1.3. Comparison 1 Azithromycin versus placebo, Outcome 3 Percentage change in FVC.



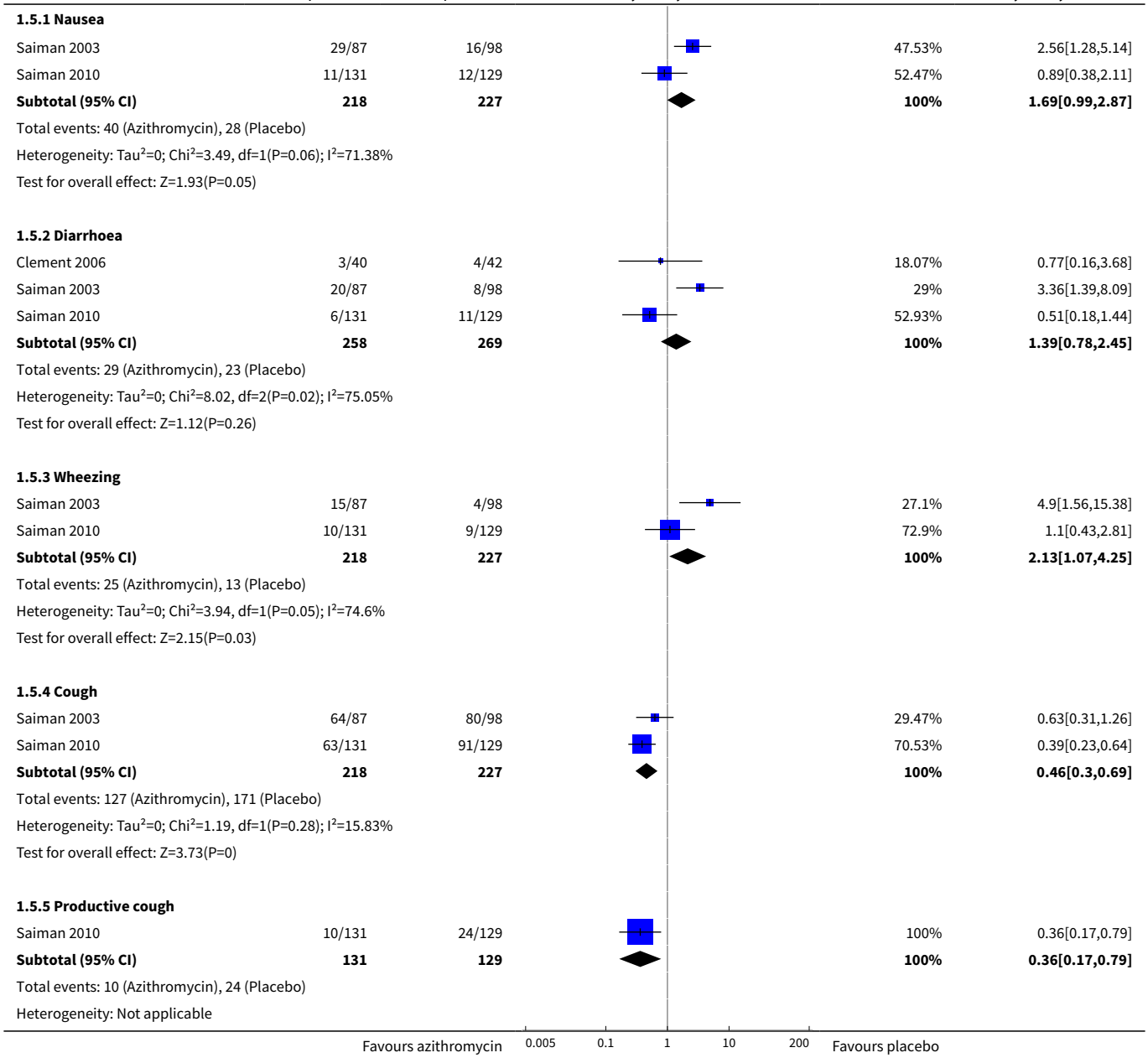


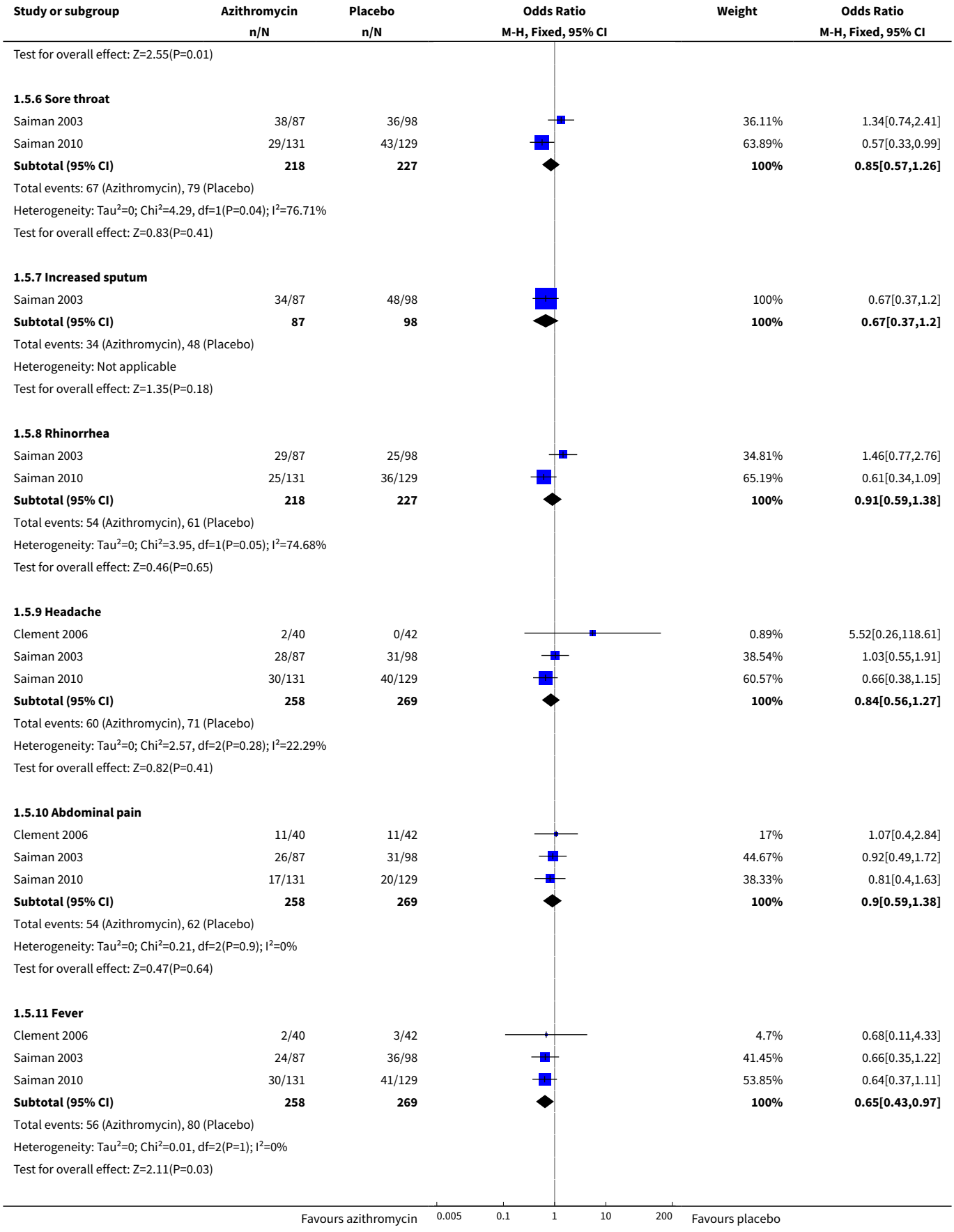
Analysis 1.4. Comparison 1 Azithromycin versus placebo, Outcome 4 Free of pulmonary exacerbation.



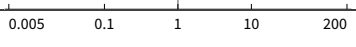


Analysis 1.5. Comparison 1 Azithromycin versus placebo, Outcome 5 Mild adverse effects of antibiotic treatment.



