# Macrolide antibiotics for cystic fibrosis (Review)

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## ABSTRACT

**Background**
Chronic severe infection with *Pseudomonas aeruginosa*, affects many people with cystic fibrosis (CF). There is evidence from the laboratory and from other disease processes that macrolide antibiotics, whilst not directly active against *Pseudomonas aeruginosa*, may have indirect actions against this organism.

**Objectives**
We aimed to test the hypotheses that, in people with CF, 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 strategy**
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 principal investigators known to work in the field, previous authors and pharmaceutical companies who manufacture macrolide antibiotics for unpublished or follow-up data (December 2003).

Most recent search of the Group's register: September 2005

**Selection criteria**
Published or unpublished randomised controlled trials of macrolide antibiotics compared to placebo, another class of antibiotic or another macrolide antibiotic. Studies comparing regimens of the same macrolide antibiotic at different doses will also be included.

**Data collection and analysis**
Two authors independently extracted data and assessed study quality. Three groups were contacted for missing data and we hope to include these in future reviews.

**Main results**
Searches identified 19 studies, four were included in this review (296 participants). Two studies enrolled adults, one children (a significant number of whom were not colonised with *Pseudomonas aeruginosa*) and one both adults and children. All the clinical studies reported small but significant improvements in respiratory function with azithromycin versus placebo. Meta-analysis at the one-month and six-month time points demonstrates a significant benefit with respect to relative change in $FEV_1$ (at six months, for n = 104, azithromycin and n = 114, placebo; weighted mean difference 5.82% (95% confidence interval 2.45 to 9.20)). The largest study reported a significant increase in mild adverse events (nausea, diarrhoea and wheezing).

**Authors' conclusions**
There is clear evidence from these studies of a small but significant improvement in respiratory function following treatment with azithromycin. The largest study employed a three times a week dose and, in this study, treatment with azithromycin was associated

with a significant increase in mild adverse events. Further studies are needed to clarify the precise role of azithromycin in the treatment of CF lung disease.

## PLAIN LANGUAGE SUMMARY

Treatment with azithromycin results in small but significant improvements in respiratory condition in people with cystic fibrosis and chronic chest infection

Cystic fibrosis is characterised by chest infection, particularly by the bacteria, *Pseudomonas aeruginosa*, which is resistant to nearly all antibiotics that can be taken by mouth. Macrolide antibiotics have no direct killing effect on *Pseudomonas aeruginosa*, however they may reduce the activity of these bacteria. Three randomised controlled trials in children and adults with cystic fibrosis (286 participants) demonstrated small but significant improvements in respiratory function after treatment with azithromycin versus placebo. Further studies are required to define the optimal role of azithromycin or other macrolide antibiotics for chest infection in people with cystic fibrosis.

## BACKGROUND

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

Cystic fibrosis is the most common inherited disease in the Caucasian population. The disease is caused by mutation of the cystic fibrosis transmembrane conductance regulator (CFTR) gene (Riordan 1989). The protein that this gene codes for, has an important role in the transport of salt and water across the surface of epithelia (Boucher 1999). The sequelae of abnormal CFTR function are apparent in a number of organs in the body, however lung involvement is the most important cause of disability and death. The CF defect results in dehydrated airway secretions (Matsui 1998). Inability to clear these secretions and an abnormal inflammatory response accounts for the lung infection and damage that characterises the condition. Recurrent bacterial infection combined with an abnormal inflammatory process leads to a cycle of lung damage and further infection.

Characteristic organisms associated with CF chest infection 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). Production of a mucoid coat by *P. aeruginosa* is characteristic and appears to increase the pathogenicity of this organism in CF. In the laboratory *P. aeruginosa* is resistant to most antibiotics that can be taken orally. The only oral antibiotics that have direct killing activity against *P. aeruginosa* are quinolones such as ciprofloxacin. All other anti-pseudomonal antibiotics need to be given intravenously or aerosolised into the lungs. Another problem in the management of people with CF is the increasing resistance of *P. aeruginosa* following prolonged use of available antibiotics.

This review focuses on macrolide antibiotics with the aim of evaluating both their long- and short-term use in CF chest infection. The oldest and most widely used macrolide (in the United Kingdom) is erythromycin. Newer antibiotics in this class include clarithromycin, roxithromycin and azithromycin. Macrolides kill a wide range of bacteria which cause respiratory disease (including *S. aureus*), but are not directly active against *P. aeruginosa*, at least when assessed in the laboratory. In Japan, macrolides have been widely used since 1982 as a treatment for diffuse panbronchiolitis, a rare inflammatory lung condition, affecting older Japanese people, until recently virtually unrecognised outside of East Asia (Hoiby 1994). *P. aeruginosa* infection in these people is associated with a very poor outcome. Evidence has been presented (including one randomised controlled trial (RCT)) that, even at low doses, the long-term use of macrolides has a beneficial effect on outcome for these people (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 a mucoid biofilm which protects *P. aeruginosa* from the host defences, are important for the pathogenicity of *P. aeruginosa* in diffuse panbronchiolitis and CF. Of the newer macrolides, an azalide, azithromycin (Retsema 1987) is reported to show the most significant evidence in laboratory studies of activity against the virulence factors of *P. aeruginosa* (Ichimiya 1996; Mizukane 1994; Molinari 1993). In addition, macrolides have been cited as having direct anti-inflammatory properties (Labro 1998). Experiments in the laboratory suggest this relates to the effects on inflammatory cells (Anderson 1996; Yanagihara 1997).

The pharmacokinetics and bioavailability of azithromycin make it a potentially useful antibiotic for lower respiratory tract infection (Ball 1991). Macrolides, in particular azithromycin, may have a role in the long- or short-term treatment of CF chest infection, given their unique activity against the virulence factors of *P. aeruginosa*. As well as direct antibacterial properties the macrolides may prove to have an important role in the treatment of CF lung disease because of their additional anti-inflammatory properties (Ianaro

2000). The effect of this class of antibiotics on the natural history of CF lung disease will require careful evaluation.

## OBJECTIVES

This review tested the hypotheses that, in people with CF, macrolide antibiotics:
(1) improve clinical status compared to placebo, no placebo or another antibiotic;
(2) do not have unacceptable adverse effects.

If efficacy of macrolide antibiotics is demonstrated, we will examine the optimum dosing regimens and durations of therapy for CF.

## CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

### Types of studies

RCTs, published or unpublished. Quasi-randomised (e.g. alternate allocation and stratification) controlled trials were included if there was sufficient evidence that intervention and control groups were similar at baseline. Cross-over trials were considered for short-term outcomes only.

### Types of participants

People included in the analysis fulfilled strict criteria for the 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 intervention

Short- or long-term (where long-term is 12 months or longer) 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) Number of days as a hospital inpatient

(2) Lung function
(a) In adults or older children who can perform spirometry
(i) forced expiratory volume at one second ($FEV_1$)
(ii) forced vital capacity (FVC)
(b) In infants non-routine tests such as
(i) thoracic gas volume (TGV)
(ii) airway conductance (Gaw)
(iii) maximum flow at functional residual capacity (Vmax FRC)
Other relevant lung function tests will also be considered.

(3) Age at which participant acquires long-term *P. aeruginosa* infection (as defined by more than two positive respiratory cultures per year) or acquisition of *P. aeruginosa* during the study period

(4) Number of additional courses of intravenous antibiotics

(5) Adverse effects of antibiotic treatment, for example, diarrhoea, skin rash and fungal infections

(6) Improvement in survival, as defined on a yearly basis starting at year one

(7) Nutritional markers such as z scores for weight and height

***Secondary outcomes***
(8) Number of additional courses of oral antibiotic required

(9) Number of courses of oral steroids

(10) Acquisition of other common pathogens such as *S. aureus* (including methicillin resistant *S. aureus*) and *Haemophilus influenzae*

(11) Development of allergic bronchopulmonary aspergillosis as defined by clinical symptoms (cough and wheeze), characteristic chest X-ray appearance, a rise in certain white blood cells (eosinophils) and positive antibodies against aspergillus

(12) Liver disease as defined by clinical measures (enlarged liver), radiographic measures (abnormal ultrasound or DISIDA scan) or biochemical measures (liver function tests abnormal on two or more occasions)

(13) Quality of life

(14) Changes in markers of inflammation, for example, cells or cytokines from samples of the lower respiratory tract

(15) Other outcomes (such as adverse events) that can not be anticipated will also be analysed

Outcomes were considered short-term if they were measured at the end of a treatment period, unless the treatment period was for 12 months or more. Outcomes were then considered long-term. Outcomes were also considered long-term if there was more than three months between the end of the treatment and the measure. Long-term outcome measures were not considered for cross-over studies.