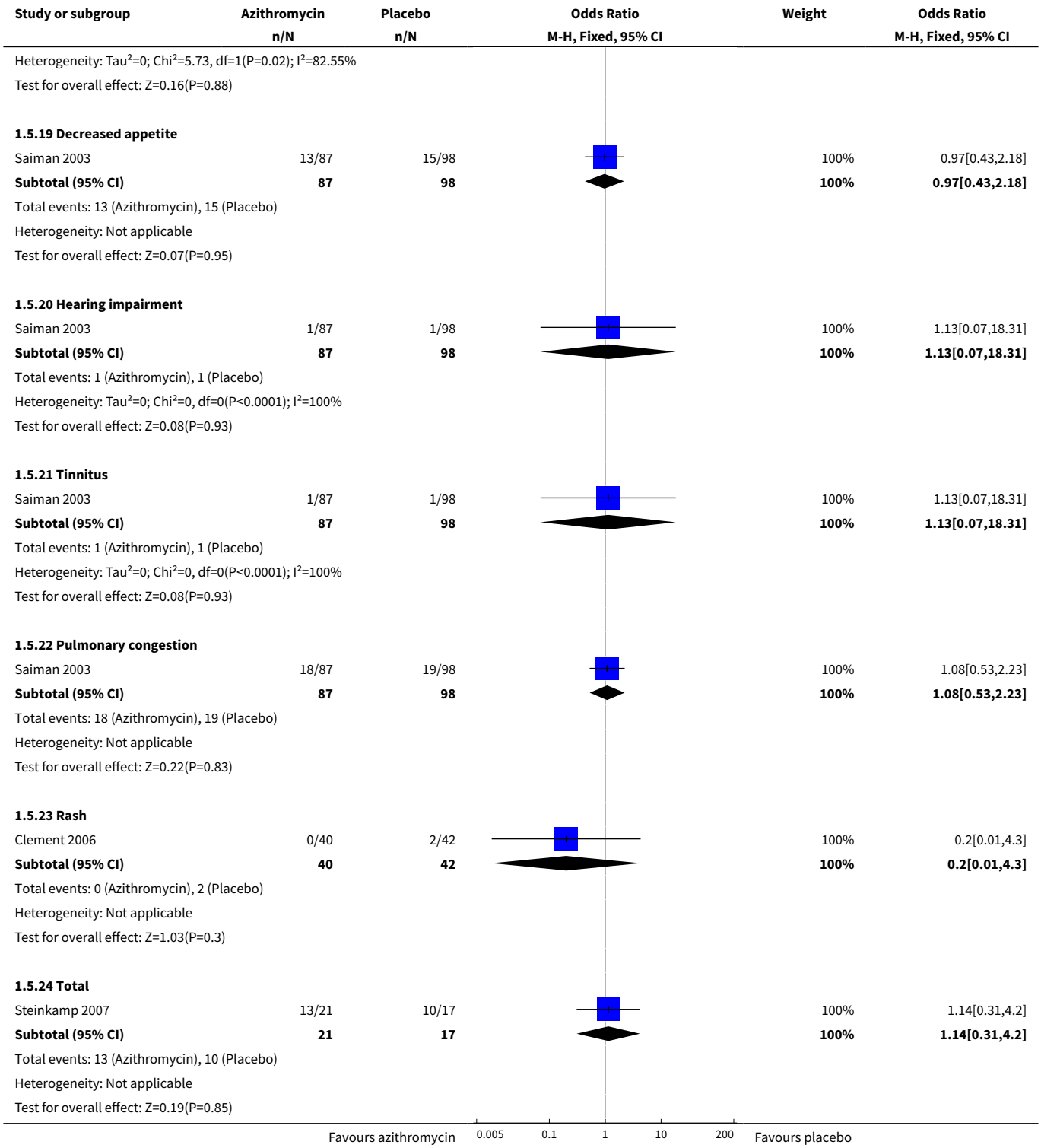


Study or subgroup	Azithromycin n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.5.12 Fatigue					
Saiman 2003	24/87	36/98		66.77%	0.66[0.35,1.22]
Saiman 2010	9/131	13/129		33.23%	0.66[0.27,1.6]
Subtotal (95% CI)	**218**	**227**		**100%**	**0.66[0.39,1.09]**
Total events: 33 (Azithromycin), 49 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=1); I^2=0%					
Test for overall effect: Z=1.61(P=0.11)					
1.5.13 Dyspnea					
Saiman 2003	23/87	24/98		100%	1.11[0.57,2.15]
Subtotal (95% CI)	**87**	**98**		**100%**	**1.11[0.57,2.15]**
Total events: 23 (Azithromycin), 24 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.3(P=0.76)					
1.5.14 Nasal congestion					
Saiman 2003	33/87	36/98		43.07%	1.05[0.58,1.91]
Saiman 2010	45/131	42/129		56.93%	1.08[0.65,1.81]
Subtotal (95% CI)	**218**	**227**		**100%**	**1.07[0.72,1.58]**
Total events: 78 (Azithromycin), 78 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.94); I^2=0%					
Test for overall effect: Z=0.34(P=0.73)					
1.5.15 Hemoptysis					
Clement 2006	0/40	2/42		11.3%	0.2[0.01,4.3]
Saiman 2003	17/87	25/98		88.7%	0.71[0.35,1.43]
Subtotal (95% CI)	**127**	**140**		**100%**	**0.65[0.33,1.28]**
Total events: 17 (Azithromycin), 27 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.63, df=1(P=0.43); I^2=0%					
Test for overall effect: Z=1.25(P=0.21)					
1.5.16 Dizziness (except vertigo)					
Saiman 2003	14/87	9/98		100%	1.9[0.78,4.63]
Subtotal (95% CI)	**87**	**98**		**100%**	**1.9[0.78,4.63]**
Total events: 14 (Azithromycin), 9 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.41(P=0.16)					
1.5.17 Vomiting					
Clement 2006	2/40	0/42		1.2%	5.52[0.26,118.61]
Saiman 2003	14/87	15/98		30.92%	1.06[0.48,2.35]
Saiman 2010	22/131	31/129		67.89%	0.64[0.35,1.18]
Subtotal (95% CI)	**258**	**269**		**100%**	**0.83[0.52,1.32]**
Total events: 38 (Azithromycin), 46 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.54, df=2(P=0.28); I^2=21.37%					
Test for overall effect: Z=0.79(P=0.43)					
1.5.18 Decreased lung function					
Saiman 2003	13/87	7/98		27%	2.28[0.87,6.02]
Saiman 2010	8/131	16/129		73%	0.46[0.19,1.11]
Subtotal (95% CI)	**218**	**227**		**100%**	**0.95[0.51,1.76]**
Total events: 21 (Azithromycin), 23 (Placebo)					



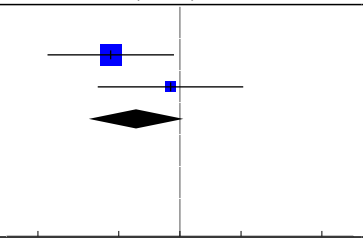
Favours azithromycin

Favours placebo



Analysis 1.6. Comparison 1 Azithromycin versus placebo, Outcome 6 Admission to hospital.

Study or subgroup	Azithromycin n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.6.1 After 6 months					
Saiman 2003	14/87	29/98		65.79%	0.46[0.22,0.94]
Saiman 2010	12/131	13/129		34.21%	0.9[0.39,2.05]
Subtotal (95% CI)	**218**	**227**		**100%**	**0.61[0.36,1.04]**
Total events: 26 (Azithromycin), 42 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=1.48, df=1(P=0.22); I^2=32.48%					
Test for overall effect: Z=1.82(P=0.07)					

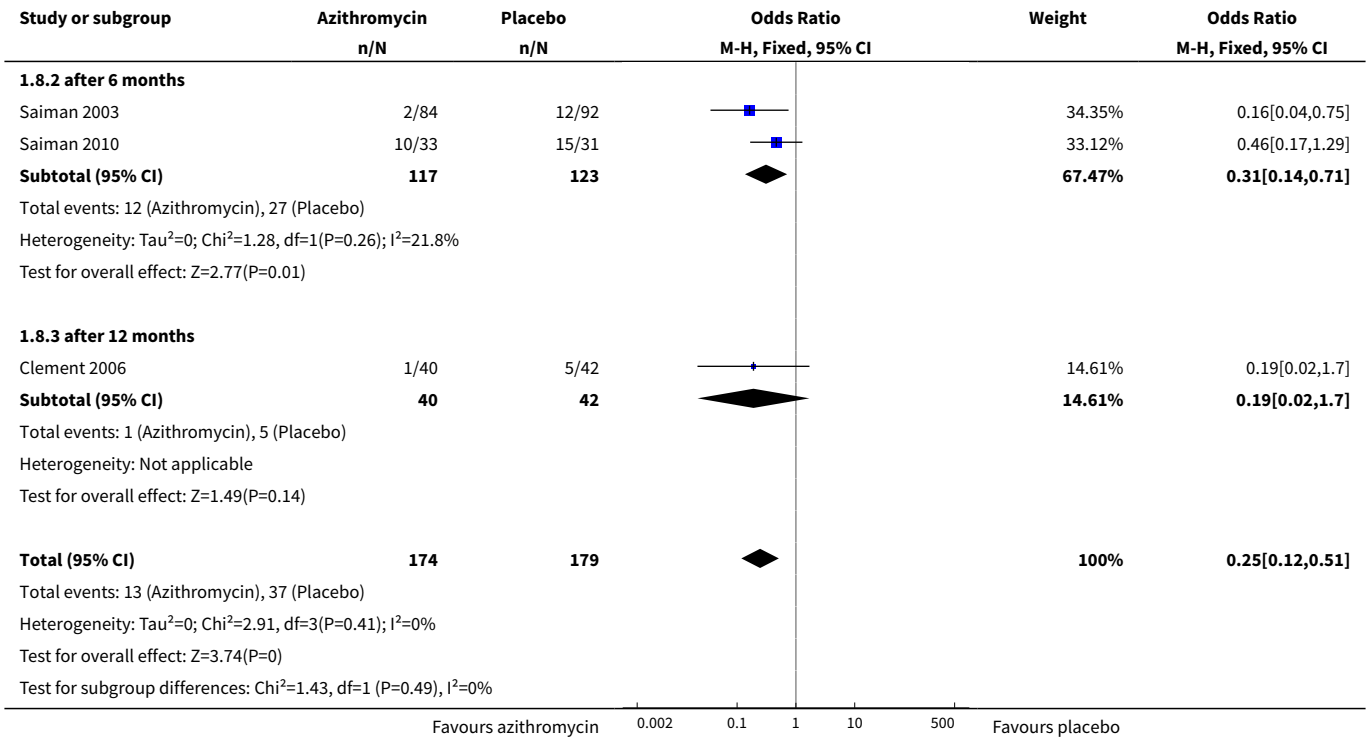


Analysis 1.7. Comparison 1 Azithromycin versus placebo, Outcome 7 Acquisition of *Pseudomonas aeruginosa*.

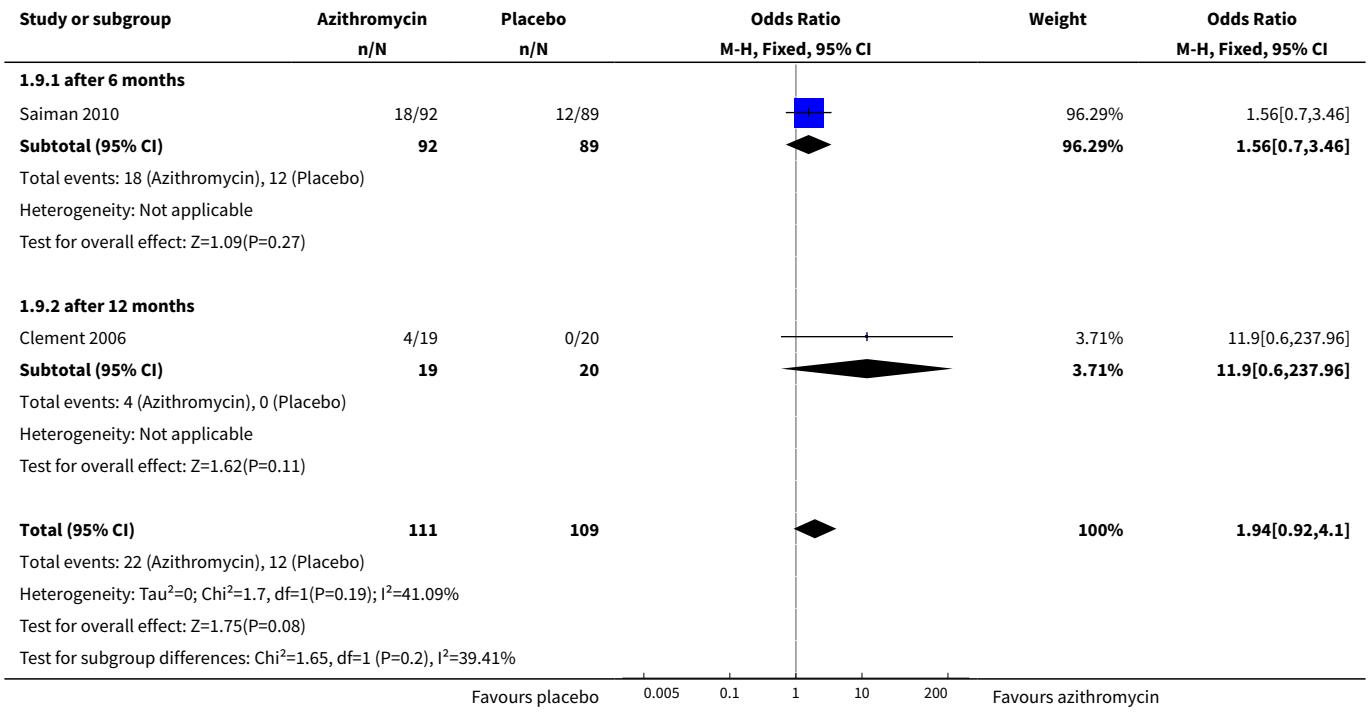
Study or subgroup	Azithromycin n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.7.1 after 6 months					
Saiman 2003	3/84	5/92		100%	0.64[0.15,2.78]
Subtotal (95% CI)	**84**	**92**		**100%**	**0.64[0.15,2.78]**
Total events: 3 (Azithromycin), 5 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.59(P=0.56)					
1.7.2 after 12 months					
Clement 2006	0/40	0/42			Not estimable
Subtotal (95% CI)	**40**	**42**			**Not estimable**
Total events: 0 (Azithromycin), 0 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**124**	**134**		**100%**	**0.64[0.15,2.78]**
Total events: 3 (Azithromycin), 5 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.59(P=0.56)					
Test for subgroup differences: Chi^2=0, df=1 (P<0.0001), I^2=100%					

Analysis 1.8. Comparison 1 Azithromycin versus placebo, Outcome 8 Acquisition of *Staphylococcal aureus*.

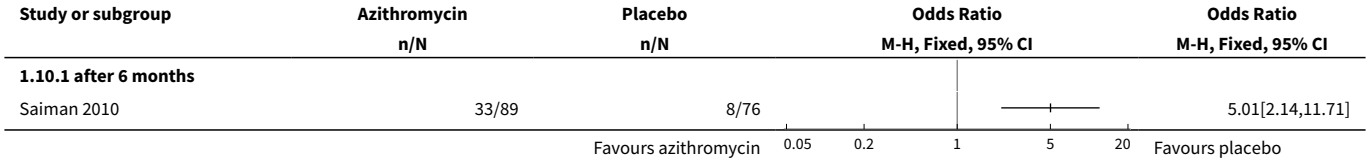
Study or subgroup	Azithromycin n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.8.1 after 2 months					
Steinkamp 2007	0/17	5/14		17.92%	0.05[0,0.99]
Subtotal (95% CI)	**17**	**14**		**17.92%**	**0.05[0,0.99]**
Total events: 0 (Azithromycin), 5 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=1.97(P=0.05)					