We intended to group outcome data into those measured at one, three, six, twelve months and annually thereafter. Outcome data were recorded at other time periods and these were also considered in this review.

## SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: Cochrane Cystic Fibrosis and Genetic Disorders Group methods used in reviews.

Relevant studies were identified from the Group's Cystic Fibrosis Trials Register using the terms: antibiotics AND (erythromycin OR azithromycin OR clarithromycin OR roxithromycin).

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.

In addition, principal investigators, known to work in the field and previous authors were contacted for unpublished or follow-up data. Pharmaceutical companies, that manufacture macrolide antibiotics, were also approached (last contacted December 2002).

Date of the most recent search of the Group's Trials Register: September 2005.

## METHODS OF THE REVIEW

Two authors (KWS and PMB) independently selected studies to be included in the review. Each author assessed the methodological quality of each study, based on a method described by Schulz (Schulz 1995). In particular, the authors examined the randomisation method, the degree of blinding in the study, whether intention-to-treat analyses were possible from the available data and if the number of participants lost to follow up or subsequently excluded from the study was recorded. Two of the authors (KS and PMB) independently extracted data from included studies, with the third reviewer (AS) arbitrating. There was no predetermined subgroup analysis.

For binary outcome measures, in order to allow an intention-to-treat analysis, we 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. We calculated a pooled estimate of the treatment effect for each outcome across studies, (using the pooled relative risk as a treatment effect estimate). For continuous outcomes, we recorded either mean change from baseline for each group or mean post-treatment or intervention values and standard deviation (SD) for each group (standard error converted to SD). We calculated a pooled estimate of treatment effect by calculating the weighted mean difference. There were not enough studies included in this review to assess heterogeneity or to undertake a sensitivity analysis based on quality. Heterogeneity between study results will be tested in future updates if further studies are included using a standard chi squared test. A sensitivity analysis based on the methodological quality of the studies, including and excluding quasi-randomised studies, will also be performed.

## DESCRIPTION OF STUDIES

Nineteen studies were identified. Four studies were included and details are listed below (Cipolli 2001; Equi 2002; Saiman 2003; Wolter 2002); seven studies were excluded (Anstead 1999; Baumann 2000; Jaffe 1998; Ordonez 2001; Pirzada 1999; Pukhalsky 2001; Jensen 2005), further details of these studies can be found in the 'Characteristics of excluded studies' section; and eight studies, published in abstract form are awaiting assessment with details of these listed below (Anstead 2001; Beringer 2005; Clement 2005; Dionyssopoulou 2005; Dogru 2004; Frederiksen 2001; Kessaris 2003; Sriram 2003).

### *Included Studies*

Wolter enrolled 60 adult participants (age range 18 years to 44 years, receiving 250 mg azithromycin once a day for three months). At baseline, mean (SD) $FEV_1$% predicted for the placebo group was 62.3% (24.8), which was significantly greater than the azithromycin group (mean $FEV_1$, 50.9% (18.3)). The placebo group contained more men (20 out of 30 compared to 9 out of 30 in the azithromycin group) who were on average taller and heavier. Fifty-seven participants provided a sputum sample at baseline; *P. aeruginosa* was isolated in 47 samples and *S. aureus* was isolated in 24 samples (Wolter 2002).

Equi enrolled 41 children (8 years to 18 years) in a cross-over study (Equi 2002). In the treatment arm they received 250 mg azithromycin (500 mg, if weight was greater than 40 kg) once a day for six months. There was a two-month 'washout' period between both interventions. Baseline characteristics of the two groups were similar (for placebo followed by azithromycin, $FEV_1$ 61% (14) compared to azithromycin followed by placebo $FEV_1$, 59% (12)). Data (kindly provided by the research team) from the first treatment arm has been included in our meta-analysis. Of the 41 children, 21 were chronically colonised with *P. aeruginosa* (as defined by three or more positive cultures in the preceding 12 months), although 38 of the 41 were receiving long-term anti-pseudomonal nebulised therapy. Twenty-five children were receiving long-term anti-staphylococcal prophylaxis and 12 had grown *S. aureus* on three or more occasions from respiratory cultures in the previous 12 months (Equi 2002).

A multicentre RCT (185 participants, children older than six years and adults) has recently been published (Saiman 2003). The study compared 250 mg azithromycin (500 mg azithromycin, if weight greater than 40 kg), given three times a week (Monday, Wednesday and Friday) for six months versus placebo. Randomisation included a valid allocation strategy to ensure equivalence between placebo and intervention with respect to weight, respiratory function and site of study. The randomisation protocol resulted in

more individuals receiving placebo (98 versus 87), however the baseline characteristics of the two groups were very similar. Eligibility criteria included documented chronic Pseudomonas infection (defined as a positive respiratory culture one year or more before screening and at screening). At screening, 99 participants grew *S. aureus* from their respiratory culture (47 from the placebo group).

The fourth study randomised 10 adult participants to receive either 500 mg or 1000 mg once a day for five days (Cipolli 2001). The primary outcomes were concentration of azithromycin in serum and bronchial secretions.

***Studies awaiting assessment and ongoing***

A total of eight studies are awaiting assessment and four studies are ongoing.

Two RCTs, examining placebo versus azithromycin, have been reported in abstract form (Anstead 2001; Clement 2005). We are awaiting data from both these studies. Four RCTs have compared placebo versus clarithromycin and have been also been reported in abstract form (Dogru 2004; Frederiksen 2001; Kessaris 2003; Sriram 2003). All these studies have been underpowered and we are communicating with authors about the possibility of sharing data for the meta-analysis. In addition, another study examining clarithromycin versus placebo has been completed and some data published on outcomes which are not pertinent to this review (Rubin 2003). We intend to undertake this analysis before the next update.

In addition to the recently completed French study (Clement 2005), another large study with more than 200 participants and examining low dose azithromycin versus placebo is nearing completion in Australia (McCormack 2003). Furthermore, the North American Macrolide Study group are planning large RCTs to examine azithromycin in people with chronic cepacia chest infection (AZ0003) and young people without Pseudomonas infection (AZ0004).

Two other studies are awaiting assessment; one study examining roxithromycin versus placebo was published in abstract form (Dionyssopoulou 2005). The final pharmacokinetic study has just been published in full form and will be included in the next update (Beringer 2005).

## METHODOLOGICAL QUALITY

The first study was of parallel design (Wolter 2002). Randomisation occurred in blocks but was not stratified. The baseline characteristics of the two treatment groups were different, with the placebo group having significantly more males with better respiratory function and nutritional status. The authors argue that this effect would bias against a positive result for the azithromycin arm, however, a counter-argument could be that the treatment arm had more room for improvement (i.e. it depends whether you look at end points or change from baseline). In the data analysis, appropriate adjustments were made for the differences between sex, body mass index (BMI) and $FEV_1$. Quality of life was assessed using the validated Chronic Respiratory Disease Questionnaire (CRDQ). Some data points were missing, however the authors undertook an intention-to-treat analysis (Wolter 2002). The study was double-blind and allocation concealment was good since this was done by the hospital pharmacy independent of the trialists.

The second published study was a randomised, double-blind, placebo-controlled cross-over study with a two-month washout between two six-month treatment blocks (Equi 2002). Allocation concealment was assessed as good, since this was performed by the hospital pharmacy independently of the trialists. This cross-over design may be inappropriate for an intervention with potentially long-term consequences. However, results from the first arm of this study have been included in the meta-analysis (relative change in $FEV_1$ and FVC). All other outcomes in the Equi study are reported as a combination of data from both arms and were inappropriate for inclusion in Statistical Analysis (Equi 2002). The study group have kindly provided individual patient data and we are currently analysing these for inclusion in future reviews. Two participants withdrew from the study but their data were included in an intention-to-treat analysis.