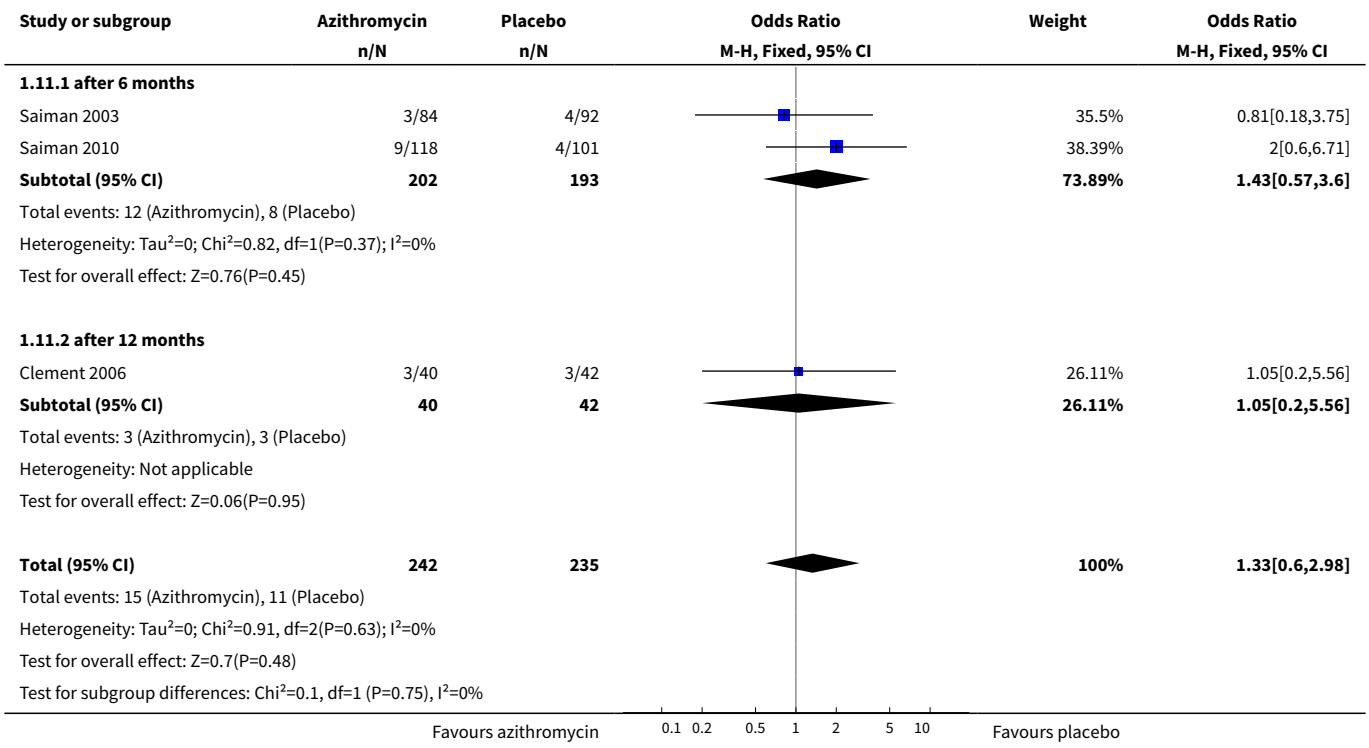
Analysis 1.9. Comparison 1 Azithromycin versus placebo, Outcome 9 Eradication of *Staphylococcal aureus* present at baseline.



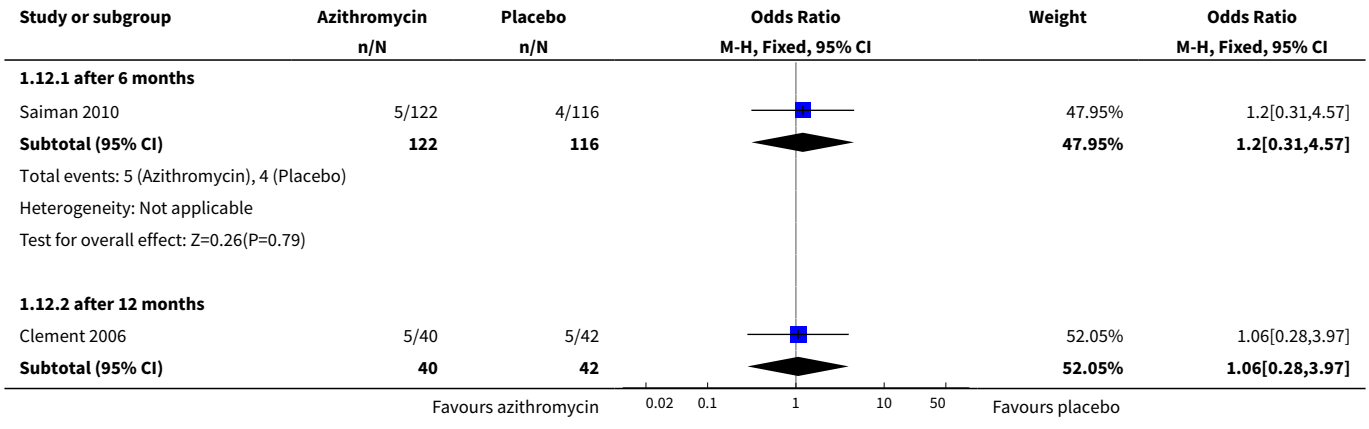
Analysis 1.10. Comparison 1 Azithromycin versus placebo, Outcome 10 Acquisition of macrolide-resistant *Staphylococcal aureus*.

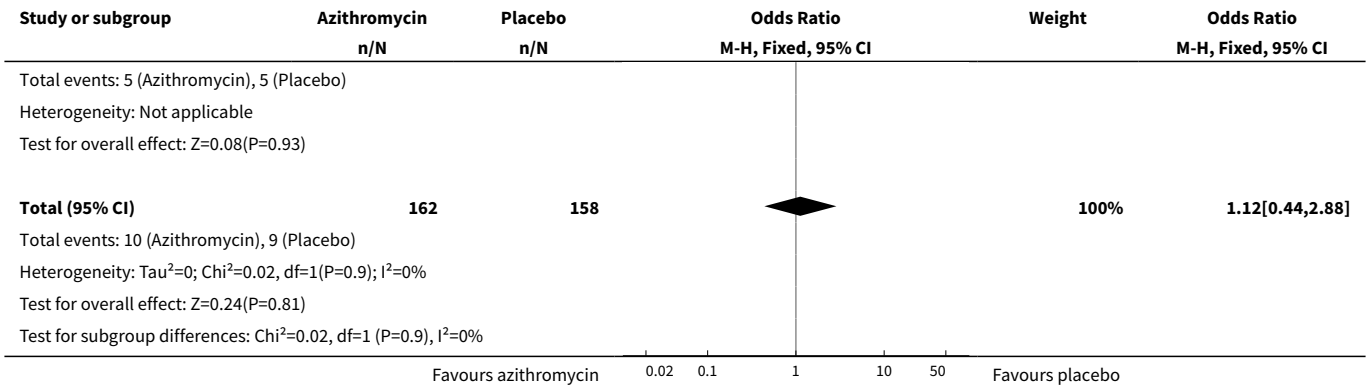


Analysis 1.11. Comparison 1 Azithromycin versus placebo, Outcome 11 Acquisition of MRSA.

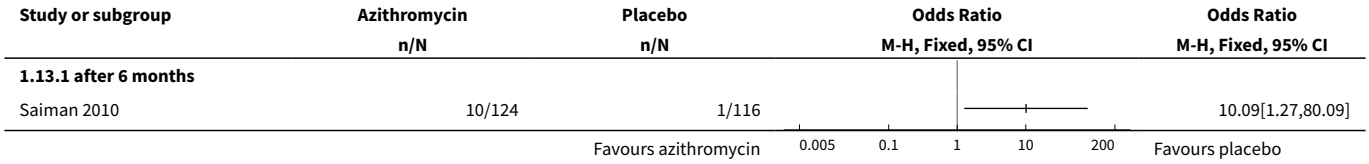


Analysis 1.12. Comparison 1 Azithromycin versus placebo, Outcome 12 Acquisition of *Haemophilus influenzae*.

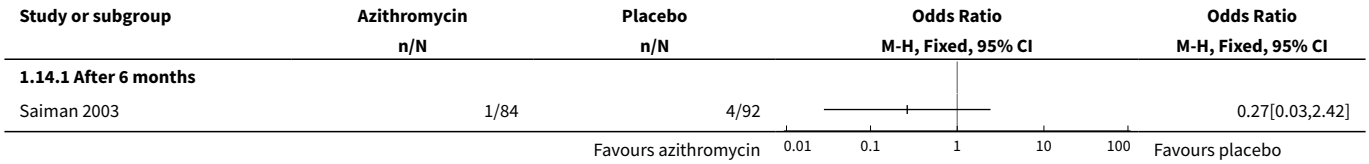




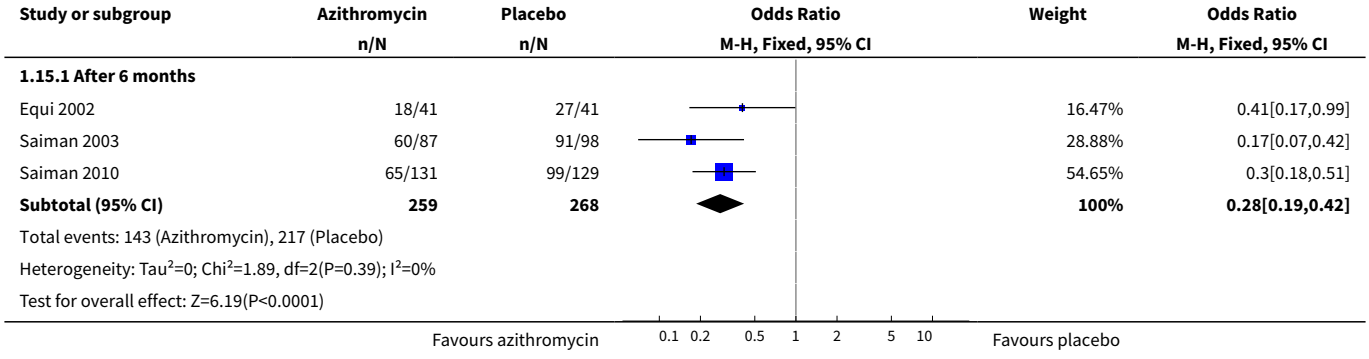
Analysis 1.13. Comparison 1 Azithromycin versus placebo, Outcome 13 Acquisition of macrolide-resistant *Haemophilus influenzae*.



Analysis 1.14. Comparison 1 Azithromycin versus placebo, Outcome 14 Acquisition of non-tuberculous mycobacterium.

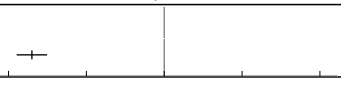


Analysis 1.15. Comparison 1 Azithromycin versus placebo, Outcome 15 Need for additional oral antibiotics.



Analysis 1.16. Comparison 1 Azithromycin versus placebo, Outcome 16 Number of courses of oral antibiotics.

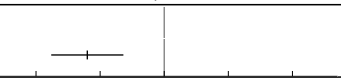
Study or subgroup	Azithromycin N	Azithromycin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.16.1 after 12 months						
Clement 2006	40	2.1 (0.4)	42	3.8 (0.5)		-1.7[-1.9,-1.5]



Favours azithromycin — Favours placebo

Analysis 1.17. Comparison 1 Azithromycin versus placebo, Outcome 17 Number of days of additional oral antibiotics.

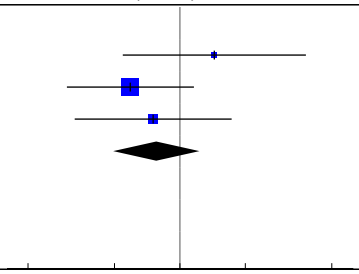
Study or subgroup	Azithromycin N	Azithromycin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.17.1 after 12 months						
Clement 2006	40	62 (13)	42	74 (13)		-12[-17.63,-6.37]



Favours azithromycin — Favours placebo

Analysis 1.18. Comparison 1 Azithromycin versus placebo, Outcome 18 Need for intravenous antibiotics.

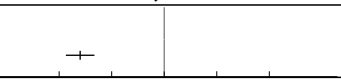
Study or subgroup	Azithromycin n/N	Placebo n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
1.18.1 After 6 months					
Equi 2002	13/41	10/41		16.21%	1.44[0.55,3.8]
Saiman 2003	18/87	30/98		53.12%	0.59[0.3,1.16]
Saiman 2010	11/131	14/129		30.67%	0.75[0.33,1.73]
Subtotal (95% CI)	**259**	**268**		**100%**	**0.78[0.49,1.23]**
Total events: 42 (Azithromycin), 54 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=2.19, df=2(P=0.33); I^2=8.63%					
Test for overall effect: Z=1.08(P=0.28)					



Favours azithromycin — Favours placebo

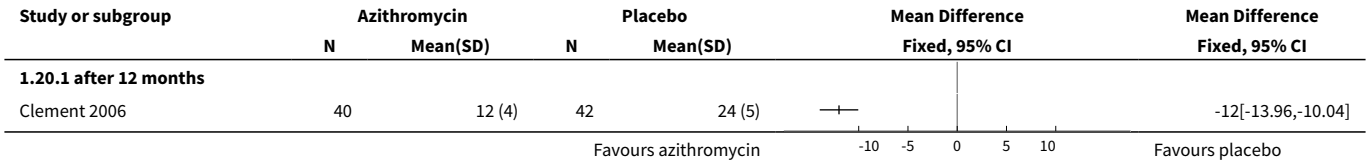
Analysis 1.19. Comparison 1 Azithromycin versus placebo, Outcome 19 Number of courses of intravenous antibiotics.

Study or subgroup	Azithromycin N	Azithromycin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.19.1 After 12 months						
Clement 2006	40	0.8 (0.2)	42	1.6 (0.4)		-0.8[-0.94,-0.66]

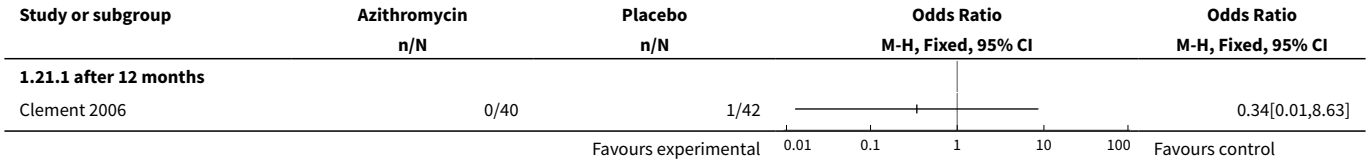


Favours azithromycin — Favours placebo

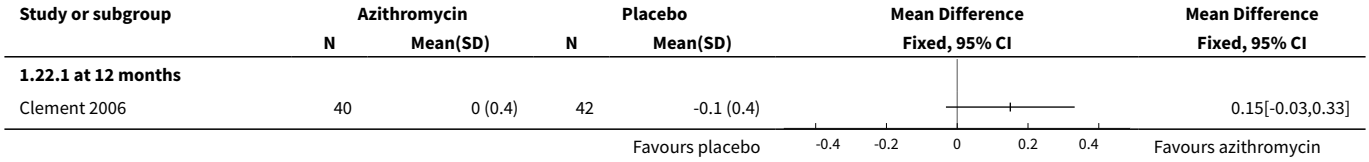
Analysis 1.20. Comparison 1 Azithromycin versus placebo, Outcome 20 Number of days of intravenous antibiotics.



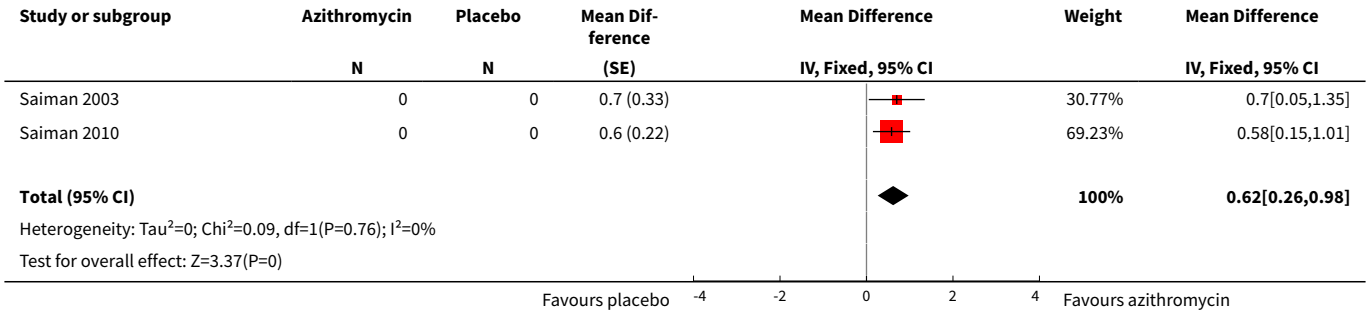
Analysis 1.21. Comparison 1 Azithromycin versus placebo, Outcome 21 Development of allergic bronchopulmonary aspergillosis.



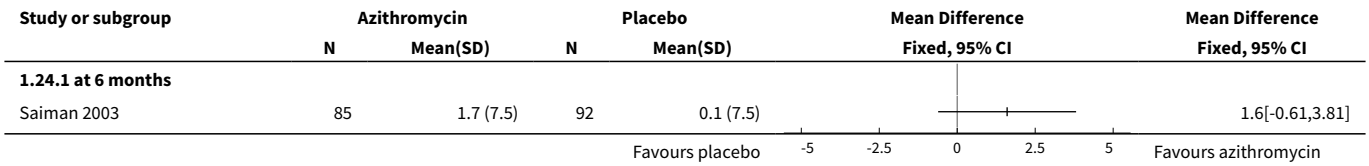
Analysis 1.22. Comparison 1 Azithromycin versus placebo, Outcome 22 Change in BMI z score.