The third study was a multicentre RCT of parallel design (Saiman 2003). An allocation strategy was employed as mentioned above, however randomisation was done independently of the trialists by the CF Therapeutics Development Network Coordinating Centre in the USA. The primary outcome was the relative change in $FEV_1$ from baseline ({[$FEV_1$% predicted at day 168 - $FEV_1$% predicted at day 0]*100}/$FEV_1$% predicted at day 0). An intention-to-treat analysis was undertaken. One participant (placebo arm) was lost to follow up having completed enrolment and baseline assessment. Seven other participants did not have data available at day 168 (at end of study). Assuming day 28 to be the point of maximal response the group employed a derived variable approach to generate individual piecewise linear regression to estimate the day 168 value for these individuals (in some cases with insufficient data the last available measurement was used).

The final study examined pharmacokinetic outcomes at two different doses (Cipolli 2001). Allocation of dose was randomised (pseudo-random number generation), but was administered in an open labelled manner. Primary outcomes were serum and bronchial secretion concentration of azithromycin, however the study group did examine for deranged liver function by measuring serum hepatic enzymes at baseline, at the end of treatment and one month later; and by undertaking liver ultrasound scan two weeks after the start of treatment.

## RESULTS

### Primary outcomes

***(1) Number of days as a hospital inpatient***

The Wolter study did not demonstrate a significant reduction in hospital inpatient days over three months (placebo mean 5.2 days (range 0 days to 36 days), azithromycin mean 2.1 days (range 0 days to 15 days), P = 0.056) (Wolter 2002). In the Saiman study, 14 (of 87) participants who received azithromycin were hospitalised compared to 29 (of 98) placebo (P = 0.05) (Saiman 2003). The azithromycin group, as a whole, had a mean (SD) of 2.0 (5.8) days in hospital during the six-month study period compared to 3.8 (8.3) days in the placebo group. As these studies examined different time scales (three and six months) it is not possible to combine these data in a meta-analysis. The Equi study did not report this outcome measure (Equi 2002).

***(2) Lung function***

*(a) In adults or older children who can perform spirometry*

(i) $FEV_1$

The primary outcome measure for all studies was change in lung function from baseline (relative change in $FEV_1$% predicted). Wolter measured respiratory function at one, two and three months (Wolter 2002). Combining results from each of these time points (and adjusting the data for the different baseline characteristics of the two groups), the study demonstrated a mean excess effect of azithromycin over placebo of 3.62% (standard error 1.78). Equi measured respiratory function at two, four and six months (Equi 2002) and calculated a similar "mean excess effect" by dividing the average values for months four and six by the baseline values (two participants had a month four or month six value missing and a single value was used) and subtracting the placebo arm from the azithromycin arm. By this method the median relative difference between azithromycin and placebo was 5.4% (95% confidence interval (CI) 0.8 to 10.5) (Equi 2002). In the Saiman study, participants in the azithromycin group had an estimated 0.097 litres (SD 0.26) improvement in $FEV_1$ after six months compared to 0.003 (0.23) in the placebo group (mean difference 0.094 litres, 95% CI 0.023 to 0.165, P = 0.009) (Saiman 2003). These results are reflected in the relative change in $FEV_1$% predicted from baseline which at six months showed a mean difference between the two groups of 6.2% (95% CI of 2.58 to 9.84) (P = 0.001). Similar results were found at one and three months. One month after the study, participants in the azithromycin group had returned their $FEV_1$ to baseline.

Due to differing study design combined data for relative change in $FEV_1$ are only available for the following time points, one month (Saiman 2003; Wolter 2002), two months (Equi 2002; Wolter 2002), three months (Saiman 2003; Wolter 2002) and six months (Equi 2002; Saiman 2003). Combined data are presented in Statistical Analysis and demonstrate significant weighted mean differences (WMDs) in favour of azithromycin at two of these time points: one month (n = 109 azithromycin and n = 120 placebo; WMD, 3.99% (95% CI 1.47 to 6.38)); and six months (n = 104 azithromycin and n = 114 placebo; WMD, 5.82% (95% CI 2.45 to 9.20)).

(ii) FVC

The WMD significantly favoured azithromycin, but at different time points (two and six months) compared to $FEV_1$ (see Statistical Analysis figure). Overall the WMD in favour of azithromycin for relative change in FVC is less impressive at all time points compared to relative change in $FEV_1$.

***(3) Age at which participant acquires long-term P. aeruginosa infection (as defined by more than two positive respiratory cultures/year) or acquisition of P. aeruginosa during the study period***

It was noted that a significant number of participants in the Equi study did not grow *P. aeruginosa* (17 out of 41 participants) during the entire study period (Equi 2002). The Wolter study did not report this outcome (Wolter 2002). In the Saiman study long-term infection with *P. aeruginosa* was one of the eligibility criteria, however, 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) Number of additional courses of intravenous antibiotics***

The Wolter study reported significant reductions in the number of courses of intravenous (IV) 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 IV 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). In the Saiman study, 18 participants in the azithromycin group and 30 in the placebo group required intravenous antibiotic treatment (mean (SD) days for azithromycin group, 4.2 (9.9) days compared to 6.9 (12.6) days, P = 0.10). (Saiman 2003). Again, because of the different study periods it is not possible to combine these data. The Equi study did not detect any difference in IV treatment during the azithromycin phase compared to the placebo phase (Equi 2002).

***(5) Adverse effects of antibiotic treatment; for example, diarrhoea, skin rash and fungal infections***

In the Wolter study, there were 16 adverse events reported in 15 participants (seven in the placebo group), exact details of these events are not reported (Wolter 2002). Of the three participants who discontinued treatment due to adverse events, urticarial reaction in a participant receiving azithromycin was reported "likely" to be related to the treatment drug, while neutropenia in a participant in the treatment group and "swelling" in a participant in the placebo group were reported as being "possibly" related to the study drug. A further two events were reported as "possibly" related to the study drug (rash in each of the treatment and placebo groups). The Saiman study reported an increased incidence of: nausea, relative risk (RR) 2.04% (95% CI 1.19 to 3.50); diarrhoea,

RR 2.82% (95% CI 1.31 to 6.07); and wheezing, RR 4.22% (95% CI 1.46 to 12.25) in the azithromycin group (Saiman 2003). In three participants azithromycin was discontinued because of sore feet and bruising; sinusitis; and rash and ankle pain. Two participants reported hearing loss and two reported tinnitus in the Saiman study (one from each group for each complaint) (Saiman 2003). Equi monitored hearing using pure tone audiometry before, during and on completion of each treatment period and detected no significant changes (Equi 2002).

***(6) Improvement in survival, as defined on a yearly basis starting at year one***

Not reported in any of the included studies.

***(7) Nutritional markers such as z scores for weight and height***

The Wolter study reported no significant change in BMI (Wolter 2002). In the Saiman study, participants in the azithromycin group gained an average 0.7 kg more than those in the placebo group (95% CI 0.1 to 1.4 kg, P = 0.02) (Saiman 2003). Equi did not report on this outcome (Equi 2002).

**Secondary outcomes**

***(8) Number of additional courses of oral antibiotic required***

The Equi study reported a significant reduction in oral antibiotic usage whilst on azithromycin (18 out of 41 participants versus 27 out of 41 participants, P = 0.005) (Equi 2002). This outcome was not assessed by the Wolter study (Wolter 2002). In the Saiman study the placebo group used significantly more days of non-quinolone oral antibiotics (mean (SD) 13.5 (31.4) days versus 5.5 (13.7) days in the azithromycin group, P = 0.03) (Saiman 2003). There was no difference in the use of quinolones in this study (Saiman 2003).

***(9) Number of courses of oral steroids***

Not reported in any of the included studies.

***(10) Acquisition of other common pathogens***

There was no significant change in pathogens isolated in the Wolter or Equi studies (Equi 2002; Wolter 2002). In the Saiman study, *S. aureus* was newly detected in 12 of the placebo group (n = 92) compared to two of the azithromycin group (n = 84) (P = 0.01) (Saiman 2003).

***(11) Development of allergic bronchopulmonary aspergillosis (ABPA) as defined by clinical symptoms (cough and wheeze), characteristic chest X-ray appearance, a rise in certain white blood cells (eosinophils) and positive antibodies against aspergillus***

Saiman reported an increase incidence of wheeze in the azithromycin group but no other evidence of ABPA (Saiman 2003).

***(12) Liver disease as defined by clinical measures (enlarged liver), radiographic measures (abnormal ultrasound or DISIDA scan) or biochemical measures (liver function tests abnormal on two or more occasions)***

An isolated case of transient raised serum liver enzymes is described by Equi, but full data are not available (Equi 2002). Wolter did not report on this outcome (Wolter 2002). There were no differences in laboratory abnormalities in the Saiman study (Saiman 2003). The study examining different doses given for five days found a significant rise in liver enzymes in one participant on 1000 mg and smaller rises in two other participants (one on 1000 mg and one on 500 mg) (Cipolli 2001). All tests returned to normal after one month and ultrasound scan two weeks after the commencement of azithromycin was normal in all cases.

***(13) Quality of life***

Wolter employed a validated questionnaire to monitor quality of life (Wolter 2002). Both placebo and treatment groups were reported to have significant improvement from baseline in their overall scores over the course of the study (P = 0.042). Improvements in specific scores (dyspnoea, emotional, mastery and total) were higher for those receiving azithromycin. Improved fatigue scores were only seen in the azithromycin group.

Equi reported no difference between the two arms of the study with respect to a visual analogue score for well being (Equi 2002).

Saiman undertook a CF quality of life questionnaire and found an improvement from baseline in the 'physical functioning' component in participants in the azithromycin group (mean difference 2.7 (95% CI 0.1 to 5.3) (P = 0.05), but no difference in other aspects of the questionnaire (psychosocial functioning and body image) (Saiman 2003).

***(14) Changes in markers of inflammation, for example, cells or cytokines from samples of the lower respiratory tract***

The Wolter 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 are stated to fall in the azithromycin group but remain stable in the placebo group (Wolter 2002). Equi did not report on this outcome (Equi 2002). There were no differences in IL8 or neutrophil elastase in the Saiman study (Saiman 2003).

***(15) Other outcomes***

There were no serious adverse events reported in any study.

The Cipolli study examined the concentration of azithromycin in the blood serum and in bronchial (airway) secretions (Cipolli 2001). The authors found higher concentrations at both doses in the bronchial secretions compared to serum, which was consistent with previous studies that have demonstrated the accumulation of azithromycin in tissues. Concentrations at the 1000 mg dose were nearly twice as high as the 500 mg dose. Six days after discontinuation of the drug, high levels of azithromycin were still detected in bronchial secretions.

## DISCUSSION

The data from the Saiman study have been a valuable addition to the review (Saiman 2003). These data are consistent with those of the previous two studies which suggest that treatment with azithromycin results in a small but significant improvement in respiratory function (Equi 2002; Wolter 2002). The Saiman study had 185 participants and the increased power is reflected in the meta-analysis of this review, which now demonstrates a significant weighted mean difference in favour of azithromycin at months one and six for relative change in $FEV_1$ % predicted. The consistency of the results of these studies is reassuring, particularly given concerns about the first two studies, namely the difference in baseline characteristics in the Wolter study (Wolter 2002) and the cross-over design of the Equi study (with the potential for hangover effects into the second arm of the study) (Equi 2002).

In total, 296 participants were enrolled in these studies and none suffered a severe or life-threatening adverse event, however, in the largest study less serious adverse events (nausea, diarrhoea and wheezing) occurred more frequently in the azithromycin group (Saiman 2003). There was no evidence of hearing impairment or deranged liver function, however the transient rise in liver enzymes in one participant on 1000 mg in the Cipolli five-day study should be noted (Cipolli 2001). In addition to the positive effect on respiratory function, Saiman demonstrated significant improvement in weight gain and in some aspects of 'quality of life' measures (Saiman 2003). Wolter had similar findings regarding quality of life (Wolter 2002). Participants in the azithromycin group of the Saiman study were less likely to be hospitalised, however, similar to the Wolter study, there was no significant reduction in overall days in hospital (Saiman 2003; Wolter 2002).

The evidence that azithromycin results in a significant improvement in respiratory function is convincing, however whether this is related to indirect anti-pseudomonal or anti-inflammatory properties remains unclear. Of note was the high incidence of all studies of *S. aureus* isolated from respiratory culture at baseline and it is possible that these results are a consequence of the anti-staphylococcal properties of azithromycin. A number of participants in these studies were on long-term anti-staphylococcal prophylaxis, however it has not been possible at the time of this update to undertake a subset analysis to determine the influence of this. Significantly more *S. aureus* was isolated from respiratory cultures in the placebo group at the end of the Saiman study (Saiman 2003).

Finally, clarification is needed as to the correct dosage regimen. Saiman employed a three-days-a-week treatment protocol (500 mg, 250 mg if under 40 kg body weight). This is attractive with respect to improving adherence to treatment and would seem logical given what is known of the tissue distribution of azithromycin. The finding of high concentrations of azithromycin in bronchial secretions six days after the end of treatment in the Cipolli study raises the intriguing possibility of even less frequent drug administration (for example, once or twice weekly) (Cipolli 2001). The issue of length of treatment needs to be addressed, as the appropriate length has not yet been determined, i.e. should this be life-long? It is important that long-term data are collected carefully from participants on azithromycin to identify consequences of treatment for longer than six months.

There is a lot of activity in this field. Large studies have either recently been completed or are nearing completion (Clement 2005; McCormack 2003). We await definitive data from these studies to include in subsequent updates.

## AUTHORS' CONCLUSIONS

### Implications for practice

The results from these studies provide evidence of a small but significant improvement in respiratory function at six months (as determined by relative change in $FEV_1$% predicted from baseline) with azithromycin versus placebo. Treatment with azithromycin is associated with a significant increase in mild adverse events, a small number of which will lead to discontinuation of the drug. The largest study, recruiting 185 children and adults, employed a dose of azithromycin of 500 mg three times a week (250 mg if body weight under 40 kg). It is not clear at what point in the life of a person with CF administration of azithromycin would be appropriate (for example, should it be commenced in young children before the acquisition of *P. aeruginosa*?). Data are only available for six months, although the benefit in respiratory function did remain at that time point. The role of clarithromycin and other macrolides is not clear.

### Implications for research

A number of questions remain concerning the potential use of macrolide antibiotics for the treatment of CF lung disease.
(1) Is the use of azithromycin for more than six months safe?
(2) What is the correct dose to be administered to people with CF (both short- and long-term)? Well-designed pharmacokinetic studies are still urgently needed.
(3) Is improvement in lung function related to an anti-pseudomonal action or merely a reflection of other antibiotic properties?
(4) Which macrolide has the greatest efficacy in CF?
(5) At which stage should macrolide therapy be initiated in CF? For example, is it more appropriate to commence this therapy at an early stage before the acquisition of *P. aeruginosa*?

## 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 is archived at: the following site and can be accesed via inserting this unique number - CD002203: http://www.update-software.com/comcritusers/

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Information on previous updates

Update: February 2004
Date of most recent search of 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.

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Update: November 2003
Following publication the Saiman 2003 reference has been moved from 'Ongoing studies' to 'Studies awaiting assessment'. The review will be updated fully in 2004.

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Update: May 2003
Date of most recent 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.

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Update: January 2001
Most recent search of Group's Trials Register January 2001.
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.
Two references by Baumann 2000 identified were excluded as they were not RCTs.

## POTENTIAL CONFLICT OF INTEREST

None known.

## ACKNOWLEDGEMENTS

The authors would like to thank members of all the study teams for their help and support and for providing extra data, in particular Scott Bell, Mark Rosenthal, Preston Campbell III and Lisa Saiman. We would also like to thank the referees for their useful comments and suggestions. Thanks to the Cystic Fibrosis and Genetic Disorders Cochrane Group; Nikki Jahnke and Tracey Remmington for continuing support with the Cochrane process; and Ashley Jones for invaluable statistical advice.

## SOURCES OF SUPPORT

**External sources of support**

- No sources of support supplied

**Internal sources of support**

- No sources of support supplied

## REFERENCES

### References to studies included in this review

**Cipolli 2001** *{published data only}*

Cipolli M, Cazzola G, Novelli A, Cassetta MI, Fallani S, Mazzei T. Azithromycin concentrations in serum and bronchial secretions of patients with cystic fibrosis. *Clinical Drug Investigation* 2001;**21**(5): 353–60.