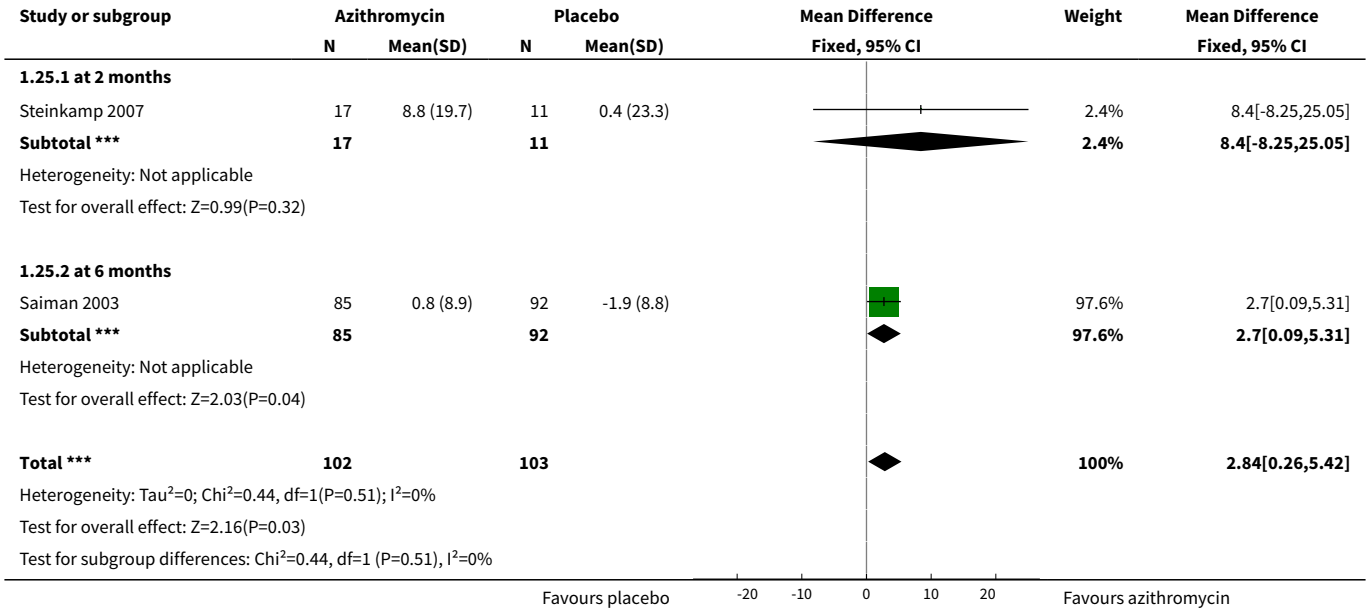
Analysis 1.23. Comparison 1 Azithromycin versus placebo, Outcome 23 Change in weight.



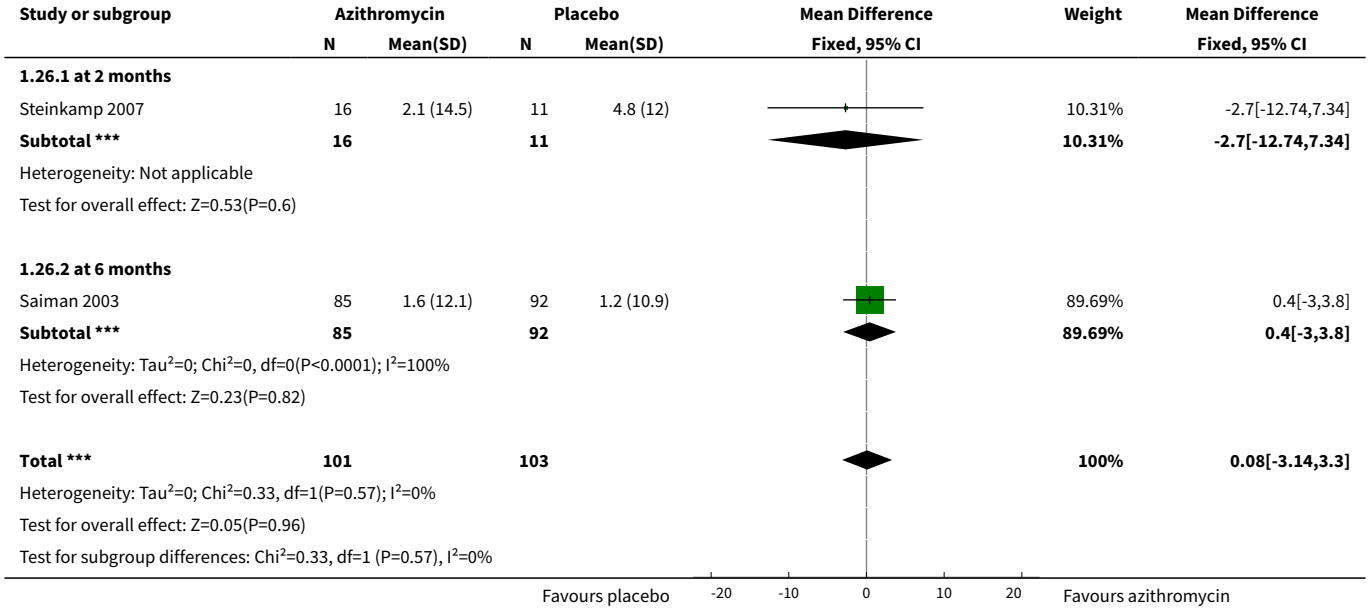
Analysis 1.24. Comparison 1 Azithromycin versus placebo, Outcome 24 Change in total quality of life score (CFQ-R).



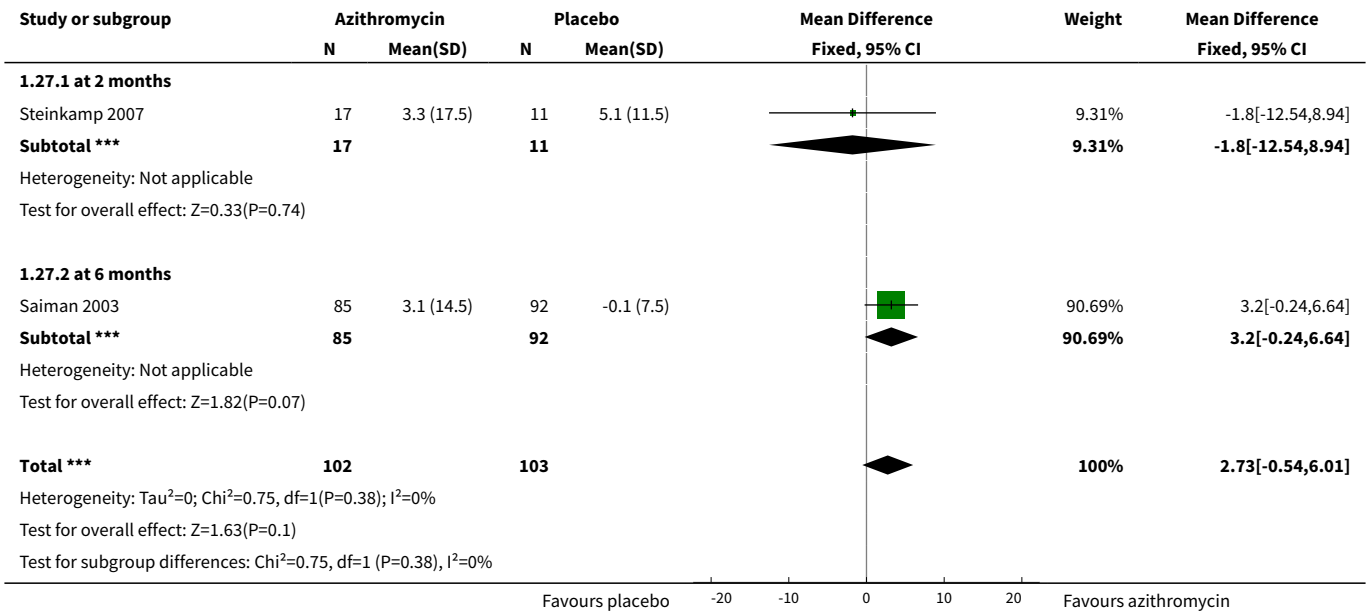
Analysis 1.25. Comparison 1 Azithromycin versus placebo, Outcome 25 Change in physical domain of CFQ-R QoL score.



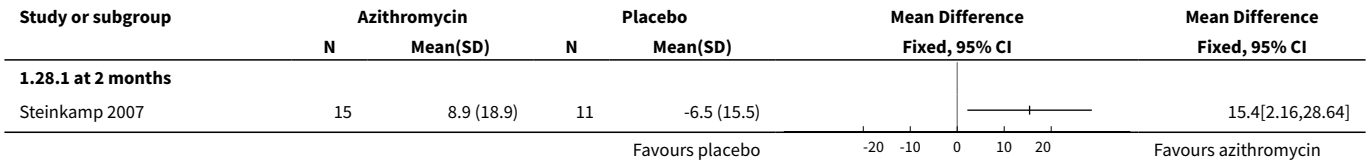
Analysis 1.26. Comparison 1 Azithromycin versus placebo, Outcome 26 Change in psychosocial domain of CFQ-R QoL score.



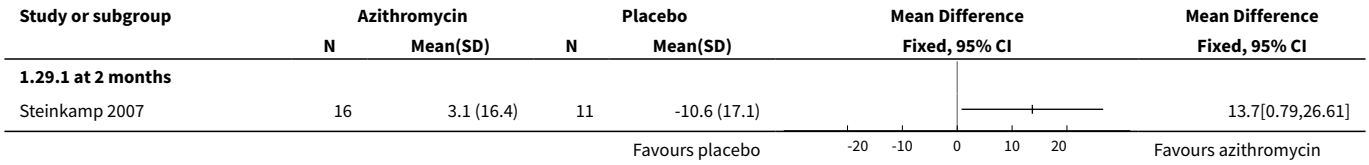
Analysis 1.27. Comparison 1 Azithromycin versus placebo, Outcome 27 Change in body image domain of CFQ-R QoL score.



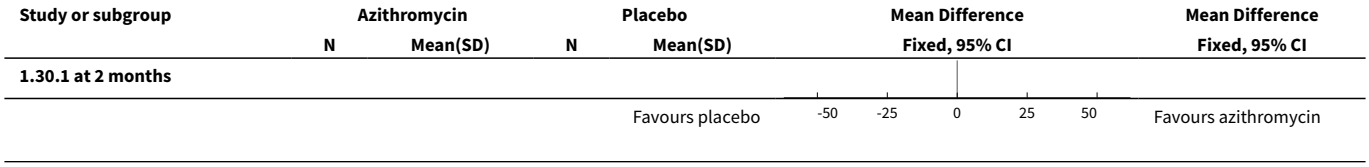
Analysis 1.28. Comparison 1 Azithromycin versus placebo, Outcome 28 Change in respiratory symptom domain of CFQ-R QoL score.



Analysis 1.29. Comparison 1 Azithromycin versus placebo, Outcome 29 Change in eating disorder domain of CFQ-R QoL score.



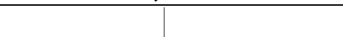
Analysis 1.30. Comparison 1 Azithromycin versus placebo, Outcome 30 Change in problems with body weight domain of the CFQ-R QoL score.



Study or subgroup	Azithromycin N	Azithromycin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Steinkamp 2007	15	20 (24.6)	11	-15.2 (27.3)		35.2[14.82,55.58]

Analysis 1.31. Comparison 1 Azithromycin versus placebo, Outcome 31 Change in CRP.

Study or subgroup	Azithromycin N	Azithromycin Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
1.31.1 After 2 months						
Steinkamp 2007	21	0.9 (6.6)	16	21.6 (60.4)		-20.7[-50.43,9.03]



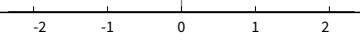
Comparison 2. Weekly versus daily azithromycin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Relative change in FEV_1 (% predicted)	1	624	Mean Difference (IV, Fixed, 95% CI)	-0.77 [-0.90, -0.65]
1.1 at 1 month	1	208	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-0.60, -0.20]
1.2 at 3 months	1	208	Mean Difference (IV, Fixed, 95% CI)	-1.20 [-1.40, 1.00]
1.3 at 6 months	1	208	Mean Difference (IV, Fixed, 95% CI)	-0.70 [-0.95, -0.45]
2 Days to first pulmonary exacerbation	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 After 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Adverse events	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Gastrointestinal	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.2 Abnormal liver transaminases	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 Total adverse events	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.4 Study withdrawal	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Days in hospital	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
4.1 after 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Number of hospital admissions	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
5.1 After 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Acquisition of azithromycin-resistant *Staphylococcal aureus*	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
6.1 After 6 months	1		Odds Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Change in CRP	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
7.1 at 1 month	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.2 at 3 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.3 at 6 months	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Analysis 2.1. Comparison 2 Weekly versus daily azithromycin, Outcome 1 Relative change in FEV_1 (% predicted).

Study or subgroup	Weekly azithromycin N	Weekly azithromycin Mean(SD)	Daily azithromycin N	Daily azithromycin Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
2.1.1 at 1 month							
McCormack 2007	105	2.4 (0.8)	103	2.8 (0.7)		37.22%	-0.4[-0.6,-0.2]
Subtotal ***	**105**		**103**			**37.22%**	**-0.4[-0.6,-0.2]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.84(P=0)							
2.1.2 at 3 months							
McCormack 2007	105	2.3 (0.7)	103	3.5 (0.8)		37.12%	-1.2[-1.4,-1]
Subtotal ***	**105**		**103**			**37.12%**	**-1.2[-1.4,-1]**
Heterogeneity: Not applicable							
Test for overall effect: Z=11.5(P<0.0001)							
2.1.3 at 6 months							
McCormack 2007	105	2.4 (1)	103	3.1 (0.8)		25.66%	-0.7[-0.95,-0.45]
Subtotal ***	**105**		**103**			**25.66%**	**-0.7[-0.95,-0.45]**
Heterogeneity: Not applicable							
Test for overall effect: Z=5.58(P<0.0001)							
Total ***	**315**		**309**			**100%**	**-0.77[-0.9,-0.65]**
Heterogeneity: Tau^2=0; Chi^2=29.92, df=2(P<0.0001); I^2=93.31%							
Test for overall effect: Z=12.18(P<0.0001)							
Test for subgroup differences: Chi^2=29.92, df=1 (P<0.0001), I^2=93.31%							



Analysis 2.2. Comparison 2 Weekly versus daily azithromycin, Outcome 2 Days to first pulmonary exacerbation.

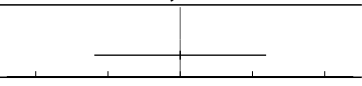
Study or subgroup	Weekly azithromycin N	Weekly azithromycin Mean(SD)	Daily azithromycin N	Daily azithromycin Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
2.2.1 After 6 months						
McCormack 2007	105	87.3 (50.6)	103	70 (44.8)		17.3[4.32,30.28]

Analysis 2.3. Comparison 2 Weekly versus daily azithromycin, Outcome 3 Adverse events.

Study or subgroup	Weekly azithromycin n/N	Daily azithromycin n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.3.1 Gastrointestinal				
McCormack 2007	27/105	9/103		3.62[1.61,8.14]
2.3.2 Abnormal liver transaminases				
McCormack 2007	1/105	4/103		0.24[0.03,2.17]
2.3.3 Total adverse events				
McCormack 2007	34/105	24/103		1.58[0.85,2.91]
2.3.4 Study withdrawal				
McCormack 2007	12/105	5/103		2.53[0.86,7.46]

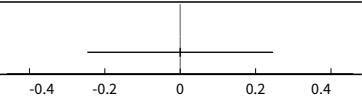
Analysis 2.4. Comparison 2 Weekly versus daily azithromycin, Outcome 4 Days in hospital.

Study or subgroup	Weekly azithromycin N	Weekly azithromycin Mean(SD)	Daily azithromycin N	Daily azithromycin Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
2.4.1 after 6 months						
McCormack 2007	105	6.5 (9.6)	103	6.5 (12.1)		0[-2.97,2.97]



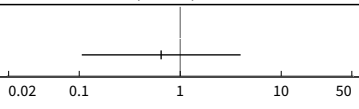
Analysis 2.5. Comparison 2 Weekly versus daily azithromycin, Outcome 5 Number of hospital admissions.

Study or subgroup	Weekly azithromycin N	Weekly azithromycin Mean(SD)	Daily azithromycin N	Daily azithromycin Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
2.5.1 After 6 months						
McCormack 2007	105	0.6 (0.8)	103	0.6 (1)		0[-0.25,0.25]



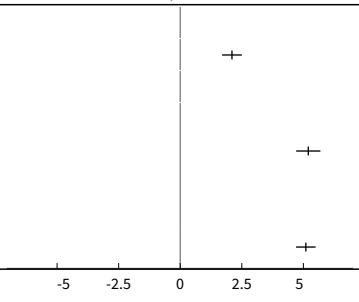
Analysis 2.6. Comparison 2 Weekly versus daily azithromycin, Outcome 6 Acquisition of azithromycin-resistant *Staphylococcal aureus*.