**Equi 2002** *{published data only}*

* Equi A, Balfour-Lynn IM, Bush A, Rosenthal M. Long term azithromycin in children with cystic fibrosis: a randomised, placebo-controlled crossover trial. *Lancet* 2002;**360**(9338):978–84.

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AZ0003. Ongoing study Starting date of trial not provided. Contact author for more information.

**AZ0004**

AZ0004. Ongoing study Starting date of trial not provided. Contact author for more information.

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Barker PM, Gillie DJ, Schechter MS, Rubin BK. Effect of macrolides on in vivo ion transport across cystic fibrosis nasal epithelium. *American journal of respiratory and critical care medicine* 2005;**171**:868–71.

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**Southern 2003**

Southern KW, Barker PM, Solis A. Macrolide antibiotics for cystic fibrosis (Cochrane Review). *The Cochrane Database of Systematic Reviews* 2003, Issue 2. Art. No.: CD002203. DOI: 10.1002/14651858.CD002203.pub2.

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Southern KW, Barker PM, Solis A. Macrolide antibiotics for cystic fibrosis (Cochrane Review). *The Cochrane Database of Systematic Reviews* 2004, Issue 1. Art. No.: CD002203. DOI: 10.1002/14651858.CD002203.pub2.

* *Indicates the major publication for the study*

# TABLES

## Characteristics of included studies

| **Study** | **Cipolli 2001** |
|---|---|
| Methods | Randomised open labelled prospective study |
| Participants | 10 adult participants. |
| Interventions | Azithromycin, 500m or 1000 mg. |
| Outcomes | Azithromycin concentration in blood and bronchial secretions. Liver function tests. |
| Notes | |
| Allocation concealment | B – Unclear |

| **Study** | **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 FEV1 (FVC and MEF), hearing, sputum bacterial densities, inflammatory markers, exercise tolerance, subjective well-being. |
| Notes | Treatment arms not reported individually. |
| Allocation concealment | A – Adequate |

| **Study** | **Saiman 2003** |
|---|---|
| Methods | Multi-centre randomised placebo controlled trial |
| Participants | 185 participants: adults and children with CF (> 6 years) with chronic Pseudomonas aeruginosa chest infection (> 1 year) and an FEV1> 30% predicted. |
| Interventions | Azithromycin, 500 mg (250 mg if weight < 40 kg) 3 days a week versus placebo. |
| Outcomes | Primary: relative change in FEV1 (% pred). Adverse events, self reported symptoms, audiology and lab tests. Respiratory cultures.<br>Secondary: relative change in FVC (% pred), body weight, pulmonary exacerbations (number and time to), hospitalisation rate, use of non-quinolone antibiotics, inflammatory markers, and quality of life. |

| | |
|---|---|
| Notes | 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 | A – Adequate |

| **Study** | **Wolter 2002** |
|---|---|
| Methods | Randomised placebo controlled trial. |
| Participants | 60 adult participants.<br>The placebo group contained more men (20/30 versus 9/30), was taller, heavier and had better lung function (FEV1 mean (SD), 62.3 (24.8) versus 50.9 (18.3)). |
| Interventions | Azithromycin, 250 mg once a day for 3 months versus placebo. |
| Outcomes | % change in FEV1 (FVC), weight, quality of life, inflammatory markers, microbiology, respiratory exacerbations. |
| Notes | Baseline characteristics of two groups significantly different. |
| Allocation concealment | A – Adequate |

FEV1: forced expiratory volume at one second
FVC: forced vital capacity
MEF: maximum expiratory flow
SD: standard deviation
Relative change in FEV1; ((Intervention value - Baseline value)*100)/Baseline value

## Characteristics of excluded studies

| **Study** | **Reason for exclusion** |
|---|---|
| Anstead 1999 | Not a randomised controlled trial. An open study. |
| Baumann 2000 | Not a randomised controlled trial. An open prospective study. |
| Jaffe 1998 | Not a randomised controlled trial. Open study. |
| Jensen 2005 | Not a randomised controlled trial |
| 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. |

## Characteristics of ongoing studies

| **Study** | **AZ0003** |
|---|---|
| Trial name or title | AZ0003 |
| Participants | CF patients with Cepacia chest infection |
| Interventions | Azithromycin v<br>Placebo |
| Outcomes | |
| Starting date | |
| Contact information | Lisa Saiman (ls5@columbia.edu) |
| Notes | About to commence recruitment |

**Characteristics of ongoing studies** (*Continued*)

| **Study** | **AZ0004** |
|---|---|
| Trial name or title | AZ0004 |
| Participants | Young CF patients without Pseudomonas chest infection |
| Interventions | Azithromycin versus placebo |
| Outcomes | |
| Starting date | |
| Contact information | Lisa Saiman (ls5@columbia.edu) |
| Notes | In design phase |

| **Study** | **McCormack 2003** |
|---|---|
| Trial name or title | Azithromycin study. |
| Participants | Target 210 participants. |
| Interventions | Azithromycin 250 mg/d versus 1200 mg/wk. |
| Outcomes | FEV1 |
| Starting date | |
| Contact information | Scott Bell<br>BellS@health.qld.gov.au |
| Notes | Recruitment complete |

| **Study** | **Rubin 2003** |
|---|---|
| Trial name or title | North Carolina |
| Participants | 30 CF patients |
| Interventions | Clarithromycin v placebo |
| Outcomes | FEV1 |
| Starting date | |
| Contact information | Pierre Barker<br>pbarker@med.unc.edu |
| Notes | Nasal PD data published |

FEV1: forced expiratory volume at one second
P. aeruginosa: Pseudomonas aeruginosa

## ANALYSES

### Comparison 01. Azithromycin versus placebo

| **Outcome title** | **No. of studies** | **No. of participants** | **Statistical method** | **Effect size** |
|---|---|---|---|---|
| 01 Percentage change in FEV1 | | | Weighted Mean Difference (Fixed) 95% CI | Subtotals only |
| 02 Percentage change in FVC | | | Weighted Mean Difference (Fixed) 95% CI | Subtotals only |
| 03 Adverse effects of antibiotic treatment | | | Relative Risk (Fixed) 95% CI | Subtotals only |

## INDEX TERMS

**Medical Subject Headings (MeSH)**

Anti-Bacterial Agents [*therapeutic use]; Cystic Fibrosis [*complications]; Macrolides; Outcome Assessment (Health Care); Pseudomonas aeruginosa; Pseudomonas Infections [*drug therapy]; Randomized Controlled Trials

**MeSH check words**

Humans

## COVER SHEET

| | |
|---|---|
| **Title** | Macrolide antibiotics for cystic fibrosis |
| **Authors** | Southern KW, Barker PM, Solis A |
| **Contribution of author(s)** | KWS conceived and drafted the review.<br>AS contributed to the content of the review.<br>PMB commented on the review.<br>All reviewers examined and evaluated studies.<br>KWS updated this review with comments from PMB and AS.<br>KWS acts as guarantor of the review. |
| **Issue protocol first published** | 2000/3 |
| **Review first published** | 2000/3 |
| **Date of most recent amendment** | 21 February 2006 |
| **Date of most recent SUBSTANTIVE amendment** | 17 February 2004 |
| **What's New** | Review updated February 2006<br>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; Dionysopoulou 2005; Dogru 2004; Kessaris 2003); and three to the list of ongoing studies (AZ003; AZ004; Rubin 2003). |
| **Date new studies sought but none found** | Information not supplied by author |
| **Date new studies found but not yet included/excluded** | Information not supplied by author |
| **Date new studies found and included/excluded** | 21 September 2005 |
| **Date authors' conclusions section amended** | Information not supplied by author |
| **Contact address** | Dr Kevin Southern<br>Senior Lecturer<br>Institute of Child Health<br>University of Liverpool<br>Alder Hey Children's Hospital<br>Eaton Road<br>Liverpool<br>Merseyside<br>L12 2AP<br>UK<br>E-mail: kwsouth@liv.ac.uk<br>Tel: +44 151 252 5693<br>Fax: +44 151 252 5456 |
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**Cochrane Library number** CD002203

**Editorial group** Cochrane Cystic Fibrosis and Genetic Disorders Group

**Editorial group code** HM-CF

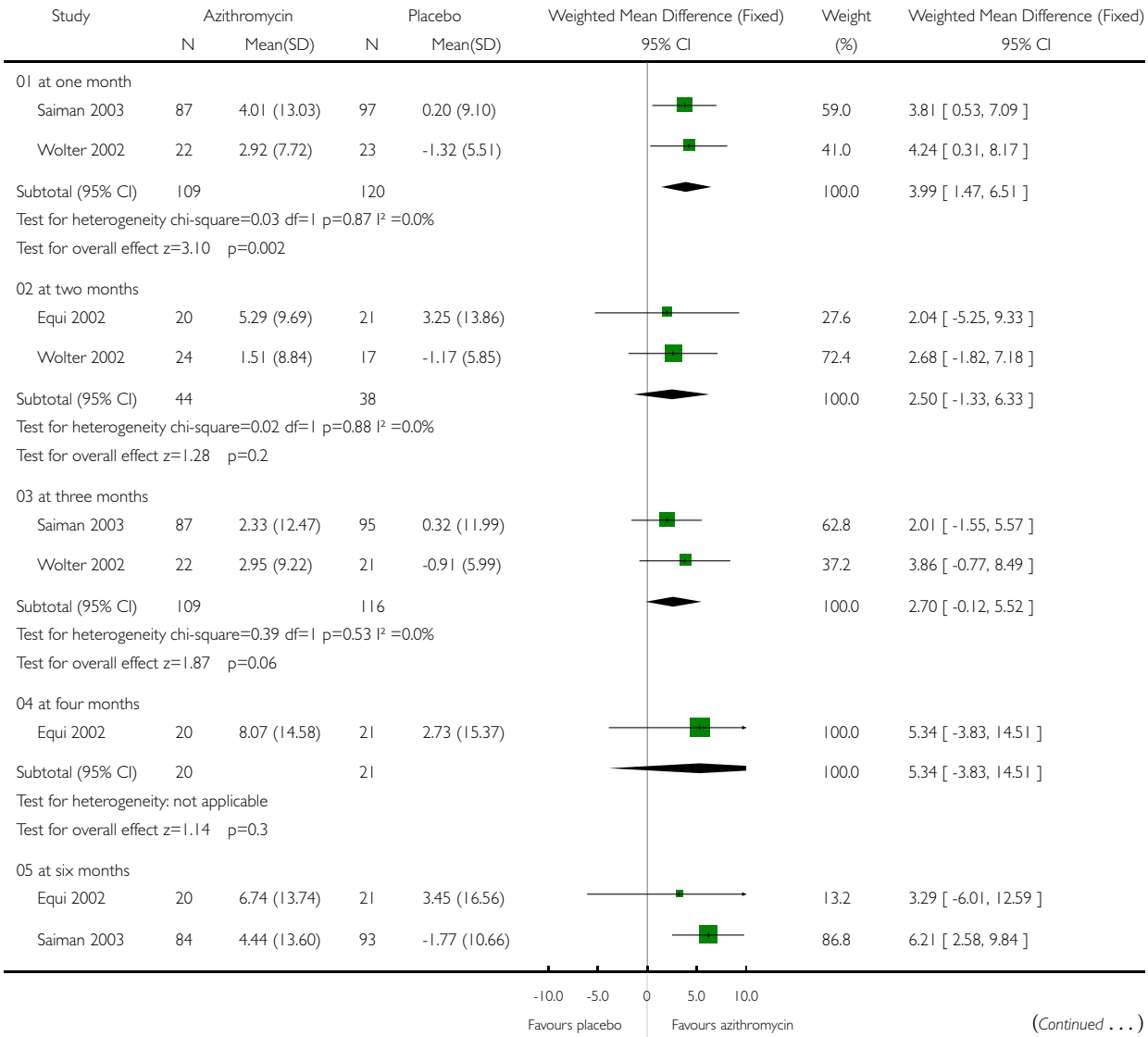
## GRAPHS AND OTHER TABLES

### Analysis 01.01. Comparison 01 Azithromycin versus placebo, Outcome 01 Percentage change in FEV1

Review: Macrolide antibiotics for cystic fibrosis

Comparison: 01 Azithromycin versus placebo

Outcome: 01 Percentage change in FEV1

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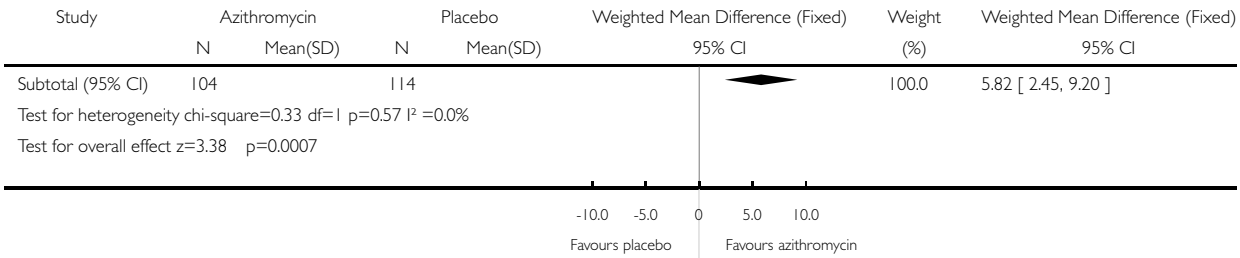
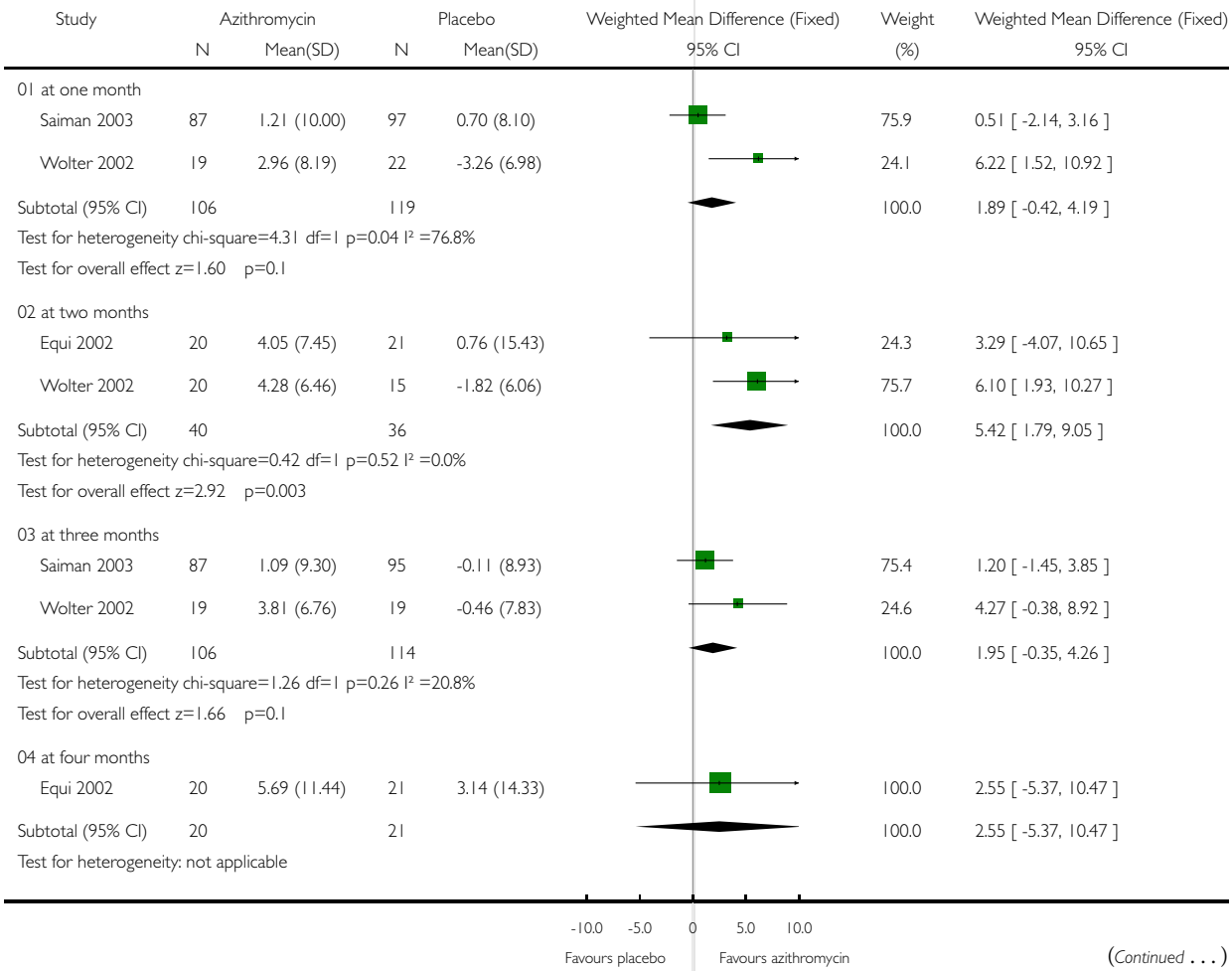



**Analysis 01.02. Comparison 01 Azithromycin versus placebo, Outcome 02 Percentage change in FVC**

Review: Macrolide antibiotics for cystic fibrosis

Comparison: 01 Azithromycin versus placebo

Outcome: 02 Percentage change in FVC

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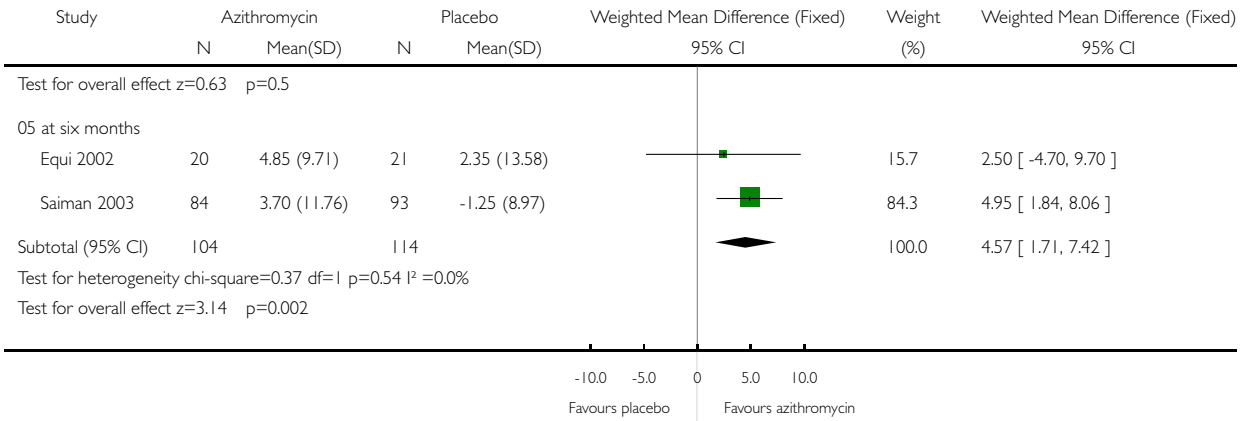
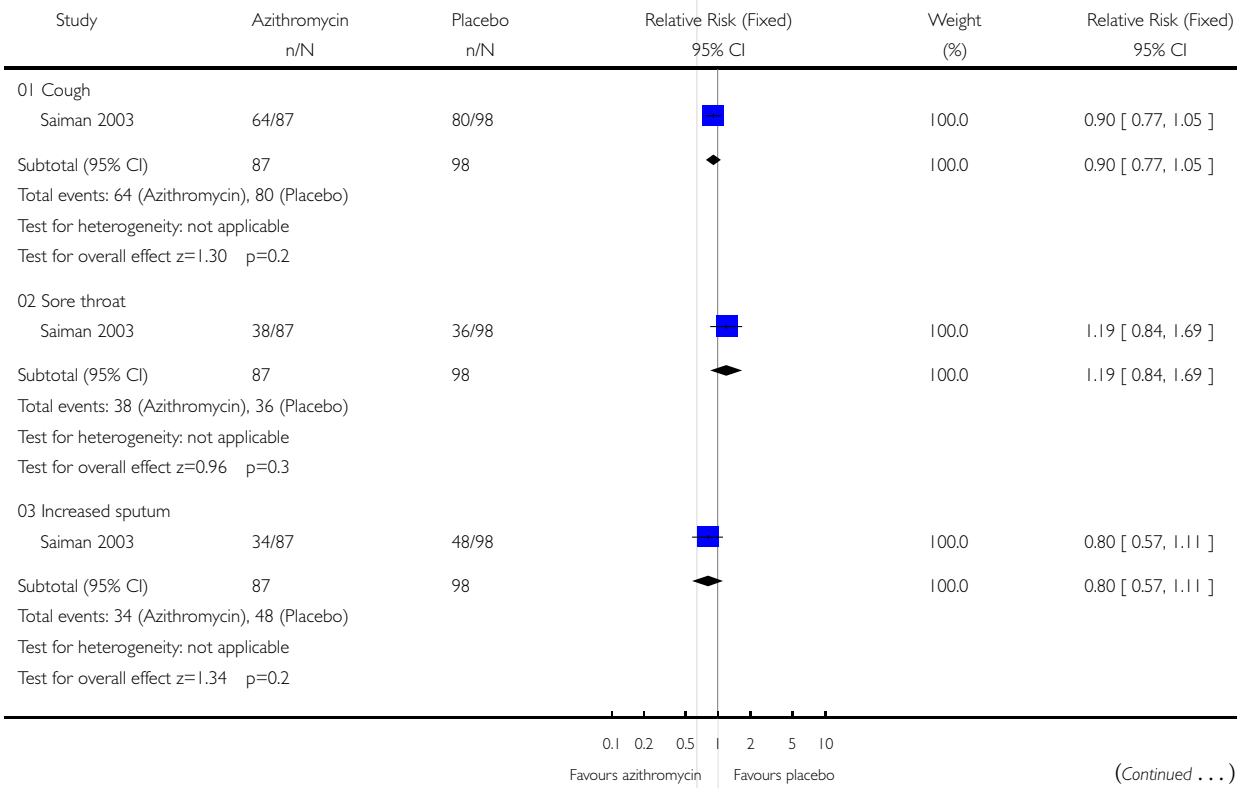



## Analysis 01.03. Comparison 01 Azithromycin versus placebo, Outcome 03 Adverse effects of antibiotic treatment

Review: Macrolide antibiotics for cystic fibrosis

Comparison: 01 Azithromycin versus placebo

Outcome: 03 Adverse effects of antibiotic treatment

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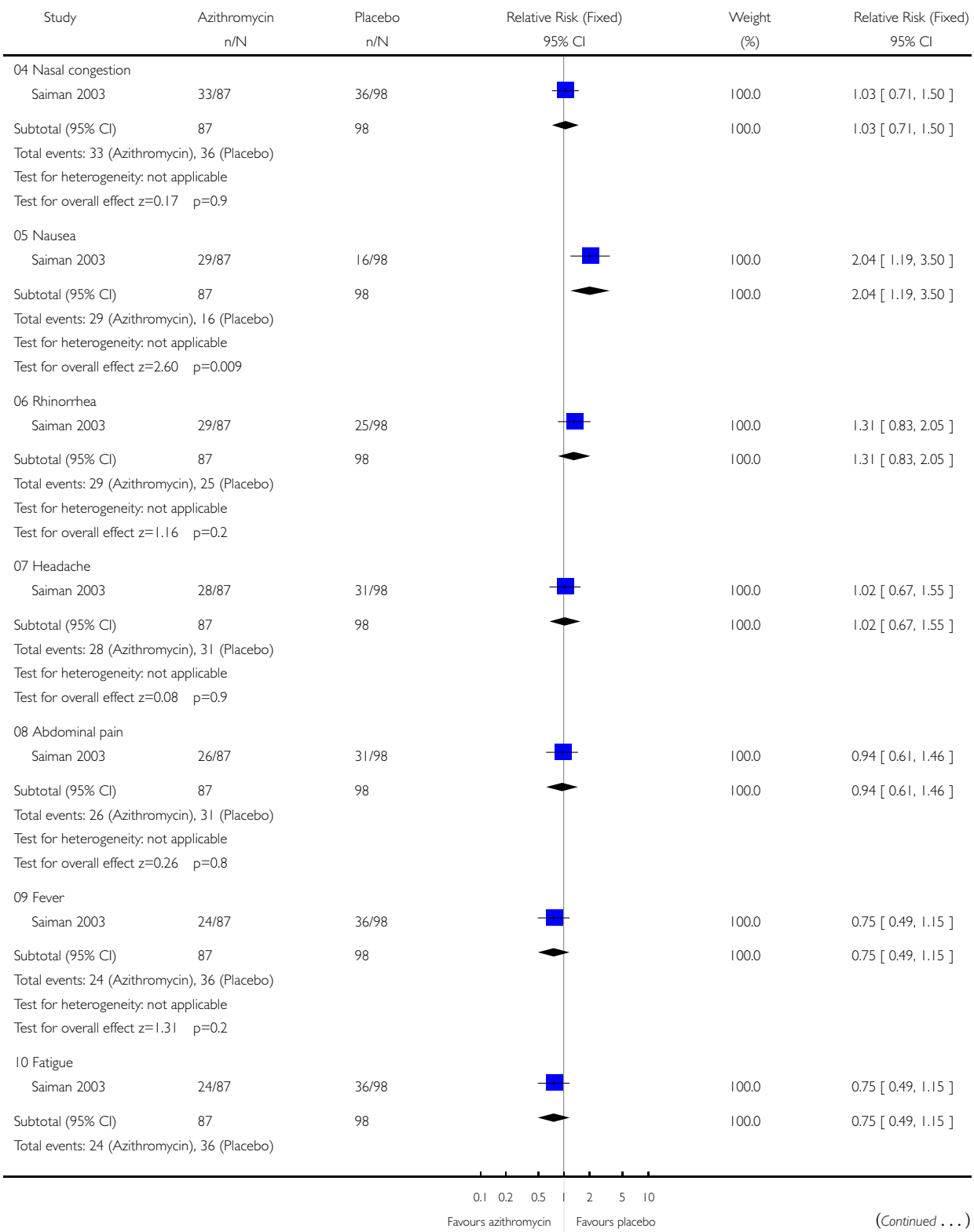


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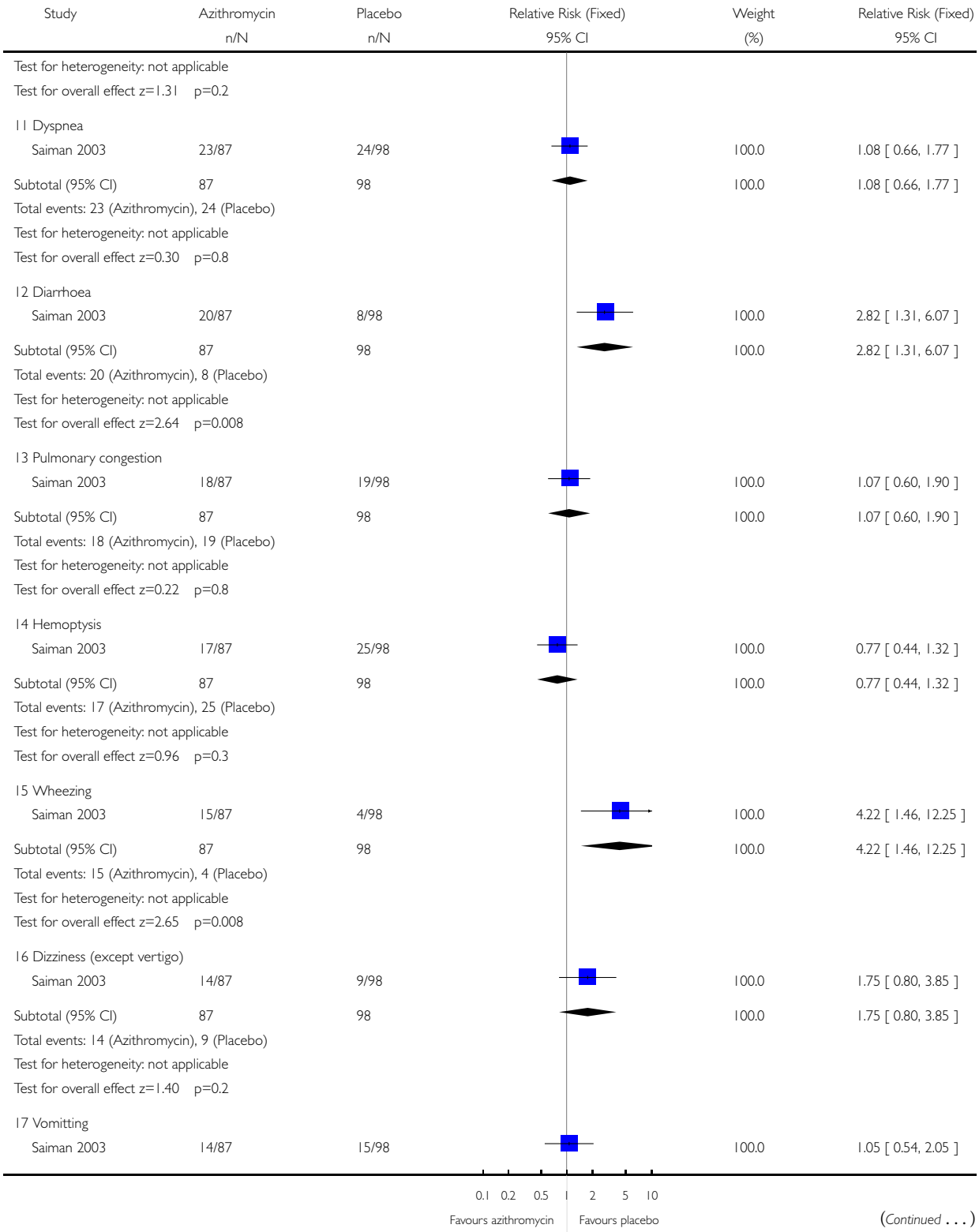


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| Study | Azithromycin n/N | Placebo n/N | Relative Risk (Fixed) 95% CI | Weight (%) | Relative Risk (Fixed) 95% CI |
|---|---|---|---|---|---|
| Subtotal (95% CI) | 87 | 98 | | 100.0 | 1.05 [ 0.54, 2.05 ] |
| Total events: 14 (Azithromycin), 15 (Placebo) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect z=0.15 p=0.9 | | | | | |
| 18 Decreased lung function | | | | | |
| Saiman 2003 | 13/87 | 7/98 | | 100.0 | 2.09 [ 0.87, 5.00 ] |
| Subtotal (95% CI) | 87 | 98 | | 100.0 | 2.09 [ 0.87, 5.00 ] |
| Total events: 13 (Azithromycin), 7 (Placebo) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect z=1.66 p=0.1 | | | | | |
| 19 Decreased appetite | | | | | |
| Saiman 2003 | 13/87 | 15/98 | | 100.0 | 0.98 [ 0.49, 1.94 ] |
| Subtotal (95% CI) | 87 | 98 | | 100.0 | 0.98 [ 0.49, 1.94 ] |
| Total events: 13 (Azithromycin), 15 (Placebo) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect z=0.07 p=0.9 | | | | | |
| 20 Hearing impairment | | | | | |
| Saiman 2003 | 1/87 | 1/98 | | 100.0 | 1.13 [ 0.07, 17.74 ] |
| Subtotal (95% CI) | 87 | 98 | | 100.0 | 1.13 [ 0.07, 17.74 ] |
| Total events: 1 (Azithromycin), 1 (Placebo) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect z=0.08 p=0.9 | | | | | |
| 21 Tinnitus | | | | | |
| Saiman 2003 | 1/87 | 1/98 | | 100.0 | 1.13 [ 0.07, 17.74 ] |
| Subtotal (95% CI) | 87 | 98 | | 100.0 | 1.13 [ 0.07, 17.74 ] |
| Total events: 1 (Azithromycin), 1 (Placebo) | | | | | |
| Test for heterogeneity: not applicable | | | | | |
| Test for overall effect z=0.08 p=0.9 | | | | | |