Study or subgroup	Weekly azithromycin n/N	Daily azithromycin n/N	Odds Ratio M-H, Fixed, 95% CI	Odds Ratio M-H, Fixed, 95% CI
2.6.1 After 6 months				
McCormack 2007	2/105	3/103		0.65[0.11,3.96]



Analysis 2.7. Comparison 2 Weekly versus daily azithromycin, Outcome 7 Change in CRP.

Study or subgroup	Weekly azithromycin N	Weekly azithromycin Mean(SD)	Daily azithromycin N	Daily azithromycin Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
2.7.1 at 1 month						
McCormack 2007	105	-2.6 (1.2)	103	-4.7 (1.7)		2.1[1.7,2.5]
2.7.2 at 3 months						
McCormack 2007	105	-1.3 (2)	103	-6.5 (1.6)		5.2[4.71,5.69]
2.7.3 at 6 months						
McCormack 2007	105	-0.7 (1.3)	103	-5.8 (1.6)		5.1[4.7,5.5]



ADDITIONAL TABLES

Table 1. Summary of included studies

Study Name	Design	Intervention	Duration	Dosing Regimen	Number	Age	PA infection	Risk of bias	Primary Outcome	Main results
Equi 2002	RCT X-over	azithromycin versus placebo	6 months each arm (2 month washout)	250 mg/day (500 mg if weight >40 kg)	41	8-18 years	+/-	Low	comparative change in FEV_1	mean relative difference of 5.4% in favour of azithromycin
Wolter 2002	RCT Parallel	azithromycin versus placebo	3 months	250 mg/day	60	adults	+/-	Low	relative change in FEV_1	mean difference 3.6% in favour of azithromycin
Saiman 2003	RCT Parallel	Azithromycin versus placebo	6 months	250 mg 3 times a week (500 if weight >40kg)	185	6-adults	+	Low	relative change in FEV_1	mean difference, 6.2% in favour of azithromycin
Rotschild 2005	RCT Parallel	azithromycin versus placebo	3 months	250 mg twice a week	21	5-36 years	+/-	Low	BPI-ANCA levels	no difference
Clement 2006	RCT Parallel	azithromycin versus placebo	12 months	250 mg 3 times a week (500 if weight >40 kg)	82	6-adults	+/-	Low	relative change in FEV_1	no difference
McCormack 2007	RCT Parallel	weekly versus daily azithromycin	6 months	250 mg daily versus 1200 mg weekly	208	6-adults	+/-	Low	relative change in FEV_1	equivalence
Steinkamp 2007	RCT Parallel	azithromycin versus placebo	2 months	500-1250 mg weekly based on weight	38	8-adults	+/-	Low	absolute change in FEV_1	no difference
O'Connor 2009	RCT X-over	azithromycin versus placebo	4 months each arm (2 month washout)	250 mg 3 times a week (500 if weight >40 kg)	17	6-18 years	+/-	High	comparative change in FEV_1	no difference
Kabra 2010	RCT Parallel	azithromycin, low versus high dose	6 months	5 versus 15 mg/kg/day	47	children	+/-	High	change in FEV_1 from baseline	no difference
Saiman 2010	RCT Parallel	azithromycin versus placebo	6 months	250 mg 3 times a week (500 if weight >36 kg)	260	6-18 years	-	Low	relative change in FEV_1	no difference

BPI-ANCA: bactericidal or permeability-increasing protein

FEV$_1$: forced expiratory volume at one second
PA: *Pseudomonas aeruginosa*
RCT: randomised controlled trial
X-over: cross-over

WHAT'S NEW

Date	Event	Description
11 September 2012	New search has been performed	A search of the Group's Cystic Fibrosis Trials Register identified five new additional references to a study already included in the review (Saiman 2010). There was some additional information identified on serum inflammatory markers, but we have only been able to include a narrative description of this so far. Data were skewed and presented as log-transformed data; we are awaiting the non-transformed data from the authors.
11 September 2012	New citation required but conclusions have not changed	Some additional narrative information has been added about serum inflammatory markers; however, the conclusions of the review remain the same.

HISTORY

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

Date	Event	Description
20 October 2011	New citation required and conclusions have changed	Due to an editorial error this review should have been flagged as a new citation due to the inclusion of large amounts of new data leading to a change in conclusions.
9 February 2011	New search has been performed	A search of the Group's Cystic Fibrosis Trials Register identified 18 new references. Five new references were to three new studies which have been included (Kabra 2010; O'Connor 2009; Saiman 2010). Four new references were to one study previously listed as ongoing which has now been included (McCormack 2007). Two new references were to a study previously listed as 'Awaiting classification' (Steinkamp 2007). This study has now been included. Two studies (with no new references found) previously listed as 'Awaiting classification' have now been included (Clement 2006; Rotschild 2005). Four new references to two new studies have been excluded (Aaron 2005; Shmarina 2004). We found one new additional reference to a study previously listed under 'Awaiting classification'; the study has now been excluded (Rubin 2003). Seven studies previously listed as 'Awaiting classification' have now been excluded (Anstead 2001; Beringer 2005; Dionysopoulou 2005; Dogru 2004; Frederiksen 2001; Kessaris 2003; Sriram 2003). One study which was previously included has now been removed from the review as it is an open label pharmacokinetic study

Date	Event	Description
		(Cipolli 2001). This has had no bearing on the overall conclusions. Two new studies have been listed as 'Awaiting classification' (Elmasry 2010; Pukhalsky 2001). A new plain language summary has been drafted in line with current guidance from The Cochrane Collaboration.
12 November 2008	Amended	Converted to new review format.
13 February 2006	New search has been performed	After a search of the Group's Cystic Fibrosis Register, a total of nine studies have been added to the review: one to the list of excluded studies (Jensen 2005); five to studies awaiting assessment (Beringer 2005; Clement 2005; Dionyssopoulou 2005; Dogru 2004; Kessaris 2003); and three to the list of ongoing studies (AZ003; AZ004; Rubin 2003).
17 February 2004	New citation required and conclusions have changed	Substantive amendment
17 February 2004	New citation required and conclusions have changed	Following a recent search of the Group's Trials Register (January 2004), Cipolli 2001 has been added to the 'Included studies', but no data were available for inclusion in MetaView. Also, this update contains recently published data from the largest RCT examining azithromycin versus placebo for CF chest disease (Saiman 2003), which has improved the impact of this review and has altered the conclusions.
18 November 2003	Amended	Following publication the Saiman 2003 reference has been moved from 'Ongoing studies' to 'Studies awaiting assessment'. The review will be updated fully in 2004.
20 May 2003	New search has been performed	After a search of Group's Trials Register (March 2003), the following studies have been added to the section 'Included studies': Equi 2002; Wolter 2003. Frederiksen 2001 has been added to the section 'Studies awaiting assessment'. We have requested data from the primary authors of this study in order to incorporate them into a later update. The following studies have been added to the section "Excluded studies": Ordonez 2001; Pukhalsky 2001. The following study has been added to the 'Ongoing studies' section: McCormack 2003.
25 January 2001	New search has been performed	After a search of Group's Trials Register two references by Baumann 2000 were identified and excluded as they were not RCTs. The descriptions of Ongoing studies were added to. New data from these ongoing studies will be incorporated when they become available and if they meet the inclusion criterion.

CONTRIBUTIONS OF AUTHORS

KWS conceived and drafted the review, assessed studies, extracted data and wrote the first and subsequent drafts.
LP assessed studies, extracted data and commented on the review.

AS contributed to the content and commented on the review.

PMB contributed to the content and commented on the review.

KWS acts as guarantor of the review.

DECLARATIONS OF INTEREST

None known.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For this review we revisited all the studies taking into account new guidance on determining risk of bias. We have extracted data again and demonstrated that this was consistent with our first review. Data extraction sheets are now available for review.

NOTES

A 'Comment and Criticism' entitled: 'Inclusion of trials and conclusions drawn' (and the response from the reviewers) was attached to this review on Issue 2, 2004. This now appears as an appendix to this review (Feedback 1).

INDEX TERMS

Medical Subject Headings (MeSH)

*Pseudomonas aeruginosa; Anti-Bacterial Agents [adverse effects] [*therapeutic use]; Azithromycin [adverse effects] [*therapeutic use]; Bacterial Infections [drug therapy] [etiology]; Cystic Fibrosis [*complications]; Disease Progression; Macrolides [adverse effects] [therapeutic use]; Outcome Assessment, Health Care; Pseudomonas Infections [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans