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[Intervention Review]

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ABSTRACT

Background

Macrolide antibiotics (macrolides) are among the most commonly prescribed antibiotics worldwide and are used for a wide range of infections. However, macrolides also expose people to the risk of adverse events. The current understanding of adverse events is mostly derived from observational studies, which are subject to bias because it is hard to distinguish events caused by antibiotics from events caused by the diseases being treated. Because adverse events are treatment-specific, rather than disease-specific, it is possible to increase the number of adverse events available for analysis by combining randomised controlled trials (RCTs) of the same treatment across different diseases.

Objectives

To quantify the incidences of reported adverse events in people taking macrolide antibiotics compared to placebo for any indication.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), which includes the Cochrane Acute Respiratory Infections Group Specialised Register (2018, Issue 4); MEDLINE (Ovid, from 1946 to 8 May 2018); Embase (from 2010 to 8 May 2018); CINAHL (from 1981 to 8 May 2018); LILACS (from 1982 to 8 May 2018); and Web of Science (from 1955 to 8 May 2018). We searched clinical trial registries for current and completed trials (9 May 2018) and checked the reference lists of included studies and of previous Cochrane Reviews on macrolides.

Selection criteria

We included RCTs that compared a macrolide antibiotic to placebo for any indication. We included trials using any of the four most commonly used macrolide antibiotics: azithromycin, clarithromycin, erythromycin, or roxithromycin. Macrolides could be administered by any route. Concomitant medications were permitted provided they were equally available to both treatment and comparison groups.

Data collection and analysis

Two review authors independently extracted and collected data. We assessed the risk of bias of all included studies and the quality of evidence for each outcome of interest. We analysed specific adverse events, deaths, and subsequent carriage of macrolide-resistant bacteria separately. The study participant was the unit of analysis for each adverse event. Any specific adverse events that occurred in 5% or more of any group were reported. We undertook a meta-analysis when three or more included studies reported a specific adverse event.

Main results

We included 183 studies with a total of 252,886 participants (range 40 to 190,238). The indications for macrolide antibiotics varied greatly, with most studies using macrolides for the treatment or prevention of either acute respiratory tract infections, cardiovascular diseases, chronic respiratory diseases, gastrointestinal conditions, or urogynaecological problems. Most trials were conducted in secondary care settings. Azithromycin and erythromycin were more commonly studied than clarithromycin and roxithromycin.

Most studies (89%) reported some adverse events or at least stated that no adverse events were observed.

Gastrointestinal adverse events were the most commonly reported type of adverse event. Compared to placebo, macrolides caused more diarrhoea (odds ratio (OR) 1.70, 95% confidence interval (CI) 1.34 to 2.16; low-quality evidence); more abdominal pain (OR 1.66, 95% CI 1.22 to 2.26; low-quality evidence); and more nausea (OR 1.61, 95% CI 1.37 to 1.90; moderate-quality evidence). Vomiting (OR 1.27, 95% CI 1.04 to 1.56; moderate-quality evidence) and gastrointestinal disorders not otherwise specified (NOS) (OR 2.16, 95% CI 1.56 to 3.00; moderate-quality evidence) were also reported more often in participants taking macrolides compared to placebo.

The number of additional people (absolute difference in risk) who experienced adverse events from macrolides was: gastrointestinal disorders NOS 85/1000; diarrhoea 72/1000; abdominal pain 62/1000; nausea 47/1000; and vomiting 23/1000.

The number needed to treat for an additional harmful outcome (NNTH) ranged from 12 (95% CI 8 to 23) for gastrointestinal disorders NOS to 17 (9 to 47) for abdominal pain; 19 (12 to 33) for diarrhoea; 19 (13 to 30) for nausea; and 45 (22 to 295) for vomiting.

There was no clear consistent difference in gastrointestinal adverse events between different types of macrolides or route of administration.

Taste disturbances were reported more often by participants taking macrolide antibiotics, although there were wide confidence intervals and moderate heterogeneity (OR 4.95, 95% CI 1.64 to 14.93; I^2 = 46%; low-quality evidence).

Compared with participants taking placebo, those taking macrolides experienced hearing loss more often, however only four studies reported this outcome (OR 1.30, 95% CI 1.00 to 1.70; I^2 = 0%; low-quality evidence).

We did not find any evidence that macrolides caused more cardiac disorders (OR 0.87, 95% CI 0.54 to 1.40; very low-quality evidence); hepatobiliary disorders (OR 1.04, 95% CI 0.27 to 4.09; very low-quality evidence); or changes in liver enzymes (OR 1.56, 95% CI 0.73 to 3.37; very low-quality evidence) compared to placebo.

We did not find any evidence that appetite loss, dizziness, headache, respiratory symptoms, blood infections, skin and soft tissue infections, itching, or rashes were reported more often by participants treated with macrolides compared to placebo.

Macrolides caused less cough (OR 0.57, 95% CI 0.40 to 0.80; moderate-quality evidence) and fewer respiratory tract infections (OR 0.70, 95% CI 0.62 to 0.80; moderate-quality evidence) compared to placebo, probably because these are not adverse events, but rather characteristics of the indications for the antibiotics. Less fever (OR 0.73, 95% 0.54 to 1.00; moderate-quality evidence) was also reported by participants taking macrolides compared to placebo, although these findings were non-significant.

There was no increase in mortality in participants taking macrolides compared with placebo (OR 0.96, 95% 0.87 to 1.06; I^2 = 11%; low-quality evidence).

Only 24 studies (13%) provided useful data on macrolide-resistant bacteria. Macrolide-resistant bacteria were more commonly identified among participants immediately after exposure to the antibiotic. However, differences in resistance thereafter were inconsistent.

Pharmaceutical companies supplied the trial medication or funding, or both, for 91 trials.

Authors' conclusions

The macrolides as a group clearly increased rates of gastrointestinal adverse events. Most trials made at least some statement about adverse events, such as "none were observed". However, few trials clearly listed adverse events as outcomes, reported on the methods

used for eliciting adverse events, or even detailed the numbers of people who experienced adverse events in both the intervention and placebo group. This was especially true for the adverse event of bacterial resistance.

PLAIN LANGUAGE SUMMARY

Adverse events in people taking macrolide antibiotics

Review question

We wanted to find out if people treated with a macrolide antibiotic experienced more adverse events than those treated with placebo.

Background

Macrolide antibiotics are a group of antibiotics that are commonly used to treat both acute and chronic infections. The four most frequently used macrolides are: azithromycin, clarithromycin, erythromycin, and roxithromycin. People taking macrolide antibiotics are at risk of experiencing adverse events such as nausea, diarrhoea, or rash.

Search date

We searched the literature up to May 2018.

Study characteristics

We included 183 studies with a total of 252,886 participants. Most studies were conducted in the hospital setting. Azithromycin and erythromycin were more commonly studied than clarithromycin and roxithromycin. Most studies (89%) reported some adverse events, or at least stated that no adverse events were observed.

Study funding sources

Drug companies supplied trial medications or funding, or both, in 91 studies. Funding sources were unclear in 59 studies.

Key results

People treated with a macrolide antibiotic experienced gastrointestinal adverse events such as nausea, vomiting, abdominal pain, and diarrhoea more often than those treated with placebo.

Taste disturbances were reported more often by people taking macrolides than those taking a placebo. However, as very few studies reported on these adverse events, these results should be interpreted with caution.

Hearing loss was reported more often by people taking macrolide antibiotics, however only four studies reported this outcome.

Macrolides caused less cough and fewer respiratory tract infections than placebo.

We did not find any evidence that macrolides caused more cardiac disorders, liver disorders, blood infections, skin and soft tissue infections, changes in liver enzymes, appetite loss, dizziness, headache, respiratory symptoms, itching, or rashes than placebo.

We did not find more deaths in people treated with macrolides than in those treated with placebo.

Very limited information was available to assess if people treated with a macrolide antibiotic were at greater risk of developing resistant bacteria than those treated with placebo. However, bacteria that did not respond to macrolide antibiotics were more commonly identified immediately after treatment in people taking a macrolide than in those taking a placebo, but differences in resistance thereafter were inconsistent.

Quality of the evidence

The quality of the evidence ranged from very low (cardiac disorders, change in liver enzymes, liver disorders) to low (abdominal pain, death, diarrhoea, dizziness, hearing loss, skin and soft tissue infections, taste disturbance, wheeze) to moderate (appetite loss, blood infection, cough, fever, headache, itching, nausea, rash, respiratory symptoms, respiratory tract infections, vomiting).

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Gastrointestinal adverse events in people taking macrolide antibiotics versus placebo for any indication

Patient or population: any indication
Setting: any setting
Intervention: macrolide antibiotics (azithromycin, clarithromycin, erythromycin, or roxithromycin, administered by any route)
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with macrolide antibiotics				
Gastrointestinal disorders not otherwise specified	90 per 1000	176 per 1000 (133 to 228)	OR 2.16 (1.56 to 3.00)	3295 (23 RCTs)	⊕⊕⊕◯ MODERATE[1]	NNTH = 12
Abdominal pain	114 per 1000	176 per 1000 (135 to 225)	OR 1.66 (1.22 to 2.26)	7776 (23 RCTs)	⊕⊕◯◯ LOW[12]	NNTH = 17
Diarrhoea	89 per 1000	143 per 1000 (116 to 175)	OR 1.70 (1.34 to 2.16)	23,754 (37 RCTs)	⊕⊕◯◯ LOW[12]	NNTH = 19
Nausea	107 per 1000	162 per 1000 (142 to 186)	OR 1.61 (1.37 to 1.90)	14,983 (28 RCTs)	⊕⊕⊕◯ MODERATE[1]	NNTH = 19
Vomiting	94 per 1000	117 per 1000 (98 to 140)	OR 1.27 (1.04 to 1.56)	5328 (15 RCTs)	⊕⊕⊕◯ MODERATE[1]	NNTH = 45

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **NNTH**: number needed to treat for an additional harmful outcome; **OR**: odds ratio; **RCT**: randomised controlled trial

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded one level due to imprecision. The outcome was reported in only a small proportion of the included studies.
[2]Downgraded one level due to inconsistency. I^2 = 59% for abdominal pain, I^2 = 74% for diarrhoea.

BACKGROUND

Description of the condition

Macrolide antibiotics, often referred to as macrolides, are among the most commonly prescribed antibiotics worldwide. Macrolides are often prescribed for the treatment of acute upper and lower respiratory infections (Laopaiboon 2015; van Driel 2016), pelvic inflammatory disease (Savaris 2017), skin and soft tissue infections (Dalal 2017), and to eradicate *Helicobacter pylori* (Ford 2016). Macrolides are frequently the drug of choice for people allergic to penicillin.

As well as antibiotic activity, macrolides have anti-inflammatory and immunomodulatory activity (Spagnolo 2013), and are used to treat several chronic respiratory tract conditions such as diffuse panbronchiolitis (Lin 2015), cystic fibrosis (Southern 2012), bronchiectasis (Hnin 2015), asthma (Kew 2015), and chronic rhinosinusitis (Head 2016). Long-term therapy has also been used for decades for the treatment of acne vulgaris, using both the antibacterial and anti-inflammatory effects of macrolides (Dawson 2013). There are various other indications for treatment with macrolide antibiotics, such as gastroparesis (Enweluzo 2013), trachoma (Evans 2011), typhoid fever (Chandey 2012), and preventing *Mycobacterium avium* complex infection in people with HIV infection (Uthman 2013). Several other indications exist or are being tested.

Description of the intervention

Erythromycin, the first discovered macrolide antibiotic, has been in use since the early 1950s. A series of semisynthetic compounds were subsequently developed, with clarithromycin, roxithromycin, and azithromycin being the most commonly used clinically (Zuckerman 2009). The availability of these new macrolides has substantially reduced the use of erythromycin over recent years, as they have greater acid stability in the digestive tract, improved oral bioavailability, longer half-lives, and diminished gastrointestinal adverse reactions (Dougherty 2012). In general, macrolides have a moderately broad spectrum of activity, which includes most gram-positive but only selected gram-negative organisms, as well as several bacteria responsible for intracellular infections, such as *Mycoplasma* spp,*Chlamydia* spp, *and Legionella* spp. Azithromycin has more potent antibacterial activity against gram-negative organisms than erythromycin and has an exceptional ability to accumulate inside eukaryotic cells, resulting in a favourable profile against intracellular bacteria (Zuckerman 2009).

In the USA, macrolides are the most commonly prescribed antibiotics together with penicillins (Hicks 2013). In Europe, macrolides are also among the most commonly prescribed antibiotics in the community (ECDC 2017a). However, resistance to macrolides has become a major problem, and macrolides are no longer always effective in treating common infections, such as community-acquired pneumonia (ECDC 2017b).

How the intervention might work

The most commonly used therapeutic macrolides are characterised by a 14-, 15- or 16-membered lactone ring, to which one or more sugars are attached (Dinos 2017). Macrolides are considered as bacteriostatic antibiotics. Macrolides are protein synthesis inhibitors, exerting their antimicrobial effect by preventing the bacterial ribosome from translating its messenger ribonucleic acid (RNA) into new proteins (Dougherty 2012). The immunomodulatory properties of macrolides are related to the lactone ring and are seen with the 14-membered ring macrolides (erythromycin, clarithromycin, and roxithromycin) and the 15-membered ring macrolides (azithromycin) (Spagnolo 2013). Although the precise mechanism of the immunomodulatory properties is unknown, it has been proposed that macrolides attenuate mucous hypersecretion, reduce production of pro-inflammatory cytokines, and have a suppressive effect on lymphocytic activity (Sadarangani 2015).

Taking macrolides also exposes people to the risk of various adverse events. For example, gastrointestinal adverse reactions such as abdominal pain, nausea, vomiting, and diarrhoea are common. The mechanism underlying these reactions is believed to be partly motilin-receptor agonism and consequently stimulation of stomach and gut motility (Abu-Gharbieh 2004). Ototoxicity (hearing loss and tinnitus) and hepatotoxicity (e.g. raised liver enzymes, hepatitis, and intrahepatic cholestasis) have also been reported in people taking macrolides. Headache, taste disturbances, and haematologic toxicity such as leukopenia, thrombocytopenia, agranulocytosis, neutropenia, and neutrophilia are also seen. Allergic reactions such as eosinophilia, fever, and rashes are rarely reported, as is *Candida* overgrowth and pseudomembranous enterocolitis caused by *Clostridium difficile* (Dougherty 2012; Zuckerman 2009).

Cardiac toxicity may complicate the use of macrolides, as macrolide antibiotics inhibit the delayed rectifier potassium current (I_{Kr}), resulting in prolongation of cardiac repolarisation (prolongation of the QT interval), which can cause cardiac arrhythmias (Owens 2006). Observational studies have shown that both azithromycin and clarithromycin are associated with a significantly increased risk of cardiovascular death (Ray 2012; Svanström 2013; Svanström 2014). However, a Danish cohort study comparing azithromycin with penicillin V found that the former was not associated with a significantly increased risk, suggesting that the increased risk of cardiovascular death observed in people taking azithromycin compared with no antibiotic use was attributable to underlying patient factors that led to the prescription of antibiotics (Svanström 2013).

Finally, there is a well-documented association between antibiotic consumption and the development of bacterial resistance at both the individual and community level, and people taking macrolides are at risk of becoming carriers of resistant bacteria (Bell 2014).

Definitions

An adverse event is an adverse outcome that occurs while a person is taking a drug, but the event is not (or not necessarily) attributable to the drug taken (Edwards 2000). It is recommended that the recording of adverse events in clinical trials should distinguish suspected adverse effects from suspected adverse reactions (Aronson 2013).

Adverse effects and adverse reactions have different manifestations by which they can be recognised (Aronson 2013):

- adverse reactions are unwanted outcomes that the person experiences and that are detected by their clinical manifestations (symptoms or signs, or both);
- adverse effects are unwanted outcomes of which the person is not aware; they are usually detected by laboratory tests (e.g. biochemical, haematological, immunological, radiological, pathological tests) or by clinical investigations (e.g. gastrointestinal endoscopy, cardiac catheterisation).

Serious adverse events are often reported separately. These are adverse events that occur at any dose and result in death or life-threatening events; requirement for hospitalisation or prolongation of existing hospitalisation; persistent or significant disability; or congenital anomalies, or are events that are considered medically important (ICH 2003).

Why it is important to do this review

The current understanding of adverse events in people taking antibiotics is largely derived from observational studies, in which estimates may be biased because it is hard to distinguish adverse drug reactions from disease-related symptoms. One way of addressing this problem is to investigate common adverse events encountered in randomised, placebo-controlled trials of antibiotics. This study design controls for disease-related symptoms, allowing for better quantification of antibiotic-related adverse events.

However, most randomised controlled trials are set up to demonstrate the benefits of antibiotic treatment for specific infections, and these studies are often not powered to quantify adverse events (Vandenbroucke 2004). The *Cochrane Handbook for Systematic Reviews of Interventions* states that "many adverse events are too uncommon or too long-term to be observed within randomised trials" (Higgins 2011). As a consequence, a typical systematic review of controlled trials focusing on a specific indication may not provide sufficient evidence on the adverse events profile of an intervention, for example antibiotics (Zorzela 2014). Because adverse events are not disease-specific (with a very few exceptions, e.g. ampicillin rash in people with Epstein-Barr virus acute infectious mononucleosis), it is possible to 'borrow strength' from studies using the same intervention for different diseases to better estimate adverse events (Chen 2014).

We undertook this review to quantify adverse events in people using macrolide antibiotics, independently of the indication or effects of the treatments. The intent is to support clinicians and patients in evaluating harms as well as benefits in the choice of management when antibiotics are contemplated.

OBJECTIVES

To quantify the incidences of reported adverse events in people taking macrolide antibiotics compared to placebo for any indication.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised, placebo-controlled trials of any of the four most commonly used macrolide antibiotics: azithromycin, clarithromycin, erythromycin, or roxithromycin. We included trials with more than two intervention arms if we could identify a macrolide arm and a placebo arm.

We excluded purely pharmacodynamic studies and purely pharmacokinetic studies, unless they also reported clinical measurements. We also excluded studies in which fewer than 20 participants were randomised to each arm.

Types of participants

We included individuals of all ages taking a macrolide antibiotic for any indication.

Types of interventions

We included trials of macrolides delivered by any route, including oral, topical, intravenous, and intramuscular. Use of concomitant medications was permitted.

Types of outcome measures

Primary outcomes

1. Any reported adverse event that occurred in 5% or more of any group (Zarin 2016).
2. Death.
3. Subsequent carriage of macrolide-resistant bacteria.

Secondary outcomes

None.

Search methods for identification of studies

Electronic searches

We searched the following databases up to 8 May 2018:

- the Cochrane Central Register of Controlled Trials, which contains the Cochrane Acute Respiratory Infections Group Specialised Register (CENTRAL; 2018, Issue 4) in the Cochrane Library using the strategy in Appendix 1;
- MEDLINE (Ovid) (from 1946 to 8 May 2018) using the search strategy in Appendix 1;
- Embase (Elsevier) (from 2010 to 8 May 2018) using the search strategy in Appendix 2;
- CINAHL (EBSCO) (Cumulative Index to Nursing and Allied Health Literature) (from 1981 to 8 May 2018) using the search strategy in Appendix 3;
- LILACS (BIREME) (Latin American and Caribbean Health Science Information database) (from 1982 to 8 May 2018) using the search strategy in Appendix 4; and
- Web of Science (Clarivate Analytics) (from 1955 to 8 May 2018) using the search strategy in Appendix 5.

We used the search strategy described in Appendix 1 to search MEDLINE and CENTRAL. We combined the search strategy with the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision); Ovid format (Higgins 2011). We adapted the search strategy to search Embase (Appendix 2), CINAHL (Appendix 3), LILACS (Appendix 4), and Web of Science (Appendix 5).

We searched the following trial registries on 9 May 2018:

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

We did not restrict the results by language or publication status (published, unpublished, in press, or in progress).

Searching other resources

We checked the reference lists of all primary studies for additional trials by performing a backward citation (cited references) search in Web of Science. We adapted the Cochrane Highly Sensitive Search Strategy for identifying randomised trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision); Ovid format, Higgins 2011, for use in EndNote 2016 on these results, before they were screened.

We searched the Cochrane Library (title, abstract, and keyword fields) using the following terms: macrolide, azithromycin, clarithromycin, erythromycin, or roxithromycin, to exploit the reference lists of previous Cochrane Reviews on macrolide antibiotics.

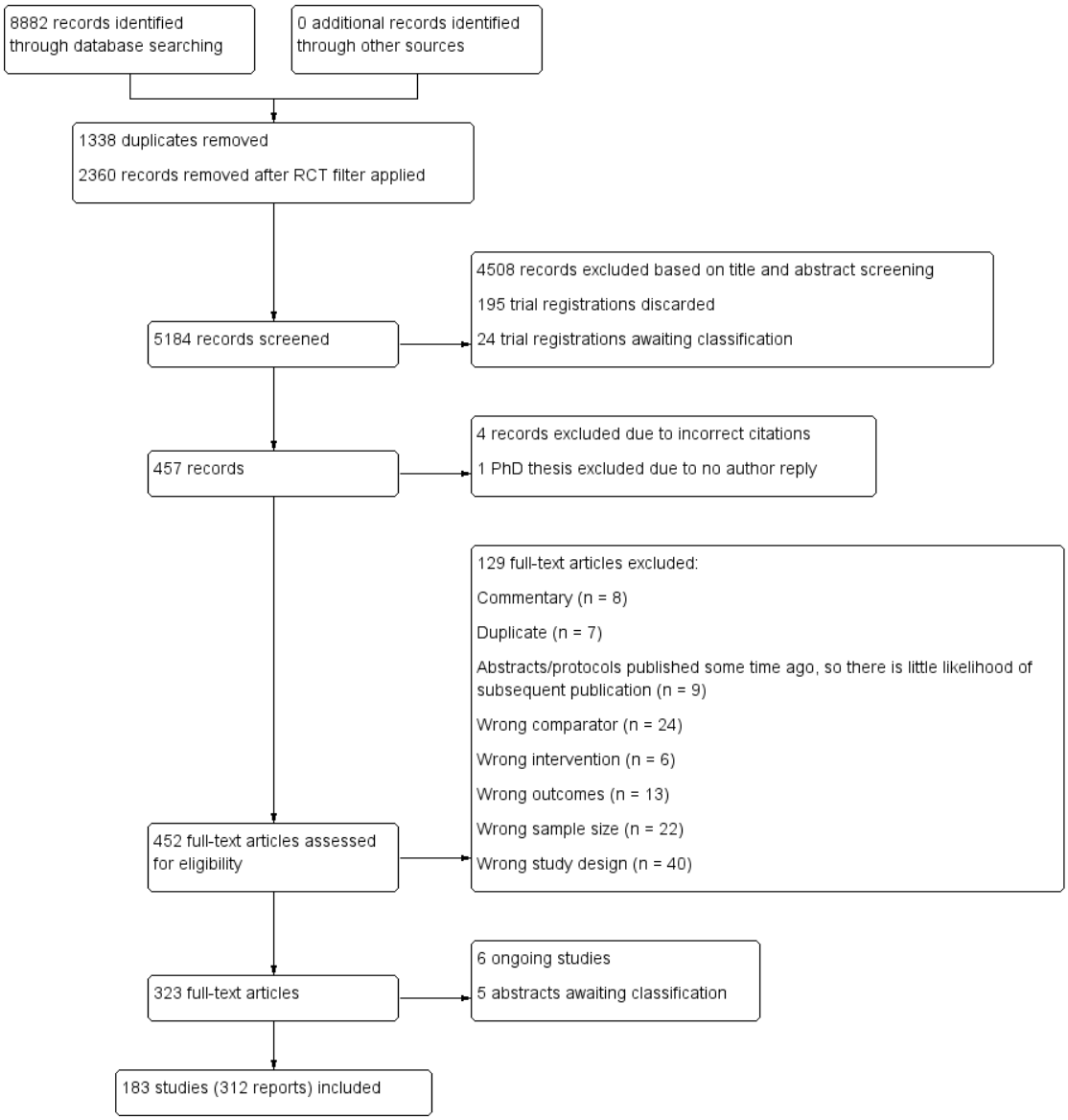
Data collection and analysis

Selection of studies

Two review authors (MPH and ST, AMcC, or AMS) independently screened the titles and abstracts of all studies identified by the searches for potential relevance. We retrieved full-text copies of all potentially relevant articles for full-text evaluation. Any disputes were resolved by consensus or by consulting a third review author (CDM).

We collated multiple reports of the same study to ensure that each study, rather than each report, was analysed. The process for selecting studies is detailed in a PRISMA flow chart (Figure 1) (Moher 2009).

Figure 1. PRISMA study flow diagram.



Data extraction and management

Two review authors (MPH and AMcC or AMS) independently extracted data from the included studies using a standardised extraction form.

We extracted the following information.

- Trial characteristics and methodological quality: year of publication, study design, number of participants, study setting, information for assessing risk of bias.
- Participant characteristics: age, sex, concomitant medications if relevant.
- Information about the intervention: indication for treatment, type of macrolide, route of administration, dose of treatment, duration of treatment, total treatment dose.
- Outcome measures: whether adverse events were stated as an outcome, any reported adverse events (including death and data on antimicrobial resistance), method of eliciting adverse events.

Assessment of risk of bias in included studies

Two review authors (MPH and AMcC or AMS) independently assessed the risks of common biases for each of the included studies using the 'Risk of bias' tool described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreements were resolved by discussion or by consulting a third review author (CDM). We assessed risk of bias according to the following seven domains:

- sequence generation (selection bias);
- allocation concealment (selection bias);
- blinding of participants and personnel (performance bias);
- blinding of outcome assessment (detection bias);
- incomplete outcome data (attrition bias);
- selective outcome reporting (reporting bias); and
- other sources of bias.

We assessed each domain as having a high, low, or unclear risk of bias and provided a justification for our judgement. Furthermore, we summarised the 'Risk of bias' judgements across different studies for each of the seven domains.

Measures of treatment effect

We expressed outcome measures as odds ratios (OR) with accompanying 95% confidence intervals (CI). When appropriate, odds ratios were also expressed as absolute risk differences (ARDs), based on average rates of adverse events in the control groups, and converted to number needed to treat for an additional harmful outcome (NNTH) to interpret the results from the meta-analysis. We calculated NNTH in the following manner:

NNTH = (PEER*(OR - 1)) + 1/(PEER*(OR - 1)*(1 - PEER))

(where PEER = patient expected event rate (i.e. the rate of events in the control population), OR = odds ratio).

Unit of analysis issues

For each of the specific adverse events, including death, the participant was the unit of analysis. We used participants and isolates (colonies of bacteria grown microbiologically that arise from one or few individual bacteria) as units of analysis when reporting subsequent carriage of macrolide-resistant bacteria. Reported data from the included large cluster-randomised controlled trial were adjusted for clustering by the trial authors and no additional adjustments were performed (Keenan 2018).

Dealing with missing data

We contacted trial authors when adverse events were incompletely reported and contact details (an e-mail address) were provided in the publication. In case of no reply or message undeliverable, we did not make a second attempt to contact authors. We did not contact authors if a study provided no information on adverse events.

Assessment of heterogeneity

We used the I^2 statistic to measure statistical heterogeneity, as recommended in the*Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Assessment of reporting biases

Outcome reporting bias is particularly important for adverse events, as they are often not the primary outcome. For each study, we searched for information about whether adverse events was predefined as an outcome, the method of eliciting adverse events, and whether adverse events were reported or not. This information is provided in Characteristics of included studies.

Data synthesis

Classification of adverse events

Some adverse events are reported under different names but are subsets of the same phenomenon. To address this, we classified the adverse events using the Medical Dictionary for Regulatory Activities (MedDRA), developed by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (MedDRA 2018). MedDRA is a clinically validated

and standardised hierarchy consisting of five levels, arranged from very specific to very general:

1. System Organ Class, e.g. gastrointestinal disorders;
2. High Level Group Term, e.g. gastrointestinal signs and symptoms;
3. High Level Term, e.g. nausea and vomiting symptoms;
4. Preferred Term, e.g. nausea;
5. Lowest Level Term, e.g. feeling queasy.

One review author (MPH) classified reported individual adverse events at the most specific level by means of the MedDRA Web-Based Browser tool (MedDRA 2018), and then grouped them under the primary System Organ Class, according to the MedDRA coding system. There are 27 System Organ Classes, as follows.

1. Blood and lymphatic system disorders.
2. Cardiac disorders.
3. Congenital, familial, and genetic disorders.
4. Ear and labyrinth disorders.
5. Endocrine disorders.
6. Eye disorders.
7. Gastrointestinal disorders.
8. General disorders and administration site conditions.
9. Hepatobiliary disorders.
10. Immune system disorders.
11. Infections and infestations.
12. Injury, poisoning, and procedural complications.
13. Investigations.
14. Metabolism and nutrition disorders.
15. Musculoskeletal and connective tissue disorders.
16. Neoplasms benign, malignant, and unspecified.
17. Nervous system disorders.
18. Pregnancy, puerperium, and perinatal conditions.
19. Product issues.
20. Psychiatric disorders.
21. Renal and urinary disorders.
22. Reproductive system and breast disorders.
23. Respiratory, thoracic, and mediastinal disorders.
24. Skin and subcutaneous tissue disorders.
25. Social circumstances.
26. Surgical and medical procedures.
27. Vascular disorders.

Two review authors (MPH and AMcC or AMS) then attempted to reclassify the adverse events to a lower common hierarchical level within each System Organ Class to enable comparisons between studies. Adverse events were most often identified at the Preferred Term level (e.g. nausea or vomiting). However, some studies only reported at the High Level Term level (e.g. nausea and vomiting symptoms) or Lowest Level Term level (e.g. gastrointestinal disorder NOS).

We needed to manage a long list of infrequently reported adverse events that were unlikely to be clinically significant, and accordingly set a threshold of ≥ 5% to analyse (Zarin 2016). However, because it is possible that less frequent adverse events might be important, we extracted these to facilitate future analysis by interested investigators (Hansen 2018a; Hansen 2018b).

Analysis

When only one or two studies reported a specific adverse event, at any MedDRA level, we reported it simply as a percentage of events in each group, and calculated P values (reported as rarely reported adverse events). We undertook a meta-analysis when ≥ 3 studies reported a specific adverse event. If studies reported more than one type of adverse event (e.g. sore throat and nasal congestion) within the same analysis (e.g. respiratory symptoms not otherwise specified), we included only the adverse event with the largest number of events in the meta-analysis to avoid the risk of double-counting. Haemoptysis is included in the meta-analysis of cough, as both types of adverse events were coded in the same adverse event group (coughing and associated symptoms).

When studies reported on deaths for several follow-up periods, we used data from the follow-up period that was mainly in line with the maximum follow-up period used in most of the included studies for the meta-analysis. We used Review Manager 5 to analyse data (Review Manager 2014). As we expected heterogeneity among the included studies, we used random-effects meta-analysis models (Higgins 2011).

Some studies reported the adverse event data of macrolide resistance by isolates rather than by participants, and we modified the protocol to include those data. Whether the data were related to participants or isolates (which include studies limiting isolates to resistant streptococci), we have reported on the absolute difference, in percentage:
([absolute value of difference in macrolide-resistant bacteria after treatment] - [absolute value of difference in macrolide-resistant bacteria before treatment]
and the relative difference:
[difference in macrolide-resistant bacteria after treatment] / [difference in macrolide-resistant bacteria before treatment]).

'Summary of findings' table and GRADE

We created two 'Summary of findings' tables. Summary of findings for the main comparison presents the following gastrointestinal outcomes: not otherwise specified gastrointestinal disorders, abdominal pain, diarrhoea, nausea, and vomiting. Summary of findings 2 presents other outcomes: cardiac disorders, hearing loss, taste disturbance, hepatobiliary disorders, and deaths. We used GRADE to rate the overall quality of evidence of each of the outcomes as either high, moderate, low, or very low, employing the five GRADE considerations (study limitations, consistency of effect, indirectness, imprecision, and publication bias) (Atkins 2004). We used methods and recommendations described in Section 8.5 and

Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011), employing GRADEpro GDT software (GRADEpro GDT 2015).

Subgroup analysis and investigation of heterogeneity

We decided a priori that if sufficient data were available we would undertake subgroup analyses according to:

1. age groups (children, adults, and elderly people);
2. type of macrolide (erythromycin, clarithromycin, roxithromycin, or azithromycin);
3. route of administration (topical, oral, intramuscular, intravenous);
4. antibiotic dosage (dose and frequency of administration); and
5. duration of therapy.

At least three studies were required for a subgroup analysis.

Sensitivity analysis

We decided a priori to perform sensitivity analyses by excluding studies with missing data on the outcome (adverse events). However, as no studies had more than 20% of randomised participants lost to follow-up, none of the studies that provided data for the meta-analyses were assessed as being at high risk of attrition bias.

RESULTS

Description of studies

We presented information about the studies in Characteristics of included studies, Characteristics of excluded studies, and Characteristics of ongoing studies.

Results of the search

We retrieved a total of 8882 records from our database searches (electronic searches, n = 8663; trial registry searches, n = 219). We removed 1338 duplicates and an additional 2360 records when the randomised controlled trial (RCT) filter was applied to the backward citation searches.

We excluded 4508 records based on title and abstract screening and discarded 195 trial registrations as they were clearly not relevant or there was little likelihood of a subsequent publication.

We excluded another four records based on incorrect citations, and one PhD thesis due to no author reply. We assessed the remaining 452 full-text articles for eligibility and excluded 129 full-text articles, of which we have reported the reasons for exclusion for 17 key studies; see the Characteristics of excluded studies table. We included 312 full-text records, comprising 183 studies (Figure 1).

A few of the included trials were published in languages other than English: Chinese (Wang 2012; Yang 2013), Farsi (Akhyani 2003; Paknejad 2010), German (Rozman 1984), Korean (Kim 2004), and Spanish (Garcia-Burguillo 1996).

We identified 64 Cochrane Reviews on macrolide antibiotics. However, we did not include any additional studies based on our exploration of the reference lists of these Cochrane Reviews.

Included studies

We included 183 randomised placebo-controlled trials involving a total of 252,886 participants.

Participants and settings

A total of 30 trials included only children aged up to 18 years; 61 trials included adults aged 18 to 64 years, and two trials included elderly people aged over 65 years; 16 trials included both children and adults; 64 trials included both adults and elderly people; three trials included children, adults, and elderly people; and seven trials did not specify the ages of participants.

Macrolide antibiotics were used for treatment or prevention of the following indications.

- Acute respiratory infections (21 studies) (Bacharier 2015; Beigelman 2015; Brickfield 1986; Dunlay 1987; Grob 1981; Halperin 1999; Haye 1998; Hyde 2001; Kaiser 2001; King 1996; Kneyber 2008; Lildholdt 2003; Mandhane 2017; McCallum 2013; McCallum 2015; McDonald 1985; Moller 1990; Petersen 1997; Pinto 2012; Schalen 1993; Van Delden 2012).
- Arthritis (4 studies) (Kvien 2004; Ogrendik 2007; Ogrendik 2011; Sadreddini 2009).
- Bacterial carriage (3 studies) (Malhotra-Kumar 2007a; Malhotra-Kumar 2007b; Wilson 1977; Wilson 1979).
- Cancer (2 studies) (Barkhordar 2018; Bergeron 2017).
- Cardiovascular diseases (24 studies) (Anderson 1999; Berg 2005; Cercek 2003; Grayston 2005; Gupta 1997; Gurfinkel 1999; Hillis 2004; Ikeoka 2007; Jackson 1999; Jespersen 2006; Joensen 2008; Kaehler 2005; Karlsson 2009; Kim 2004; Leowattana 2001; Neumann 2001; O'Connor 2003; Parchure 2002; Sander 2002; Sinisalo 2002; Vainas 2005; Vammen 2001; Wiesli 2002; Zahn 2003).
- Chronic respiratory diseases (39 studies) (Albert 2011; Altenburg 2013; Amali 2015; Anthony 2014; Ballard 2011; Banerjee 2004; Berkhof 2013; Black 2001; Branden 2004; Brill 2015; Brusselle 2013; Cameron 2013; Clement 2006; Corris 2015; Fonseca-Aten 2006; Gibson 2017; Hahn 2006; Hahn 2012; Haxel 2015; Hodgson 2016; Johnston 2016; Kostadima 2004; Kraft 2002; Ozdemir 2011; Saiman 2003; Saiman 2010; Seemungal 2008; Serisier 2013; Shafuddin 2015; Simpson 2008; Uzun 2014; Valery 2013; Veskitkul 2017; Videler 2011; Vos 2011; Wallwork 2006; Wang 2012; Wolter 2002; Wong 2012).

- Dental problems (15 studies) (Agarwal 2012; Agarwal 2017; Andere 2017; Bajaj 2012; Botero 2013; Bystedt 1980; Kathariya 2014; Martande 2015; Martande 2016; Paknejad 2010; Pradeep 2011; Pradeep 2013; Sampaio 2011; Shanson 1985; Smith 2002).
- Eye infections (Yang 2013).
- Gastrointestinal conditions (31 studies) (Altraif 2011; Aly 2007; Andremont 1981; Bala 2008; Berne 2002; Bonacini 1993; Carbonell 2006; Curry 2004; Czarnetzki 2015; Ehsani 2013; Frossard 2002; Gharpure 2001; Gokmen 2012; Jun 2014; Kalliafas 1996; Lanza 1998; Mandal 1984; Mathai 2007; Memis 2002; Narchi 1993; Ng 2007; Nuntnarumit 2006; Oei 2001; Patole 2000; Peterson 1996; Reignier 2002; Robins-Browne 1983; Roy 1998; Sirinavin 2003; Smith 2000; Yeo 1993).
- Infections associated with HIV infection (5 studies) (Currier 2000; El-Sadr 2000; Jablonowski 1997; Oldfield 1998; Pierce 1996).
- Improvement of immune responses (Grassly 2016).
- Malaria (3 studies) (Andersen 1998; Heppner 2005; Taylor 1999).
- Prevention of childhood mortality (Keenan 2018).
- Sepsis (2 studies) (Giamarellos-Bourboulis 2008; Giamarellos-Bourboulis 2014).
- Skin or soft tissue complaints (9 studies) (Ahmed 2014; Akhyani 2003; Amer 2006; Amland 1995; Avci 2013; Glass 1999; Pandhi 2014; Rozman 1984; Schwameis 2017)
- Urogynaecological problems (22 studies) (Alger 1991; Eschenbach 1991; Garcia-Burguillo 1996; Hooton 1990; Kaul 2004; Kenyon 2001a; Kenyon 2001b; Klebanoff 1995; Martin 1997; McCormack 1987; McGregor 1986; McGregor 1990; McGregor 1991; Mercer 1992; Paul 1998; Rajaei 2006; Roca 2016a; Sorensen 1992; Tita 2016; Van den Broek 2009; Walsh 1998; Winkler 1988).

Of the 183 included studies, 129 were conducted in secondary care, nine in primary care (Brickfield 1986; Dunlay 1987; Grob 1981; Hahn 2006; Hahn 2012; Haye 1998; King 1996; McDonald 1985; Petersen 1997), two in both primary and secondary care (Brill 2015; Johnston 2016), and 14 in dental care (Agarwal 2012; Agarwal 2017; Andere 2017; Bajaj 2012; Botero 2013; Kathariya 2014; Martande 2015; Martande 2016; Paknejad 2010; Pradeep 2011; Pradeep 2013; Sampaio 2011; Shanson 1985; Smith 2002). Another 22 trials were conducted in various settings, including: villages in sub-Saharan Africa (Andersen 1998; Keenan 2018), among residents travelling to Mexico (Andremont 1981), centres or clinics not specified (Bacharier 2015; Hodgson 2016; Jablonowski 1997; Lanza 1998; O'Connor 2003; Pierce 1996; Walsh 1998), antenatal clinics in Southern Malawi (Van den Broek 2009), university-based outpatient clinics (Currier 2000), households (Halperin 1999), remote forest and scrub-covered foothills in Thailand (Heppner 2005), an urban slum area of Nairobi in Kenya (Kaul 2004), universities (Malhotra-Kumar 2007a; Malhotra-Kumar 2007b; Wilson 1977; Wilson 1979), food factories in Thailand (Sirinavin 2003), soldiers and civilians in Indonesia (Taylor 1999), community clinics in Australia and a tertiary paediatric hospital in New Zealand (Valery 2013), and infants living in the Vellore district in India (Grassly 2016). The setting was not specified clearly in seven trials (Cameron 2013; El-Sadr 2000; Jackson 1999; Kraft 2002; Oldfield 1998; Rozman 1984; Schwameis 2017).

Interventions

Azithromycin was used as one of the treatment arms in 80 studies, erythromycin in 66 studies, clarithromycin in 23 studies, and roxithromycin in 14 studies. Five studies had two intervention arms, both using one of the four included macrolides. In Andersen 1998, one arm received azithromycin 250 mg per day for 10 weeks and one arm received azithromycin 1000 mg per week for 10 weeks. In Gupta 1997, both arms were treated with azithromycin for three or six days. Kostadima 2004 had two intervention arms, both treated with clarithromycin 250 mg, one twice, and one three times a day. In the study by Malhotra-Kumar and colleagues, one arm received azithromycin 500 mg for three days (Malhotra-Kumar 2007a), and the other arm received clarithromycin 1000 mg for seven days (Malhotra-Kumar 2007b). In McCormack 1987, the form of erythromycin was changed from the estolate to the stearate about halfway through the study after reports of liver damage due to the former appeared; these two treatment arms were reported separately.

Some studies specified the form of erythromycin used: 12 studies used erythromycin base, 3 erythromycin estolate, 10 studies erythromycin ethylsuccinate, 11 studies erythromycin lactobionate, and 5 studies erythromycin stearate.

Macrolides were delivered orally in 154 studies, intravenously in 20 studies (Altraif 2011; Ballard 2011; Berne 2002; Bonacini 1993; Carbonell 2006; Czarnetzki 2015; Ehsani 2013; Frossard 2002; Gharpure 2001; Giamarellos-Bourboulis 2008; Giamarellos-Bourboulis 2014; Jun 2014; Kalliafas 1996; Narchi 1993; Ozdemir 2011; Reignier 2002; Smith 2000; Tita 2016; Van Delden 2012; Yeo 1993), and topically in nine studies (Agarwal 2012; Agarwal 2017; Bajaj 2012; Glass 1999; Kathariya 2014; Pradeep 2013; Rozman 1984; Schwameis 2017; Yang 2013). None of the included studies administered the macrolides intramuscularly.

In 131 of the 183 studies, the study participants used concomitant medications. One study advised participants not to use concomitant medications (Avci 2013). In 51 studies, the authors did not clearly specify if concomitant medications were permitted.

Outcomes

Adverse events were reported in 146 studies. Three of these studies reported only the number of adverse events, rather than the numbers of participants with adverse events (Andersen 1998;

Bergeron 2017; Brusselle 2013), and were therefore excluded from the analyses to avoid the potential problem of double-counting of events. In 17 studies, the authors stated that no adverse events were observed or reported (Agarwal 2012; Agarwal 2017; Altraif 2011; Andremont 1981; Bajaj 2012; Bala 2008; Carbonell 2006; Kathariya 2014; Mandal 1984; Martande 2016; Mathai 2007; McCallum 2013; Memis 2002; Moller 1990; Oei 2001; Vammen 2001; Veskitkul 2017). Twenty studies did not report adverse events (excluding data on death or resistant bacteria, or both) (Berg 2005; Ehsani 2013; Fonseca-Aten 2006; Garcia-Burguillo 1996; Grob 1981; Jablonowski 1997; Kalliafas 1996; Kneyber 2008; Leowattana 2001; Neumann 2001; Paknejad 2010; Parchure 2002; Paul 1998; Pinto 2012; Robins-Browne 1983; Roy 1998; Sander 2002; Schalen 1993; Wang 2012; Winkler 1988).

A few studies provided additional information on adverse events (Ahmed 2014; Cameron 2013; Gibson 2017; Grassly 2016; Pradeep 2011; Roca 2016a), and when authors were contacted by e-mail (Ahmed 2016 [pers comm]; Grassly 2017 [pers comm]; Kathariya 2016 [pers comm]; Powell 2018 [pers comm]; Roca 2016b [pers comm]; Thomsen 2016 [pers comm]).

Thirteen studies reported on participants with subsequent carriage of macrolide-resistant bacteria; eight studies reported isolates with macrolide-resistant bacteria; and three studies specifically reported the proportion of macrolide-resistant streptococci. Fifty-two studies reported on deaths.

Study funding sources

Funding sources of the 183 included studies are reported in the Characteristics of included studies table. Pharmaceutical companies supplied the trial medication, funding, or both for 91 of the included studies; 33 studies were non-industry funded; and the funding sources were unclear in 59 studies.

Excluded studies

We excluded 129 studies. However, for brevity, we elected to report only 17 key studies. See the Characteristics of excluded studies table. We excluded these 17 studies for the following reasons.

- Cross-over trial, reporting adverse events only after cross-over (Ferahbas 2004).
- Only reported on pharmacodynamic outcomes (microbiome) (Doan 2017; Parker 2017).
- Not placebo-controlled (Pazoki-Toroudi 2010; Rasi 2008; Weber 1993).
- Not possible to identify if participants were treated with clarithromycin or azithromycin (Figueiredo-Mello 2018).
- Participants randomised to receive both a macrolide antibiotic and metronidazole (Aboud 2009).
- Participants received erythromycin on top of placebo if feed failure (Makkar 2016).
- Sample size too small (Ballard 2007; Gong 2014; Nielsen 2016).
- The unit of randomisation was asthma episodes rather than participants (Stokholm 2016).
- Quasi-randomised or non-randomised design (Batieha 2002; Sharma 2000; Yamamoto 1992; Zhang 2006).

Ongoing studies

We identified six ongoing studies (Chang 2012; Gonzalez-Martinez 2017; Kobbernagel 2016; Mosquera 2016; Pavlinac 2017; Vermeersch 2016). The macrolide used in all six studies was azithromycin.

Studies awaiting classification

Twenty-four trials identified by the clinical trial registry searches are awaiting classification and are listed in the Characteristics of studies awaiting classification table. We identified five abstracts based on four trials in the database searches (Dicko 2016; Gregersen 2017; Milito 2017; Ramsey 2017), however we were not able to locate peer-reviewed publications of these trials.

Risk of bias in included studies

We assessed all 183 included studies using the six domains in the Cochrane 'Risk of bias' tool as described in the *Cochrane Handbook for Systematic Review of Interventions* (Higgins 2011). Details of the 'Risk of bias' assessments are provided in Characteristics of included studies and summarised in Figure 2 and Figure 3.

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

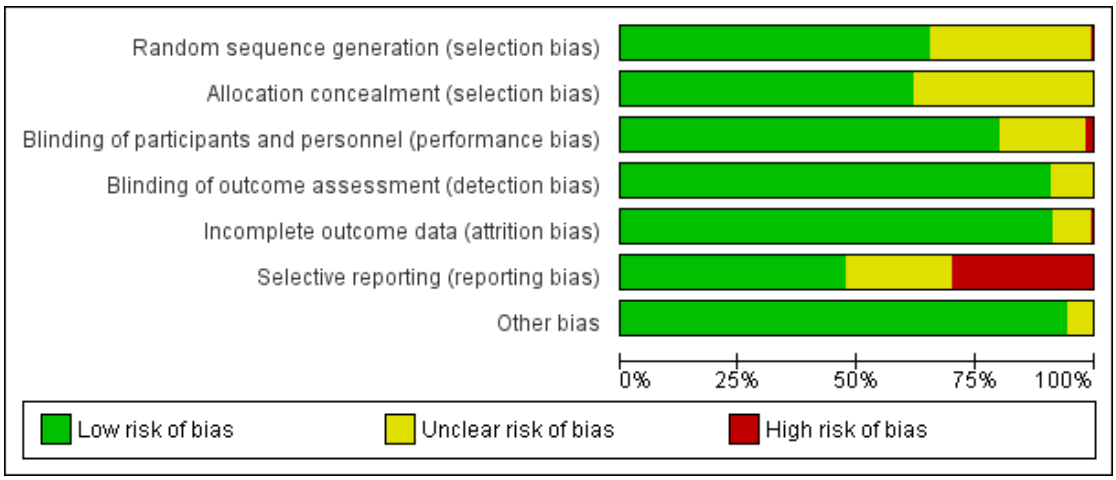


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Allocation

Random sequence generation

We assessed 119 studies, most of which used either computer-generated randomisation or random number tables, as at low risk of bias. We assessed one study as at high risk of bias because randomisation was by lottery (Ahmed 2014). We assessed 63 studies that did not provide detailed information about the randomisation method used as at unclear risk of bias.

Allocation concealment

We assessed 112 studies as at low risk of bias for allocation concealment. Most studies used central allocation, but some also used sequentially numbered, identical drug containers, or sealed, opaque envelopes. We assessed studies with either insufficient or no information about allocation concealment as at unclear risk of bias.

Blinding

Blinding of participants and personnel

We assessed three studies as at high risk of bias for this domain (Brill 2015; Wilson 1977; Wilson 1979). Wilson 1977 and Wilson 1979 did not use an identical placebo. In the four-armed study by Brill 2015, the placebo was given as one tablet daily, while the macrolide treatment was taken three times per week.

We assessed 34 studies as at unclear risk of bias because the placebo was not described in sufficient detail to judge whether blinding of participants and personnel was sufficient. The remaining studies used an identical placebo and were assessed as at low risk of bias.

Blinding of outcome assessment

We assessed 158 studies as at low risk of bias for blinding of outcome assessment. We assessed studies as at low risk of bias if blinding of all possible outcome assessors was judged sufficient; if studies only reported objective outcomes (death, data on antimicrobial resistance); or if no relevant outcomes were reported. We assessed 17 studies at unclear risk of bias because it was unclear if study participants, clinicians, and other possible outcome assessors were blinded.

Incomplete outcome data

We assessed one study as at high risk of bias for incomplete data reporting because over 20% of study participants were excluded from the final analysis without providing reasons (Paul 1998). We assessed 15 studies as at unclear risk of bias. We assessed most studies as at low risk of bias, with no or limited participant dropout, or with reasons for dropouts provided.

Selective reporting

We assessed 56 studies that either did not report adverse events or where reporting was incomplete as at high risk of selective reporting. We assessed 42 studies as at unclear risk of bias for this domain. We judged 85 studies, all of which reported on adverse events and most of which reported on the method for eliciting adverse events, as at low risk of bias.

Other potential sources of bias

We assessed 174 studies as at low risk of other bias. We assessed nine studies as at unclear risk of bias: four had an uneven distribution of participants allocated to the trial arms (Amali 2015; Lanza 1998; Peterson 1996; Taylor 1999), and five had baseline imbalances (Frossard 2002; Gokmen 2012; Gurfinkel 1999; Mathai 2007; Wolter 2002).

Effects of interventions

See: **Summary of findings for the main comparison** Gastrointestinal adverse events in people taking macrolide antibiotics versus placebo for any indication; **Summary of findings 2** Other adverse events in people taking macrolide antibiotics versus placebo for any indication

See Summary of findings for the main comparison for adverse events in people taking macrolide antibiotics versus placebo for any indication.

Primary outcomes

1. Any reported adverse event that occurred in 5% or more of any group

Sufficient numbers of adverse events were reported to perform meta-analyses for 11 of the 27 System Organ Classes.

i. Cardiac disorders

Seven studies reported cardiac disorders as adverse events, involving 1715 participants with 115 events (Albert 2011; Berkhof 2013; Gupta 1997; Kim 2004; Smith 2000; Vammen 2001; Vos 2011). The cardiovascular adverse events reported were arrhythmias, acute coronary syndrome, and not specified cardiac events.

We found no difference in cardiac disorders in participants taking macrolide antibiotics compared to participants taking placebo (odds ratio (OR) 0.87, 95% confidence interval (CI) 0.54 to 1.40; I^2 = 9%; Analysis 1.1). We judged the evidence for cardiac disorders to be of very low-quality due to high risk of reporting bias and imprecision.

ii. Ear and labyrinth disorders

Hearing loss was reported in four studies, involving 1369 participants with 284 events (Albert 2011; Altenburg 2013; Hahn 2012; Saiman 2003). None of the studies explicitly stated if they reported on short- or long-term hearing loss. Participants taking macrolides experienced hearing loss more often than those taking placebo (OR 1.30, 95% CI 1.00 to 1.70; I^2 = 0%; Analysis 2.1), although the findings are non-significant. The absolute risk difference (ARD) of experiencing hearing loss was 42/1000 people, and the number of people treated with macrolides for one to experience the adverse event of hearing loss (number needed to treat for an additional harmful outcome (NNTH)) was 24 (95% CI 11 to infinity). We judged the evidence for hearing loss as of low-quality due to high risk of reporting bias and imprecision.

iii. Gastrointestinal disorders

Nausea was an outcome in 28 studies (14,983 participants), and vomiting an outcome of 15 studies (5328 participants). Participants taking macrolides had more nausea (OR 1.61, 95% CI 1.37 to 1.90; I^2 = 35%; Analysis 3.1) and vomiting (OR 1.27, 95% CI 1.04 to 1.56; I^2 = 6%; Analysis 3.4) than participants taking placebo. When reported together, macrolides were not associated with nausea and vomiting (High Level Term) (OR 0.92, 95% CI 0.60 to 1.42; I^2 = 0%; Analysis 3.7).

Compared to those taking placebo, participants taking a macrolide antibiotic more often experienced abdominal pain (OR 1.66, 95% CI 1.22 to 2.26; I^2 = 58%; Analysis 3.8); diarrhoea (OR 1.70, 95% CI 1.34 to 2.16; I^2 = 74%; Analysis 3.10); and gastrointestinal disorders not otherwise specified (NOS) (when gastrointestinal disorders were reported together) (OR 2.16, 95% CI 1.56 to 3.00; I^2 = 42%; Analysis 3.12).

The number of additional people who experienced adverse events from macrolides compared to placebo (ARD) was: gastrointestinal disorders NOS: 85/1000; diarrhoea: 72/1000; abdominal pain: 62/1000; nausea: 47/1000; and vomiting: 23/1000. The NNTH ranged from 12 (95% CI 8 to 23) for gastrointestinal disorders NOS to 17 (9 to 47) for abdominal pain; 19 (12 to 33) for diarrhoea; 19 (13 to 30) for nausea; and 45 (22 to 295) for vomiting. We judged the evidence for abdominal pain and diarrhoea to be of low-quality due to inconsistency and imprecision, and the evidence of nausea, vomiting, nausea and vomiting, and gastrointestinal disorders NOS to be of moderate quality due to imprecision.

iv. Nervous system disorders

There was insufficient evidence to determine whether macrolides caused dizziness based on the three studies reporting this outcome (376 participants, 31 events) (OR 1.83, 95% CI 0.85 to 3.95; I^2 = 0%; Analysis 4.1). Macrolides were not associated with headache in 12 trials with 1386 participants, 195 events (OR 0.81, 95% CI 0.58 to 1.11; I^2 = 0%; Analysis 4.2). However, macrolides did cause taste disturbance in five trials, involving 932 participants, reporting 81 instances (OR 4.95, 95% CI 1.64 to 14.93; I^2 = 46%; Analysis 4.3). The ARD of experiencing taste disturbances was 117/1000 people, and the number of people treated with macrolides for one to experience the adverse event of taste disturbance (NNTH) was 11 (4 to 62).

We judged the evidence for taste disturbance and dizziness as of low-quality due to very serious imprecision, and the evidence for headache as moderate quality due to imprecision.

v. Skin and subcutaneous tissue disorders

Macrolides did not cause increased itching in four trials with 1388 participants reporting 99 events (OR 1.11, 95% CI 0.73 to 1.67; I^2 = 0%; Analysis 5.1) or rash in eight trials of 5314 participants reporting rash in 360 instances (OR 1.13, 95% CI 0.91 to 1.41; I^2 = 0%; Analysis 5.2). We judged the evidence of itching and rash as of moderate quality due to imprecision.

vi. General disorders and administration site conditions

Seven studies (2451 participants) reported fever (Bonacini 1993; Clement 2006; Grassly 2016; Heppner 2005; Roca 2016a; Saiman 2003; Saiman 2010). We found that fever was reduced in participants taking macrolides compared to placebo (OR 0.73, 95% CI 0.54 to 1.00; I^2 = 35%; Analysis 6.1), although the findings were non-significant. We judged the evidence for fever as of moderate quality due to imprecision.

vii. Hepatobiliary disorders

Four trials reported 23 hepatobiliary disorders as adverse events (cholestatic jaundice, cholangitis, or abnormal hepatic function) (Aly 2007; Black 2001; Nuntnarumit 2006; Yeo 1993). We did not find a difference in the occurrence of hepatobiliary disorders between the participants in the macrolides and placebo groups (OR 1.04, 95% CI 0.27 to 4.09; I^2 = 47%; Analysis 7.1). We judged the evidence for hepatobiliary disorders as of very low-quality due to indirectness and very serious imprecision.

viii. Infections and infestations

Four studies reported blood infections (356 participants with 99 events) (Aly 2007; Berne 2002; Ng 2007; Nuntnarumit 2006). We found no difference in the number of blood infections in

participants taking macrolide antibiotics compared to those taking placebo (OR 0.83, 95% CI 0.52 to 1.34; I^2 = 0%; Analysis 8.1). Macrolides reduced respiratory tract infections (11 trials, 11,062 participants, 1078 events) (OR 0.70, 95% CI 0.62 to 0.80; I^2 = 0%; Analysis 8.2), while for skin and soft tissue infections (3 trials, 263 participants, and only 9 events) there was no difference between groups (OR 1.57, 95% CI 0.53 to 4.64; I^2 = 0%; Analysis 8.3). We judged the evidence for blood infections and respiratory tract infections as of moderate quality due to imprecision, and the evidence for skin and soft tissue infections as of low-quality due to very serious imprecision.

ix. Investigations

There was insufficient evidence to determine whether macrolides caused changes in liver enzymes (reported as either "elevated" or "abnormal") in the six trials reporting these adverse events (144 events among 1187 participants) (OR 1.56, 95% CI 0.73 to 3.37) because of wide confidence intervals and high heterogeneity (I^2 = 71%; Analysis 9.1). We judged the evidence for changes in liver enzymes as of very low-quality due to inconsistency and very serious imprecision.

x. Metabolism and nutrition disorders

Five studies reported appetite loss (2183 participants with 248 events) (Eschenbach 1991; Heppner 2005; Martin 1997; Petersen 1997; Saiman 2003). We found no difference in appetite loss between participants taking macrolide antibiotics and those taking placebo (OR 1.10, 95% CI 0.84 to 1.43; I^2 = 16%; Analysis 10.1). We judged the evidence for appetite loss as of moderate quality due to imprecision.

xi. Respiratory, thoracic and mediastinal disorders

Six trials reported that macrolides reduced cough (1587 participants with 390 events) (OR 0.57, 95% CI 0.40 to 0.80; I^2 = 14%; Analysis 11.1). We did not find evidence that macrolides caused more respiratory symptoms NOS in eight trials of 2176 participants reporting 461 events (OR 1.02, 95% CI 0.82 to 1.25; I^2 = 0%; Analysis 11.2) or wheeze in three trials of 484 participants reporting 41 events (OR 2.20, 95% 0.74 to 6.52; I^2 = 49%; Analysis 11.3). We judged the evidence for cough and respiratory symptoms NOS as of moderate quality due to imprecision, and the evidence for wheeze as of low-quality due to very serious imprecision.

xii. Rarely reported adverse events

Rarely reported adverse events are presented in a separate table according to System Organ Classes (Table 1). No differences were observed for most rarely reported adverse events between the macrolides and placebo groups. The exceptions are listed below.

Adverse events significantly more common in people treated with a macrolide

- Rectal disorder (P = 0.004) (Pierce 1996).
- Flatulence (P < 0.001) (Jespersen 2006).
- Upset stomach (P < 0.001) (Jespersen 2006).
- Infusion site pain (P < 0.001) (Giamarellos-Bourboulis 2014).
- Allergic reactions (P = 0.041) (Hyde 2001).
- Gastroenteritis (P = 0.006) (Cameron 2013).

Adverse events significantly more common in people taking a placebo

- Dyspepsia (P = 0.040) (Lanza 1998).
- Puerperal pyrexia (P = 0.001) (Tita 2016).
- Infections NOS (P = 0.001) (Roca 2016a).
- Otitis (P = 0.005) (Cameron 2013).

2. Death

Macrolides did not cause increased mortality in 52 studies with 216,246 participants reporting 6923 events (OR 0.96, 95% 0.87 to 1.06; I^2 = 11%; Analysis 12.1). Five studies reported on number of deaths at various time points; see Table 2 for details (Giamarellos-Bourboulis 2008; Gurfinkel 1999; Jespersen 2006; Keenan 2018; Van den Broek 2009). We obtained number of deaths (all-cause mortality) at 10-year follow-up of the CLARICOR trial, Jespersen 2006, by e-mail correspondence with Winkel 2017 [pers comm]. We judged the evidence for death as of low-quality due to indirectness and imprecision.

3. Subsequent carriage of macrolide-resistant bacteria

Thirteen studies reported on participants with macrolide-resistant bacteria following treatment with macrolide antibiotics (Table 3). The range of absolute increases across the studies in the numbers of participants carrying macrolide-resistant organisms was 0% to 43%. No clear trend was observed in studies reporting on resistant bacteria at multiple time points: two trials showed an absolute decrease in resistance over time (Berg 2005; Valery 2013); one showed an absolute increase over time (Roca 2016a); and one initially reported an absolute increase followed by a decrease (Sirinavin 2003). Four studies reported a small (< 10%) relative increase in resistance (Bacharier 2015; Brusselle 2013; McCallum 2015; Wilson 1977), and three studies reported a small relative decrease in resistance (Berkhof 2013; Gibson 2017; Uzun 2014). Valery 2013 and Sirinavin 2003 showed an initial relative increase in resistance followed by a decrease over time.

Eight studies reported on the proportion of macrolide-resistant isolates following macrolide treatment. The absolute increase in resistance ranged from 0% to 55% for studies reporting on

macrolide-resistant isolates at a single follow-up point (Albert 2011; Altenburg 2013; Berg 2005; Seemungal 2008; Tita 2016; Videler 2011; Wilson 1979). A single trial reported on macrolide-resistant isolates at multiple time points, showing an initial absolute increase (at week 26) followed by a gradual decrease to 0% at week 78 (Lildholdt 2003). There was a mixed picture for relative increase in resistance, with three trials showing a small (< 10%) relative decrease in resistance (Albert 2011; Berg 2005; Videler 2011); one showing a small relative increase (Altenburg 2013); and one trial showing an initial relative increase followed by a decrease over time (Lildholdt 2003) (Table 4).

Three trials reported the proportion of macrolide-resistant streptococci isolates (Brusselle 2013; Serisier 2013), of which one trial had two active treatment arms (Malhotra-Kumar 2007a; Malhotra-Kumar 2007b). Absolute increase in resistance decreased over time in Brusselle 2013, Malhotra-Kumar 2007a, and Malhotra-Kumar 2007b. Two trials also reported an initial relative increase in macrolide-resistant bacteria followed by a decrease over time (Brusselle 2013; Malhotra-Kumar 2007b); and Malhotra-Kumar 2007a reported an initial decrease in relative resistance, but its magnitude decreased over time (Table 5).

Subgroup analysis

The protocol prespecified the following subgroup analyses: age groups, type of macrolide, route of administration, antibiotic dosage, and duration of therapy. However, we were unable to undertake all planned subgroup analyses because either there were too few studies in the subgroup (< 3); data were confounded (e.g. subgroups not reported separately); or we decided against 'duration of therapy' from which, together with daily dose, we had hoped to estimate peak or steady-state blood concentrations, but could not. We conducted the following subgroup analyses.

i. Nausea

Type of macrolide: the increased nausea caused by roxithromycin (OR 3.29, 95% CI 1.15 to 9.43) compared with either azithromycin (OR 1.66, 95% CI 1.27 to 2.16) or erythromycin (OR 1.58, 95% CI 1.23 to 2.04) was not significant (test for subgroup differences P = 0.41) (Analysis 3.2).

Route of administration: intravenous administration of macrolides (OR 3.04, 95% CI 0.69 to 13.51) was not significantly different from oral administration (OR 1.57, 95% CI 1.35 to 1.81; P = 0.38; Analysis 3.3).

ii. Vomiting

Type of macrolide: erythromycin was not significantly more likely to cause vomiting (OR 1.46, 95% CI 1.07 to 1.98) than azithromycin (OR 1.06, 95% CI 0.76 to 1.49; P = 0.17; Analysis 3.5).

Route of administration: intravenous administration of macrolides (OR 1.21, 95% CI 0.88 to 1.66) was not significantly different from oral administration (OR 1.32, 95% CI 0.97 to 1.78; P = 0.70; Analysis 3.6).

iii. Abdominal pain

Type of macrolide: erythromycin and azithromycin caused similar increases of abdominal pain (OR 3.16, 95% CI 1.14 to 8.75) and (OR 1.47, 95% CI 1.01 to 2.13), respectively; P = 0.16 (Analysis 3.9).

iv. Diarrhoea

Type of macrolide: clarithromycin did not cause diarrhoea significantly more often (OR 2.09, 95% CI 1.70 to 2.56) than azithromycin (OR 1.96, 95% CI 1.37 to 2.81), erythromycin (OR 1.36, 95% CI 0.94 to 1.98), or roxithromycin (OR 0.88, 95% CI 0.38 to 2.07); P = 0.07 (Analysis 3.11).

v. Gastrointestinal NOS

Type of macrolide: erythromycin was not significantly more likely to cause gastrointestinal adverse events NOS (OR 4.00, 95% 1.83 to 8.74) than azithromycin (OR 1.77, 95% CI 1.30 to 2.42); P = 0.06 (Analysis 3.13).

vi. Deaths

Type of macrolide: roxithromycin did not cause death significantly more often (OR 1.03, 95% CI 0.76 to 1.41) than azithromycin (OR 0.97, 95% 0.85 to 1.10), clarithromycin (OR 0.86, 95% 0.59 to 1.24), or erythromycin (OR 0.73, 95% 0.38 to 1.40); P = 0.74 (Analysis 12.2).

Route of administration: intravenous administration of macrolides (OR 0.83, 95% CI 0.63 to 1.10) was not significantly different from oral administration (OR 0.98, 95% CI 0.88 to 1.10); P = 0.28 (Analysis 12.3).

Sensitivity analyses

We decided a priori to perform sensitivity analyses by excluding those studies with missing data on the outcome (adverse events). However, none of the studies that provided data for the meta-analyses had more than 20% of randomised participants lost to follow-up, that is were assessed as being at high risk of attrition bias.

Supplementary data

In this Cochrane Review we have reported on any reported adverse event that occurred in 5% or more of any group. However, we extracted all adverse events and grouped them by primary System Organ Class, according to the MedDRA coding system (MedDRA 2018). See adverse events by System Organ Classes: threshold ≥

5%, Hansen 2018a, and adverse events by System Organ Classes
< 5%, Hansen 2018b.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Other adverse events in people taking macrolide antibiotics versus placebo for any indication

Patient or population: any indication
Setting: any setting
Intervention: macrolide antibiotics (azithromycin, clarithromycin, erythromycin, or roxithromycin, administered by any route)
Comparison: placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with placebo	Risk with macrolide antibiotics				
Cardiac disorders	73 per 1000	64 per 1000 (41 to 99)	OR 0.87 (0.54 to 1.40)	1715 (7 RCTs)	⊕◯◯◯ VERY LOW [12]	
Hearing loss	187 per 1000	230 per 1000 (187 to 281)	OR 1.30 (1.00 to 1.70)	1369 (4 RCTs)	⊕⊕◯◯ LOW [13]	NNTH = 24
Taste disturbance	27 per 1000	119 per 1000 (43 to 290)	OR 4.95 (1.64 to 14.93)	932 (5 RCTs)	⊕⊕◯◯ LOW [4]	NNTH = 11
Hepatobiliary disorders	48 per 1000	50 per 1000 (14 to 172)	OR 1.04 (0.27 to 4.09)	443 (4 RCTs)	⊕◯◯◯ VERY LOW [45]	
Deaths	34 per 1000	32 per 1000 (29 to 35)	OR 0.96 (0.87 to 1.06)	216,246 (52 RCTs)	⊕⊕◯◯ LOW [16]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **NNTH**: number needed to treat for an additional harmful outcome; **OR**: odds ratio; **RCT**: randomised controlled trial

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1]Downgraded one level due to imprecision. The outcome was reported in only a small proportion of the included studies.
[2]Downgraded two levels due to risk of bias. High risk of reporting bias for Kim 2004, as they only report on major cardiac events and no other possible adverse events. Importantly, the study population consists of participants with acute coronary syndrome who underwent percutaneous coronary intervention. High risk of bias for Gupta 1997, as they report on adverse events as a total for both treatment regimens (azithromycin dose 1500 mg or 3000 mg). Importantly, the study population consists of male survivors of myocardial infarction, and the events are reported as adverse cardiovascular events.
[3]Downgraded one level due to risk of bias. High risk of reporting bias for Saiman 2003, as hearing loss (judged by audiology testing) was only reported for about 50% of participants assigned.
[4]Downgraded two levels due to very serious imprecision. The outcome was reported in only a very small proportion of the included studies, and there were large confidence intervals.
[5]Downgraded one level due to indirectness. Two out of four studies did not clearly state adverse events as an outcome or did not report on standardised adverse event ascertainment (Aly 2007; Black 2001).
[6]Downgraded one level due to indirectness. Death is reported in this review regardless if reported as a primary outcome or adverse event in the primary studies.

DISCUSSION

Summary of main results

This multi-indication review included 183 randomised, placebo-controlled trials (RCTs) involving a total of 252,886 participants. The indications for macrolide antibiotics varied greatly, with most studies using macrolides for the treatment or prevention of acute respiratory tract infections, cardiovascular diseases, chronic respiratory diseases, gastrointestinal conditions, or urogynaecological problems. Azithromycin and erythromycin were more commonly studied than clarithromycin and roxithromycin.

The most commonly reported adverse events were gastrointestinal. Participants taking macrolide antibiotics experienced vomiting, nausea, diarrhoea, abdominal pain, and gastrointestinal disorders NOS significantly more often than those taking a placebo.

We found low-quality evidence that macrolides caused taste disturbances, although there were wide confidence intervals and moderate heterogeneity.

Participants taking macrolides experienced hearing loss more often than those taking a placebo, although the findings were non-significant.

We did not find any evidence that macrolides caused more cardiac disorders, hepatobiliary disorders, or changes in liver enzymes compared to placebo.

In the overall meta-analysis there was no evidence of an increase in deaths in participants treated with macrolides compared to those treated with placebo.

Very few of the included studies reported on macrolide-resistant bacteria. Macrolide-resistant bacteria were more commonly identified among participants immediately after exposure to the antibiotic, as expected, but there was little pattern of the decay of resistance thereafter.

Pharmaceutical companies supplied the trial medication or provided funding, or both, for about 50% of the included studies.

Overall completeness and applicability of evidence

Some of the outcomes were based on very few studies, despite the large total (183 trials) of included studies. However, most studies did report on some adverse events, and only 20 studies did not report on any adverse events.

The strengths of this review include the large set of RCTs to analyse. Randomised controlled trials avoid the complexity of attempting to distinguish symptoms caused by the treatment (antibiotics) or the disease (for which antibiotics were used), which makes observational studies weak for answering this question. Additionally, we included trials that allowed concomitant medications (when they were equally available in the placebo group), which might have caused drug interactions, and possibly have amplified any adverse event rates, which is an advantage when generalising to normal use.

One limitation is the assumptions made to decide what outcomes are adverse events and which are disease outcomes (for trials testing antibiotic efficacy); deaths, cardiac disorders, and symptoms of acute respiratory infections are examples. Furthermore, it was not possible to test dose effects because of the confusion surrounding the different forms of macrolide, especially erythromycin (which was used in estolate, stearate, base, and ethylsuccinate forms). A failure of most studies to report participant age groups' data discretely meant that we could not analyse the effect of age on adverse events.

When trial authors reported adverse events, it was not always obvious if they reported the numbers of adverse events or the numbers of participants with adverse events. Consequently, there is a risk of double-counting when performing a systematic review reporting adverse events data. In this systematic review, we aimed to report only adverse events from trials that reported the numbers of participants with adverse events. However, some of the included studies did not clearly specify if they reported on participants with adverse events, and in those cases our assessments have been based on inferences made by comparing the total numbers of participants and events they reported.

We tried to collect information on the follow-up period for reporting on adverse events from all of the included studies. However, in most cases it was not possible to calculate the follow-up period for the reporting of adverse events, as most trial authors only clearly reported the follow-up period for the main outcome(s) and not for adverse events.

We did not plan to perform a subgroup analysis based on indications for macrolide treatment, as we anticipated that adverse events are not disease-specific. However, different populations might experience different adverse events. For example, people with certain susceptibility factors have an increased risk of arrhythmias in response to macrolides (Albert 2014). Nevertheless, such differences need not necessarily be related to different indications for treatment rather than differences in individual susceptibility.

Quality of the evidence

The quality of evidence according to GRADE assessment ranged from very low (cardiac disorders, change in liver enzymes, hepatobiliary disorders) to low (abdominal pain, death, diarrhoea, dizziness, hearing loss, skin and soft tissue infections, taste disturbance, wheeze) to moderate (appetite loss, blood infection, cough, fever, gastrointestinal disorders NOS, headache, itching, nausea, nausea and vomiting, rash, respiratory symptoms NOS, respiratory tract infections, vomiting). We downgraded the quality of the evidence due to high risk of reporting bias, inconsistency, indirectness, and imprecision.

Potential biases in the review process

The interpretation of an adverse event differed significantly between trial authors. For example, some authors reported on pneumonia as a complication and wheezing as a disease-specific symptom, while others reported on these as an adverse event. When extracting data from the included trials, two review authors independently searched for any information that could be interpreted as an adverse event, regardless of how this was reported in the original trial. Consequently, this review may report on outcomes that some trial authors did not consider to be an adverse event. An exception was the study by Andremont 1981, which we excluded from the meta-analysis on diarrhoea as the trial tested a macrolide antibiotic versus placebo for the prevention of traveller's diarrhoea and reported on diarrhoea as a primary outcome. We assessed the reported cases of diarrhoea (four participants in the placebo group) as caused by virus/bacteria, rather than by treatments.

Less than one-third of the included RCTs reported on death (52 studies), and even fewer reported on data on macrolide-resistant bacteria (24 studies). There is strong evidence that much of the information on adverse events remains unpublished, and that the number - and range - of adverse events is higher in unpublished versions of the same study (Golder 2016). We searched six databases, the reference lists of included trials, the World Health Organization (WHO) International Clinical Trials Registry Platform and ClinicalTrials.gov for ongoing trials, and exploited the reference lists of previous Cochrane Reviews on macrolide antibiotics. We also contacted authors if they reported incompletely on adverse events and contact details (an e-mail address) were available. However, we did not contact each of the 183 trial authors asking for unpublished data on adverse events, and consequently it is possible that we missed information on adverse events, including death and data on macrolide-resistant bacteria.

The methods used for eliciting adverse events varied greatly between the included trials and included spontaneous reporting, asking participants, use of a questionnaire, identification during a clinical examination, and/or laboratory testing. Also, many studies did not provide any information on how the information on adverse events was obtained. A newly published Cochrane Review raises concerns that methods used for eliciting adverse events may influence the detection of these data (Allen 2018). The review authors found that there was a risk for underdetection of adverse events in studies using a more general elicitation method compared to those using a comprehensive method (Allen 2018). This possible underdetection of adverse events might have compromised our ability to pool data, as we required at least three studies reporting on a specific adverse event in order to perform a meta-analysis.

Agreements and disagreements with other studies or reviews

This Cochrane Review is the first multi-indication review on adverse events in people taking macrolides that includes studies using the same intervention for different diseases (Chen 2014). However, several other reviews have presented data on adverse events in people taking macrolides for various indications. Some reviews, such as Ni 2015, have only presented the total number of adverse events, whilst other authors have presented data for specific adverse events (Shi 2014). Shi 2014 studied macrolides for bronchiectasis, presenting both efficacy and adverse outcomes, and finding abdominal pain (risk ratio (RR) 6.2, 95% CI 1.43 to 26.83) and diarrhoea (RR 2.89, 95% CI 1.13 to 7.35) significantly more often in participants treated with a macrolide than in those treated with a placebo. Also, in line with our findings, that review found no increased risk of headache in participants treated with a macrolide (RR 0.62, 95% CI 0.17 to 2.29). Reporting of other adverse events in the Cochrane Review by Shi and colleagues was limited by lack of statistical power (Shi 2014).

The absence of a signal of liver damage in this review contrasts with older reports that macrolide antibiotics, erythromycin in particular, can cause two different types of liver damage - changes in liver enzymes and cholestatic jaundice (Braun 1976; Ginsburg 1976). There are several possible explanations for the dissonance between our review and the previous reports. Because many of the older reports were anecdotal, the associations may have occurred purely by chance; alternatively, newer formulations of erythromycin may be less hepatotoxic; previous observational studies may have been confounded by indication, hepatobiliary adverse effects having been caused by the infections being treated; or the risk of hepatotoxicity may be real but too small to have met our eligibility entry requirement that adverse events should have affected $\geq$ 5% of participants. Settling this question may need interrogation of large data sets beyond the remit of this review.

Findings when cardiovascular adverse events are reported in people taking macrolide antibiotics are contradictory. Observational studies have shown that treatment with macrolide antibiotics is associated with an increased risk of cardiovascular outcomes, including cardiovascular deaths, myocardial infarction, and arrhythmias (Wong 2017). In contrast, meta-analyses of RCTs did not show an increased cardiovascular risk (Wong 2017). Our findings concur with the RCT-derived data, as we did not find evidence of an increased risk of cardiac disorders in participants taking a macrolide antibiotic compared with placebo.

AUTHORS' CONCLUSIONS

Implications for practice

Antimicrobial resistance is one of the key global health problems facing our generation, with antibiotic use being the main driver (O'Neill 2014; WHO 2018). Most antibiotics used in humans are used in primary care (DANMAP 2016), and particularly in general practice (Aabenhus 2016). For some infections, such as

acute respiratory infections, the benefits of antibiotic treatment are minimal, if any. We undertook this systematic review to quantify adverse events in people using macrolide antibiotics, independently of the indication or effects of treatment, and found that macrolides as a group increased rates of gastrointestinal adverse events. The intention of this review is to support clinicians and patients in evaluating harms as well as benefits in the choice of management when antibiotics are contemplated.

Implications for research

Poor and inconsistent reporting of adverse events in clinical trials is well known (Hodkinson 2013). Most trials reported on some adverse events, or at least stated that no adverse events were observed. Nonetheless, trial authors are encouraged to clearly state adverse events (including data on resistant bacteria) as outcomes; to report on the methods used for eliciting adverse events; and preferably to report both the number of each specific adverse event and the number of people with each event in both the intervention and control groups.

Most systematic reviews of antimicrobial treatments ignore the problem of antimicrobial resistance (Leibovici 2003), and a framework for addressing antibiotic resistance in systematic reviews has recently been proposed for use in Cochrane Review protocols and Cochrane Reviews (Leibovici 2016). A revised version of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) framework was published in 2016 to increase the appropriateness of reporting for epidemiological studies, focusing on the link between resistant bacteria and antibiotic use (Tacconelli 2016). Only 24 (13%) of the trials included in our review provided useful data on macrolide-resistant bacteria. Consequently, not only review authors, but also authors conducting primary research on antimicrobial treatments are encouraged to measure and report on resistance data in future research projects.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Agarwal 2012

Methods	**Design:** randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 61 adults (macrolide n = 31, placebo n = 30) **Age in years** (range): 30 to 50 **Setting:** dental care
Interventions	**Indication:** chronic periodontitis **Type of macrolide:** clarithromycin **Route:** topical **Dose per day:** 0.5% gel x 1 **Duration of treatment:** 1 day **Total treatment dose:** N/A
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper:** no **Ascertainment of adverse events:** unclear **Adverse events:** states that no adverse events were observed or reported **Antimicrobial resistance:** not reported **Death:** not reported
Funding sources	None reported.
Notes	**Concomitant medication:** unclear

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo used.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of both participant and examiner/ clinicians
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, similar across groups

Agarwal 2012 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Adverse events not stated as an outcome, unclear ascertainment. However, report on adverse events
Other bias	Low risk	None were identified.

Agarwal 2017

Methods	**Design:** randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 63 adults (macrolide n = 31, placebo n = 32) **Age in years** (range): 30 to 50 **Setting:** dental care
Interventions	**Indication:** chronic periodontitis in people with type 2 diabetes mellitus **Type of macrolide:** azithromycin **Route:** topical **Dose per day:** 0.2 mL of 0.5% gel **Duration of treatment:** 1 day **Total treatment dose:** N/A
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper:** unclear **Ascertainment of adverse events:** participants asked **Adverse event:** authors state that no adverse events were observed or reported **Antimicrobial resistance:** not reported **Death:** not reported
Funding sources	None reported. Authors thank supplying companies.
Notes	**Concomitant medication:** unclear

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear if matching placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of both participant and examiner

Agarwal 2017 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, similar across groups
Selective reporting (reporting bias)	Low risk	Adverse events not stated as an outcome. However, clear ascertainment and report on (no) adverse events
Other bias	Low risk	None were identified.

Ahmed 2014

Methods	**Design:** randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 60 children and adults (macrolide n = 30, placebo n = 30) **Age in years** (mean ± SD): macrolide: 23.13 ± 10.34, placebo: 21.67 ± 7.42 **Setting:** secondary care
Interventions	**Indication:** pityriasis rosea **Type of macrolide:** clarithromycin **Route:** per oral **Dose per day:** 250 mg (child)/500 mg (adult) x 2 **Duration of treatment:** 7 days **Total treatment dose:** 7000 mg (maximum)
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper:** no **Ascertainment of adverse events:** unclear **Adverse event:** incomplete reporting, author contacted **Antimicrobial resistance:** not reported **Death:** not reported
Funding sources	None stated.
Notes	**Concomitant medication:** unclear

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Randomisation was done by lottery method.
Allocation concealment (selection bias)	Unclear risk	Allocation not described in detail.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo

Ahmed 2014 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of both participant and examiner/ clinicians
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	High risk	Adverse events not stated as an outcome, unclear ascertainment and incomplete reporting of adverse events
Other bias	Low risk	None were identified.

Akhyani 2003

Methods	**Design:** randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 46 children and adults (macrolide n = 23, placebo n = 23) **Age in years** (mean (range)): 21.5 (11 to 36) **Setting:** secondary care
Interventions	**Indication:** pityriasis rosea **Type of macrolide:** erythromycin **Route:** per oral **Dose per day:** 1000 mg **Duration of treatment:** 7 days **Total treatment dose:** 7000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper:** no **Ascertainment of adverse events:** unclear **Adverse events:** incomplete reporting, however no contact details for author **Antimicrobial resistance:** not reported **Death:** not reported
Funding sources	None reported.
Notes	**Concomitant medication:** unclear

Risk of bias

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

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear if matching placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	High risk	Adverse events not stated as an outcome, unclear ascertainment and incomplete reporting of adverse events
Other bias	Low risk	None were identified.

Albert 2011

Methods	**Design:** randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 1142 adults and elderly (macrolide n = 570, placebo n = 572) **Age in years** (mean ± SD): macrolide: 65 ± 9, placebo: 66 ± 8 **Setting:** secondary care
Interventions	**Indication:** prevention of an exacerbation in people with chronic obstructive pulmonary disease **Type of macrolide:** azithromycin **Route:** per oral **Dose per day:** 250 mg **Duration of treatment:** 1 year **Total treatment dose:** 91,250 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper:** yes **Adverse events ascertainment:** participants asked and clinical examination/laboratory tests **Adverse events:** data reported **Antimicrobial resistance:** data reported **Death:** data reported
Funding sources	Funded by the National Institutes of Health. Several authors are on pharmaceutical boards
Notes	**Concomitant medication:** yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Albert 2011 (*Continued*)

Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of both participant and examiner/ clinician
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, similar across groups
Selective reporting (reporting bias)	Low risk	Adverse events stated as an outcome in the protocol, and participants were asked about adverse events/were examined
Other bias	Low risk	None were identified.

Alger 1991

Methods	**Design:** randomised, placebo-controlled, 3-armed trial
Participants	**Number assigned:** 84 children and adults (macrolide n = 40, placebo n = 44) **Age in years** (mean ± SD): macrolide: 21.7 ± 4.2, placebo: 21.3 ± 4.0 **Setting:** secondary care
Interventions	**Indication:** antenatal *Chlamydia trachomatis* infection **Type of macrolide:** erythromycin base **Route:** per oral **Dose per day:** 1332 mg **Duration of treatment:** 14 days **Total treatment dose:** 18,648 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper:** no **Adverse events ascertainment:** unclear **Adverse events:** data reported **Antimicrobial resistance:** not reported **Death:** not reported
Funding sources	Study supported by a grant from the Upjohn Company. Role of funding source unclear
Notes	**Concomitant medication:** unclear
Risk of bias	

Alger 1991 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Unclear if the placebo group was generated from another trial
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear if identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear if participants and clinicians were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout
Selective reporting (reporting bias)	Low risk	Adverse events not stated as an outcome and unclear ascertainment. However, adverse events reported
Other bias	Low risk	None were identified.

Altenburg 2013

Methods	**Design:** randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 89 adults and elderly (macrolide n = 45, placebo n = 44) **Age in years** (mean ± SD): macrolide: 59.9 ± 12.3, placebo: 64.6 ± 9.1 **Setting:** secondary care
Interventions	**Indication:** prevention of pulmonary exacerbations in people with non-cystic fibrosis bronchiectasis **Type of macrolide:** azithromycin **Route:** per oral **Dose per day:** 250 mg **Duration of treatment:** 12 months **Total treatment dose:** 91,250 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper:** yes **Adverse events ascertainment:** participant diary and clinical examination/laboratory tests A**dverse events:** data reported **Antimicrobial resistance:** data reported **Death:** not reported

Altenburg 2013 (*Continued*)

Funding sources	A research grant from the Foreest Medical School was used for paying salaries. The study was supported by an unrestricted grant from GlaxoSmithKline. Azithromycin tablets were supplied by Teva Netherlands
Notes	**Concomitant medication:** yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centralised computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Numbers on the boxes matched a treatment allocation, in accordance with a computer-generated allocation sequence that was kept in a safe place in the pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of both participant and examiner/clinician
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, similar across groups
Selective reporting (reporting bias)	Low risk	Adverse events stated as an outcome, standardised ascertainment, adverse events reported
Other bias	Low risk	None were identified.

Altraif 2011

Methods	**Design:** randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 102 adults and elderly (macrolide n = 53, placebo n = 49) **Age in years** (mean ± SD): macrolide: 62.3 ± 9.8, placebo: 62.7 ± 14.7 **Setting:** secondary care
Interventions	**Indication:** variceal bleeding in people with liver cirrhosis **Type of macrolide:** erythromycin lactobionate **Route:** intravenous **Dose per day:** 125 mg **Duration of treatment:** 1 day

Altraif 2011 (*Continued*)

	Total treatment dose: 125 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper:** yes **Adverse events ascertainment:** unclear A**dverse events:** states that no adverse events were observed or reported **Antimicrobial resistance:** not reported **Death:** not reported
Funding sources	None stated.
Notes	**Concomitant medication:** yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of both participant and endoscopist/clinician
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, similar across groups
Selective reporting (reporting bias)	Unclear risk	Adverse events stated as an outcome. However, unclear ascertainment and states that no adverse events were observed
Other bias	Low risk	None were identified.

Aly 2007

Methods	**Design:** randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 60 children (macrolide n = 30, placebo n = 30) **Age in days** (median (range)): macrolide: 2.0 (2.0 to 24.0), placebo: 2.0 (2.0 to 10.0) **Setting:** secondary care
Interventions	**Indication:** feeding intolerance in preterm infants **Type of macrolide:** erythromycin ethylsuccinate

	Route: per oral **Dose per day:** 3 mg/kg **Duration of treatment:** the study medicine was to stop once the primary endpoint was achieved **Total treatment dose:** N/A
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper:** no **Adverse events ascertainment:** unclear **Adverse events:** data reported **Antimicrobial resistance:** not reported **Death:** data reported
Funding sources	None reported.
Notes	**Concomitant medication:** yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomisation
Allocation concealment (selection bias)	Low risk	Allocation concealed by cards provided in consecutively numbered, opaque, sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both active drug and placebo were mixed thoroughly into the milk feeds by designated staff not involved in the clinical management of the infants
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Parents and staff blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, similar across groups
Selective reporting (reporting bias)	Unclear risk	Adverse events not stated as an outcome and unclear ascertainment. Adverse events/complications reported
Other bias	Low risk	None were identified.

Amali 2015

Methods	**Design:** randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 66 children and adults (macrolide n = 22, placebo n = 44) **Age in years** (mean ± SD (range)): macrolide: 34.9 ± 9.2 (18 to 57), placebo: 39.1 ± 10.7 (15 to 62) **Setting:** secondary care
Interventions	**Indication:** chronic rhinosinusitis **Type of macrolide:** azithromycin **Route:** per oral **Dose per day:** 250 mg **Duration of treatment:** 84 days **Total treatment dose:** 21,000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper:** no **Adverse events ascertainment:** unclear **Adverse events:** incomplete reporting, author contacted **Antimicrobial resistance:** not reported **Death:** not reported
Funding sources	None reported.
Notes	**Concomitant medication:** yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described in detail.
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo not described.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, investigators, and individuals analysing data were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, similar across groups. Reasons for dropout given
Selective reporting (reporting bias)	High risk	Adverse events not stated as an outcome, unclear ascertainment, incomplete reporting of adverse events

Amali 2015 (*Continued*)

Other bias	Unclear risk	2:1 randomisation design

Amer 2006

Methods	**Design:** randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 49 children (macrolide n = 25, placebo n = 24) **Age in years** (mean): macrolide: 8.0, placebo: 8.4 **Setting:** secondary care
Interventions	**Indication:** pityriasis rosea **Type of macrolide:** azithromycin **Route:** per oral **Dose per day:** 500 mg (maximum) **Duration of treatment:** 5 days **Total treatment dose:** 2500 mg (maximum)
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper:** unclear **Adverse events ascertainment:** participant asked **Adverse events:** data reported **Antimicrobial resistance:** not reported **Death:** not reported
Funding sources	Study supported by a grant from Pfizer Inc.
Notes	**Concomitant medication:** unclear

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described in detail.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of both participants and clinicians
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropout

Amer 2006 (*Continued*)

Selective reporting (reporting bias)	Low risk	Adverse events not clearly stated as an outcome. However, standardised ascertainment of adverse events at each follow-up visit and adverse events reported
Other bias	Low risk	None were identified.

Amland 1995

Methods	**Design:** randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 339 children, adults, and elderly (macrolide n = 171, placebo n = 168) **Age in years** mean (range): male: macrolide: 30 (7 to 85), placebo: 28 (6 to 84); female: macrolide 33 (6 to 84), placebo: 33 (7 to 82) **Setting:** secondary care
Interventions	**Indication:** prevention of postoperative wound infections **Type of macrolide:** azithromycin **Route:** per oral **Dose per day:** 1000 mg (maximum) **Duration of treatment:** 1 day **Total treatment dose:** 1000 mg (maximum)
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper:** no **Adverse events ascertainment:** unclear **Adverse events:** data reported **Antimicrobial resistance:** not reported **Death:** not reported
Funding sources	None stated. Reports that the study was supported by Pfizer, who provided the study medication
Notes	**Concomitant medication:** yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was performed in blocks of 10 using a computer-generated chart
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo not described.

Amland 1995 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear if participants and clinicians were blinded to treatment groups
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, similar across groups
Selective reporting (reporting bias)	Unclear risk	Adverse events not stated as an outcome, unclear ascertainment. However, adverse events reported
Other bias	Low risk	None were identified.

Andere 2017

Methods	**Design:** randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 40 adults (macrolide n = 20, placebo n = 20) **Age in years** (mean (range)): 32.2 (22 to 35) **Setting:** dental care
Interventions	**Indication:** generalised aggressive periodontitis **Type of macrolide:** clarithromycin **Route:** per oral **Dose per day:** 1000 mg **Duration of treatment:** 3 days **Total treatment dose:** 3000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper:** unclear **Ascertainment of adverse events:** participant diary **Adverse event:** data reported **Antimicrobial resistance:** not reported **Death:** not reported
Funding sources	Funded by Research Funding Agency from Sao Paulo State and National Council for Science and Technological Development
Notes	**Concomitant medication:** unclear

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Central allocation

Andere 2017 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo used.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of both participant and examiner/ clinicians
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropout
Selective reporting (reporting bias)	Low risk	Adverse events not stated as an outcome. However, clear ascertainment and adverse events reported
Other bias	Low risk	None were identified.

Andersen 1998

Methods	**Design:** randomised, placebo-controlled, 4-armed trial
Participants	**Number assigned:** 177 adults (macrolide (daily dose) n = 59, macrolide (weekly dose) n = 58, placebo n = 60) **Age in years** (range): 18 to 55 **Setting:** 2 villages in western Kenya
Interventions	**Indication:** malaria prophylaxis **Type of macrolide:** azithromycin **Route:** per oral **Dose per day/week:** arm 1: 250 mg/day; arm 2: 1000 mg/week **Duration of treatment:** 10 weeks **Total treatment dose:** arm 1: 17,500 mg; arm 2: 10,000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper:** yes **Adverse events ascertainment:** participants asked + clinical examination/lab tests A**dverse events:** data reported. Adverse events are reported as "number of events" and not as "patients with events" **Antimicrobial resistance:** not reported **Death:** not reported
Funding sources	Kenya Medical Research Institute through the US Army Medical Material Development Activity and Pfizer Central Research. Pfizer provided the study drugs and placebo
Notes	**Concomitant medication:** yes **Note:** a 4th group of people were treated with doxycyclin.
Risk of bias	

Andersen 1998 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Separate placebos were used for different treatment groups to preserve the blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and staff
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, similar across groups
Selective reporting (reporting bias)	Low risk	Adverse events stated as an outcome and were assessed by a daily symptom questionnaire. Adverse events reported
Other bias	Low risk	None were identified.

Anderson 1999

Methods	**Design:** randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 302 adults and elderly (macrolide n = 150, placebo n = 152) **Age in years** (mean ± SD)**:** macrolide: 64 ± 10, placebo: 63 ± 11 **Setting:** secondary care
Interventions	**Indication:** secondary prevention in people with coronary artery disease and seropositivity to *Chlamydia pneumoniae* **Type of macrolide:** azithromycin **Route:** per oral **Dose:** 500 mg/day for 3 days, then 500 mg/week for 3 months **Duration of treatment:** 93 days **Total treatment dose:** 7500 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper:** yes **Adverse events ascertainment:** unclear **Adverse event**: data reported **Antimicrobial resistance:** not reported **Death:** data reported
Funding sources	Study supported in part by a grant from the Deseret Foundation, LDS Hospital, Salt Lake City, Utah. Azithromycin and placebo purchased from pharmacies

Anderson 1999 (*Continued*)

Notes	**Concomitant medication:** unclear	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomisation (alternating blocks of 4 and 6)
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and clinicians
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, similar across groups
Selective reporting (reporting bias)	Low risk	Adverse events stated as an outcome. Unclear ascertainment, but adverse events reported
Other bias	Low risk	None were identified.

Andremont 1981

Methods	**Design:** randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 48 adults (macrolide n = 24, placebo n = 24) **Age in years:** N/A **Setting:** healthy US residents travelling to Mexico to attend a professional meeting
Interventions	**Indication:** prevention of traveller's diarrhoea **Type of macrolide:** erythromycin base **Route:** per oral **Dose per day:** 1000 mg **Duration of treatment:** mean days of treatment 6 (range 4 to 13 days) **Total treatment dose:** 6000 mg (mean)
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper:** no **Adverse events ascertainment:** unclear **Adverse events:** states that no adverse events were reported **Antimicrobial resistance:** not reported **Death:** not reported

Andremont 1981 (*Continued*)

Funding sources	Study supported by a "contrat de recherche clinique" from Institut Gustave Roussy and a grant from Roussel-Uclaf Laboratories
Notes	**Concomitant medication:** unclear **Note:** gastrointestinal symptoms were reported as the primary outcome in this study and not reported/regarded as an adverse event

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and clinicians
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropout
Selective reporting (reporting bias)	Unclear risk	Adverse events not stated as an outcome and unclear ascertainment. However, states that no adverse events were reported
Other bias	Low risk	None were identified.

Anthony 2014

Methods	**Design:** randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 78 adults and elderly (macrolide n = 39, placebo n = 39) **Age in years** (mean ± SD): azithromycin: 65.94 ± 11.77, placebo: 59.75 ± 15.03 **Setting:** secondary care
Interventions	**Indication:** bronchiectasis **Type of macrolide:** azithromycin **Route:** per oral **Dose:** 1000 mg/week **Duration of treatment:** 12 weeks **Total treatment dose:** 12,000 mg

Anthony 2014 (*Continued*)

Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper:** unclear **Adverse events ascertainment:** participants asked + clinical examination/lab tests **Adverse events:** data reported **Antimicrobial resistance:** not reported **Death:** data reported
Funding sources	Study supported by a grant approved by the Ministry of Health of Malaysia. Study medication was manufactured and provided by Pfizer Inc
Notes	**Concomitant medication:** unclear

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and clinicians
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout in both groups
Selective reporting (reporting bias)	Low risk	Adverse events not clearly stated as an outcome. However, standardised ascertainment at each follow-up visit and adverse events reported
Other bias	Low risk	None were identified.

Avci 2013

Methods	**Design:** randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 60 adults and elderly (macrolide n = 30, placebo n = 30) **Age in years** (mean age ± SD (range)): 50.68 ± 12.92 (18 to 78) **Setting:** secondary care

Avci 2013 (*Continued*)

Interventions	**Indication:** erythrasma **Type of macrolide:** erythromycin **Route:** per oral **Dose per day:** 1000 mg **Duration of treatment:** 14 days **Total treatment dose:** 14,000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper:** unclear **Adverse events ascertainment:** participants asked **Adverse events:** data reported **Antimicrobial resistance:** not reported **Death:** not reported
Funding sources	None reported. Authors thank supplying companies.
Notes	**Concomitant medication:** no

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described in detail.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear if identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear if participants and clinicians were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropout
Selective reporting (reporting bias)	Low risk	Adverse events not clearly stated as an outcome. However, standardised ascertainment of adverse events at each follow-up visit and adverse events reported
Other bias	Low risk	None were identified.

Bacharier 2015

Methods	**Design:** randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 607 children (macrolide n = 307, placebo n = 300) **Age in months** (mean ± SD): 41.5 ± 16.5 **Setting:** 9 US academic medical centres in the National Heart, Lung, and Blood Institute's AsthmaNet network
Interventions	**Indication:** recurrent severe lower respiratory tract illness **Type of macrolide:** azithromycin **Route:** per oral **Dose per day:** 12 mg/kg **Duration of treatment:** 5 days (per treatment course) **Total treatment dose:** N/A
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper:** yes **Adverse events ascertainment:** spontaneously reporting + clinical examination **Adverse events:** data reported **Antimicrobial resistance:** data reported **Death:** not reported
Funding sources	Study supported by the National Heart, Lung, and Blood Institute as part of AsthmaNet. Several authors have received personal fees and grants from various pharmaceutical companies
Notes	**Concomitant medication:** yes **Note:** during the 78-week follow-up included children could use the study treatment during a maximum of 4 treated respiratory tract infection episodes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Placebo-controlled, double-blind trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	17% and 18% withdrew for reasons other than "early termination" or were lost to follow-up, respectively. Reasons not given

Bacharier 2015 (*Continued*)

Selective reporting (reporting bias)	Low risk	Adverse events stated as an outcome, standardised ascertainment, and adverse events reported
Other bias	Low risk	None were identified.

Bajaj 2012

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 63 adults (macrolide n = 32, placebo n = 31) **Age in years** (range): 30 to 50 **Setting**: dental care
Interventions	**Indication**: chronic periodontitis in people with type 2 diabetes mellitus **Type of macrolide**: clarithromycin **Route**: topical **Dose per day:** 0.5% gel once **Duration of treatment:** 1 day **Total treatment dose:** N/A
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: states that no adverse events were observed or reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	None stated. Authors thank Micro Labs, India, and Purac Biomaterials, the Netherlands, for providing active drug and placebo
Notes	**Concomitant medication**: unclear

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	Allocation not described in detail.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo gel used.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of both the participant and the clinician, who provided treatment

Bajaj 2012 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, similar across groups
Selective reporting (reporting bias)	Unclear risk	Adverse events not stated as an outcome, unclear ascertainment. Authors state that no adverse events were reported
Other bias	Low risk	None were identified.

Bala 2008

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 40 adults (macrolide n = 20, placebo n = 20) **Age in years** (mean ± SD): macrolide: 28 ± 10.2, placebo: 35 ± 10.4 **Setting**: secondary care
Interventions	**Indication**: gastric fluid pH and volume during surgery **Type of macrolide**: erythromycin **Route:** per oral **Dose per day:** 250 mg **Duration of treatment:** 1 day **Total treatment dose:** 250 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: authors state that "no adverse effects could be attributed to the test drugs" **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	Institutional funding
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Central randomisation
Allocation concealment (selection bias)	Low risk	Allocation by statistician off-site
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo

Bala 2008 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of both participant and clinicians
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropout
Selective reporting (reporting bias)	Unclear risk	Adverse events not stated as an outcome and unclear ascertainment. Authors report that no adverse events were observed
Other bias	Low risk	None were identified.

Ballard 2011

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 220 children (macrolide n = 111, placebo n = 109) **Age in weeks** (mean ± SD): macrolide: 25.7 ± 1.5, placebo: 26 ± 1.6 **Setting**: secondary care
Interventions	**Indication**: prevention of bronchopulmonary dysplasia in preterm infants **Type of macrolide**: azithromycin **Route:** intravenous (study drugs were initially administered intravenously, but switched to enteral route once the infant reached full enteral feeds) **Dose per day:** 10 mg/kg for 7 days, followed by 5 mg/kg for 5 weeks **Duration of treatment:** 42 days **Total treatment dose**: N/A
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: clinical examination **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: data reported
Funding sources	None reported.
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomisation
Allocation concealment (selection bias)	Low risk	Central allocation

Ballard 2011 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of caretakers and staff
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, reasons given
Selective reporting (reporting bias)	Unclear risk	Adverse events not clearly stated as an outcome. Audiometry and lab tests performed, however not complete reporting of adverse events
Other bias	Low risk	None were identified.

Banerjee 2004

Methods	**Design**: randomised, placebo-controlled, parallel-group trial	
Participants	**Number assigned:** 67 adults and elderly (macrolide n = 31, placebo n = 36) **Age in years** (mean ± SE): macrolide: 65.1 ± 1.4, placebo: 68.1 ± 1.2 **Setting**: secondary care	
Interventions	**Indication**: chronic obstructive pulmonary disease **Type of macrolide**: clarithromycin **Route**: per oral **Dose per day:** 500 mg **Duration of treatment:** 90 days **Total treatment dose:** 45,000 mg	
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participants asked + sputum **Adverse events:** incomplete reporting, author contacted **Antimicrobial resistance**: not reported **Death**: not reported	
Funding sources	Funded by a research grant from Abbott Laboratories Ltd, Maidenhead, UK	
Notes	**Concomitant medication**: yes	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Banerjee 2004 (*Continued*)

Random sequence generation (selection bias)	Low risk	Block randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and clinicians
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, similar across groups
Selective reporting (reporting bias)	Unclear risk	Adverse events not clearly stated as an outcome. Participants were contacted and asked about adverse events regularly, however no reporting of adverse events in published paper
Other bias	Low risk	None were identified.

Barkhordar 2018

Methods	**Design:** randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 96 adults (macrolide n = 48, placebo n = 48) **Age in years** (mean ± SD (range)): macrolide: 35.5 ± 12.0 (16 to 62), placebo: 36.1 ± 11.5 (18 to 62) **Setting:** secondary care
Interventions	**Indication:** prevention of graft versus host disease in people with acute leukaemia **Type of macrolide:** azithromycin **Route:** per oral **Dose per day:** 500 mg **Duration of treatment:** 18 days **Total treatment dose:** 9000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper:** no (mortality stated as outcome) **Ascertainment of adverse events:** unclear **Adverse event:** not reported. States that "the medication was well tolerated by all patients" **Antimicrobial resistance:** not reported **Death:** data reported
Funding sources	None reported.

Barkhordar 2018 (*Continued*)

Notes	**Concomitant medication:** yes	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described in detail.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants, nursing staff, outcome assessor, and attending physician
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, similar across groups, reasons given
Selective reporting (reporting bias)	High risk	Adverse events not stated as an outcome, unclear ascertainment and incomplete reporting of adverse events
Other bias	Low risk	None were identified.

Beigelman 2015

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 40 children (macrolide n = 20, placebo n = 20) **Age in years** (mean ± SD): 3.8 ± 2.9 **Setting**: secondary care
Interventions	**Indication**: respiratory syncytial virus bronchiolitis **Type of macrolide**: azithromycin **Route**: per oral **Dose per day:** 10 mg/kg once daily for 7 days, followed by 5 mg/kg once daily for an additional 7 days **Duration of treatment:** 14 days **Total treatment dose**: N/A
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: contacting participants' families 3 times a week during the treatment period **Adverse events**: data reported

Beigelman 2015 (*Continued*)

	Antimicrobial resistance: not reported **Death**: not reported
Funding sources	Study supported by Washington University Institute of Clinical and Translational Sciences grant from the National Center for Advancing Translational Sciences and the Children's Discovery Institute of Washington University and St Louis Children's Hospital. Supported in part by CTSA grant and Siteman Comprehensive Cancer Center and NCI Cancer Center support grant
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of all participants, their families, investigators, and study staff
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 child lost to follow-up
Selective reporting (reporting bias)	Low risk	Adverse events stated as an outcome, standardised ascertainment and adverse events reported
Other bias	Low risk	None were identified.

Berg 2005

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 473 adults and elderly (macrolide n = 238, placebo n = 235) **Age in years** (mean ± SD): macrolide: 64.9 ± 8.7, placebo: 63.8 ± 10.8 **Setting**: secondary care
Interventions	**Indication**: coronary artery disease **Type of macrolide**: clarithromycin **Route**: per oral

Berg 2005 (*Continued*)

	Dose per day: 500 mg **Duration of treatment:** 16 days (mean) **Total treatment dose:** 8000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: not reported **Antimicrobial resistance**: data reported **Death**: data reported
Funding sources	Unrestricted grant from Abbott Pharmaceuticals
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	Allocation not described in detail.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and research physician
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout
Selective reporting (reporting bias)	High risk	Adverse events not stated as an outcome, unclear ascertainment and no reporting of adverse events
Other bias	Low risk	None were identified.

Bergeron 2017

Methods	**Design:** randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 480 adults and elderly (macrolide n = 243, placebo n = 237, excluded n = 15) **Age in years:** median (IQR): macrolide: 57.5 (45.0 to 63.6), placebo: 55.6 (40.3 to 63.2)

Bergeron 2017 (*Continued*)

	Setting: secondary care	
Interventions	**Indication:** improvement of airflow decline-free survival after allogenic haematopoietic stem cell transplant **Type of macrolide:** azithromycin **Route:** per oral **Dose:** 250 mg 3 times per week **Duration of treatment:** 730 days **Total treatment dose:** 78,000 mg	
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper:** yes **Ascertainment of adverse events:** participants asked + clinical examination **Adverse event:** data reported. Adverse events are reported as "number of events" and not as "patients with events" **Antimicrobial resistance:** not reported **Death:** data reported	
Funding sources	Supported by the French Ministry of Health, SFGM-TC Capucine association, and SOS Oxygene	
Notes	**Concomitant medication:** unclear	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Central computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and clinicians
Incomplete outcome data (attrition bias) All outcomes	Low risk	Adverse events reported for all allocated participants (safety population)
Selective reporting (reporting bias)	Unclear risk	Adverse events stated as an outcome, clear ascertainment. However, only serious adverse events are reported on
Other bias	Low risk	None were identified.

Berkhof 2013

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 84 adults and elderly (macrolide n = 42, placebo n = 42) **Age in years** (mean ± SD): macrolide: 67 ± 9, placebo: 68 ± 10 **Setting**: secondary care
Interventions	**Indication**: chronic obstructive pulmonary disease **Type of macrolide**: azithromycin **Route**: per oral **Dose:** 750 mg/week **Duration of treatment:** 12 weeks **Total treatment dose:** 9000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: participant asked + lab tests **Adverse events**: data reported **Antimicrobial resistance**: data reported **Death**: not reported
Funding sources	None stated. However, the authors thank Stichting Astma Bestrijding for financial support and Teva Pharma for providing the azithromycin tablets
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated block randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of investigators, research nurses, and participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout. Higher dropout in azithromycin group because of adverse events, however they are reported
Selective reporting (reporting bias)	Low risk	Adverse events stated as an outcome, standardised ascertainment and adverse events reported

Other bias	Low risk	None were identified.

Berne 2002

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 68 adults (macrolide n = 32, placebo n = 36) **Age in years** (mean): macrolide: 40.0, placebo: 34.1 **Setting**: secondary care
Interventions	**Indication**: gastric emptying in critically trauma participants **Type of macrolide**: erythromycin lactobionate **Route:** intravenous **Dose per day:** 1000 mg **Duration of treatment:** 2 days **Total treatment dose:** 2000 mg (maximum)
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events:** incomplete reporting, however no contact details for author **Antimicrobial resistance**: not reported. Report on 1 participant developing a penicillin-resistant *Streptococcus pneumoniae* pneumonia **Death**: data reported
Funding sources	None reported.
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described in detail.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of staff and participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropout

Berne 2002 (*Continued*)

Selective reporting (reporting bias)	High risk	Adverse events not stated as an outcome, unclear ascertainment and incomplete reporting of adverse events
Other bias	Low risk	None were identified.

Black 2001

Methods	**Design**: randomised, placebo-controlled, parallel-group trial	
Participants	**Number assigned:** 232 adults (macrolide n = 105, placebo n = 114, excluded n = 13) **Age in years** (mean ± SD): macrolide: 40 ± 11.6, placebo: 42 ± 11.9 **Setting**: secondary care	
Interventions	**Indication**: asthma participants infected with *Chlamydia pneumoniae* **Type of macrolide**: roxithromycin **Route**: per oral **Dose per day:** 300 mg **Duration of treatment:** 42 days **Total treatment dose:** 12,600 mg	
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: not reported	
Funding sources	Study supported by Aventis Pharma.	
Notes	**Concomitant medication**: yes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described in detail.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of both participant and examiner/clinician

Black 2001 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout
Selective reporting (reporting bias)	Unclear risk	Adverse events not stated as an outcome and unclear ascertainment. Adverse events reported
Other bias	Low risk	None were identified.

Bonacini 1993

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 80 adults and elderly (macrolide n = 41, placebo n = 36, excluded n = 3) **Age in years** (median (range)): macrolide: 42 (18 to 80), placebo: 40 (18 to 81) **Setting**: secondary care
Interventions	**Indication**: postoperative ileus **Type of macrolide**: erythromycin lactobionate **Route:** intravenous **Dose per day:** 750 mg **Duration of treatment:** 3 days **Total treatment dose:** 2250 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	None reported.
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described in detail.
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo

Bonacini 1993 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and clinicians blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout. However, 3 assigned participants (4%) were excluded from analysis based on unclear reasons
Selective reporting (reporting bias)	Unclear risk	Adverse events not stated as an outcome and unclear ascertainment. Adverse events reported
Other bias	Low risk	None were identified.

Botero 2013

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 70 adults and elderly (macrolide n = 33, placebo n = 37) **Age in years** (mean ± SD): macrolide: 55.9 ± 12.6, placebo: 58.2 ± 11.1 **Setting**: dental care
Interventions	**Indication**: periodontitis in people with diabetes mellitus **Type of macrolide**: azithromycin **Route**: per oral **Dose per day:** 500 mg **Duration of treatment:** 3 days **Total treatment dose:** 1500 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: spontaneously reporting (participants were instructed to report any side effects) **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	Partially supported by a grant from Colgate-Palmolive and the Universidad de Antioquia. Authors thank supplying companies
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation

Botero 2013 (*Continued*)

Allocation concealment (selection bias)	Low risk	Opaque, sealed, and coded envelopes used for allocation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and clinicians
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, similar across groups
Selective reporting (reporting bias)	Low risk	Adverse events not clearly stated as an outcome. However, standardised ascertainment and adverse events reported
Other bias	Low risk	None were identified.

Branden 2004

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 103 adults and elderly (macrolide n = 51, placebo n = 52) **Age in years** (mean ± SD): macrolide: 61.1 ± 10.5, placebo: 59.8 ± 13.4 **Setting**: secondary care
Interventions	**Indication**: chronic *Chlamydia pneumoniae*-infected participants with longstanding airway and/or pharyngeal symptoms **Type of macrolide**: azithromycin **Route**: per oral **Dose per day:** 500 mg **Duration of treatment:** 15 days in total (5 days treatment, repeated 3 times with 23-day intervals) **Total treatment dose:** 7500 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participants asked + lab tests **Reporting of adverse events**: yes **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	Study supported by Karolinska Institutet, Stockholm, Sweden and the Swedish Heart and Lung Foundation. Pfizer AB, Sweden supplied the study medication
Notes	**Concomitant medication**: yes

Branden 2004 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and clinicians
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout. Adverse events leading to discontinuation reported
Selective reporting (reporting bias)	Low risk	Adverse events not clearly stated as an outcome, standardised ascertainment of adverse events at follow-up visits. Adverse events clearly presented in a table
Other bias	Low risk	None were identified.

Brickfield 1986

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 52 adults (macrolide n = 27, placebo n = 25) **Age in years** (mean): macrolide: 32.0, placebo: 32.5 **Setting**: primary care
Interventions	**Indication**: acute bronchitis **Type of macrolide**: erythromycin base **Route**: per oral **Dose per day:** 999 mg **Duration of treatment:** 7 days **Total treatment dose:** 6993 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear A**dverse events:** incomplete reporting. However, no contact details for author **Antimicrobial resistance**: not reported **Death**: not reported

Brickfield 1986 (*Continued*)

Funding sources	Study supported by a grant from the American Academy of Family Physicians. Authors acknowledge supplying companies
Notes	**Concomitant medication**: unclear

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Independent company generated numbered, sealed bottles containing tablets of placebo or erythromycin
Allocation concealment (selection bias)	Low risk	Participants received a numbered, sealed bottle with tablets
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo not described.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear if participants and clinicians were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant withdrew from each group, no reasons given.
Selective reporting (reporting bias)	High risk	Adverse events not stated as an outcome, unclear ascertainment and incomplete reporting of adverse events
Other bias	Low risk	None were identified.

Brill 2015

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 49 adults and elderly (macrolide n = 25, placebo n = 24) **Age in years** (mean ± SD): macrolide: 67.9 ± 8.6, placebo: 68.7 ± 9.8 **Setting**: participants were recruited from both primary and secondary care
Interventions	**Indication**: chronic obstructive pulmonary disease **Type of macrolide**: azithromycin **Route**: per oral **Dose:** 250 mg 3 times a week **Duration of treatment:** 13 weeks **Total treatment dose:** 9750 mg

Brill 2015 (*Continued*)

Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: participant asked + swabs **Adverse events**: incomplete reporting, author contacted **Antimicrobial resistance**: incomplete reporting, author contacted **Death**: not reported
Funding sources	Study supported by the National Institute for Health Research (NIHR) under the Programme Grants for Applied Research programme and the NIHR Royal Brompton Respiratory Biomedical Research Unit. Many of the authors have received honoraria, consulting, and board membership fees from pharmaceutical companies. Authors state that the study presents independent research
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Azithromycin was taken 3 times per week, while placebo was given as 1 tablet per day
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessors probably not blinded. However, only report on AMR data, which is an objective outcome and not influenced by blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, reasons given
Selective reporting (reporting bias)	High risk	Adverse events stated as an outcome and standardised ascertainment. However, incomplete reporting of adverse events including data on antimicrobial resistance
Other bias	Low risk	None were identified.

Brusselle 2013

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 109 adults and elderly (macrolide n = 55, placebo n = 54) **Age in years** median (range): macrolide: 53 (19 to 76), placebo: 53 (20 to 74) **Setting**: secondary care
Interventions	**Indication**: severe asthma **Type of macrolide**: azithromycin **Route**: per oral **Dose:** 250 mg per day for 5 days, then 250 mg 3 times/week for 25 weeks **Duration of treatment:** 26 weeks **Total treatment dose:** 20,000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: unclear **Adverse events**: data reported. Adverse events are reported as "number of events" and not as "patients with events" **Antimicrobial resistance**: data reported **Death**: not reported
Funding sources	The study was funded by the Agency for Innovation by Science and Technology, Flanders, Belgium
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Used a central, web-based tool
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo not described in detail. However, both active treatment and placebo were formulated at the same pharmacy
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Double-blinded trial and presumably matching placebo used
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout. Adverse events resulting in discontinuation are reported
Selective reporting (reporting bias)	Low risk	Adverse events stated as an outcome, unclear ascertainment. Adverse events reported

Brusselle 2013 (*Continued*)

Other bias	Low risk	None were identified.

Bystedt 1980

Methods	**Design**: randomised, placebo-controlled, 7-armed trial
Participants	**Number assigned:** 40 children, adults, and elderly (macrolide n = 20, placebo n = 20) **Age in years** (mean (range)): 29 (17 to 79) **Setting**: secondary care
Interventions	**Indication**: impacted mandibular 3rd molars **Type of macrolide**: erythromycin stearate **Route**: per oral **Dose per day:** 500 mg at day 1, then 250 mg x 4 for 7 days **Duration of treatment:** 8 days **Total treatment dose:** 7500 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participants asked **Adverse events**: incomplete reporting. However, no contact details for author **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	None reported.
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear if identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear if participants and staff were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts not reported.

Bystedt 1980 (*Continued*)

Selective reporting (reporting bias)	High risk	Adverse events not clearly stated as an outcome, standardised ascertainment, adverse events not reported
Other bias	Low risk	None were identified.

Cameron 2013

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 77 adults (macrolide n = 39, placebo n = 38) **Age in years** (mean ± SD): macrolide: 46.4 ± 8.8, placebo: 42.8 ± 9.4 **Setting**: unclear
Interventions	**Indication**: smokers with chronic asthma **Type of macrolide**: azithromycin **Route**: per oral **Dose per day:** 250 mg **Duration of treatment:** 84 days **Total treatment dose:** 21,000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: incomplete reporting, author contacted **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	Study funded by the Medical Research Council UK and supported financially by NHS Research Scotland (NRS), through the Scottish Primary Care Research Network Authors purchased study medication with an educational grant from AstraZeneca. Some authors were on advisory boards, received consultancy fee or grants for institutions from pharmaceutical companies
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear if identical-appearing placebo

Cameron 2013 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear if participants and clinicians were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout
Selective reporting (reporting bias)	High risk	Adverse events not stated as an outcome, unclear ascertainment, and incomplete reporting of adverse events. However, information on adverse events was clearly presented upon contacting authors
Other bias	Low risk	None were identified.

Carbonell 2006

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 100 adults and elderly (macrolide n = 50, placebo n = 50) **Age in years** (mean ± SD): macrolide: 59.3 ± 14.6, placebo: 57.0 ± 13.4 **Setting**: secondary care
Interventions	**Indication**: endoscopy for acute upper gastrointestinal bleeding **Type of macrolide**: erythromycin **Route**: intravenous **Dose per day:** 250 mg **Duration of treatment:** 1 day **Total treatment dose:** 250 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: participants asked + clinical examination **Adverse events**: states that no adverse events were observed **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	Supported by Assistance Publique Hopitanx de Paris, France. Erythromycin produced by Abbott France
Notes	**Concomitant medication**: unclear

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation

Carbonell 2006 (*Continued*)

Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Active treatment or placebo was mixed with saline before infusion and administered intravenously
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded participants and staff
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropout, except 1 participant randomised to erythromycin who was withdrawn before treatment as he had advanced hepatocellular carcinoma
Selective reporting (reporting bias)	Low risk	Adverse events stated as an outcome, standardised ascertainment, and adverse events reported
Other bias	Low risk	None were identified.

Cercek 2003

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 1439 adults and elderly (macrolide n = 716, placebo n = 723) **Age in years** (mean ± SE): macrolide: 65.2 ± 0.5, placebo: 64.7 ± 0.5 **Setting**: secondary care
Interventions	**Indication**: unstable angina or acute myocardial infarction **Type of macrolide**: azithromycin **Route**: per oral **Dose per day:** 500 mg day 1 followed by 250 mg/day for 4 days **Duration of treatment:** 5 days **Total treatment dose:** 1500 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: laboratory tests **Reporting of adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: data reported
Funding sources	Funded by The Heart Foundation at Cedars-Sinai (formerly the Steven S Cohen Heart Fund) and institutional funds of the participating centres
Notes	**Concomitant medication**: yes

Cercek 2003 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stratified randomisation
Allocation concealment (selection bias)	Low risk	Sealed, tamper-evident envelopes used.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Active drugs and matched placebo delivered in identical bottles
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded evaluators and participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, reasons given
Selective reporting (reporting bias)	Unclear risk	Adverse events not clearly stated as an outcome. Standardised ascertainment, except for liver function tests. Adverse events reported
Other bias	Low risk	None were identified.

Clement 2006

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 82 children (macrolide n = 40, placebo n = 42) **Age in years** (mean ± SD): macrolide: 10.9 ± 3.5, placebo: 11.1 ± 3.2 **Setting**: secondary care
Interventions	**Indication**: cystic fibrosis **Type of macrolide**: azithromycin **Route**: per oral **Dose:** 250 mg if < 40 kg or 500 mg if ≥ 40 kg, 3 days/week **Duration of treatment:** 1 year **Total treatment dose:** 78,000 mg (maximum)
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participants asked + clinical examination/lab tests **Reporting of adverse events**: yes **Antimicrobial resistance**: data reported **Death**: not reported

Clement 2006 (*Continued*)

Funding sources	Study supported by the Cystic Fibrosis Association Vaincre la Mucoviscidose, Paris, France	
Notes	**Concomitant medication**: yes	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Central computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and study investigators blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, similar across groups
Selective reporting (reporting bias)	Unclear risk	Adverse events not clearly stated as an outcome. Standardised ascertainment and adverse events presented clearly. However, liver function measured but not reported
Other bias	Low risk	None were identified.

Corris 2015

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 48 adults (macrolide n = 25, placebo n = 23) **Age in years** (median (IQR)): macrolide: 51.0 (35 to 56), placebo: 51.0 (44 to 59) **Setting**: secondary care
Interventions	**Indication:** bronchiolitis obliterans syndrome post-lung transplantation **Type of macrolide**: azithromycin **Route**: per oral **Dose:** 250 mg on alternate days **Duration of treatment:** 84 days **Total treatment dose:** 10,500 mg

Corris 2015 (*Continued*)

Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: incomplete reporting, author contacted **Antimicrobial resistance**: data reported **Death**: no deaths during the study period
Funding sources	Study funded by a Medical Research Council project grant and a British Lung Foundation Trevor Clay Award
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomly assigned in a 1:1 ratio using random permuted blocks within strata
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo not described in detail. However, active treatment and placebo were formulated by the same company
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and clinicians blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	None lost to follow-up. 1 adverse event leading to discontinuation reported
Selective reporting (reporting bias)	High risk	Adverse events not stated as an outcome and unclear ascertainment. Adverse events not presented clearly
Other bias	Low risk	None were identified.

Currier 2000

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 644 adults (macrolide n = 322, placebo n = 321, mistakenly enrolled n = 1) **Age in years** (median): 40 **Setting**: AIDS clinical trial study sites at university-based outpatient clinics

Currier 2000 (*Continued*)

Interventions	**Indication**: mycobacterium avium complex infection in people with AIDS and increased CD4+ cell counts **Type of macrolide**: azithromycin **Route**: per oral **Dose:** 1200 mg/week **Duration of treatment:** 69 weeks (median) **Total treatment dose:** 82,800 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: participant asked **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: data reported
Funding sources	Study supported by the AIDS Clinical Trials Group and National Institute of Allergy and Infectious Diseases and in part by Pfizer Inc. 1 of the authors was a representative for Pfizer Inc and reviewed the protocol, statistical reports, and manuscript
Notes	**Concomitant medication**: yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned in permuted blocks of 4 within each stratification level
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and staff
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, similar across groups. Discontinuation due to adverse events was larger in azithromycin group than in placebo group (8% versus 2%), but this is reported
Selective reporting (reporting bias)	Low risk	Adverse events stated as an outcome, standardised ascertainment, and adverse events reported

Currier 2000 (*Continued*)

Other bias	Low risk	None were identified.

Curry 2004

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 62 children (macrolide n = 32, placebo n = 30) **Age in weeks** (mean ± SD): macrolide: 36.3 ± 2.1, placebo: 36.3 ± 1.1 **Setting**: secondary care
Interventions	**Indication**: infants with gastroschisis **Type of macrolide**: erythromycin **Route**: per oral **Dose per day:** 12 mg/kg **Duration of treatment:** 13 days (mean) **Total treatment dose:** 377 mg (mean weight used)
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: laboratory tests and ECG **Adverse events**: incomplete reporting, however no contact details for author **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	The BAPS Multicentre Research Fellow was funded by Dunhill Medical Trust. Authors acknowledge supplying company (Rosemont Pharmaceuticals)
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Central computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of investigators and caretakers
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, reasons given

Curry 2004 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Adverse events stated as an outcome, laboratory tests and ECG performed regularly. However, unclear reporting of adverse events
Other bias	Low risk	None were identified.

Czarnetzki 2015

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 132 adults (macrolide n = 66, placebo n = 66) **Age in years** (median (IQR)): macrolide: 40.5 (31 to 58), placebo: 45.0 (29 to 55) **Setting**: secondary care
Interventions	**Indication**: gastric emptying in people undergoing general anaesthesia for emergency surgery **Type of macrolide**: erythromycin lactobionate **Route**: intravenous **Dose per day:** 3 mg/kg **Duration of treatment:** 1 day **Total treatment dose:** 223.5 mg (mean weight in macrolide group used)
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: participant asked + clinical examination **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	Study supported by institutional funds from the Division of Anestesiology, Geneva University Hospitals
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo

Czarnetzki 2015 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and staff
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Low risk	Adverse events stated as an outcome, standardised ascertainment, and adverse events reported
Other bias	Low risk	None were identified.

Dunlay 1987

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 63 adults (macrolide n = 32, placebo n = 31) **Age in years** (mean): macrolide: 43.0, placebo: 44.0 **Setting**: primary care
Interventions	**Indication**: acute bronchitis **Type of macrolide**: erythromycin base **Route**: per oral **Dose per day:** 999 mg **Duration of treatment:** 10 days **Total treatment dose:** 9990 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participant diary used **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	None reported. Authors acknowledge supplying company (Upjohn Company)
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomisation
Allocation concealment (selection bias)	Low risk	Used sequentially numbered, identical drug containers

Dunlay 1987 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, physician, and investigators were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, discontinuation due to adverse events reported
Selective reporting (reporting bias)	Unclear risk	Adverse events not clearly stated as an outcome. Standardised ascertainment, however unclear reporting of adverse events as only reported on how many participants withdrew due to adverse events
Other bias	Low risk	None were identified.

Ehsani 2013

Methods	**Design**: randomised, placebo-controlled, parallel-group trial	
Participants	**Number assigned:** 40 adults and elderly (macrolide n = 20, placebo n = 20) **Age in years** (mean ± SD): macrolide: 61 ± 15, placebo: 62 ± 17 **Setting**: secondary care	
Interventions	**Indication**: upper gastrointestinal bleeding **Type of macrolide**: erythromycin **Route**: intravenous **Dose per day:** 3 mg/kg in 100 mL saline **Duration of treatment:** 1 day **Total treatment dose**: N/A	
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: not reported **Antimicrobial resistance**: not reported **Death**: data reported	
Funding sources	None reported.	
Notes	**Concomitant medication**: yes	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Ehsani 2013 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear blinding as placebo not described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Unclear if participants and staff were blinded, however the only reported outcome is death, which is objective
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropout
Selective reporting (reporting bias)	High risk	Adverse events not stated as an outcome. States that adverse events were recorded, but unclear ascertainment, and adverse events not reported
Other bias	Low risk	None were identified.

El-Sadr 2000

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 520 adults (macrolide n = 258, placebo n = 262) **Age in years** (mean ± SD): macrolide: 41.7 ± 7.4, placebo: 41.9 ± 8.5 **Setting**: not specified
Interventions	**Indication**: mycobacterium avium complex infection in people with HIV and increased CD4+ cell counts **Type of macrolide**: azithromycin **Route**: per oral **Dose:** 1200 mg/week **Duration of treatment**: 12.7 months (median in azithromycin group) **Total treatment dose:** 66,000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: unclear **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: data reported
Funding sources	Study supported by a grant from the National Institute of Allergy and Infectious Diseases. Authors acknowledge supplying company (Pfizer)

El-Sadr 2000 (*Continued*)

Notes	**Concomitant medication**: yes	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stratified randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and clinicians were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, discontinuation due to adverse events reported
Selective reporting (reporting bias)	Low risk	Adverse events stated as an outcome, unclear ascertainment. Adverse events presented clearly
Other bias	Low risk	None were identified.

Eschenbach 1991

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 1181 adults (macrolide n = 605, placebo n = 576) **Age in years** (mean ± SD): macrolide: 23.9 ± 5.3, placebo: 23. 6 ± 5.6 **Setting**: secondary care
Interventions	**Indication**: pregnant women with *Ureaplasma urealyticum* **Type of macrolide**: erythromycin base **Route**: per oral **Dose per day:** 999 mg **Duration of treatment**: maximum of 70 days (starting between 26 and 30 weeks' gestation and continuing through 35 completed weeks of pregnancy. Instructed to take the medication for 10 weeks or until the end of the 35th week of pregnancy, whichever came first) **Total treatment dose:** 69,930 mg (maximum)

Eschenbach 1991 (*Continued*)

Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: spontaneously + asked **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: data reported for babies
Funding sources	Study supported by the National Institutes of Health. Authors acknowledge supplying company (The Upjohn Company)
Notes	**Concomitant medication**: unclear

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Pregnant women and staff blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, similar across groups
Selective reporting (reporting bias)	Low risk	Adverse events not clearly stated as an outcome. Standardised ascertainment, and adverse events presented clearly
Other bias	Low risk	None were identified.

Fonseca-Aten 2006

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 43 children (macrolide n = 22, placebo n = 21) **Age in months** (median (range)): macrolide: 112.5 (62 to 187), placebo: 100 (50 to 181) **Setting**: emergency department of Children's Medical Center

Fonseca-Aten 2006 (*Continued*)

Interventions	**Indication**: acute exacerbation of recurrent wheezing or asthma **Type of macrolide**: clarithromycin **Route**: per oral **Dose per day:** 15 mg/day, in 2 divided doses (maximum of 1000 mg) **Duration of treatment:** 5 days **Total treatment dose:** 5000 mg (maximum)
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: not reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	Supported by Abbott Laboratories and Children's Medical Center of Dallas Research Advisory committee
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo not described, however active treatment and placebo prepared by the same company
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No outcomes reported. Children, caretakers, and staff were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Lost to follow-up not reported.
Selective reporting (reporting bias)	High risk	Adverse events not stated as an outcome, unclear ascertainment, and adverse events not reported
Other bias	Low risk	None were identified.

Frossard 2002

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 105 adults and elderly (macrolide n = 51, placebo n = 54) **Age in years** (mean ± SD): macrolide: 59.2 ± 15, placebo: 64.5 ± 16 **Setting**: secondary care
Interventions	**Indication**: acute upper gastrointestinal bleeding **Type of macrolide**: erythromycin **Route**: intravenous **Dose per day:** 250 mg (mixed with 50 mL saline) **Duration of treatment:** 1 day **Total treatment dose:** 250 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: spontaneously **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: incomplete reporting
Funding sources	None reported.
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Low risk	Allocation done off-site at a central pharmacy.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and staff
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropout
Selective reporting (reporting bias)	Low risk	Adverse events stated as an outcome, standardised ascertainment, and adverse events reported

Frossard 2002 (*Continued*)

Other bias	Unclear risk	Small, significant age difference between the 2 groups

Garcia-Burguillo 1996

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 60 adults (macrolide n = 30, placebo n = 30) **Age in years** (mean ± SD): macrolide: 28.3 ± 5.9, placebo: 27.4 ± 6 **Setting**: secondary care
Interventions	**Indication**: preterm rupture of the amniotic membranes **Type of macrolide**: erythromycin ethyl succinate **Route**: per oral **Dose per day:** 2000 mg **Duration of treatment:** 8 days (mean duration of treatment in erythromycin group) **Total treatment dose:** 16,000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: not reported **Antimicrobial resistance**: not reported **Death**: reported for babies of treated mothers
Funding sources	None reported.
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear blinding as placebo not described
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only reported on death in babies, which is an objective outcome not influenced by blinding or not
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts

Selective reporting (reporting bias)	High risk	Adverse events not stated as an outcome, unclear ascertainment, adverse events not reported (only death in babies)
Other bias	Low risk	None were identified.

Gharpure 2001

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 74 children (macrolide n = 37, placebo n = 37) **Age in years** (mean (range)): macrolide: 3.5 (0.1 to 16), placebo: 1.8 (0.1 to 17) **Setting**: secondary care
Interventions	**Indication**: tube placement in critically ill children **Type of macrolide**: erythromycin lactobionate **Route**: intravenous **Dose per day:** 10 mg/kg for every 6 hours (maximum 3 doses) **Duration of treatment:** 1 day **Total treatment dose**: N/A
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: continuous electrocardiogram monitoring and adverse events defined before study start **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	Study supported by Children's Research Center of Michigan.
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Central computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Saline used as placebo and equal amounts.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of children, parents, and staff

Gharpure 2001 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, report on reason for discontinuation
Selective reporting (reporting bias)	Low risk	Adverse events not clearly stated as an outcome. However, adverse events defined before study start and reported
Other bias	Low risk	None were identified.

Giamarellos-Bourboulis 2008

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 200 adults and elderly (macrolide n = 100, placebo n = 100) **Age in years** (mean ± SD): macrolide: 58.4 ± 20.7, placebo: 58.4 ± 17.4 **Setting**: secondary care
Interventions	**Indication**: sepsis associated with ventilator-associated pneumonia **Type of macrolide**: clarithromycin **Route**: intravenous **Dose per day:** 1000 mg **Duration of treatment:** 3 days **Total treatment dose:** 3000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: clinical examination (lab tests, ECG) **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: data reported
Funding sources	Study supported by Abbott Laboratories. No information about their role in the study
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The sequence was generated by an independent biostatistician and stratified by study site
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo

Giamarellos-Bourboulis 2008 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of staff and participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	None lost to follow-up. Report on reasons for discontinuation
Selective reporting (reporting bias)	Unclear risk	Adverse events not stated as an outcome. Only serious adverse events reported; info on QTc interval not presented even though ECG was performed
Other bias	Low risk	None were identified.

Giamarellos-Bourboulis 2014

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 600 adults and elderly (macrolide n = 302, placebo n = 298) **Age in years** (mean ± SD): macrolide: 67.8 ± 19.3, placebo: 65.9 ± 19.9 **Setting**: secondary care
Interventions	**Indication**: suspected gram-negative sepsis **Type of macrolide**: clarithromycin **Route**: intravenous **Dose per day:** 1000 mg **Duration of treatment:** 4 days **Total treatment dose:** 4000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: data reported
Funding sources	Study supported by Abbott Laboratories (Hellas) SA. The first author serves as an advisor of Astellas Hellas and The Medicines Company and has received honoraria from AbbVie
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The sequence was generated by an independent biostatistician and stratified by study site

Giamarellos-Bourboulis 2014 (*Continued*)

Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of staff and participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	None lost to follow-up. Report on reasons for discontinuation
Selective reporting (reporting bias)	Low risk	Adverse events not stated as an outcome and unclear ascertainment. However, adverse events reported in detail
Other bias	Low risk	None were identified.

Gibson 2017

Methods	**Design:** randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 420 adults and elderly (macrolide n = 213, placebo n = 207) **Age in years** (median (IQR)): macrolide: 60.01 (49.58 to 67.98), placebo: 61.02 (50.62 to 68.74) **Setting:** secondary care
Interventions	**Indication:** persistent uncontrolled asthma **Type of macrolide:** azithromycin **Route:** per oral **Dose:** 500 mg 3 times per week **Duration of treatment:** 336 days **Total treatment dose:** 72,000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper:** yes **Ascertainment of adverse events:** participants asked + clinical examination **Adverse event:** data reported **Antimicrobial resistance:** data reported **Death:** not reported
Funding sources	Supported by the National Health and Medical Research Council of Australia and the John Hunter Hospital Charitable Trust
Notes	**Concomitant medication:** yes
Risk of bias	

Gibson 2017 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of staff and participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	About 20% of participants in each group were withdrawn, however reasons (including adverse events) for withdrawal were provided
Selective reporting (reporting bias)	Low risk	Adverse events stated as an outcome and clear ascertainment. Adverse events reported
Other bias	Low risk	None were identified.

Glass 1999

Methods	**Design**: randomised, placebo-controlled, 4-armed trial
Participants	**Number assigned:** 80 children and adults (macrolide n = 39, placebo n = 41) **Age in years** (mean ± SD): macrolide: 18.8 ± 2.5, placebo: 18.3 ± 1.9 **Setting**: secondary care
Interventions	**Indication**: acne vulgaris **Type of macrolide**: erythromycin **Route**: topical **Dose per day:** 2% gel twice a day **Duration of treatment:** 84 days **Total treatment dose**: N/A
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participants asked + clinician assessment **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	None reported.

Glass 1999 (*Continued*)

Notes	**Concomitant medication**: unclear	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo not described (4 arms in study).
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear if participants or staff or both were blinded to treatments
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, reasons given
Selective reporting (reporting bias)	Unclear risk	Adverse events not clearly stated as an outcome. Standardised ascertainment and adverse events reported. However, only report "overall" on participants with adverse events
Other bias	Low risk	None were identified.

Gokmen 2012

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned**: 47 children (macrolide n = 24, placebo n = 23) **Gestational age in weeks** (median (range)): macrolide: 28.5 (26 to 32), placebo: 27 (25 to 30) **Setting**: secondary care
Interventions	**Indication**: preventing feeding intolerance and liver function abnormalities in premature infants **Type of macrolide**: erythromycin **Route**: per oral **Dose per day:** 12.5 mg/kg (mixed into milk feeds) **Duration of treatment:** 14 days **Total treatment dose**: N/A

Gokmen 2012 (*Continued*)

Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: electrocardiography was performed before drug treatment began and after the 1st and 2nd week of treatment to assess the QTc intervals **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: data reported
Funding sources	None reported.
Notes	**Concomitant medication**: unclear

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo solution was given as an equivalent volume of normal saline. All the medications were mixed thoroughly into milk feeds to mask their appearance
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Medicine or placebo addition to the milk was performed by a dietitian so that the neonatal nurses were blinded to the particular intervention in each infant. Death is an objective outcome, not influenced by blinding or not
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, none caused by adverse events
Selective reporting (reporting bias)	Unclear risk	Adverse events not clearly stated as an outcome. State that ECG was performed during study period, but no reporting of ECG measures
Other bias	Unclear risk	Infants in the macrolide group had higher gestational age and birthweight than those assigned placebo

Grassly 2016

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 754 children (macrolide n = 376, placebo n = 378) **Age in months** (mean ± SE): azithromycin: 7.46 ± 0.08, placebo: 7.49 ± 0.08 **Setting:** healthy infants living in 14 blocks of Vellore district, India
Interventions	**Indication**: improve immune response to oral poliovirus vaccination **Type of macrolide**: azithromycin **Route**: per oral **Dose per day:** 10 mg/kg **Duration of treatment:** 3 days **Total treatment dose:** 219 mg (mean weight in macrolide group used)
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: participants asked **Adverse events**: incomplete reporting, author contacted **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	Study supported by Bill & Melinda Gates Foundation. 1 author declared unrelated collaborations with pharmaceutical companies
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Central computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Children, parents, and staff blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout
Selective reporting (reporting bias)	Unclear risk	Adverse events stated as an outcome. However, unclear ascertainment and incomplete reporting of adverse events (do not report on each adverse event separately)

Grassly 2016 (*Continued*)

Other bias	Low risk	None were identified.

Grayston 2005

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 4012 adults and elderly (macrolide n = 2004, placebo n = 2008) **Age in years** (mean): macrolide: 65, placebo: 65 **Setting**: secondary care
Interventions	**Indication**: secondary prevention in people with stable coronary heart disease **Type of macrolide**: azithromycin **Route**: per oral **Dose:** 600 mg/week **Duration of treatment:** 1 year **Total treatment dose:** 31,200 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participant asked **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: data reported (part of composite primary outcome)
Funding sources	Study supported by the National Heart, Lung, and Blood Institute and Pfizer
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of staff and participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, none due to adverse events

Grayston 2005 (*Continued*)

Selective reporting (reporting bias)	Low risk	Adverse events not clearly stated as an outcome. However, standardised ascertainment and adverse events reported
Other bias	Low risk	None were identified.

Grob 1981

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 91 children (macrolide n = 52, placebo n = 39) **Age in years** (range): 0 to 8 **Setting**: primary care
Interventions	**Indication:** *Bordetella pertussis* prevention **Type of macrolide:** erythromycin ethyl succinate **Route**: per oral **Dose per day:** 500 mg if aged < 2 years and 1000 mg if aged 2 to 8 years **Duration of treatment:** 14 days **Total treatment dose:** 14,000 mg (maximum)
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: not reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	Study funded by the Medical Research Council.
Notes	**Concomitant medication**: unclear

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Unclear sequence generation
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No relevant outcomes reported.

Grob 1981 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout not reported.
Selective reporting (reporting bias)	High risk	Adverse events not stated as an outcome, unclear ascertainment, and adverse events not reported
Other bias	Low risk	None were identified.

Gupta 1997

Methods	**Design**: randomised, placebo-controlled, 3-armed trial
Participants	**Number assigned:** 60 adults and elderly (macrolide (3-day course) n = 28, macrolide (6-day course) n = 12, placebo n = 20) **Age in years** (mean ± SD): macrolide (both arms): 58 ± 7, placebo: 60 ± 9 **Setting**: secondary care
Interventions	**Indication**: male survivors of myocardial infarction **Type of macrolide**: azithromycin **Route**: per oral **Dose per day:** 500 mg **Duration of treatment**: arm 1: 3 days, arm 2: 6 days **Total treatment dose**: arm 1: 1500 mg, arm 2: 3000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: unclear **Adverse events**: data reported (note: do not report on "common adverse events") **Antimicrobial resistance**: not reported **Death**: data reported
Funding sources	Supported by the British Heart Foundation. Authors acknowledge supplying company (Pfizer Ltd)
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo and azithromycin supplied by the same company. However, unclear if placebo

Gupta 1997 (*Continued*)

		matched the single course of azithromycin (3 days) or the 2 courses (2 x 3 days)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only report on objective outcomes (death/ myocardial infarction) not influenced by blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts.
Selective reporting (reporting bias)	High risk	Adverse events stated as an outcome. Unclear ascertainment. Report on outcomes for the 2 treatment regimens as 1 group and do not report on common adverse events
Other bias	Low risk	None were identified.

Gurfinkel 1999

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 202 adults and elderly (macrolide n = 102, placebo n = 100) **Age in years** (mean ± SD): macrolide: 61 ± 12, placebo: 61 ± 12 **Setting**: secondary care
Interventions	**Indication**: non-Q-wave coronary syndrome **Type of macrolide**: roxithromycin **Route**: per oral **Dose per day:** 300 mg **Duration of treatment:** 30 days **Total treatment dose:** 9000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: electrocardiogram **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: data reported
Funding sources	Study funded by the Favaloro Foundation. Authors acknowledge supplying company (Hoechst Marion Roussel)
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Gurfinkel 1999 (*Continued*)

Random sequence generation (selection bias)	Low risk	Central computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and staff blinded to treatments.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout
Selective reporting (reporting bias)	Low risk	Adverse events not clearly stated as an outcome and unclear ascertainment, except from ECG. However, adverse events reported
Other bias	Unclear risk	More participants with diabetes were randomised to macrolide group

Hahn 2006

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 45 adults (macrolide n = 24, placebo n = 21) **Age in years** (mean ± SD): macrolide: 50 ± 14, placebo: 45 ± 12 **Setting**: primary care
Interventions	**Indication**: asthma **Type of macrolide**: azithromycin **Route**: per oral **Dose:** 600 mg/day for 3 days, followed by 600 mg weekly **Duration of treatment:** 6 weeks **Total treatment dose:** 4800 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participant asked **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: data reported
Funding sources	Study supported by the National Institutes of Health, the American Academy of Family Physicians Foundation Joint Grant Awards Program, the Wisconsin Academy of Family Physicians, under the auspices of the Wisconsin Research Network, the Dean Foundation

Hahn 2006 (*Continued*)

	for Health Research and Education. Study supported by an unrestricted educational grant from Pfizer
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study physicians, research staff, participants, and data analysts were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, similar across groups
Selective reporting (reporting bias)	Low risk	Adverse events not stated clearly as an outcome, however standardised ascertainment and adverse events reported
Other bias	Low risk	None were identified.

Hahn 2012

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 75 adults (macrolide n = 38, placebo n = 37) **Age in years** (mean ± SD): macrolide: 45.7 ± 15.5, placebo: 47.4 ± 14.2 **Setting**: primary care
Interventions	**Indication**: asthma **Type of macrolide**: azithromycin **Route**: per oral **Dose:** 600 mg/day for 3 days, followed by 600 mg weekly **Duration of treatment:** 12 weeks **Total treatment dose:** 8400 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: participant asked

Hahn 2012 (*Continued*)

	Adverse events: data reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	Study supported by the Wisconsin Academy of Family Physicians, the American Academy of Family Physicians Foundation, the Dean Foundation for Health Research and Education, and private donors provided financial support for direct costs of AZMATICS (AZithroMycin/Asthma: Trial in Community Settings). Authors acknowledge supplying company (Pfizer Inc)
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Central computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of staff and participants
Incomplete outcome data (attrition bias) All outcomes	Low risk	42% lost to follow-up in azithromycin group versus 30% in placebo group. However, authors report on adverse events for 92% to 95% of participants in macrolide group and 92% in placebo group
Selective reporting (reporting bias)	Low risk	Adverse events stated as an outcome, standardised ascertainment, and adverse events reported
Other bias	Low risk	None were identified.

Halperin 1999

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 362 children and adults (macrolide n = 170, placebo n = 192) **Age in years** (mean): macrolide: 26.6, placebo: 24.9 **Setting**: community based (households)

Halperin 1999 (*Continued*)

Interventions	**Indication:** *Bordetella pertussis* prevention **Type of macrolide**: erythromycin estolate **Route**: per oral **Dose per day:** 40 mg/kg (max 1000 mg) **Duration of treatment:** 10 days **Total treatment dose:** 10,000 mg (maximum)
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participant asked **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	Study supported by the National Health Research and Development Program, Health Canada. Authors acknowledge supplying company (Eli Lilly Canada Inc)
Notes	**Concomitant medication**: unclear

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number table used.
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and staff blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, similar across groups
Selective reporting (reporting bias)	Low risk	Adverse events not clearly stated as an outcome. However, standardised ascertainment and reporting of adverse events
Other bias	Low risk	None were identified.

Haxel 2015

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number:** 58 adults (macrolide n = 29, placebo n = 29) **Age in years** (mean ± SD): macrolide: 45.7 ± 12.8, placebo: 47.7 ± 12.5 **Setting**: secondary care
Interventions	**Indication**: chronic rhinosinusitis **Type of macrolide**: erythromycin **Route**: per oral **Dose per day:** 250 mg **Duration of treatment:** 90 days **Total treatment dose:** 22,500 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: unclear **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	None stated.
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and staff blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout. More participants dropped out in macrolide group. However, adverse events reported
Selective reporting (reporting bias)	Unclear risk	Adverse events stated as an outcome. However, unclear ascertainment and authors only report on gastrointestinal adverse events, although it reads as there might have been other kinds of adverse events to re-

Haxel 2015 (*Continued*)

		port ("Adverse events such as gastrointestinal disorders...")
Other bias	Low risk	None were identified.

Haye 1998

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 169 adults and elderly (macrolide n = 87, placebo n = 82) **Age in years** (mean (range)): macrolide: 40.2 (21 to 70), placebo: 43.2 (18 to 68) **Setting**: primary care
Interventions	**Indication**: acute maxillary sinusitis **Type of macrolide**: azithromycin **Route**: per oral **Dose per day:** 500 mg **Duration of treatment:** 3 days **Total treatment dose:** 1500 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participant asked **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	None stated.
Notes	**Concomitant medication**: unclear

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomisation
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo used.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and clinicians blinded.

Haye 1998 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropout and no participants discontinued treatment due to adverse events
Selective reporting (reporting bias)	Low risk	Adverse events not stated clearly as an outcome. However, standardised ascertainment and adverse events reported
Other bias	Low risk	None were identified.

Heppner 2005

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 292 adults (macrolide n = 190, placebo n = 102) **Age in years** (mean ± SD): macrolide: 29.3 ± 8, placebo: 29.1 ± 8 **Setting**: the remote forest and scrub-covered foothills at the AFRIMS-Kwai River Christian Hospital field site in western Thailand
Interventions	**Indication**: *Plasmodium vivax* malaria prophylaxis **Type of macrolide**: azithromycin **Route**: per oral **Dose per day**: loading dose on day 1 of 750 mg, then 250 mg per day **Duration of treatment:** 74 days (on average) **Total treatment dose:** 19,000 mg (average duration of treatment used)
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: participants asked + clinical examination **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	Study supported by the US Army Medical Materiel Development Activity and by the Military Infectious Diseases Research Program. Azithromycin and placebo were provided by Pfizer Central Research
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomisation
Allocation concealment (selection bias)	Low risk	Central allocation

Heppner 2005 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and trial personnel blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Lost to follow-up 28% (macrolide) versus 25% (placebo). However, adverse events reported for > 90% of participants
Selective reporting (reporting bias)	Low risk	Adverse events stated as an outcome, standardised ascertainment, and adverse events reported
Other bias	Unclear risk	2:1 randomisation design

Hillis 2004

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 141 adults and elderly (macrolide n = 72, placebo n = 69) **Age in years** (mean ± SD): macrolide: 66 ± 11, placebo: 65 ± 12 **Setting**: secondary care
Interventions	**Indication**: survivors of acute coronary syndrome **Type of macrolide**: azithromycin **Route**: per oral **Dose per day:** 500 mg **Duration of treatment:** 5 days **Total treatment dose:** 2500 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participants asked **Adverse events**: data reported, but only those resulting in discontinuation **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	Study supported by the British Heart Foundation.
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Hillis 2004 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo used.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and clinicians blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant dropped out in each group.
Selective reporting (reporting bias)	High risk	Adverse events not stated clearly as an outcome. Standardised ascertainment. However, only adverse events resulting in discontinuation were reported on
Other bias	Low risk	None were identified.

Hodgson 2016

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned**: 44 adults and elderly (macrolide n = 22, placebo n = 22) **Age in years** (mean ± SD): macrolide: 59.6 ± 11.0, placebo: 56.9 ± 9.0 **Setting**: respiratory clinics
Interventions	**Indication**: chronic cough **Type of macrolide**: azithromycin **Route**: per oral **Dose:** 500 mg daily for 3 days, followed by 250 mg 3 times/week **Duration of treatment:** 59 days **Total treatment dose:** 7500 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: unclear (ECG and phlebotomy prior to study entry) **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	Study supported by a National Institute for Health Research Biomedical Research fellowship
Notes	**Concomitant medication**: yes

Hodgson 2016 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and clinicians blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, similar across groups. Reasons given.
Selective reporting (reporting bias)	Low risk	Adverse events stated as an outcome. Unclear ascertainment. However, adverse events reported
Other bias	Low risk	None were identified.

Hooton 1990

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 87 adults (macrolide n = 36, placebo n = 41) **Age in years** (mean ± SD): macrolide: 26 ± 6, placebo: 29 ± 8 **Setting**: secondary care
Interventions	**Indication**: non-gonococcal urethritis **Type of macrolide**: erythromycin estolate **Route**: per oral **Dose per day:** 1000 mg **Duration of treatment:** 21 days **Total treatment dose:** 21,000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	None stated. Erythromycin and placebo were provided by The Upjohn Company

Hooton 1990 (*Continued*)

Notes	**Concomitant medication**: unclear	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random numbers table used.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and clinicians blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, similar across groups
Selective reporting (reporting bias)	Low risk	Adverse events not stated as an outcome. Unclear ascertainment, although follow-up visits scheduled. Adverse events reported
Other bias	Low risk	None were identified.

Hyde 2001

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 147 adults (macrolide n = 73, placebo n = 74) **Age in years** (mean (range)): macrolide: 44 (25 to 63), placebo: 46 (19 to 64) **Setting**: secondary care
Interventions	**Indication**: *Mycoplasma pneumoniae* prophylaxis **Type of macrolide**: azithromycin **Route**: per oral **Dose:** 500 mg on day 1, followed by 250 mg on days 2 to 5 **Duration of treatment:** 5 days **Total treatment dose:** 1500 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: not reported

Hyde 2001 (*Continued*)

Funding sources	None stated. Authors acknowledge supplying company (Pfizer).
Notes	**Concomitant medication**: unclear

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Residents and staff blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, similar across groups
Selective reporting (reporting bias)	Low risk	Adverse events not stated as an outcome, unclear ascertainment. However, adverse events reported
Other bias	Low risk	None were identified.

Ikeoka 2007

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 90 adults and elderly (macrolide n = 42, placebo n = 40, excluded n = 8) **Age in years** (mean ± SD): macrolide: 62 ± 10, placebo: 59 ± 9 **Setting**: secondary care
Interventions	**Indication**: stable coronary disease **Type of macrolide**: azithromycin **Route**: per oral **Dose:** 500 mg x 1 for 3 days in week 1, followed by 500 mg x 1 weekly for 12 weeks, then 500 mg x 1 for 3 days in week 14 **Duration of treatment:** 14 weeks **Total treatment dose:** 9000 mg

Ikeoka 2007 (*Continued*)

Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participants asked + clinical examination **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: data reported
Funding sources	None stated. Authors acknowledge supplying company (Pfizer).
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated, block randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo used.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and clinicians blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, similar across groups
Selective reporting (reporting bias)	Low risk	Adverse events not stated clearly as an outcome. However, standardised ascertainment and adverse events reported
Other bias	Low risk	None were identified.

Jablonowski 1997

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned**: 682 adults (macrolide n = 341, placebo n = 341) **Age in years** (range): 20 to 60 **Setting**: multicentre trial
Interventions	**Indication**: mycobacterium avium-intracellulare complex prophylaxis in HIV-infected individuals **Type of macrolide**: clarithromycin **Route**: per oral

	Dose per day: 1000 mg **Duration of treatment**: N/A **Total treatment dose**: N/A
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: not reported **Antimicrobial resistance**: no surveillance system was used to study the emergence of resistant bacteria. However, authors state that there were no reports of infections with clarithromycin-resistant organisms during the study, and no pneumonia due to a clarithromycin-resistant organism was observed **Death**: data reported
Funding sources	None stated.
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear if identical-appearing placebo was used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only report on objective outcomes, blinding not relevant
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, similar across groups
Selective reporting (reporting bias)	High risk	Adverse events not stated as an outcome, unclear ascertainment, adverse events not reported
Other bias	Low risk	None were identified.

Jackson 1999

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 88 adults and elderly (macrolide n = 44, placebo n = 44) **Age in years** (mean (range)): 57 (37 to 79) **Setting**: unclear
Interventions	**Indication**: coronary artery disease **Type of macrolide**: azithromycin **Route**: per oral **Dose:** 500 mg on days 1 and 2, then 250 mg on days 3 to 28 **Duration of treatment:** 28 days **Total treatment dose:** 8000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: participant asked **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	None stated. Authors acknowledge supplying company (Pfizer Inc)
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo not described in detail. However, active treatment and placebo were formulated by the same company
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and clinicians blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, similar across groups
Selective reporting (reporting bias)	Low risk	Adverse events stated as an outcome, standardised ascertainment, adverse events reported
Other bias	Low risk	None were identified.

Jespersen 2006

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned**: 4373 adults and elderly (macrolide n = 2172, placebo n = 2201) **Age in years** (mean ± SD): macrolide: 65.4 ± 10.3, placebo: 65.2 ± 10.4 **Setting**: secondary care
Interventions	**Indication**: stable coronary heart disease **Type of macrolide**: clarithromycin **Route**: per oral **Dose per day:** 500 mg **Duration of treatment:** 14 days **Total treatment dose:** 7000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: participant diary used **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: data reported
Funding sources	Study supported by the Danish Heart Foundation, Copenhagen Hospital Corporation, Danish Research Council, and 1991 Pharmacy Foundation. Authors acknowledge supplying company (Abbott Laboratories)
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Central computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and clinicians blinded, death is an objective outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	About 1% in each group did not return the participant diary.
Selective reporting (reporting bias)	Low risk	Adverse events stated as an outcome, standardised ascertainment, and adverse events reported

Jespersen 2006 (*Continued*)

Other bias	Low risk	None were identified.

Joensen 2008

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 507 adults and elderly (macrolide n = 250, placebo n = 257) **Age in years** (mean ± SD): macrolide: 64.8 ± 8.8, placebo: 66.6 ± 10.1 **Setting**: secondary care
Interventions	**Indication**: peripheral arterial disease **Type of macrolide**: roxithromycin **Route**: per oral **Dose per day:** 300 mg **Duration of treatment:** 28 days **Total treatment dose:** 8400 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participant asked **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: data reported (primary outcome)
Funding sources	Study supported by the Danish Heart Foundation, the Rosa and Asta Jensen Foundation, the Danish Medical Research Council, and the Health Department of Viborg County
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Nurses at the department gave participants a glass of pills (unaware of content)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Nurse, other team members, and participants blinded. Death is an objective outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	None lost to follow-up

Joensen 2008 (*Continued*)

Selective reporting (reporting bias)	Low risk	Adverse events not clearly stated as an outcome. However, standardised ascertainment and adverse events reported
Other bias	Low risk	None were identified.

Johnston 2016

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 199 adults (macrolide n = 97, placebo n = 102) **Age in years** (median (IQR)): macrolide: 39.1 (28.9 to 49.5), placebo: 36.2 (25.4 to 49.3) **Setting:** 30 secondary care hospitals and 1 primary centre
Interventions	**Indication**: acute asthma exacerbation **Type of macrolide**: azithromycin **Route**: per oral **Dose per day:** 500 mg **Duration of treatment:** 3 days **Total treatment dose:** 1500 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participant diary used **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	Study funded by the Efficacy and Mechanisms Evaluation programme of the Medical Research Council, in partnership with the National Institute for Health Research
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	ID numbers assigned sequentially.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo used.

Johnston 2016 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and clinicians blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear how many participants included in safety assessments, numbers not stated. However, authors report that 80% attended all follow-up visits
Selective reporting (reporting bias)	Low risk	Adverse events not clearly stated as an outcome. However, standardised ascertainment and adverse events are reported
Other bias	Low risk	None were identified.

Jun 2014

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 116 adults and elderly (macrolide n = 58, placebo n = 58) **Age in years** (mean ± SD): macrolide: 56.6 ± 10.3, placebo: 59 ± 11.6 **Setting**: secondary care
Interventions	**Indication**: subtotal gastrectomy **Type of macrolide**: erythromycin lactobionate **Route**: intravenous **Dose per day:** 125 mg **Duration of treatment:** 1 day **Total treatment dose:** 125 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: unclear **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	Study supported by Business of Globalization for Science and Technology, Seoul, Republic of South Korea
Notes	**Concomitant medication**: unclear

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation

Jun 2014 (*Continued*)

Allocation concealment (selection bias)	Low risk	Sequentially numbered, sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both groups received infusion of saline (+/- antibiotics).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and clinicians blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Unclear risk	Adverse events not stated as an outcome and unclear ascertainment. Some adverse events reported (nausea, vomiting)
Other bias	Low risk	None were identified.

Kaehler 2005

Methods	**Design**: randomised, placebo-controlled, parallel-group trial	
Participants	**Number assigned:** 327 adults and elderly (macrolide n = 165, placebo n = 162) **Age in years** (mean ± SD): macrolide: 62 ± 16, placebo: 63 ± 14 **Setting**: secondary care	
Interventions	**Indication**: coronary artery disease **Type of macrolide**: roxithromycin **Route**: per oral **Dose per day:** 300 mg **Duration of treatment:** 42 days **Total treatment dose:** 12,600 mg	
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: incomplete reporting, author contacted **Antimicrobial resistance**: not reported **Death**: data reported	
Funding sources	Study supported by Aventis Pharma GmbH, Germany.	
Notes	**Concomitant medication**: yes	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Kaehler 2005 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear if identical-appearing placebo was used
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No adverse events reported, death is an objective outcome.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	High risk	Adverse events not stated as an outcome, unclear ascertainment, incomplete reporting of adverse events
Other bias	Low risk	None were identified.

Kaiser 2001

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 269 adults and elderly (macrolide n = 133, placebo n = 132, excluded n = 4) **Age in years** (median (range)): 35 (18 to 93) **Setting**: secondary care
Interventions	**Indication**: common cold and acute rhinosinusitis **Type of macrolide**: azithromycin **Route**: per oral **Dose per day:** 500 mg **Duration of treatment:** 3 days **Total treatment dose:** 1500 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participant asked **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	Study supported by a grant from Pfizer AG, Switzerland.
Notes	**Concomitant medication**: yes

Kaiser 2001 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo used.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and clinicians blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout
Selective reporting (reporting bias)	Unclear risk	Adverse events not clearly stated as an outcome and unclear ascertainment. However, gastrointestinal adverse events reported
Other bias	Low risk	None were identified.

Kalliafas 1996

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 57 adults and elderly (macrolide n = 31, placebo n = 26) **Age in years** (mean (range)): macrolide: 54.7 (19 to 84), placebo: 57.8 (19 to 86) **Setting**: secondary care
Interventions	**Indication**: critically ill individuals assessed as needing nutrition support **Type of macrolide**: erythromycin lactobionate **Route**: intravenous **Dose per day:** 200 mg **Duration of treatment:** 1 day **Total treatment dose:** 200 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: not reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	None stated.

Kalliafas 1996 (*Continued*)

Notes	**Concomitant medication**: unclear	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number table used.
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Saline used as placebo.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No reporting of relevant outcomes. Participants and clinicians blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	High risk	Adverse events not stated as an outcome, unclear ascertainment, adverse events not reported
Other bias	Low risk	None were identified.

Karlsson 2009

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 247 elderly (macrolide n = 122, placebo n = 125) **Age in years** (median (IQR)): macrolide: 71 (67 to 74), placebo: 71 (67 to 76) **Setting**: secondary care
Interventions	**Indication**: abdominal aortic aneurysms **Type of macrolide**: azithromycin **Route**: per oral **Dose per day:** 600 mg x 1 daily for 3 days, then 600 mg once weekly for 15 weeks **Duration of treatment:** 16 weeks **Total treatment dose:** 10,800 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: data reported

Karlsson 2009 (*Continued*)

Funding sources	Study supported by County of Gävleborg Research and Development Center, Gore Swedish Research Foundation, Pfizer AB Sweden, Schyberg medical research fund, and Zoega medical research fund
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and clinicians blinded. Death is an objective outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 person in each group was lost to follow-up.
Selective reporting (reporting bias)	High risk	Adverse events not stated as an outcome, unclear ascertainment, and only non-specific adverse events are reported on
Other bias	Low risk	None were identified.

Kathariya 2014

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 100 adults (macrolide n = 50, placebo n = 50) **Age in years** (mean ± SD): macrolide: 39.3 ± 7.4, placebo: 37.4 ± 7.3 **Setting**: dental care
Interventions	**Indication**: chronic periodontitis **Type of macrolide**: clarithromycin **Route**: topical **Dose per day:** 0.5% gel once **Duration of treatment:** 1 day **Total treatment dose**: N/A

Kathariya 2014 (*Continued*)

Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participant asked **Adverse events**: states that no adverse events were observed or reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	Self funded project
Notes	**Concomitant medication**: unclear

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Allocation done by a study co-ordinator not involved in the clinical treatment/assessments
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and clinicians blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 participants lost to follow-up in placebo group: 1 migrated and 1 was unwilling to continue
Selective reporting (reporting bias)	Low risk	Adverse events not clearly stated as an outcome. However, standardised ascertainment and states that no adverse events were observed or reported
Other bias	Low risk	None were identified.

Kaul 2004

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 466 adults (macrolide n = 230, placebo n = 236) **Age in years** (mean ± SD): macrolide: 29.1 ± 7.8, placebo: 28.1 ± 7.7 **Setting**: urban slum area of Nairobi, Kenya

Kaul 2004 (*Continued*)

Interventions	**Indication**: prevention of sexually transmitted infections and HIV-1 infection **Type of macrolide**: azithromycin **Route**: per oral **Dose:** 1000 mg once a month **Duration of treatment:** 26 months (on average) **Total treatment dose:** 26,000 mg (on average)
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: data reported
Funding sources	Study supported by the Rockefeller Foundation, the European Commission, the Canada Research Chairs Program, Ontario HIV Treatment Network, the Canadian Institutes of Health Research, and the Canadian Infectious Disease Society. Authors acknowledge supplying company (Pfizer Inc)
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomisation
Allocation concealment (selection bias)	Low risk	Clinic staff assigned study numbers consecutively at enrolment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and clinicians blinded. Death is an objective outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	> 20% lost to follow-up after 2 years in the 2 groups, but adverse events as a source of dropout reported
Selective reporting (reporting bias)	Unclear risk	Adverse events not stated as an outcome, unclear ascertainment. However, adverse events considered to be possibly or likely related to treatments are reported on
Other bias	Low risk	None were identified.

Keenan 2018

Methods	**Design:** cluster-randomised placebo-controlled trial
Participants	**Number assigned:** 1533 communities (macrolide n = 767 communities (97,047 children), placebo n = 766 communities (93,191 children), excluded n = 20 communities, declined n = 1 community) **Age in months** (range): 1 to 59 **Setting:** communities in Malawi, Niger, and Tanzania
Interventions	**Indication:** mass distribution of antibiotics to reduce mortality **Type of macrolide:** azithromycin **Route:** per oral **Dose:** minimum 20 mg/kg once. Repeated twice yearly **Duration of treatment:** 4 years **Total treatment dose:** N/A
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper:** unclear **Ascertainment of adverse events:** parents asked **Adverse event:** data reported **Antimicrobial resistance:** not reported **Death:** data reported
Funding sources	Supported by a grant from the Bill & Melinda Gates Foundation. Pfizer provided both the azithromycin and the placebo
Notes	**Concomitant medication:** unclear

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants, observers, and investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	Reasons for exclusion of 20 communities explained, no communities were lost to follow-up after the initial census
Selective reporting (reporting bias)	High risk	Unclear if adverse events were stated as an outcome, standardised ascertainment. Re-

		port on very few adverse events in a large trial population
Other bias	Low risk	None were identified.

Kenyon 2001a

Methods	**Design**: randomised, placebo-controlled, factorial trial
Participants	**Number assigned:** 3180 adults (macrolide n = 1611, placebo n = 1569) **Age in years** (mean ± SD): macrolide: 26.5 ± 6.1, placebo: 26.7 ± 5.7 **Setting**: secondary care
Interventions	**Indication**: spontaneous preterm labour **Type of macrolide**: erythromycin **Route**: per oral **Dose per day:** 1000 mg **Duration of treatment:** 10 days (or until delivery) **Total treatment dose:** 10,000 mg (maximum)
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: incomplete reporting, author contacted **Antimicrobial resistance**: not reported **Death**: report on death of babies born to women with preterm labour
Funding sources	Study supported by the UK Medical Research Council. Authors acknowledge supplying company (Parke-Davis)
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Each woman was assigned a sequentially numbered study-drug pack
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, clinicians, and trial staff blinded.

Kenyon 2001a (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, similar across groups (note 50% completion at 7 years follow-up)
Selective reporting (reporting bias)	High risk	Adverse events not stated as an outcome, unclear ascertainment, and adverse events not reported
Other bias	Low risk	None were identified.

Kenyon 2001b

Methods	**Design**: randomised, placebo-controlled, factorial trial
Participants	**Number assigned:** 2422 adults (macrolide n = 1197, placebo n = 1225) **Age in years** (mean ± SD): macrolide: 27.5 ± 6.1, placebo: 27.9 ± 6.1 **Setting**: secondary care
Interventions	**Indication**: preterm pre-labour rupture of foetal membranes **Type of macrolide**: erythromycin **Route**: per oral **Dose per day:** 1000 mg **Duration of treatment:** 10 days (or until delivery) **Total treatment dose:** 10,000 (maximum)
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: incomplete reporting, author contacted **Antimicrobial resistance**: not reported **Death**: report on death of babies born to women with PPROM
Funding sources	Study supported by the UK Medical Research Council. Authors acknowledge supplying company (Parke-Davis)
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Each woman was assigned a sequentially numbered study-drug pack

Kenyon 2001b (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, clinicians, and trial staff blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, similar across groups (69% completion at 7 years follow-up)
Selective reporting (reporting bias)	High risk	Adverse events not stated as an outcome, unclear ascertainment. Most adverse events presented as a total, and it was not possible to determine how many there were in each of the 4 groups (erythromycin, erythromycin and co-amoxiclav, co-amoxiclav, or placebo)
Other bias	Low risk	None were identified.

Kim 2004

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 129 adults and elderly (macrolide n = 64, placebo n = 65) **Age in years** (mean ± SD): macrolide: 60.0 ± 10.0, placebo: 59.6 ± 10.1 **Setting**: secondary care
Interventions	**Indication**: acute coronary syndrome who underwent PCI **Type of macrolide**: azithromycin **Route**: per oral **Dose:** 500 mg daily for 3 days before and after PCI, followed by 500 mg/week **Duration of treatment:** 3 weeks **Total treatment dose:** 4000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: clinical examination (lab tests) **Adverse events**: incomplete reporting, author contacted **Antimicrobial resistance**: not reported **Death**: data reported
Funding sources	Not stated
Notes	**Concomitant medication**: yes
Risk of bias	

Kim 2004 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear if matching placebo used.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No adverse events reported, death is an objective outcome.
Incomplete outcome data (attrition bias) All outcomes	Low risk	12 months follow-up in 95% of participants.
Selective reporting (reporting bias)	High risk	Adverse events not stated clearly as an outcome, unclear ascertainment, adverse events not reported (only adverse cardiac outcomes are reported on)
Other bias	Low risk	None were identified.

King 1996

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 91 adults (macrolide n = 49, placebo n = 42) **Age in years** (mean ± SD): macrolide: 36.0 ± 13, placebo: 38.2 ± 14.5 **Setting**: primary care
Interventions	**Indication**: acute bronchitis **Type of macrolide**: erythromycin **Route**: per oral **Dose per day:** 1000 mg **Duration of treatment:** 10 days **Total treatment dose:** 10,000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participant asked **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: not reported

King 1996 (*Continued*)

Funding sources	Study supported by the Division of Primary Care of the Agency for Health Care Policy and Research. Authors acknowledge supplying company (Parke-Davis, Morris Plane, New Jersey)
Notes	**Concomitant medication**: yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and clinicians.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	> 20% lost to follow-up, unclear from which groups.
Selective reporting (reporting bias)	Low risk	Adverse events were stated clearly as an outcome. Standardised ascertainment and adverse events presented
Other bias	Low risk	None were reported.

Klebanoff 1995

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 938 women (macrolide n = 469, placebo n = 469) **Age in years**: N/A **Setting**: secondary care
Interventions	**Indication**: pregnant women colonised with group B streptococci **Type of macrolide**: erythromycin base **Route**: per oral **Dose per day:** 999 mg **Duration of treatment:** 10 weeks or until the end of the 35th week of pregnancy, whichever came first **Total treatment dose:** 69,930 mg (maximum)

Klebanoff 1995 (*Continued*)

Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: spontaneously **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: report on death in babies of mothers treated
Funding sources	Study supported by the National Institutes of Health. Authors acknowledge supplying company (The Upjohn Company)
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Pregnant women and clinicians blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 1% of women not included in reporting of adverse events
Selective reporting (reporting bias)	Unclear risk	Adverse events not stated clearly as an outcome. Standardised ascertainment. However, adverse events not presented clearly
Other bias	Low risk	None were identified.

Kneyber 2008

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 71 children (macrolide n = 32, placebo n = 39) **Age in months** (mean (IQR)): macrolide: 3.0 (1.0 to 4.0), placebo: 3.6 (1.0 to 6.0) **Setting**: secondary care
Interventions	**Indication**: respiratory syncytial virus lower respiratory tract disease **Type of macrolide**: azithromycin

Kneyber 2008 (*Continued*)

	Route: per oral **Dose per day:** 10 mg/kg **Duration of treatment:** 3 days **Total treatment dose:** 276 mg (mean weight in macrolide group used)
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: not reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	None stated.
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No relevant outcomes reported. Children, parents, and clinicians blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 child in placebo group dropped out.
Selective reporting (reporting bias)	Unclear risk	Adverse events not stated as an outcome, unclear ascertainment, and no reporting of adverse events
Other bias	Low risk	None were identified.

Kostadima 2004

Methods	**Design**: randomised, placebo-controlled, 3-armed trial
Participants	**Number assigned:** 75 adults (macrolide (twice a day) n = 25, macrolide (3 times a day) n = 25, placebo n = 25) **Age in years** (mean ± SD): macrolide (twice a day): 48 ± 16, macrolide (3 times a day): 42 ± 12, placebo: 41 ± 16

Kostadima 2004 (*Continued*)

	Setting: secondary care
Interventions	**Indication**: asthma **Type of macrolide**: clarithromycin **Route**: per oral **Dose per day**: arm 1: 500 mg, arm 2: 750 mg **Duration of treatment:** 8 weeks **Total treatment dose**: arm 1: 28,000 mg, arm 2: 42,000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: clinical examination (lab tests) **Adverse events**: incomplete reporting, author contacted **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	None stated.
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Low risk	Allocation done by an independent nurse.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	States that the placebo tablets were indistinguishable from the clarithromycin tablets. However, there are 2 active groups with 2 or 3 doses/day, unclear how many placebo tablets/day
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No relevant outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, reasons given
Selective reporting (reporting bias)	High risk	Adverse events not stated clearly as an outcome. States that laboratory assessment was done, however values/changes not reported. Incomplete reporting of adverse events
Other bias	Low risk	None were identified.

Kraft 2002

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 52 adults (macrolide n = 26, placebo n = 26) **Age in years** (mean ± SD): 33.4 ± 1.2 **Setting**: unclear
Interventions	**Indication**: asthma **Type of macrolide**: clarithromycin **Route**: per oral **Dose per day:** 1000 mg **Duration of treatment:** 6 weeks **Total treatment dose:** 42,000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events reported**: incomplete reporting, author contacted **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	Study supported by the American Lung Association Asthma Research Center Grant and Abbott Laboratories
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear if placebo was identical appearing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No relevant outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts not reported.
Selective reporting (reporting bias)	High risk	Adverse events not reported as an outcome, unclear ascertainment, and incomplete reporting of adverse events
Other bias	Low risk	None were identified.

Kvien 2004

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 152 adults (macrolide n = 81, placebo n = 71) **Age in years** (mean ± SD): macrolide: 33.0 ± 9.8, placebo: 34.7 ± 8.9 **Setting**: secondary care
Interventions	**Indication**: reactive arthritis **Type of macrolide**: azithromycin **Route**: per oral **Dose:** 1000 mg per week (starting after a single 1 g dose of azithromycin) **Duration of treatment:** 12 weeks **Total treatment dose:** 13,000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participants asked + clinical examination/lab tests **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	Study supported by Pfizer.
Notes	**Concomitant medication:** yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear if placebo was identical appearing
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear if participants and clinicians were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropout was 30% and 34% in macrolide and placebo groups, respectively. However, reasons reported
Selective reporting (reporting bias)	Low risk	Adverse events not clearly stated as an outcome. However, standardised ascertainment and adverse events reported

Kvien 2004 (*Continued*)

Other bias	Low risk	None were identified.

Lanza 1998

Methods	**Design**: randomised, placebo-controlled, 4-armed trial
Participants	**Number assigned:** 89 adults and elderly (macrolide n = 60, placebo n = 29) **Age in years** (mean (range)): macrolide: 45.0 (28 to 76), placebo: 49.9 (24 to 78) **Setting:** "47-Center U.S study"
Interventions	**Indication**: duodenal ulcer **Type of macrolide**: clarithromycin **Route**: per oral **Dose per day:** 1500 mg **Duration of treatment:** 14 days **Total treatment dose:** 21,000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: participant asked + clinical examination **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	Study sponsored by Glaxo Wellcome Inc.
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear if placebo was identical appearing
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear if participants and clinicians were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Adverse events reported for all randomised participants.

Lanza 1998 (*Continued*)

Selective reporting (reporting bias)	Low risk	Adverse events stated as an outcome, standardised ascertainment, and adverse events reported
Other bias	Unclear risk	Uneven distribution of number of participants in the 2 arms (2:1 allocation)

Leowattana 2001

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 84 adults and elderly (macrolide n = 43, placebo n = 41) **Age in years** (mean ± SD): macrolide: 62.9 ± 9.6, placebo: 60.4 ± 12.6 **Setting**: secondary care
Interventions	**Indication**: secondary prevention of acute coronary syndrome **Type of macrolide**: roxithromycin **Route**: per oral **Dose per day:** 300 mg **Duration of treatment:** 30 days **Total treatment dose:** 9000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: not reported **Antimicrobial resistance**: not reported **Death**: data reported
Funding sources	Study supported by Siriraj Grant for Research Development and Medical Education. Authors acknowledge supplying company (Hoechst Marion Roussel)
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Sequentially numbered, sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identically appearing placebo

Leowattana 2001 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and clinicians blinded. Death is an objective outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropout
Selective reporting (reporting bias)	High risk	Adverse events not stated as an outcome, unclear ascertainment, and no reporting of adverse events
Other bias	Low risk	None were identified.

Lildholdt 2003

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 124 children and adults (macrolide n = 53, placebo n = 57, excluded n = 10) **Age in years** (mean (range)): 23.4 (6 to 58) **Setting**: secondary care
Interventions	**Indication**: recurrent acute tonsillitis **Type of macrolide**: azithromycin **Route**: per oral **Dose:** 500 mg/week **Duration of treatment:** 26 weeks **Total treatment dose:** 13,000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: data reported **Antimicrobial resistance**: data reported **Death**: not reported
Funding sources	Study supported by Pfizer APS, Denmark.
Notes	**Concomitant medication**: unclear

Risk of bias

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

Lildholdt 2003 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear if placebo was identical appearing
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear if participants and clinicians were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, unclear in which group
Selective reporting (reporting bias)	Unclear risk	Adverse events not stated as an outcome and unclear ascertainment. However, adverse events are reported
Other bias	Low risk	None were identified.

Malhotra-Kumar 2007a

Methods	**Design**: randomised, placebo-controlled, 3-armed trial
Participants	**Number assigned**: 112 adults (macrolide n = 74, placebo n = 38) **Age in years**: (mean (range)): macrolide: 24 (19 to 56), placebo: 24 (18 to 57) **Setting:** volunteers were selected from the University of Antwerp, Belgium
Interventions	**Indication**: pharyngeal carriage of macrolide-resistant streptococci in healthy volunteers **Type of macrolide**: azithromycin **Route**: per oral **Dose per day:** 500 mg **Duration of treatment:** 3 days **Total treatment dose:** 1500 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes (only AMR) **Adverse events ascertainment**: clinical examination (oral swabs) **Adverse events**: incomplete reporting, author contacted **Antimicrobial resistance**: data reported **Death**: not reported
Funding sources	Study supported by Abbott Laboratories.
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Malhotra-Kumar 2007a (*Continued*)

Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Volunteers allocated by an administrator with no further role in the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	2 placebo groups (1 for each of the macrolide arms) were used to ensure complete blinding (Malhotra-Kumar 2007b).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Volunteers and trial staff blinded. Objective outcomes (data on AMR)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, similar across groups
Selective reporting (reporting bias)	Unclear risk	Standardised ascertainment and subsequent carriage of resistant bacteria reported. However, no reporting on other adverse events
Other bias	Low risk	None were identified.

Malhotra-Kumar 2007b

Methods	**Design**: randomised, placebo-controlled, 3-armed trial
Participants	**Number assigned:** 112 adults (macrolide n = 74, placebo n = 38) **Age in years** (mean (range)): macrolide: 24 (19 to 58), placebo: 24 (18 to 57) **Setting:** volunteers were selected from the University of Antwerp, Belgium
Interventions	**Indication**: pharyngeal carriage of macrolide-resistant streptococci in healthy volunteers **Type of macrolide**: clarithromycin **Route**: per oral **Dose per day:** 1000 mg **Duration of treatment:** 7 days **Total treatment dose:** 7000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes (only AMR) **Adverse events ascertainment**: clinical examination (oral swabs) **Adverse events**: incomplete reporting, author contacted **Antimicrobial resistance**: data reported **Death**: not reported
Funding sources	Study supported by Abbott Laboratories.

Malhotra-Kumar 2007b (*Continued*)

Notes	**Concomitant medication**: yes	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Volunteers allocated by an administrator with no further role in the study
Blinding of participants and personnel (performance bias) All outcomes	Low risk	2 placebo groups (1 for each of the macrolide arms) were used to ensure complete blinding (Malhotra-Kumar 2007a).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Volunteers and trial staff blinded. Objective outcomes (data on AMR)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, similar across groups
Selective reporting (reporting bias)	Unclear risk	Standardised ascertainment and subsequent carriage of resistant bacteria reported. However, no reporting on other adverse events
Other bias	Low risk	None were identified.

Mandal 1984

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 80 children and adults (macrolide n = 35, placebo n = 37, excluded n = 8) **Age in years** (mean ± SD): macrolide: 31.93 ± 16.59, placebo: 31.18 ± 21.15 **Setting**: secondary care
Interventions	**Indication**: *Campylobacter jejuni* infection **Type of macrolide**: erythromycin **Route**: per oral **Dose per day:** 50 mg/kg/child, 1000 mg/adult **Duration of treatment:** 5 days **Total treatment dose:** 5000 mg (maximum)

Mandal 1984 (*Continued*)

Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participant asked **Adverse events**: authors state that "no incidence of adverse drug reaction was recorded". Nausea, vomiting, and abdominal pain are reported as a primary outcome and are not considered to be adverse events **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	None stated. Authors acknowledge supplying company (Abbott Laboratories)
Notes	**Concomitant medication**: unclear

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo used.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and clinicians blinded, none experienced adverse events
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, unclear which group
Selective reporting (reporting bias)	Low risk	Adverse events not clearly stated as an outcome. However, standardised ascertainment and authors state that no adverse events were noted
Other bias	Low risk	None were identified.

Mandhane 2017

Methods	**Design:** randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 300 children (macrolide n = 150, placebo n = 150) **Age in months** (mean ± SD): macrolide: 34.8 ± 13.6, placebo: 30.5 ± 13.9 **Setting:** secondary care

Interventions	**Indication:** wheezing **Type of macrolide:** azithromycin **Route:** per oral **Dose per day:** 10 mg/kg for 1 day, then 5 mg/kg for 4 days **Duration of treatment:** 5 days **Total treatment dose:** N/A
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper:** unclear **Ascertainment of adverse events:** participant diary **Adverse event:** data reported **Antimicrobial resistance:** not reported **Death:** not reported
Funding sources	Supported by The Lung Association - Alberta and Northwest Territories - TLA-IKON Pediatric Team Grant
Notes	**Concomitant medication:** yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated stratified block randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of children/parents and study investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	Information on adverse events provided for 93% of participants in each group, reasons for dropouts given
Selective reporting (reporting bias)	Low risk	Unclear if adverse events were stated as an outcome and unclear ascertainment. However, protocol clearly states times for adverse event monitoring, and adverse events are reported
Other bias	Low risk	None were identified.

Martande 2015

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 70 adults (macrolide n = 35, placebo n = 35) **Age in years** (range): 20 to 60 **Setting**: dental care
Interventions	**Indication**: chronic periodontitis **Type of macrolide**: roxithromycin **Route**: per oral **Dose per day:** 300 mg **Duration of treatment:** 5 days **Total treatment dose:** 1500 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participant asked **Adverse events**: incomplete reporting, author contacted **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	None stated. Authors acknowledge supplying company (Micro Labs)
Notes	**Concomitant medication**: unclear

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Allocation not described in detail.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No relevant outcomes reported. Participants and clinicians blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, similar across groups
Selective reporting (reporting bias)	High risk	Adverse events not clearly stated as an outcome. Standardised ascertainment. However, incomplete reporting of adverse events
Other bias	Low risk	None were identified.

Martande 2016

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 70 adults (macrolide n = 35, placebo n = 35) **Age in years** (mean ± SD): macrolide: 32.6 ± 5.4, placebo: 33.3 ± 7.3 **Setting**: dental care
Interventions	**Indication**: *Aggregatibacter actinomycetemcomitans*-associated periodontitis **Type of macrolide**: azithromycin **Route**: per oral **Dose per day:** 500 mg **Duration of treatment:** 3 days **Total treatment dose:** 1500 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participant asked **Adverse events**: authors state that "(n)one of the individuals reported any adverse effect due to the medications" **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	None stated. Authors thank supplying companies (Micro Labs, Government College of Pharmacy, Bangalore, India)
Notes	**Concomitant medication**: unclear

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No relevant outcomes reported. Clinicians and participants blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Low risk	Adverse events not clearly stated as an outcome. However, standardised ascertainment and authors state that no adverse events were identified

Martande 2016 (*Continued*)

Other bias	Low risk	None were identified.

Martin 1997

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 414 children and adults (macrolide n = 205, placebo n = 209) **Age in years** (mean ± SD): macrolide: 21.5 ± 4.2, placebo: 21.1 ± 4.3 **Setting**: secondary care
Interventions	**Indication**: pregnant women infected with *Chlamydia trachomatis* **Type of macrolide**: erythromycin base **Route**: per oral **Dose per day:** 999 mg **Duration of treatment**: N/A **Total treatment dose**: N/A
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participant asked **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: data reported on death in babies of treated mothers
Funding sources	Study supported by the National Institute of Child Health and Human Development and the National Institute of Allergy and Infectious Diseases. Authors acknowledge supplying company (The Upjohn Company)
Notes	**Concomitant medication**: unclear

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Pregnant women and clinicians blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, similar across groups

Martin 1997 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Adverse events not clearly stated as an outcome. Standardised ascertainment. However, adverse events not presented clearly
Other bias	Low risk	None were identified.

Mathai 2007

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 50 children (macrolide n = 27, placebo n = 23) **Age in weeks** (mean): macrolide: 35.5, placebo: 37.2 **Setting**: secondary care
Interventions	**Indication**: gastric emptying of low-birthweight babies **Type of macrolide**: erythromycin **Route**: per oral **Dose per day:** 6 mg/kg **Duration of treatment:** 4 days **Total treatment dose:** 47 mg (used mean birthweight in erythromycin group)
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: clinician assessment + clinical examination **Adverse events**: authors state that "no side effects of the drug were seen" **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	Study supported by the office of Director General Armed Forces Medical Services
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear if placebo was identical appearing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No relevant outcomes reported.

Mathai 2007 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Low risk	Adverse events not clearly stated as an outcome. However, standardised ascertainment, and authors state that no adverse events were identified
Other bias	Unclear risk	Infants in the erythromycin group had lower gestational age and birthweight than those in the placebo group

McCallum 2013

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 97 children (macrolide n = 50, placebo n = 47) **Age in months** (median (IQR)): macrolide: 5.3 (3 to 9.4), placebo: 5 (3 to 8.5) **Setting**: secondary care
Interventions	**Indication:** bronchiolitis **Type of macrolide**: azithromycin **Route**: per oral **Dose per day:** 30 mg/kg **Duration of treatment:** 1 day **Total treatment dose**: N/A
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: clinician assessment **Adverse events**: authors state that "there were no adverse events or serious adverse events" **Antimicrobial resistance**: not reported **Death**: no deaths reported
Funding sources	Funded by the National Health and Medical Research Council, the Channel 7 Foundation, and the Financial Markets Foundation for Children
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stratified block randomisation
Allocation concealment (selection bias)	Low risk	Sequentially numbered, identical drug containers

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No relevant outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Low risk	Adverse events stated as a primary outcome, and adverse events monitored by study staff every 12 hours until discharge
Other bias	Low risk	None were identified.

McCallum 2015

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 219 children (macrolide n = 106, placebo n = 113) **Age in months** (median (IQR)): macrolide: 5.7 (3 to 10), placebo: 5.6 (3 to 9) **Setting**: secondary care
Interventions	**Indication:** bronchiolitis **Type of macrolide**: azithromycin **Route**: per oral **Dose:** 30 mg/kg once weekly **Duration of treatment:** 3 weeks **Total treatment dose**: N/A
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: participants asked + clinical examination (swabs) **Adverse events**: data reported **Antimicrobial resistance**: data reported **Death**: not reported
Funding sources	Study supported by the National Health and Medical Research Council and by a Centre for Research Excellence in Lung Health of Aboriginal and Torres Strait Islander Children
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

McCallum 2015 (*Continued*)

Random sequence generation (selection bias)	Low risk	Computer-generated randomisation.
Allocation concealment (selection bias)	Low risk	Sealed, opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Children, parents, and clinicians blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	6% and 3% did not attend the day 21 follow-up interview in the macrolide and placebo groups, respectvely
Selective reporting (reporting bias)	Low risk	Adverse events stated as an outcome, standardised ascertainment, and adverse events reported
Other bias	Low risk	None were identified.

McCormack 1987

Methods	**Design**: randomised, placebo-controlled, 3-armed trial
Participants	**Number assigned:** 825 women (macrolide arm 1, n = 174; macrolide arm 2, n = 224; placebo, n = 427) **Age in years**: N/A **Setting**: secondary care
Interventions	**Indication**: pregnant women harbouring genital *Ureaplasma urealyticum* or *Mycoplasma hominis*, or both **Type of macrolide**: arm 1: erythromycin estolate, arm 2: erythromycin stearate **Route**: per oral **Dose per day:** 1000 mg (both arms) **Duration of treatment:** 6 weeks (both arms) **Total treatment dose:** 42,000 mg (both arms)
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participant asked + clinical examination/lab tests **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	Study supported by the National Institute of Child Health and Human Development

McCormack 1987 (*Continued*)

Notes	**Concomitant medication**: unclear **Note**: type of erythromycin used is changed roughly halfway through the study period (stearate to estolate) due to the reporting of many adverse events

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Pregnant women and clinicians blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Large dropout in all 3 groups - only about 40% of women completed the study. However, adverse events presented for 91% of participants
Selective reporting (reporting bias)	Low risk	Adverse events not clearly stated as an outcome. Standardised ascertainment and adverse events reported
Other bias	Low risk	None were identified.

McDonald 1985

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 114 adults (macrolide n = N/A, placebo n = N/A) **Age in years**: N/A **Setting**: primary care
Interventions	**Indication**: non-streptococcal pharyngitis **Type of macrolide**: erythromycin **Route**: per oral **Dose per day:** 1000 mg **Duration of treatment:** 7 days **Total treatment dose:** 7000 mg

McDonald 1985 (*Continued*)

Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participant diary used **Adverse events**: incomplete reporting, however no contact details for author **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	Study supported by the National Institute of Allergy and Infectious Diseases
Notes	**Concomitant medication**: unclear

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No relevant outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Reasons given for 16 dropouts, unclear in what groups. Unclear how many participants are actually included in the final analysis
Selective reporting (reporting bias)	Unclear risk	Adverse events not clearly stated as an outcome. Standardised ascertainment, however incomplete reporting of adverse events
Other bias	Low risk	None were identified.

McGregor 1986

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 58 women (macrolide n = 29, placebo n = 29) **Age in years**: N/A **Setting**: secondary care

McGregor 1986 (*Continued*)

Interventions	**Indication**: idiopathic preterm labour **Type of macrolide**: erythromycin base **Route**: per oral **Dose per day:** 999 mg **Duration of treatment:** 7 days **Total treatment dose:** 6993 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	Study supported by The Upjohn Company, Kalamazoo, Michigan.
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation.
Allocation concealment (selection bias)	Low risk	Sequentially numbered, identical drug bottles.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Active drug and placebo supplied by the same company.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Pregnant women and staff blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant lost to follow-up in each group.
Selective reporting (reporting bias)	High risk	Adverse events not stated as an outcome, unclear ascertainment, and unclear reporting of adverse events
Other bias	Low risk	None were identified.

McGregor 1990

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 235 children and adults (macrolide n = 119, placebo n = 110, excluded n = 6) **Age in years** (mean (range)): macrolide: 23.0 (13 to 37), placebo: 23.2 (16 to 34) **Setting**: secondary care
Interventions	**Indication**: impact on cervicovaginal microflora and pregnancy outcomes **Type of macrolide**: erythromycin base **Route**: per oral **Dose per day:** 999 mg **Duration of treatment:** 7 days **Total treatment dose:** 6993 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participant asked **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death:** only intrauterine foetal death is reported on.
Funding sources	Funding not stated. The Upjohn Company prepared the treatments
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Pregnant women and staff blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	6 participants lost to follow-up (3%), unclear in which group
Selective reporting (reporting bias)	Low risk	Adverse events not clearly stated as an outcome. However, standardised ascertainment and adverse events reported

McGregor 1990 (*Continued*)

Other bias	Low risk	None were identified.

McGregor 1991

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 65 adults (macrolide n = 28, placebo n = 27, excluded n = 10) **Age in years** (mean (range)): macrolide: 25.4 (18 to 41), placebo: 24.2 (18 to 38) **Setting**: secondary care
Interventions	**Indication**: preterm premature rupture of the membranes **Type of macrolide**: erythromycin base **Route**: per oral **Dose per day:** 999 mg **Duration of treatment**: until active labour or for maximum 7 days **Total treatment dose:** 6993 mg (maximum)
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death:** only foetal or neonatal death reported on.
Funding sources	Funding not stated. The Upjohn Company prepared the treatments
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Pregnant women and staff blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, reasons stated

McGregor 1991 (*Continued*)

Selective reporting (reporting bias)	Low risk	Adverse events not clearly stated as an outcome and unclear ascertainment. However, adverse events are reported
Other bias	Low risk	None were identified.

Memis 2002

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 40 adults and elderly (macrolide n = 20, placebo n = 20) **Age in years** (mean (SD)): macrolide: 47 (22), placebo: 49 (16) **Setting**: secondary care
Interventions	**Indication**: effect of preoperative erythromycin on gastric acidity and volume **Type of macrolide**: erythromycin **Route**: per oral **Dose per day:** 200 mg **Duration of treatment:** 1 day **Total treatment dose:** 200 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participant asked **Adverse events**: authors state that "there were no side-effects observed in any of the groups" **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	None stated.
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study drugs prepared by the same pharmacy.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and clinicians blinded. No relevant outcomes reported

Memis 2002 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Low risk	Adverse events not clearly stated as an outcome. Standardised ascertainment for 24 hours after surgery, and authors report that no adverse events were observed
Other bias	Low risk	None were identified.

Mercer 1992

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 220 adults (macrolide n = 106, placebo n = 114) **Age in years** (mean (SD)): macrolide: 23.7 (5.7), placebo: 24.1 (5.6) **Setting**: secondary care
Interventions	**Indication**: preterm premature rupture of the membranes **Type of macrolide**: erythromycin base **Route**: per oral **Dose per day:** 999 mg **Duration of treatment**: N/A (until delivery) **Total treatment dose**: N/A
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death:** only death in babies of treated mothers reported on.
Funding sources	None stated. Boots Pharmaceuticals supplied the treatments.
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo

Mercer 1992 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigators, participant caregivers, and participants were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	3 participants lost to follow-up (1%).
Selective reporting (reporting bias)	Unclear risk	Adverse events not stated as an outcome, unclear ascertainment, and only gastrointestinal discomfort mentioned as a possible adverse event
Other bias	Low risk	None were identified.

Moller 1990

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 147 children (macrolide n = 69, placebo n = 72, excluded n = 6) **Age in years** (range): 1 to 15 **Setting**: secondary care
Interventions	**Indication:** otitis media with effusion **Type of macrolide**: erythromycin ethylsuccinate **Route**: per oral **Dose per day:** 50 mg/kg **Duration of treatment:** 14 days **Total treatment dose**: N/A
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events reported**: stated that no adverse events were reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	None stated.
Notes	**Concomitant medication**: unclear

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation not described in detail.

Moller 1990 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear if placebo was identical appearing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No relevant outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	4% dropout, unclear in which group
Selective reporting (reporting bias)	Unclear risk	Unclear if adverse events were stated as an outcome, unclear ascertainment. Authors state that no adverse events were reported
Other bias	Low risk	None were identified.

Narchi 1993

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 50 adults (macrolide n = 25, placebo n = 25) **Age in years** (mean ± SD): macrolide: 33 ± 5, placebo: 36 ± 9 **Setting**: secondary care
Interventions	**Indication**: gastric acidity and volume in people scheduled for diagnostic laparoscopy **Type of macrolide**: erythromycin lactobionate **Route**: intravenous **Dose per day:** 500 mg **Duration of treatment:** 1 day **Total treatment dose:** 500 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participant asked **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	None stated.
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.

Narchi 1993 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo appears similar.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and clinicians blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, similar across groups
Selective reporting (reporting bias)	Low risk	Adverse events not clearly stated as an outcome. However, standardised ascertainment and adverse events reported
Other bias	Low risk	None were identified.

Neumann 2001

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 1010 adults and elderly (macrolide n = 506, placebo n = 504) **Age in years** (mean ± SD): macrolide: 64.6 ± 11.4, placebo: 64.3 ± 11.4 **Setting**: secondary care
Interventions	**Indication**: restenosis after coronary stent replacement **Type of macrolide**: roxithromycin **Route**: per oral **Dose per day:** 300 mg **Duration of treatment:** 28 days **Total treatment dose:** 8400 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: not reported **Antimicrobial resistance**: not reported **Death**: data reported
Funding sources	Study supported by funds from the Medical Faculty of Technische Universität München. Aventis provided the study medication and funded participant insurance and cost of reagents for titre assays
Notes	**Concomitant medication**: yes
Risk of bias	

Neumann 2001 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and clinicians blinded. Death is an objective outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout
Selective reporting (reporting bias)	High risk	Adverse events not stated as an outcome, unclear ascertainment, and adverse events not presented
Other bias	Low risk	None were identified.

Ng 2007

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 182 children (macrolide n = 91, placebo n = 91) **Age in weeks** (median (range)): macrolide: 28.6 (27.3 to 30.5), placebo: 28.9 (26.6 to 30.6) **Setting**: secondary care
Interventions	**Indication**: parenteral nutrition-associated cholestasis in preterm, very low-birthweight infants **Type of macrolide**: erythromycin ethylsuccinate **Route**: per oral **Dose per day:** 50 mg/kg **Duration of treatment:** 14 days **Total treatment dose:** 767 mg (mean birthweight in macrolide group used)
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: clinician assessment + clinical examination (ECG, lab tests) **Adverse events**: authors state that "no serious adverse effects were associated with erythromycin treatment", data on complications reported **Antimicrobial resistance**: not reported **Death**: data reported

Ng 2007 (*Continued*)

Funding sources	Supported by Department of Pediatrics, Chinese University of Hong Kong, Research Grant Council of the Government of Hong Kong SAR and by the HM Lui Memorial Fund
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Both active drug and normal saline (placebo) were mixed thoroughly into the milk feeds
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Parents and clinicians blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Unclear risk	Adverse events stated as an outcome. Standardised ascertainment. However, only complications were reported
Other bias	Low risk	None were identified.

Nuntnarumit 2006

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 46 children (macrolide n = 23, placebo n = 23) **Age in weeks** (median (range)): macrolide: 30 (29 to 32), placebo: 29 (28 to 31) **Setting**: secondary care
Interventions	**Indication:** feeding intolerance in preterm infants **Type of macrolide**: erythromycin ethylsuccinate **Route**: per oral **Dose per day:** 40 mg/kg/day for 2 days, then 16 mg/kg/day for 5 days **Duration of treatment:** 7 days **Total treatment dose:** 176 mg (median birthweight in macrolide group used)

Nuntnarumit 2006 (*Continued*)

Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: clinician assessment + clinical examination (ECG, lab tests) **Adverse events**: authors state that "(n)o significant adverse effects related to erythromycin were observed" **Antimicrobial resistance**: not reported **Death**: data reported
Funding sources	Supported by Ramathibodi Fund. Authors acknowledge supplying company (Siam Pharmaceutical Ltd)
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Stratified randomisation (by age)
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Parents, participant-care team, and assessors blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Unclear risk	Adverse events stated as an outcome, standardised ascertainment, however only complications reported
Other bias	Low risk	None were identified.

O'Connor 2003

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 7747 adults and elderly (macrolide n = 3879, placebo n = 3868) **Age in years** (mean): 62 **Setting**: clinical practices in North America, Europe, Argentina, and India

O'Connor 2003 (*Continued*)

Interventions	**Indication**: coronary artery disease and known *Chlamydia pneumoniae* exposure **Type of macrolide**: azithromycin **Route**: per oral **Dose per day:** 600 mg/day for 3 days during week 1, then 600 mg/week during weeks 2 to 12 **Duration of treatment:** 84 days **Total treatment dose:** 8400 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participants asked + clinical examination/lab tests **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	Study was sponsored by Pfizer Global Research and Development
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomisation
Allocation concealment (selection bias)	Low risk	Identical drug containers
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, investigators, clinical site monitors, and the sponsor project team were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout. Adverse events resulting in discontinuation are reported
Selective reporting (reporting bias)	Unclear risk	Adverse events not clearly stated as an outcome, standardised ascertainment. Authors only report on gastrointestinal complaints, not lab tests. Adverse events are reported as %, not numbers, assume that this is out of the total analysed
Other bias	Low risk	None were identified.

Oei 2001

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 50 children (macrolide n = 25, placebo n = 25) **Gestational age in weeks** (mean (range)): macrolide: 28.6 (24 to 32), placebo: 29.3 (27 to 32) **Setting**: secondary care
Interventions	**Indication:** feeding intolerance in preterm infants **Type of macrolide**: erythromycin ethylsuccinate **Route**: per oral **Dose per day:** 10 mg/day **Duration of treatment:** 10 days **Total treatment dose:** 123 mg (mean birthweight in macrolide group used)
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: authors state that no adverse events were noted during the trial. Vomiting is reported as a primary outcome and is not considered to be an adverse event **Antimicrobial resistance**: not reported **Death**: data reported
Funding sources	None stated. Authors acknowledge supplying company (Abbott Australasia Ltd)
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Parents and clinicians blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, similar across groups
Selective reporting (reporting bias)	Unclear risk	Adverse events not stated as an outcome, unclear ascertainment. However, authors state that no adverse events were noted

Oei 2001 (*Continued*)

Other bias	Low risk	None were identified.

Ogrendik 2007

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned**: 81 adults (macrolide n = 41, placebo n = 40) **Age in years** (mean ± SD): macrolide: 42 ± 9, placebo: 38 ± 10 **Setting**: secondary care
Interventions	**Indication**: rheumatoid arthritis **Type of macrolide**: clarithromycin **Route**: per oral **Dose per day:** 500 mg **Duration of treatment:** 6 months **Total treatment dose:** 90,000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participant asked **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: reported that no deaths occurred
Funding sources	Supported by Sanovel, Istanbul
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Central computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and clinicians blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, most discontinued because of lack of efficacy of treatments

Ogrendik 2007 (*Continued*)

Selective reporting (reporting bias)	Low risk	Adverse events not clearly stated as an outcome. Standardised ascertainment, only most frequently reported adverse events reported (5% cut-off)
Other bias	Low risk	None were identified.

Ogrendik 2011

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 100 adults (macrolide n = 50, placebo n = 50) **Age in years** (mean ± SD): macrolide: 49 ± 7, placebo: 45 ± 8 **Setting**: secondary care
Interventions	**Indication**: rheumatoid arthritis **Type of macrolide**: roxithromycin **Route**: per oral **Dose per day:** 300 mg **Duration of treatment:** 6 months **Total treatment dose:** 54,000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participant asked **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: reported that no deaths occurred
Funding sources	None stated.
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Central computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias)	Low risk	Participants and clinicians blinded.

Ogrendik 2011 (*Continued*)

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, most discontinued because of lack of efficacy of treatments
Selective reporting (reporting bias)	Low risk	Unclear if adverse events were stated as an outcome. Standardised ascertainment, only most frequently reported adverse events reported (5% cut-off)
Other bias	Low risk	None were identified.

Oldfield 1998

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 182 adults (macrolide n = 89, placebo n = 93) **Age in years** (mean (range)): macrolide: 41.1 (24 to 63), placebo: 38.2 (24 to 61) **Setting**: unclear
Interventions	**Indication**: prevention of *Mycobacterium avium* complex infection in people with AIDS **Type of macrolide**: azithromycin **Route**: per oral **Dose:** 1200 mg once a week **Duration of treatment:** 400 days (mean duration of therapy in macrolide group) **Total treatment dose:** 68,571 mg (used mean days in macrolide group)
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participant asked + clinical examination (biaural audiograms) **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: data reported
Funding sources	Supported by Pfizer and the Military Medical Consortium for Applied Retroviral Research
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	Allocation not described in detail.

Oldfield 1998 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and staff
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unclear how many are analysed for various outcomes. Reported n = 90 in adverse events section, although only 89 people were randomised
Selective reporting (reporting bias)	Low risk	Adverse events not clearly stated as an outcome. However, standardised ascertainment and reporting of adverse events
Other bias	Low risk	None were identified.

Ozdemir 2011

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 74 children (macrolide n = 37, placebo, n = 37) **Gestational age in years** (mean ± SD): macrolide: 27.4 ± 1.3, placebo: 27.3 ± 1.8 **Setting**: secondary care
Interventions	**Indication**: prevention of bronchopulmonary dysplasia in *Ureaplasma urealyticum*-positive preterm infants **Type of macrolide**: clarithromycin **Route**: intravenous **Dose per day:** 20 mg/kg **Duration of treatment:** 10 days **Total treatment dose:** 198 mg (mean birthweight in macrolide group used)
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: incomplete reporting, author contacted. Author reply: "We didn't see any adverse events in both groups" **Antimicrobial resistance**: not reported **Death**: data reported
Funding sources	None stated.
Notes	**Concomitant medication**: yes
Risk of bias	

Ozdemir 2011 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear if placebo was identical appearing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only objective outcomes (death) reported on.
Incomplete outcome data (attrition bias) All outcomes	Low risk	None lost to follow-up
Selective reporting (reporting bias)	High risk	Adverse events not stated as an outcome, unclear ascertainment, and incomplete reporting of adverse events
Other bias	Low risk	None were identified.

Paknejad 2010

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 40 adults (macrolide n = 20, placebo n = 20) **Age in years** (min to max): 18.0 to 46.7 **Setting**: dental care
Interventions	**Indication**: chronic periodontitis **Type of macrolide**: azithromycin **Route**: per oral **Dose per day:** 500 mg **Duration of treatment:** 3 days **Total treatment dose:** 1500 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: not reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	None stated.
Notes	**Concomitant medication**: unclear

Paknejad 2010 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No relevant outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, unclear which group, reasons given
Selective reporting (reporting bias)	Low risk	Adverse events not stated as an outcome, unclear ascertainment, and no reporting of adverse events
Other bias	Low risk	None were identified.

Pandhi 2014

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 70 children and adults (macrolide n = 35, placebo n = 35) **Age in years** (mean ± SD): macrolide: 23.00 ± 8.96, placebo: 23.66 ± 8.35 **Setting**: secondary care
Interventions	**Indication**: pityriasis rosea **Type of macrolide**: azithromycin **Route**: per oral **Dose per day:** 500 mg (maximum) **Duration of treatment:** 5 days **Total treatment dose:** 2500 mg (maximum)
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: participant asked **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	None stated.

Pandhi 2014 (*Continued*)

Notes	**Concomitant medication**: unclear	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and clinicians blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout
Selective reporting (reporting bias)	Low risk	Adverse events stated as an outcome, standardised ascertainment, and adverse events reported
Other bias	Low risk	None were identified.

Parchure 2002

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 40 adults and elderly (macrolide n = 20, placebo n = 20) **Age in years** (mean ± SD): macrolide: 56 ± 9, placebo: 54 ± 10 **Setting**: secondary care
Interventions	**Indication**: coronary artery disease and antibodies positive to *Chlamydia pneumoniae* **Type of macrolide**: azithromycin **Route**: per oral **Dose per day:** 500 mg for 3 days, then 500 mg once a week for an additional 4 weeks **Duration of treatment:** 5 weeks **Total treatment dose:** 3500 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: not reported **Antimicrobial resistance**: not reported **Death**: not reported

Parchure 2002 (*Continued*)

Funding sources	Supported by the British Heart Foundation	
Notes	**Concomitant medication**: yes	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and clinicians blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	High risk	Adverse events not stated as an outcome, unclear ascertainment, and no reporting of adverse events
Other bias	Low risk	None were identified.

Patole 2000

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 73 children (macrolide n = 36, placebo n = 37) **Gestational age in weeks** (median (IQR)): macrolide: 29 (27 to 30), placebo: 30 (27 to 31) **Setting**: secondary care
Interventions	**Indication:** full enteral feeds in preterm infants **Type of macrolide**: erythromycin ethylsuccinate **Route**: per oral **Dose per day:** 48 mg/kg **Duration of treatment**: until full feeds or maximum of 14 days **Total treatment dose:** 230 mg (mean birthweight in macrolide group and median time taken to full feeds used)

Patole 2000 (*Continued*)

Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: incomplete reporting, however no contact information for author **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	Authors acknowledge Abbott Australasia.
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Sealed, coded envelopes
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Parents and clinicians blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	High risk	Adverse events not stated as an outcome, unclear ascertainment, and incomplete reporting of adverse events
Other bias	Low risk	None were identified.

Paul 1998

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 437 women (macrolide n = 219, placebo n = 218) **Age in years**: N/A **Setting**: secondary care
Interventions	**Indication**: low birthweight and preterm delivery **Type of macrolide**: erythromycin stearate **Route**: per oral **Dose per day:** 1000 mg

Paul 1998 (*Continued*)

	Duration of treatment: 6 weeks **Total treatment dose:** 42,000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: not reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	None stated.
Notes	**Concomitant medication**: unclear

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear if placebo was identical appearing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No relevant outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	High risk	27% and 24% excluded from the final analysis in the macrolide and placebo groups, respectively; 29 lost to follow-up. Reasons not given
Selective reporting (reporting bias)	High risk	Adverse events not stated as an outcome, unclear ascertainment, and incomplete reporting of adverse events
Other bias	Low risk	None were identified.

Petersen 1997

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 212 adults (macrolide n = 93, placebo n = 93, excluded n = 26) **Age in years** (median): macrolide: 25, placebo: 26 **Setting**: primary care

Interventions	**Indication**: pharyngitis not caused by group A *Streptococcus* **Type of macrolide**: erythromycin base **Route**: per oral **Dose per day:** 999 mg **Duration of treatment:** 10 days **Total treatment dose:** 9990 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participant diary used **Adverse events**: data reported on day 1, 3, and 6 **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	Supported by Henry J Kaiser Foundation and The Upjohn Company
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and clinicians blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, similar between groups
Selective reporting (reporting bias)	Low risk	Adverse events not clearly stated as an outcome. However, standardised ascertainment and adverse events reported. Reported on adverse events as %, not numbers, assume that this is out of the total analysed
Other bias	Low risk	None were identified.

Peterson 1996

Methods	**Design**: randomised, placebo-controlled, 4-armed trial
Participants	**Number assigned:** 89 adults and elderly (macrolide n = 55, placebo n = 34) **Age in years** (mean (range)): macrolide: 51.7 (26 to 77), placebo: 48.4 (22 to 76) **Setting**: secondary care
Interventions	**Indication**: duodenal ulcer **Type of macrolide**: clarithromycin **Route**: per oral **Dose per day:** 1500 mg **Duration of treatment:** 14 days **Total treatment dose:** 21,000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: physical + clinical examination (lab tests) **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	Study supported by Glaxo Wellcome Inc.
Notes	**Concomitant medication**: yes **Note**: this is a 4-armed randomised controlled trial (placebo, clarithromycin, ranitidine bismuth citrate, ranitidine bismuth citrate + clarithromycin). Importantly, the participants in both the macrolide and the placebo group received a placebo at some time to ensure blinding in all groups

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and clinicians blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Dropouts due to adverse events reported.

Peterson 1996 (*Continued*)

Selective reporting (reporting bias)	Low risk	Adverse events stated as an outcome, standardised ascertainment, and adverse events reported
Other bias	Unclear risk	Participants were assigned in a 2:1 ratio.

Pierce 1996

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 682 adults and elderly (macrolide n = 341, placebo n = 341) **Age in years** (mean (range)): macrolide: 37.5 (22 to 60), placebo: 37.6 (20 to 65) **Setting**: unclear
Interventions	**Indication**: prevention of disseminated *Mycobacterium avium* complex infection in people with AIDS **Type of macrolide**: clarithromycin **Route**: per oral **Dose per day:** 1000 mg **Duration of treatment:** 315 days (mean duration of treatment in macrolide group used) **Total treatment dose:** 315,000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: unclear **Adverse events**: data reported **Antimicrobial resistance**: data reported **Death**: data reported
Funding sources	Supported by a grant from Abbott Laboratories
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated block randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias)	Low risk	Participants and staff blinded.

Pierce 1996 (*Continued*)

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	Few participants lost to follow-up. Withdrawal due to adverse events reported
Selective reporting (reporting bias)	Low risk	Adverse events stated as an outcome. Unclear ascertainment, but clear statement about the approach used to summarise adverse events. Adverse events reported in detail. Authors only present adverse events as % - calculations done on all participants enrolled/treated
Other bias	Low risk	None were identified.

Pinto 2012

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 185 children (macrolide n = 88, placebo n = 97) **Age in months** (mean ± SD): macrolide: 3.08 ± 2.23, placebo: 3.12 ± 2.29 **Setting**: secondary care
Interventions	**Indication**: acute bronchiolitis **Type of macrolide**: azithromycin **Route**: per oral **Dose per day:** 10 mg/kg **Duration of treatment:** 7 days **Total treatment dose:** 394 mg (current weight in macrolide group used)
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: not reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	Supported by Fundacao de Amparo a Pesquisa do Estado do Rio Grande do Sul
Notes	**Concomitant medication**: yes

Risk of bias

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

Pinto 2012 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear if placebo was identical appearing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No relevant outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant in placebo group lost to follow-up.
Selective reporting (reporting bias)	High risk	Adverse events not stated as an outcome, unclear ascertainment, and no reporting of adverse events
Other bias	Low risk	None were identified.

Pradeep 2011

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 40 adults (macrolide n = 20, placebo n = 20) **Age in years** (mean ± SD (range)): macrolide: 35.2 ± 6.0 (26 to 45), placebo: 37.3 ± 5.7 (29 to 48) **Setting**: dental care
Interventions	**Indication**: chronic periodontitis **Type of macrolide**: clarithromycin **Route**: per oral **Dose per day:** 1000 mg **Duration of treatment:** 3 days **Total treatment dose:** 3000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: incomplete reporting, author contacted **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	Stated that project is self funded
Notes	**Concomitant medication**: unclear

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Pradeep 2011 (*Continued*)

Random sequence generation (selection bias)	Low risk	Computer-generated randomisation.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Examiner and participant blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	10% and 5% of participants were lost to follow-up in the macrolide and placebo groups, respectively
Selective reporting (reporting bias)	Low risk	Adverse events not stated as an outcome, unclear ascertainment, and incomplete reporting of adverse events
Other bias	Low risk	None were identified.

Pradeep 2013

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 61 adults (macrolide n = 31, placebo n = 30) **Age in years** (range): 30 to 50 **Setting**: dental care
Interventions	**Indication**: chronic periodontitis in smokers **Type of macrolide**: azithromycin **Route**: topical **Dose per day:** 0.5% gel **Duration of treatment:** 1 day **Total treatment dose**: N/A
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participant asked **Adverse events**: incomplete reporting, author contacted **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	None stated. Authors acknowledge Micro Labs and Purac Biomaterials for providing samples of gel and antibiotics
Notes	**Concomitant medication**: unclear

Pradeep 2013 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	Allocation not described in detail.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Placebo gel not described.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No adverse events reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, similar across groups
Selective reporting (reporting bias)	High risk	Adverse events not clearly stated as an outcome. Standardised ascertainment, but incomplete reporting of adverse events
Other bias	Low risk	None were identified.

Rajaei 2006

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 94 children and adults (macrolide n = 38, placebo n = 42, excluded n = 12) **Age in years** (mean ± SD): macrolide: 23.87 ± 4.99, placebo: 22.59 ± 5.06 **Setting**: secondary care
Interventions	**Indication**: idiopathic preterm labor **Type of macrolide**: erythromycin **Route**: per oral **Dose per day:** 1600 mg **Duration of treatment:** 10 days **Total treatment dose:** 16,000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participant asked **Adverse events**: incomplete reporting, author contacted **Antimicrobial resistance**: not reported **Death**: not reported

Rajaei 2006 (*Continued*)

Funding sources	None stated.	
Notes	**Concomitant medication**: yes	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation not described in detail.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No adverse events reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	5 participants had no follow-up, and a further 3 stopped medication (9%). Reasons not given, unclear in which group
Selective reporting (reporting bias)	High risk	Adverse events not clearly stated as an outcome. Standardised ascertainment, but incomplete reporting of adverse event
Other bias	Low risk	None were identified.

Reignier 2002

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 48 adults and elderly (macrolide n = 25, placebo n = 23) **Age in years** (mean ± SD): macrolide: 70 ± 2, placebo: 66 ± 3 **Setting**: secondary care
Interventions	**Indication**: enteral feeding in mechanically ventilated, critically ill individuals **Type of macrolide**: erythromycin lactobionate **Route**: intravenous **Dose per day:** 1000 mg **Duration of treatment:** 5 days **Total treatment dose:** 5000 mg

Reignier 2002 (*Continued*)

Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: incomplete reporting, however no contact details for author **Antimicrobial resistance**: not reported **Death**: data reported
Funding sources	None stated.
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear if placebo was identical appearing
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear if participants and clinicians were blinded. Death is an objective outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, reasons given
Selective reporting (reporting bias)	High risk	Adverse events not stated as an outcome, unclear ascertainment, and incomplete reporting of adverse events
Other bias	Low risk	None were identified.

Robins-Browne 1983

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 78 children (macrolide n = 39, placebo n = 39) **Age in months:** (mean): macrolide: 9.1, placebo: 7.4 **Setting**: secondary care
Interventions	**Indication**: acute non-specific gastroenteritis **Type of macrolide**: erythromycin ethylsuccinate **Route**: per oral **Dose per day:** 40 mg/kg

Robins-Browne 1983 (*Continued*)

	Duration of treatment: 5 days **Total treatment dose**: N/A
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: not reported **Antimicrobial resistance**: not reported (only at baseline) **Death**: data reported
Funding sources	Study supported by the South African Medical Research Council, the University of Natal, and Abbott Laboratories
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Low risk	Sequentially numbered, identical drug containers
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Paediatricians, nurses, and children/parents blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, similar between groups. Reasons given.
Selective reporting (reporting bias)	High risk	Adverse events not stated as an outcome, unclear ascertainment, and no reporting of adverse events
Other bias	Low risk	None were identified.

Roca 2016a

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 829 adults (macrolide n = 414, placebo n = 415) **Age in years** (median (IQR)): macrolide: 26.0 (22.0 to 30.0), placebo: 25.0 (22.0 to 30.0) **Setting**: secondary care

Roca 2016a (*Continued*)

Interventions	**Indication:** bacterial carriage in mothers and their offspring **Type of macrolide**: azithromycin **Route**: per oral **Dose per day:** 2000 mg **Duration of treatment:** 1 day **Total treatment dose:** 2000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: participants asked + clinical examination **Adverse events**: incomplete reporting, author contacted **Antimicrobial resistance**: data reported **Death**: data reported
Funding sources	Study supported by the UK Medical Research Council, the UK Department for International Development, and the EDCTP2 programme supported by the European Union
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomisation.
Allocation concealment (selection bias)	Low risk	Central allocation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Mothers and clinicians blinded. Death and AMR objective outcomes
Incomplete outcome data (attrition bias) All outcomes	Low risk	5% and 4% dropouts in the macrolide and placebo groups, respectively
Selective reporting (reporting bias)	Unclear risk	Adverse events stated as an outcome, standardised ascertainment, but incomplete reporting of adverse events (complete after author reply)
Other bias	Low risk	None were identified.

Roy 1998

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 94 children (macrolide n = 46, placebo n = 48) **Age in months** (mean ± SD): macrolide: 43.5 ± 12.2, placebo: 43.6 ± 10.6 **Setting**: secondary care
Interventions	**Indication**: cholera **Type of macrolide**: erythromycin **Route**: per oral **Dose per day:** 50 mg/kg **Duration of treatment:** 3 days **Total treatment dose:** 1560 mg (mean weight in macrolide group used)
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: clinical examination (lab tests) **Adverse events**: not reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	Supported by the International Centre for Diarrhoeal Disease Research, Bangladesh
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear if placebo was identical appearing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Dropouts not reported. However, it seems like all participants are included in the final analysis
Incomplete outcome data (attrition bias) All outcomes	Low risk	No adverse events reported.
Selective reporting (reporting bias)	High risk	Adverse events not clearly stated as an outcome. Standardised ascertainment, but no adverse events reported
Other bias	Low risk	None were identified.

Rozman 1984

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 282 participants (macrolide n = 146, placebo n = 136) **Age in years**: N/A **Setting**: unclear
Interventions	**Indication**: acne **Type of macrolide**: erythromycin **Route**: topical **Dose per day:** 1% gel/cream twice a day **Duration of treatment:** 3 months **Total treatment dose**: N/A
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	None stated.
Notes	**Concomitant medication**: unclear

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and clinicians blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	7% dropout, unclear in which group. Reasons unclear
Selective reporting (reporting bias)	Low risk	Adverse events not stated as an outcome, unclear ascertainment. However, adverse events reported
Other bias	Low risk	None were identified.

Sadreddini 2009

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 108 adults and elderly (macrolide n = 54, placebo n = 54) **Age in years** (mean ± SD): macrolide: 55.71 ± 11.19, placebo: 52.73 ± 10.25 **Setting**: secondary care
Interventions	**Indication:** knee effusion due to osteoarthritis **Type of macrolide**: erythromycin **Route**: per oral **Dose per day:** 800 mg **Duration of treatment:** 12 weeks **Total treatment dose:** 67,200 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: unclear **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	None stated.
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number table.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and clinicians blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	6% and 2% dropout in the macrolide and placebo groups, respectively
Selective reporting (reporting bias)	Low risk	Adverse events not clearly stated as an outcome and unclear ascertainment. However, adverse events reported
Other bias	Low risk	None were identified.

Saiman 2003

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 185 children and adults (macrolide n = 87, placebo n = 98) **Age in years** (mean ± SD): macrolide: 20.2 ± 7.9, placebo: 20.6 ± 8.6 **Setting**: secondary care
Interventions	**Indication**: people with cystic fibrosis chronically infected with *Pseudomonas aeroginosa* **Type of macrolide**: azithromycin **Route**: per oral **Dose per week:** 1500 mg (maximum) **Duration of treatment:** 168 days **Total treatment dose:** 36,000 mg (maximum)
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: participant asked + clinical examination **Adverse events**: data reported **Antimicrobial resistance**: data reported **Death**: not reported
Funding sources	Study supported by the Cystic Fibrosis Foundation. Authors acknowledge supplying company (Pfizer Pharmaceuticals)
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Central computer-generated randomisation.
Allocation concealment (selection bias)	Low risk	Central allocation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Active treatment and placebo supplied from the same company and packed identically
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All study personnel and participants were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	5% and 6% lost to follow-up in the macrolide and placebo groups, respectively. Reasons given
Selective reporting (reporting bias)	High risk	Adverse events stated as an outcome. Standardised ascertainment, adverse events reported. However, adverse events were only reported if at least 15% of participants in

Saiman 2003 (*Continued*)

		the macrolide group experienced the adverse event
Other bias	Low risk	None were identified.

Saiman 2010

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 263 children (macrolide n = 131, placebo n = 132) **Age in years** (mean ± SD): macrolide: 10.7 ± 3.25, placebo: 10.6 ± 3.10 **Setting**: secondary care
Interventions	**Indication**: cystic fibrosis (uninfected with *Pseudomonas aeruginosa*) **Type of macrolide**: azithromycin **Route**: per oral **Dose per week:** 1500 mg (maximum) **Duration of treatment:** 168 days **Total treatment dose:** 36,000 mg (maximum)
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: participants asked + clinical examination/lab tests **Adverse events**: data reported **Antimicrobial resistance**: data reported **Death**: not reported
Funding sources	Study funded by CF Foundation Therapeutics Inc. Authors acknowledge supplying company (Pfizer)
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Centralised computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All study personnel and participants were blinded.

Saiman 2010 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, similar across groups
Selective reporting (reporting bias)	High risk	Adverse events stated as an outcome, standardised ascertainment, and reporting of adverse events. However, adverse events were only reported on if at least 10% of participants in either of the groups experienced the adverse event
Other bias	Low risk	None were identified.

Sampaio 2011

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 40 adults (macrolide n = 20, placebo n = 20) **Age in years** (mean ± SD): macrolide: 44.40 ± 7.42, placebo: 43.52 ± 5.90 **Setting**: dental care
Interventions	**Indication**: chronic periodontitis **Type of macrolide**: azithromycin **Route**: per oral **Dose per day:** 500 mg **Duration of treatment:** 5 days **Total treatment dose:** 2500 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participant asked **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	Study supported by Conselho Nacional de Desenvolvimento Cientifico e Tecnologico, Brazil
Notes	**Concomitant medication**: unclear

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Independent person did the allocation.

Sampaio 2011 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Examiners, participants, and biostatisticians blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Low risk	Adverse events not clearly stated as an outcome. However, standardised ascertainment and adverse events reported
Other bias	Low risk	None were identified.

Sander 2002

Methods	**Design**: randomised, placebo-controlled, 4-armed trial
Participants	**Number assigned:** 272 adults and elderly (macrolide n = 136, placebo n = 136) **Age in years** (range): 61 to 69 **Setting**: secondary care
Interventions	**Indication**: carotid atherosclerosis **Type of macrolide**: roxithromycin **Route**: per oral **Dose per day:** 300 mg **Duration of treatment:** 30 days **Total treatment dose:** 9000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: not reported **Antimicrobial resistance**: not reported **Death**: data reported
Funding sources	None stated.
Notes	**Concomitant medication**: yes **Note:** within the 2 groups (macrolide versus placebo) *Chlamydia pneumoniae* positive and negative are presented as 1 group - i.e. 2 arms instead of 4 arms

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Sander 2002 (*Continued*)

Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and clinicians. Only report on objective outcome (death)
Incomplete outcome data (attrition bias) All outcomes	Low risk	< 5% dropout during the 4-year follow-up. All reported as deaths
Selective reporting (reporting bias)	High risk	Adverse events not stated as an outcome, unclear ascertainment, no reporting of adverse events
Other bias	Low risk	None were identified.

Schalen 1993

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 106 adults (macrolide n = 53, placebo n = 53) **Age in years** (mean): macrolide: 33.6, placebo: 38.3 **Setting**: secondary care
Interventions	**Indication**: acute laryngitis **Type of macrolide**: erythromycin **Route**: per oral **Dose per day:** 1000 mg **Duration of treatment:** 5 days **Total treatment dose:** 5000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: not reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	Study supported by Abbott Scandinavia AB, Sweden.
Notes	**Concomitant medication**: unclear
Risk of bias	

Schalen 1993 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and clinicians blinded. No relevant outcome reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	7% dropout, unclear which group. Reasons given.
Selective reporting (reporting bias)	High risk	Adverse events not stated as an outcome, unclear ascertainment, no reporting of adverse events
Other bias	Low risk	None were identified.

Schwameis 2017

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 1371 adults (macrolide n = 685, placebo n = 686) **Age in years** (mean ± SD): macrolide: 44.2 ± 15.3, placebo: 43.7 ± 14.8 **Setting**: unclear
Interventions	**Indication**: prevention of Lyme borreliosis in people bitten by European ticks **Type of macrolide**: azithromycin **Route**: topical **Dose per day**: N/A (10% gel twice per day) **Duration of treatment:** 3 days **Total treatment dose**: N/A
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: participants asked + clinical examination **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: data reported
Funding sources	Study supported by Ixodes AG.

Schwameis 2017 (*Continued*)

Notes	**Concomitant medication**: unclear **Note**: trial stopped early as a futility analysis showed that the prespecified primary endpoint was not reached in the intention-to-treat population

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and trial staff blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Adverse events reported for all allocated participants.
Selective reporting (reporting bias)	Low risk	Adverse events stated as an outcome, standardised ascertainment, and adverse events reported
Other bias	Low risk	None were identified.

Seemungal 2008

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 109 adults and elderly (macrolide n = 53, placebo n = 56) **Age in years** (mean ± SD): macrolide: 66.54 ± 8.10, placebo: 67.79 ± 9.08 **Setting**: secondary care
Interventions	**Indication**: chronic obstructive pulmonary disease **Type of macrolide**: erythromycin stearate **Route**: per oral **Dose per day:** 500 mg **Duration of treatment:** 1 year **Total treatment dose:** 182,500 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participant diary + clinical examination/lab tests **Adverse events**: data reported

Seemungal 2008 (*Continued*)

	Antimicrobial resistance: data reported **Death**: data reported
Funding sources	Supported by the British Lung Foundation
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation.
Allocation concealment (selection bias)	Low risk	Central allocation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and clinicians blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	17% and 18% dropout in the macrolide and placebo groups, respectively. However, reasons given
Selective reporting (reporting bias)	Low risk	Adverse events not clearly stated as an outcome. However, standardised ascertainment and adverse events reported
Other bias	Low risk	None were identified.

Serisier 2013

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 117 adults and elderly (macrolide n = 59, placebo n = 58) **Age in years** (mean ± SD): macrolide: 63.5 ± 9.5, placebo: 61.1 ± 10.5 **Setting**: secondary care
Interventions	**Indication**: non-cystic fibrosis bronchiectasis **Type of macrolide**: erythromycin ethylsuccinate **Route**: per oral **Dose per day:** 800 mg **Duration of treatment:** 336 days **Total treatment dose:** 268,800 mg

Serisier 2013 (*Continued*)

Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: clinical examination (laboratory tests, audiometry) **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: reported that no deaths occurred
Funding sources	Study funded by Mater Adult Respiratory Research Trust Fund.
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated block randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, trial supervisors, and all staff directly involved in participant care were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout. Adverse events resulting in discontinuation are reported
Selective reporting (reporting bias)	Low risk	Adverse events stated as an outcome, standardised ascertainment, adverse events reported
Other bias	Low risk	None were identified.

Shafuddin 2015

Methods	**Design**: randomised, placebo-controlled, 3-armed trial
Participants	**Number assigned:** 191 adults and elderly (macrolide n = 97, placebo n = 94) **Age in years** (mean ± SD): macrolide: 67.6 ± 7.85, placebo: 66.7 ± 8.7 **Setting**: secondary care
Interventions	**Indication**: chronic obstructive pulmonary disease **Type of macrolide**: roxithromycin **Route**: per oral **Dose per day:** 300 mg

Shafuddin 2015 (*Continued*)

	Duration of treatment: 84 days **Total treatment dose:** 25,200 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: participant diary + clinical examination/lab tests **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: data reported
Funding sources	Study supported by Sanofi-Aventis Australia Pty.
Notes	**Concomitant medication**: unclear

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomisation sequence not described.
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo and active treatment supplied by same company.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and clinicians blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, reasons given
Selective reporting (reporting bias)	Low risk	Adverse events stated as an outcome, standardised ascertainment, and adverse events reported
Other bias	Low risk	None were identified.

Shanson 1985

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 109 adults and elderly (macrolide n = 56, placebo n = 53) **Age in years** (range): 18 to 78 **Setting**: dental care

Shanson 1985 (*Continued*)

Interventions	**Indication**: prophylaxis of streptococcal bacteraemia after dental extraction **Type of macrolide:** erythromycin stearate **Route**: per oral **Dose per day:** 1500 mg **Duration of treatment:** 1 day **Total treatment dose:** 1500 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: participant diary used **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	Supported by a grant from Abbott Laboratories
Notes	**Concomitant medication**: yes **Note**: randomised participants were also allocated alternatively for different measurement methods for adverse events (1 with leading questions about adverse events and 1 without) . However, adverse events are reported as a total

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Low risk	Coded envelopes were used with identical-appearing content. Allocation done by nurse
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and clinicians blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Low risk	Adverse events stated as an outcome, standardised ascertainments, and adverse events reported
Other bias	Low risk	None were identified.

Simpson 2008

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 46 adults and elderly (macrolide n = 23, placebo n = 23) **Age in years** (mean (range)): macrolide: 60 (27 to 80), placebo: 55 (27 to 77) **Setting**: secondary care
Interventions	**Indication**: refractory asthma **Type of macrolide**: clarithromycin **Route**: per oral **Dose per day:** 1000 mg **Duration of treatment:** 8 weeks **Total treatment dose:** 56,000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participant asked **Adverse events**: incomplete reporting, author contacted **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	Supported by the National Health and Medical Research Council of Australia
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and clinicians blinded. No adverse events reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant in placebo group was withdrawn as the participant did not complete first week treatment
Selective reporting (reporting bias)	High risk	Adverse events not clearly stated as an outcome. Standardised ascertainment. However, incomplete reporting of adverse events

Simpson 2008 (*Continued*)

Other bias	Low risk	None were identified.

Sinisalo 2002

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 152 adults and elderly (macrolide n = 74, placebo n = 74, excluded n = 4) **Age in years** (mean ± SD): macrolide: 64 ± 10, placebo: 63 ± 11 **Setting**: secondary care
Interventions	**Indication**: unstable angina or non-Q-wave myocardial infarction **Type of macrolide**: clarithromycin **Route**: per oral **Dose per day:** 500 mg **Duration of treatment:** 85 days **Total treatment dose:** 42,500 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: clinical examination (ECG, lab tests) **Adverse events reported**: data reported **Antimicrobial resistance:** not reported **Death**: data reported
Funding sources	Supported by the Aarno Koskelo Foundation and the Finnish Foundation for Cardiovascular Research. Authors acknowledge Abbott Laboratories for supplying trial medication
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and clinicians blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants were lost to follow-up. Reasons for dropouts given

Sinisalo 2002 (*Continued*)

Selective reporting (reporting bias)	Low risk	Adverse events not clearly stated as an outcome, however standardised ascertainment and reporting of adverse events
Other bias	Low risk	None were identified.

Sirinavin 2003

Methods	**Design**: randomised, placebo-controlled, 3-armed trial
Participants	**Number assigned:** 191 children and adults (macrolide n = 95, placebo n = 96) **Age in years** (mean (range)): macrolide: 25 (15 to 55), placebo: 22 (15 to 48) **Setting:** 4 food factories in Thailand
Interventions	**Indication**: eradication of non-typhoidal *Salmonella* **Type of macrolide**: azithromycin **Route**: per oral **Dose per day:** 500 mg **Duration of treatment:** 5 days **Total treatment dose:** 2500 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: participant asked + clinical examination (swabs) **Adverse events**: data reported **Antimicrobial resistance**: data reported **Death**: not reported
Funding sources	Supported by Bureau of General Communicable Diseases, Department of Disease Control, Ministry of Public Health, Nonthaburi, Thailand
Notes	**Concomitant medication**: unclear

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear if matching placebo used. Two placebo groups in lieu of 2 different antibiotic regimens (azithromycin, norfloxacin)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear if participant and trial investigators were blinded for assessment of adverse

Sirinavin 2003 (*Continued*)

		events. Data on AMR should be considered an objective outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	19% of participants missed more than 1 follow-up visit, however reasons given
Selective reporting (reporting bias)	Low risk	Adverse events stated as an outcome, standardised ascertainment, and adverse events reported
Other bias	Low risk	None were identified.

Smith 2000

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 150 adults and elderly (macrolide n = 75, placebo n = 75) **Age in years** (mean ± SD): macrolide: 63.2 ± 12.6, placebo: 61.4 ± 11.7 **Setting**: secondary care
Interventions	**Indication**: postoperative ileus after colorectal surgery **Type of macrolide**: erythromycin lactobionate **Route**: intravenous **Dose per day:** 800 mg **Duration of treatment:** 5 days (maximum) **Total treatment dose:** 4000 mg (maximum)
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: clinical examination (ECG) **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	None stated.
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described in detail.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.

Smith 2000 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and staff blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, reasons given.
Selective reporting (reporting bias)	Low risk	Adverse events not clearly stated as an outcome. However, standardised ascertainment and adverse events reported
Other bias	Low risk	None were identified.

Smith 2002

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 46 adults (macrolide n = 23, placebo n = 21, excluded n = 2) **Age in years** (mean ± SD): macrolide: 41.87 ± 7.09, placebo: 43.57 ± 10.22 **Setting**: dental care
Interventions	**Indication**: periodontitis **Type of macrolide**: azithromycin **Route**: per oral **Dose per day:** 500 mg **Duration of treatment:** 3 days **Total treatment dose:** 1500 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: clinical examination (lab tests) **Adverse events**: incomplete reporting, author contacted **Antimicrobial resistance**: incomplete reporting, author contacted **Death**: not reported
Funding sources	Study supported by Pfizer Ltd Sandwich.
Notes	**Concomitant medication**: unclear

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.

Smith 2002 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and clinicians blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	4% dropout, reasons given
Selective reporting (reporting bias)	High risk	Adverse events not clearly stated as an outcome. Standardised ascertainment, however incomplete reporting of adverse events, including AMR
Other bias	Low risk	None were identified.

Sorensen 1992

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 432 children and adults (macrolide n = 216, placebo n = 216) **Age in years** (median (range)): macrolide: 28 (14 to 46), placebo: 27 (14 to 46) **Setting**: secondary care
Interventions	**Indication**: prevention of postabortal pelvic inflammatory disease **Type of macrolide**: erythromycin **Route**: per oral **Dose per day:** 1000 mg **Duration of treatment:** 7.5 days **Total treatment dose:** 7500 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: incomplete reporting, however no contact details for author **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	None stated. Abbott supplied treatments.
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Sorensen 1992 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Active treatment and placebo supplied by the same company.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Women and clinicians blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout. Reasons given.
Selective reporting (reporting bias)	High risk	Adverse events not stated as an outcome, unclear ascertainment, incomplete reporting of adverse events
Other bias	Low risk	None were identified.

Taylor 1999

Methods	**Design**: randomised, placebo-controlled, 3-armed trial
Participants	**Number assigned:** 225 adults (macrolide n = 148, placebo n = 77) **Age in years** (median (range)): macrolide: 27 (18 to 52), placebo: 26 (20 to 50) **Setting**: army soldiers and civilians in Indonesia
Interventions	**Indication**: malaria prophylaxis **Type of macrolide**: azithromycin **Route**: per oral **Dose per day**: loading dose on day 1 of 750 mg, then 250 mg per day **Duration of treatment:** 141 days **Total treatment dose:** 35,750 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participant asked + clinical examination (lab tests) **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	Supported by the US Army Medical Materiel Development Activity and the US Naval Medical Research and Development Command. Authors acknowledge supplying company (Pfizer Central Research)
Notes	**Concomitant medication**: yes

Taylor 1999 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation.
Allocation concealment (selection bias)	Low risk	Sequentially numbered, identical drug containers.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and trial staff blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	21% and 17% dropout in the macrolide and placebo groups, respectively. Reasons (including withdrawal due to adverse events) given. However, unclear how many people adverse events data were based on, and numbers change throughout the reporting
Selective reporting (reporting bias)	High risk	Adverse events not clearly stated as an outcome, however standardised ascertainment. Incomplete reporting of adverse events
Other bias	Unclear risk	2:1 allocation to macrolide and placebo group.

Tita 2016

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 2013 adults (macrolide n = 1019, placebo n = 994) **Age in years** (mean ± SD): macrolide: 28.2 ± 6.1, placebo: 28.4 ± 6.5 **Setting**: secondary care
Interventions	**Indication**: non-elective Caesarean delivery **Type of macrolide**: azithromycin **Route**: intravenous **Dose per day:** 500 mg **Duration of treatment:** 1 hour **Total treatment dose:** 500 mg

Tita 2016 (*Continued*)

Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: medical records review and participant asked **Adverse events**: data reported **Antimicrobial resistance**: data reported **Death**: data reported
Funding sources	Supported by a grant from the Eunice Kennedy Shriver National Institute of Child Health and Human Development
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo saline
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Women and clinicians blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts for reporting of adverse events
Selective reporting (reporting bias)	Low risk	Adverse events stated as an outcome, standardised ascertainment, and adverse events are reported
Other bias	Low risk	None were identified.

Uzun 2014

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 92 adults and elderly (macrolide n = 47, placebo n = 45) **Age in years** (mean ± SD): macrolide: 64.7 ± 10.2, placebo: 64.9 ± 10.2 **Setting**: secondary care
Interventions	**Indication**: chronic obstructive pulmonary disease **Type of macrolide**: azithromycin **Route**: per oral

Uzun 2014 (*Continued*)

	Dose: 500 mg 3 times a week **Duration of treatment:** 52 weeks **Total treatment dose:** 78,000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: participant asked + clinical examination (lab tests, swabs) **Adverse events**: data reported **Antimicrobial resistance**: data reported **Death**: data reported
Funding sources	Supported by SoLong Trust
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear if placebo was identical appearing
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear if participants and trial staff were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	13% and 16% withdrew in the macrolide and placebo groups, respectively. However, reasons given, including adverse events
Selective reporting (reporting bias)	Low risk	Adverse events stated as an outcome, standardised ascertainment, and adverse events reported
Other bias	Low risk	None were identified.

Vainas 2005

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 509 adults and elderly (macrolide n = 257, placebo n = 252) **Age in years** (mean ± SD): macrolide: 64.4 ± 9.9, placebo: 65.5 ± 9.7 **Setting**: secondary care

Vainas 2005 (*Continued*)

Interventions	**Indication**: peripheral arterial disease **Type of macrolide**: azithromycin **Route**: per oral **Dose per day:** 500 mg **Duration of treatment:** 3 days **Total treatment dose:** 1500 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participant diary used **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: data reported
Funding sources	Supported by the Netherlands Heart Foundation
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, attending surgeons, and the co-ordinating scientist blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	94% and 95% completed treatments in the macrolide and placebo groups, respectively. Reasons for dropouts given
Selective reporting (reporting bias)	Low risk	Adverse events not clearly stated as an outcome. However, standardised ascertainment and adverse events reported
Other bias	Low risk	None were identified.

Valery 2013

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 89 children (macrolide n = 45, placebo n = 44) **Age in years** (mean ± SD): macrolide: 3.99 ± 2.14, placebo: 4.22 ± 2.30 **Setting**: community clinics in central and northern Australia, and urban Maori and Pacific Island children from a tertiary paediatric hospital in Auckland, New Zealand
Interventions	**Indication:** bronchiectasis **Type of macrolide**: azithromycin **Route**: per oral **Dose:** 30 mg/kg (max 600 mg) once weekly **Duration of treatment:** 24 months (maximum) **Total treatment dose:** 62,400 (maximum)
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: participant asked + clinical examination (swabs) **Adverse events**: data reported **Antimicrobial resistance**: data reported **Death**: not reported
Funding sources	Supported by the National Health and Medical Research Council of Australia and Health Research Council, New Zealand
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation.
Allocation concealment (selection bias)	Low risk	Sequentially numbered, double-sealed, opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, families, health professionals, and study personnel blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	11% and 21% dropouts in the macrolide and placebo groups, respectively. However, reasons given

Valery 2013 (*Continued*)

Selective reporting (reporting bias)	Low risk	Adverse events stated as an outcome, standardised ascertainment, and adverse events reported
Other bias	Low risk	None were identified.

Vammen 2001

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 92 elderly (macrolide n = 43, placebo n = 49) **Age in years** (mean ± SD): macrolide: 72 ± 3.7, placebo: 73 ± 3.7 **Setting**: secondary care
Interventions	**Indication**: abdominal aortic aneurysms **Type of macrolide**: roxithromycin **Route**: per oral **Dose per day:** 300 mg **Duration of treatment**: annual 4 weeks' treatment. Followed/treated annually for a mean of 5.27 years **Total treatment dose:** 44,268 mg (mean follow-up used)
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: unclear **Adverse events**: stated that no participants stopped their medication due to side effects and that no adverse events were observed **Antimicrobial resistance**: not reported **Death**: data reported
Funding sources	Supported by the Danish Heart Foundation, the Foundation of Asta and Rosa Jensen, and the Health Department of Viborg County
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation.
Allocation concealment (selection bias)	Unclear risk	Alocation not described in detail.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo.

Vammen 2001 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and clinicians blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout. Stated that no participants stopped their medication due to side effects
Selective reporting (reporting bias)	Low risk	Adverse events stated as an outcome. Unclear ascertainment, but reported that no adverse events were observed
Other bias	Low risk	None were identified.

Van Delden 2012

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 92 adults and elderly (macrolide n = 47, placebo n = 45) **Age in years** (mean ± SD): macrolide: 59.3 ± 16.98, placebo: 59.7 ± 15.18 **Setting**: secondary care
Interventions	**Indication**: prevention of *Pseudomonas aeruginosa* ventilator-associated pneumonia **Type of macrolide**: azithromycin **Route**: intravenous **Dose per day:** 300 mg **Duration of treatment:** 20 days (maximum) **Total treatment dose:** 6000 mg (maximum)
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: spontaneously **Adverse events**: data reported **Antimicrobial resistance**: stated that azithromycin did lead to an increase in minimum inhibitory concentration when comparing initial and last *P aeruginosa* isolate. **Death**: data reported
Funding sources	Study supported by Anbics Corporation, the Swiss Ministry of Technolog, and the Swiss National Science Foundation
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomisation.
Allocation concealment (selection bias)	Low risk	Central allocation.

Van Delden 2012 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo (saline).
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Investigator, staff, participants, and monitor blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low dropout, similar across groups.
Selective reporting (reporting bias)	Low risk	Adverse events stated as an outcome, standardised ascertainment, and adverse events reported
Other bias	Low risk	None were identified.

Van den Broek 2009

Methods	**Design**: randomised, placebo-controlled, parallel-group trial	
Participants	**Number assigned:** 2297 children and adults (macrolide n = 1149, placebo n = 1148) **Age in years** (mean ± SD): azithromycin: 22.8 ± 5.1, placebo: 23.0 ± 5.2 **Setting**: 3 rural and 1 peri-urban antenatal clinic in southern Malawi	
Interventions	**Indication**: preterm birth **Type of macrolide**: azithromycin **Route**: per oral **Dose:** 1000 mg given 1 time between 16 to 24 weeks and 1 time between 28 to 32 weeks **Duration of treatment**: N/A **Total treatment dose:** 2000 mg	
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Reporting of adverse events**: yes **Antimicrobial resistance**: not reported **Death**: data reported	
Funding sources	Study funded by Wellcome Trust. Authors acknowledge supplying company (Pfizer) and state that Pfizer had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript	
Notes	**Concomitant medication**: yes	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Van den Broek 2009 (*Continued*)

Random sequence generation (selection bias)	Low risk	Block randomisation
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Placebo not described in detail, however drug and placebo were supplied by the same pharmaceutical company
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants, study midwives, and trial statistician
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Similar dropouts across groups. Unclear reasons for loss to follow-up: "Missed visit, could not be traced, declined to continue and did not attend". Possibly missed reporting on some adverse events as discontinuation due to adverse events was not reported
Selective reporting (reporting bias)	Unclear risk	Adverse events not stated as an outcome and unclear ascertainment. However, adverse events reported
Other bias	Low risk	None were identified.

Veskitkul 2017

Methods	**Design:** randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 40 children (macrolide n = 20, placebo n = 20) **Age in years** (median (range)): macrolide: 5.8 (5.0 to 9.2), placebo: 5.9 (5.0 to 12.3) **Setting:** secondary care
Interventions	**Indication:** recurrent acute rhinosinusitis **Type of macrolide:** azithromycin **Route:** per oral **Dose per day:** 5 mg/kg/day for 3 days/week **Duration of treatment:** 12 months **Total treatment dose:** N/A
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper:** unclear **Ascertainment of adverse events:** participants/parents asked **Adverse event:** stated that "adverse events were not reported in either group" **Antimicrobial resistance:** not reported **Death:** not reported

Veskitkul 2017 (*Continued*)

Funding sources	Supported by a Siriraj Grant for Research Development from the Faculty of Medicine, Siriraj Hospital, Bangkok, Thailand
Notes	**Concomitant medication:** yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomisation
Allocation concealment (selection bias)	Unclear risk	Allocation not described in detail.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants and assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropout
Selective reporting (reporting bias)	Low risk	Unclear if adverse events were stated as an outcome. However, standardised ascertainment and reported on (no) adverse events
Other bias	Low risk	None were identified.

Videler 2011

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 60 adults and elderly (macrolide n = 29, placebo n = 31) **Age in years** (median (range)): macrolide: 49 (20 to 70), placebo: 49 (20 to 70) **Setting**: secondary care
Interventions	**Indication**: chronic rhinosinusitis **Type of macrolide**: azithromycin **Route**: per oral **Dose:** 500 mg once a day for 3 days for the first week, then once a week for 11 weeks **Duration of treatment:** 12 weeks **Total treatment dose:** 7000 mg

Videler 2011 (*Continued*)

Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participant asked + clinical examination (swabs) **Adverse events**: data reported **Antimicrobial resistance**: data reported **Death**: not reported
Funding sources	None stated. Authors acknowledge Pliva Hrvatska d.o.o., Zagreb, Croatia for supplying treatments
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described in detail.
Allocation concealment (selection bias)	Low risk	Central allocation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and clinicians blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	13% and 10% dropout at follow-up 2 weeks after treatment finished in the macrolide and placebo groups, respectively. However, reasons given
Selective reporting (reporting bias)	Unclear risk	Adverse events not clearly stated as an outcome. Standardised ascertainment and adverse events reported. However, lab tests for liver function were performed but the results were not provided
Other bias	Low risk	None were identified.

Vos 2011

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 83 adults (macrolide n = 40, placebo n = 43) **Age in years** (median (range)): macrolide: 56.1 (47.7 to 61.2), placebo: 55.1 (44.2 to 59.4) **Setting**: secondary care
Interventions	**Indication**: prevention of bronchiolitis obliterans syndrome post-lung transplantation **Type of macrolide**: azithromycin **Route**: per oral **Dose per day:** 250 mg daily for 5 days, followed by 250 mg 3 times a week for 2 years **Duration of treatment:** 2 years **Total treatment dose:** 79,250 mg (maximum)
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participants asked **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: data reported
Funding sources	None stated.
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Low risk	Central allocation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and clinicians blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	70% and 41.9% completed 2 years' treatment in the macrolide and placebo groups, respectively. However, reasons given for discontinuation/entering open-label treatment
Selective reporting (reporting bias)	Low risk	Adverse events not clearly stated as an outcome. Standardised ascertainment, and ad-

Vos 2011 (*Continued*)

		verse events reported
Other bias	Low risk	None were identified.

Wallwork 2006

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 64 participants (macrolide n = 29, placebo n = 35) **Age in years**: N/A **Setting**: secondary care
Interventions	**Indication**: chronic rhinosinusitis **Type of macrolide**: roxithromycin **Route**: per oral **Dose per day:** 150 mg **Duration of treatment:** 3 months **Total treatment dose:** 13,500 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: clinical examination (swabs) **Adverse events**: incomplete reporting, author contacted **Antimicrobial resistance**: authors state that "no macrolide-resistant organisms were noted to develop" **Death**: not reported
Funding sources	None stated.
Notes	**Concomitant medication:** unclear

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random number table.
Allocation concealment (selection bias)	Low risk	Central allocation.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear if placebo was identical appearing.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear if participants and clinicians were blinded.

Wallwork 2006 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	7% and 9% withdrew in the macrolide and placebo groups, respectively. Reasons given
Selective reporting (reporting bias)	High risk	Adverse events not clearly stated as an outcome. Unclear ascertainment, only swabs mentioned. Reported solely on adverse events leading to discontinuation
Other bias	Low risk	None were identified.

Walsh 1998

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 1985 adults (macrolide n = 996, placebo n = 989) **Age in years** (mean ± SD): macrolide: 30.4 ± 6.3, placebo: 30.5 ± 6.5 **Setting:** 11 clinics in Los Angeles County, USA. Clinics represented several provider types
Interventions	**Indication**: intrauterine device insertion **Type of macrolide**: azithromycin **Route**: per oral **Dose per day:** 500 mg **Duration of treatment:** 1 day **Total treatment dose:** 500 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participants asked **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	Supported by the National Institute of Child Health and Human Development, National Institutes of Health
Notes	**Concomitant medication**: unclear

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Sequentially numbered, identical, opaque, sealed pill bottles

Walsh 1998 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Clinicians, research personnel, and participants blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2% lost to follow-up in both groups.
Selective reporting (reporting bias)	Low risk	Adverse events not clearly stated as an outcome. However, standardised ascertainment and adverse events reported
Other bias	Low risk	None were identified.

Wang 2012

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 45 adults and elderly (macrolide n = 23, placebo n = 22) **Age in years** (mean (range)): macrolide: 60 (27 to 80), placebo: 55 (27 to 80) **Setting**: secondary care
Interventions	**Indication**: non-eosinophilic refractory asthma **Type of macrolide**: clarithromycin **Route**: per oral **Dose per day:** 1000 mg **Duration of treatment:** 56 days **Total treatment dose:** 56,000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participants asked **Adverse events**: not reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	None stated.
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Wang 2012 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear if placebo was identical appearing
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear if participants and clinicians were blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	1 participant dropped out, reason unclear.
Selective reporting (reporting bias)	High risk	Adverse events not clearly stated as an outcome. Standardised ascertainment. However, no reporting about adverse events
Other bias	Low risk	None were identified.

Wiesli 2002

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 40 adults and elderly (macrolide n = 20, placebo n = 20) **Age in years** (mean ± SD): macrolide: 72.4 ± 7.7, placebo: 70.3 ± 9.1 **Setting**: secondary care
Interventions	**Indication**: peripheral arterial occlusive disease in *Chlamydia pneumoniae* seropositive men **Type of macrolide**: roxithromycin **Route**: per oral **Dose per day:** 300 mg **Duration of treatment:** 28 days **Total treatment dose:** 8400 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: data reported
Funding sources	Study supported by Aventis Pharma AG, Switzerland and the Lixmar foundation, Switzerland
Notes	**Concomitant medication**: yes

Wiesli 2002 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Clinicians and participants blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	Unclear risk	Adverse events not stated as an outcome and unclear ascertainment. However, adverse events are reported
Other bias	Low risk	None were identified.

Wilson 1977

Methods	**Design**: randomised, placebo-controlled, 3-armed trial
Participants	**Number assigned:** 51 adults (macrolide n = 26, placebo n = 25) **Age in years**: N/A **Setting:** healthy volunteers at the Baylor College of Medicine
Interventions	**Indication**: nasal carriage of *Staphylococcus aureus* **Type of macrolide**: erythromycin **Route**: per oral **Dose per day:** 1000 mg **Duration of treatment:** 7 days **Total treatment dose:** 7000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participant diary + clinical examination/lab tests **Adverse events**: data reported **Antimicrobial resistance**: data reported **Death**: not reported

Wilson 1977 (*Continued*)

Funding sources	Study supported by the EI duPont de Nemours and Company and the National Institute of Allergy and Infectious Diseases
Notes	**Concomitant medication**: unclear **Note**: a third group of people were treated with josamycin

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Placebo not identical appearing, orange vs pink tablet.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear who was blinded. Data on AMR assessed as an objective outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	A total of 4 dropouts in the 3 arms before medication was given, unclear in which groups
Selective reporting (reporting bias)	Low risk	Adverse events not clearly stated as an outcome. However, standardised ascertainment and adverse events reported
Other bias	Low risk	None were identified.

Wilson 1979

Methods	**Design**: randomised, placebo-controlled, 3-armed trial
Participants	**Number assigned:** 57 adults (macrolide n = 27, placebo n = 30) **Age in years** (range): 18 to 43 **Setting:** healthy volunteers at the Baylor College of Medicine
Interventions	**Indication**: nasal carriage of *Staphylococcus aureus* **Type of macrolide**: erythromycin **Route**: per oral **Dose per day:** 1000 mg **Duration of treatment:** 7 days **Total treatment dose:** 7000 mg

Wilson 1979 (*Continued*)

Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participant diary + clinical examination/lab tests **Adverse events**: data reported **Antimicrobial resistance**: data reported **Death**: not reported
Funding sources	Study supported by Schering Laboratories, The Council for Tobacco Research, and the National Institutes of Health
Notes	**Concomitant medication**: unclear **Note**: a third group of people were treated with rosaramicin.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Unclear if placebo was identical appearing. Authors state only that the placebo was identical in appearance to the rosaramicin capsules (the third arm)
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unclear who was blinded. Data on AMR assessed as an objective outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	13% and 3% dropout in the macrolide and placebo groups, respectively. Reasons given
Selective reporting (reporting bias)	Low risk	Adverse events not clearly stated as an outcome. However, standardised ascertainment and adverse events reported
Other bias	Low risk	None were identified.

Winkler 1988

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 43 pregnant women (macrolide n = 20, placebo n = 23) **Age in years**: N/A **Setting**: secondary care

Interventions	**Indication**: preterm delivery **Type of macrolide**: erythromycin **Route**: per oral **Dose per day:** 1200 mg **Duration of treatment:** 7 days **Total treatment dose:** 8400 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: not reported **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	None stated.
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear if placebo was identical appearing
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Dropouts not reported.
Selective reporting (reporting bias)	High risk	Adverse events not stated as an outcome, unclear ascertainment, and adverse events not reported
Other bias	Low risk	None were identified.

Wolter 2002

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 60 adults (macrolide n = 30, placebo n = 30) **Age in years** (mean (range)): 27.9 (18 to 44) **Setting**: secondary care
Interventions	**Indication**: cystic fibrosis **Type of macrolide**: azithromycin **Route**: per oral **Dose per day:** 250 mg **Duration of treatment:** 90 days **Total treatment dose:** 22,500 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: incomplete reporting, author contacted **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	Study supported by the John P Kelly Mater Research Foundation and the Mater Hospital Private Practice Fund. Authors thank supplying company (Pfizer)
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomisation.
Allocation concealment (selection bias)	Low risk	Randomised by independent pharmacy staff, and participants were automatically dispensed the next allocated treatment
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of participants, clinicians, and statistician. No relevant outcomes reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	6 participants (25%) and 9 participants (30%) did not complete the treatment in the macrolide and placebo groups, respectively. However, adverse events are reported for 3 participants, while the remainder dropped out due to non-compliance or per-

Wolter 2002 (*Continued*)

		sonal request
Selective reporting (reporting bias)	High risk	Adverse events not stated as an outcome, unclear ascertainment, and incomplete reporting of adverse events
Other bias	Unclear risk	The placebo group contained more men, and they were also taller, heavier, and had a better lung function

Wong 2012

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 141 adults and elderly (macrolide n = 71, placebo n = 70) **Age in years** (mean ± SD): macrolide: 60.9 ± 13.6, placebo: 59.0 ± 13.3 **Setting**: secondary care
Interventions	**Indication**: non-cystic fibrosis bronchiectasis **Type of macrolide**: azithromycin **Route**: per oral **Dose:** 500 mg 3 times a week **Duration of treatment:** 6 months **Total treatment dose:** 39,000 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: participant asked **Adverse events**: data reported **Antimicrobial resistance**: reported on participants diagnosed with macrolide-resistant *Streptococcus pneumoniae* following macrolide treatment **Death**: not reported
Funding sources	Study funded by the Health Research Council of New Zealand and the Auckland District Health Board Charitable Trust
Notes	**Concomitant medication**: yes

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Central allocation

Wong 2012 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, clinicians, and investigators blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	6% in macrolide group versus 10% in placebo group withdrew. However, reasons for dropout are clearly presented
Selective reporting (reporting bias)	Unclear risk	Adverse events stated as an outcome, standardised ascertainment, and adverse events reported. Note that only adverse events with an incidence of more than 2.5% in either group were presented
Other bias	Low risk	None were identified.

Yang 2013

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 180 children, adults, and elderly (macrolide n = 89, placebo n = 91) **Age in years** (mean (range)): 41 (9 to 87) **Setting**: secondary care
Interventions	**Indication:** bacterial conjunctivitis **Type of macrolide**: azithromycin **Route**: topical **Dose**: a 1% drop of gel twice a day for 2 days, then 1 drop once a day for the next 3 to 7 days **Duration of treatment:** 7 days **Total treatment dose**: N/A
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: yes **Adverse events ascertainment**: participants asked + clinical examination (swabs) **Adverse events**: incomplete reporting, author contacted **Antimicrobial resistance**: not reported **Death**: not reported
Funding sources	None stated.
Notes	**Concomitant medication**: unclear
Risk of bias	

Yang 2013 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described in detail.
Allocation concealment (selection bias)	Low risk	Central allocation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and clinicians blinded. No outcomes reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No dropouts
Selective reporting (reporting bias)	High risk	Adverse events stated as an outcome, standardised ascertainment. However, incomplete reporting of adverse events
Other bias	Low risk	None were identified.

Yeo 1993

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 128 adults and elderly (macrolide n = 58, placebo n = 60) **Age in years** (mean ± SD): macrolide: 65.6 ± 1.6, placebo: 63.7 ± 1.4 **Setting**: secondary care
Interventions	**Indication**: gastric emptying after pancreaticoduodenectomy **Type of macrolide**: erythromycin lactobionate **Route**: intravenous **Dose per day:** 800 mg **Duration of treatment:** 8 days **Total treatment dose:** 6400 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: unclear **Adverse events ascertainment**: participant asked **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: no deaths reported
Funding sources	None stated.
Notes	**Concomitant medication**: yes

Yeo 1993 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Sequence generation not described in detail.
Allocation concealment (selection bias)	Unclear risk	Allocation not described.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Nursing staff, physicians, and participants blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	10 participants (8%) excluded from analysis, unclear which group. However, reasons given
Selective reporting (reporting bias)	Low risk	Adverse events not clearly stated as an outcome. However, standardised ascertainment and adverse events reported
Other bias	Low risk	None were identified.

Zahn 2003

Methods	**Design**: randomised, placebo-controlled, parallel-group trial
Participants	**Number assigned:** 872 adults and elderly (macrolide n = 433, placebo n = 439) **Age in years** (mean (IQR)): macrolide: 60.4 (51.3 to 69.1), placebo: 61.0 (52.2 to 68.6) **Setting**: secondary care
Interventions	**Indication**: acute myocardial infarction **Type of macrolide**: roxithromycin **Route:** per oral **Dose per day:** 300 mg **Duration of treatment:** 42 days **Total treatment dose:** 12,600 mg
Outcomes	**Adverse events stated as an outcome in trial registration/protocol/paper**: no **Adverse events ascertainment**: unclear **Adverse events**: data reported **Antimicrobial resistance**: not reported **Death**: data reported (death is reported as a primary outcome)

Zahn 2003 (*Continued*)

Funding sources	Supported by Aventis Pharma GmbH	
Notes	**Concomitant medication:** yes	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomisation.
Allocation concealment (selection bias)	Low risk	Central allocation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Identical-appearing placebo.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants and clinicians blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	18% and 11% dropouts in the macrolide and placebo groups, respectively. Reasons given
Selective reporting (reporting bias)	High risk	Adverse events not stated as an outcome, unclear ascertainment. Only adverse events resulting in discontinuation were reported
Other bias	Low risk	None were identified.

AMR: antimicrobial resistance
ECG: electrocardiogram
IQR: interquartile range
N/A: not applicable
PCI: percutaneous coronary intervention
PPROM: preterm pre-labour rupture of membrane
SD: standard deviation
SE: standard error

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

Study	Reason for exclusion
Aboud 2009	Participants in treatment group were randomised to receive both a macrolide (erythromycin) and metronidazole
Ballard 2007	Too-small sample size. 19 infants were allocated to macrolide treatment and 16 infants were allocated to placebo
Batieha 2002	Quasi-randomised trial. Participants were allocated by alternate assignment to either macrolide or placebo group
Doan 2017	Only report on pharmacodynamic outcomes (microbiome)
Ferahbas 2004	Cross-over trial. Adverse events were only reported after cross-over
Figueiredo-Mello 2018	Participants in the intervention group were allocated to 1 of 2 types of macrolides (clarithromycin or azithromycin). However, it was not possible to identify those participants treated with clarithromycin and those treated with azithromycin
Gong 2014	Too-small sample size. Only 17 participants were allocated in each arm
Makkar 2016	Not possible to extract data on participants only treated with placebo. Participants allocated to placebo also received erythromycin if feed failure
Nielsen 2016	Too-small sample size. Only 12 participants were allocated in each arm
Parker 2017	Only report on pharmacodynamic outcomes (microbiome)
Pazoki-Toroudi 2010	Not placebo controlled. Participants allocated to topical macrolide gel were treated for 12 weeks, while participants allocated to topical placebo gel were treated for 4 weeks
Rasi 2008	Not placebo controlled. Participants allocated to macrolides were treated with tablets, while participants allocated to placebo were treated with an emollient cream
Sharma 2000	Quasi-randomised trial. Participants were allocated by alternate assignment to either macrolide treatment or placebo
Stokholm 2016	Asthma-like episodes, not participants, randomised to either macrolide treatment or placebo
Weber 1993	Not placebo controlled. Participants allocated to macrolides were treated with a cream, while participants allocated to placebo were treated with tablets
Yamamoto 1992	Participants were not randomly assigned to treatment or placebo group
Zhang 2006	Quasi-randomised trial. Participants were allocated by alternate assignment to either macrolide treatment or placebo

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

ACTRN12617000531314

Methods	Randomised, placebo-controlled clinical trial
Participants	Adults with chronic periodontitis
Interventions	**Arm 1:** azithromycin (+ non-surgical periodontal scaling and root planing + use of mouthwashes) **Arm 2:** placebo (+ non-surgical periodontal scaling and root planing + use of mouthwash)
Outcomes	Adverse events, antimicrobial resistance, and death
Notes	

ChiCTR-INR-17013272

Methods	Randomised, placebo-controlled clinical trial
Participants	Women having Caesarean section
Interventions	**Arm 1:** azithromycin (+ usual antibiotic regimen = cefuroxime) **Arm 2:** placebo (+ usual antibiotic regimen = cefuroxime)
Outcomes	Adverse events, antimicrobial resistance, and death
Notes	

ChiCTR-IOR-16008820

Methods	Randomised, placebo-controlled clinical trial
Participants	Adults with chronic obstructive pulmonary disease
Interventions	**Arm 1:** erythromycin **Arm 2:** placebo
Outcomes	Adverse events, antimicrobial resistance, and death
Notes	

CTRI/2017/07/009017

Methods	Randomised, placebo-controlled clinical trial
Participants	Children with acute diarrhoea
Interventions	**Arm 1:** azithromycin **Arm 2:** placebo

CTRI/2017/07/009017 (*Continued*)

Outcomes	Adverse events including data on antimicrobial resistance and death
Notes	

Dicko 2016

Methods	Randomised, placebo-controlled clinical trial
Participants	African children
Interventions	**Arm 1**: azithromycin (+ usual malaria prevention = sulfadoxine/pyrimethamine + amodiaquine) **Arm 2**: placebo (+ usual malaria prevention = sulfadoxine/pyrimethamine + amodiaquine)
Outcomes	Adverse events including data on antimicrobial resistance and death
Notes	

EUCTR2011-004351-39-IT

Methods	Randomised, placebo-controlled clinical trial
Participants	Adolescents and adults with primary immunodeficiency and chronic obstructive pulmonary disease
Interventions	**Arm 1**: azithromycin **Arm 2**: placebo
Outcomes	Adverse events including data on antimicrobial resistance and death
Notes	

EUCTR2012-002792-34-GB

Methods	Randomised, placebo-controlled clinical trial
Participants	Adults and elderly with bronchiectasis
Interventions	**Arm 1:** erythromycin **Arm 2**: placebo
Outcomes	Adverse events including data on antimicrobial resistance and death
Notes	

EUCTR2015-004306-42-SI

Methods	Randomised, placebo-controlled clinical trial
Participants	Adults with chronic periodontitis
Interventions	**Arm 1**: azithromycin **Arm 2**: placebo
Outcomes	Adverse events including data on antimicrobial resistance and death
Notes	

Gregersen 2017

Methods	Randomised, placebo-controlled clinical trial
Participants	Adults and elderly with multiple myeloma
Interventions	**Arm 1:** clarithromycin **Arm 2**: placebo
Outcomes	Adverse events including data on antimicrobial resistance and death
Notes	Extended abstract identified. However, we could not identify a peer-reviewed publication of this study

IRCT2015052322383N1

Methods	Randomised, placebo-controlled clinical trial
Participants	Adults residing in endemic area of leptospirosis and working in the paddy field
Interventions	**Arm 1**: azithromycin **Arm 2:** doxycycline **Arm 3**: placebo
Outcomes	Adverse events including data on antimicrobial resistance and death
Notes	

KCT0002373

Methods	Randomised, placebo-controlled clinical trial
Participants	*Ureaplasma*-positive preterm infants
Interventions	**Arm 1**: azithromycin **Arm 2**: placebo

KCT0002373 (*Continued*)

Outcomes	Adverse events including data on antimicrobial resistance and death
Notes	

Milito 2017

Methods	Randomised, placebo-controlled clinical trial
Participants	Children and adults with primary antibody deficiency and chronic obstructive pulmonary disease with recurrent exacerbations
Interventions	**Arm 1**: azithromycin **Arm 2**: placebo
Outcomes	Adverse events including data on antimicrobial resistance and death
Notes	

NCT01270074

Methods	Randomised, placebo-controlled clinical trial
Participants	Children with cystic fibrosis
Interventions	**Arm 1**: azithromycin **Arm 2**: placebo
Outcomes	Adverse events including data on antimicrobial resistance and death
Notes	

NCT01778634

Methods	Randomised, placebo-controlled clinical trial
Participants	Preterm infants with indwelling intravenous line for drug administration
Interventions	**Arm 1**: azithromycin **Arm 2**: placebo
Outcomes	Adverse events including data on antimicrobial resistance and death
Notes	Study results posted on ClinicalTrials.gov in May 2018. However, we could not identify a peer-reviewed publication of this study

NCT02003911

Methods	Randomised, placebo-controlled clinical trial
Participants	Children hospitalised with acute asthma exacerbations
Interventions	**Arm 1**: azithromycin **Arm 2**: placebo
Outcomes	Adverse events including data on antimicrobial resistance and death
Notes	

NCT02307825

Methods	Randomised, placebo-controlled clinical trial
Participants	Adults with chronic rhinosinusitis
Interventions	**Arm 1**: azithromycin **Arm 2**: placebo
Outcomes	Adverse events including data on antimicrobial resistance and death
Notes	

NCT02336516

Methods	Randomised, placebo-controlled clinical trial
Participants	Children diagnosed with postdiarrhoeal haemolytic and uraemic syndrome
Interventions	**Arm 1**: azithromycin **Arm 2**: placebo
Outcomes	Adverse events including data on antimicrobial resistance and death
Notes	

NCT02677701

Methods	Randomised, placebo-controlled clinical trial
Participants	Children and adults with cystic fibrosis and chronic airway infection with *Pseudomonas aeruginosa*
Interventions	**Arm 1**: azithromycin + tobramycin **Arm 2**: placebo + tobramycin
Outcomes	Adverse events including data on antimicrobial resistance and death

NCT02677701 (*Continued*)

Notes	

NCT02756403

Methods	Randomised, placebo-controlled clinical trial
Participants	Women having a first trimester abortion
Interventions	**Arm 1**: azithromycin **Arm 2:** doxycycline **Arm 3:** metronidazole **Arm 4**: placebo
Outcomes	Adverse events including data on antimicrobial resistance and death
Notes	

NCT02911935

Methods	Randomised, placebo-controlled clinical trial
Participants	Children hospitalised with respiratory syncytial virus bronchiolitis
Interventions	**Arm 1**: azithromycin **Arm 2**: placebo
Outcomes	Adverse events including data on antimicrobial resistance and death
Notes	

NCT02960503

Methods	Randomised, placebo-controlled clinical trial
Participants	Adults with sickle cell disease
Interventions	**Arm 1**: azithromycin **Arm 2**: placebo
Outcomes	Adverse events including data on antimicrobial resistance and death
Notes	

NCT03130114

Methods	Randomised, placebo-controlled clinical trial
Participants	Children with severe diarrhoea
Interventions	**Arm 1**: azithromycin **Arm 2**: placebo
Outcomes	Adverse events including data on antimicrobial resistance and death
Notes	

NCT03233880

Methods	Randomised, placebo-controlled clinical trial
Participants	Healthy primigravidae: prevention of pre-eclampsia
Interventions	**Arm 1**: azithromycin **Arm 2**: placebo
Outcomes	Adverse events including data on antimicrobial resistance and death
Notes	

NCT03248297

Methods	Randomised, placebo-controlled clinical trial
Participants	High-risk labouring women in low-income countries
Interventions	**Arm 1**: azithromycin **Arm 2**: azithromycin + amoxicillin **Arm 3**: placebo
Outcomes	Adverse events including data on antimicrobial resistance and death
Notes	

NCT03341273

Methods	Randomised, placebo-controlled clinical trial
Participants	Adults with a suspected lower respiratory tract infection
Interventions	**Arm 1**: azithromycin (+ procalcitonin test) **Arm 2**: placebo (+ procalcitonin test)

NCT03341273 (*Continued*)

Outcomes	Adverse events including data on antimicrobial resistance and death
Notes	

NCT03345992

Methods	Randomised, placebo-controlled clinical trial
Participants	Adults with sepsis and respiratory and multiple organ dysfunction syndrome
Interventions	**Arm 1**: clarithromycin **Arm 2**: placebo
Outcomes	Adverse events including data on antimicrobial resistance and death
Notes	

Ramsey 2017

Methods	Randomised, placebo-controlled clinical trial
Participants	Children with cystic fibrosis with early *Pseudomonas aeruginosa*
Interventions	**Arm 1**: azithromycin **Arm 2**: placebo
Outcomes	Adverse events including data on antimicrobial resistance and death
Notes	

RBR-9pqqpb

Methods	Randomised, placebo-controlled clinical trial
Participants	Adults with eosinophilic nasosinusinal polyposis
Interventions	**Arm 1**: azithromycin **Arm 2**: placebo
Outcomes	Adverse events including data on antimicrobial resistance and death
Notes	

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

Chang 2012

Trial name or title	A randomised, double-blind, placebo-controlled trial of azithromycin versus amoxicillin-clavulanic acid to treat mild to moderate respiratory exacerbations in children with non-cystic fibrosis bronchiectasis, study one
Methods	Randomised, double-blind, double-dummy, placebo-controlled, parallel-group trial
Participants	Children aged less than 18 years, diagnosed with non-cystic fibrosis bronchiectasis
Interventions	Arm 1: oral azithromycin 5 mg/kg x 1 for 14 days Arm 2: oral amoxicillin-clavulanic acid 22.5 mg/kg x 2 for 14 days Arm 3: oral placebo for 14 days
Outcomes	Adverse events including data on antimicrobial resistance
Starting date	15 March 2012
Contact information	annechang@ausdoctors.net
Notes	**Author reply in April 2018**: Dr Anne Chang reports that the trial has completed recruitment and data are being analysed. No publication yet **Trial registration**: Australia and New Zealand Clinical Trials Register ACTRN12612000011886

Gonzalez-Martinez 2017

Trial name or title	Azithromycin versus placebo for the treatment of HIV-associated chronic lung disease in children and adolescents (BREATHE trial): study protocol for a randomised controlled trial
Methods	Randomised, double-blind, placebo-controlled, parallel-group trial
Participants	Children and adolescents aged 6 to 19 years, diagnosed with HIV-associated chronic lung disease
Interventions	Arm 1: oral azithromycin (10 to 19.9 kg, 250 mg; 20 to 29.9 kg, 500 mg; 30 to 39.9 kg, 750 mg; > 40 kg, 1250 mg) once a week for 12 months Arm 2: oral placebo for 12 months
Outcomes	Adverse events including data on antimicrobial resistance and death
Starting date	June 2016
Contact information	rashida.ferrand@lshtm.ac.uk
Notes	**Author reply in June 2018**: Dr Rashida Ferrand reports that the trial will be completed shortly and that they plan to publish the results in 2019 **Trial registration**: ClinicalTrials.gov NCT02426112

Kobbernagel 2016

Trial name or title	Randomised controlled trial to determine the efficacy and safety of azithromycin maintenance for 6 months in participants with primary ciliary dyskinesia - a double-blind, parallel-group study
Methods	Randomised, double-blind, placebo-controlled, parallel-group trial
Participants	Children and adults aged 7 to 50 years, diagnosed with primary ciliary dyskinesia
Interventions	Arm 1: oral azithromycin 250 mg/500 mg (according to body weight) x 1, 3 times a week for 6 months Arm 2: oral placebo for 6 months
Outcomes	Adverse events including data on antimicrobial resistance
Starting date	26 August 2014
Contact information	helene_kobber@hotmail.com
Notes	**Author reply in April 2018**: Dr Helene Kobbernagel reports that the trial has completed recruitment and data are being analysed. No publication yet **Trial registration**: EU Clinical Trials Register EudraCT 2013-004664-58

Mosquera 2016

Trial name or title	The anti-inflammatory effect of prophylactic macrolides on children with chronic lung disease
Methods	Randomised, double-blind, placebo-controlled, parallel-group trial
Participants	Children aged 6 months to 6 years with chronic lung disease secondary to bronchopulmonary dysplasia
Interventions	Arm 1: oral azithromycin 5 mg/kg x 1, 3 times a week for 3 to 6 months Arm 2: oral placebo for 3 to 6 months
Outcomes	Adverse events
Starting date	October 2015
Contact information	Richardo.A.Mosquera@uth.tmc.edu
Notes	**Author reply in April 2018**: Dr Richardo Mosquera reports that the trial has completed recruitment and data are being analysed. No publication yet **Trial registration**: ClinicalTrials.gov NCT02544984

Pavlinac 2017

Trial name or title	Azithromycin to prevent post-discharge morbidity and mortality in Kenyan children: a protocol for a randomised, double-blind, placebo-controlled trial (the Toto Bora trial)
Methods	Randomised, double-blind, placebo-controlled, parallel-group trial
Participants	Children aged 1 to 59 months discharged from hospitals
Interventions	Arm 1: oral azithromycin, 10 mg/kg on day 1, followed by 5 mg/kg for days 2 to 5 Arm 2: oral placebo for 5 days
Outcomes	Adverse events including data on antimicrobial resistance and death
Starting date	28 June 2016
Contact information	ppav@uw.edu
Notes	**Author reply in June 2018**: Dr Patricia Pavlinac reports that they are still recruiting patients and anticipate publishing results in late 2019/late 2020 **Trial registration**: ClinicalTrials.gov NCT02414399

Vermeersch 2016

Trial name or title	Belgian trial with azithromycin during acute COPD exacerbations
Methods	Randomised, double-blind, placebo-controlled, parallel-group trial
Participants	Adults aged 18 years or older hospitalised for an acute exacerbation in chronic obstructive pulmonary disease (COPD)
Interventions	Arm 1: oral azithromycin: 500 mg x 1 for 3 days, followed by 250 mg once every 2 days for the remainder of the 90-day treatment period Arm 2: oral placebo for 90 days
Outcomes	Adverse events including data on deaths
Starting date	1 August 2014
Contact information	wim.janssens@uzleuven.be
Notes	**Author reply in April 2018**: Dr Wim Janssens reports that the trial has completed recruitment and data are being analysed. No publication yet **Trial registration**: ClinicalTrials.gov NCT02135354

DATA AND ANALYSES

Comparison 1. Cardiac disorders

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cardiac disorders	7	1715	Odds Ratio (M-H, Random, 95% CI)	0.87 [0.54, 1.40]

Comparison 2. Ear and labyrinth disorders

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hearing loss	4	1369	Odds Ratio (M-H, Random, 95% CI)	1.30 [1.00, 1.70]

Comparison 3. Gastrointestinal disorders

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Nausea	28	14983	Odds Ratio (M-H, Random, 95% CI)	1.61 [1.37, 1.90]
2 Nausea - subgroup analysis by macrolide	26	10572	Odds Ratio (M-H, Random, 95% CI)	1.67 [1.39, 2.00]
2.1 Azithromycin	10	5437	Odds Ratio (M-H, Random, 95% CI)	1.66 [1.27, 2.16]
2.2 Erythromycin	13	4625	Odds Ratio (M-H, Random, 95% CI)	1.58 [1.23, 2.04]
2.3 Roxithromycin	3	510	Odds Ratio (M-H, Random, 95% CI)	3.29 [1.15, 9.43]
3 Nausea - subgroup analysis by route of administration	28	14983	Odds Ratio (M-H, Random, 95% CI)	1.61 [1.37, 1.90]
3.1 Intravenous	3	396	Odds Ratio (M-H, Random, 95% CI)	3.04 [0.69, 13.51]
3.2 Peroral	25	14587	Odds Ratio (M-H, Random, 95% CI)	1.57 [1.35, 1.81]
4 Vomiting	15	5328	Odds Ratio (M-H, Random, 95% CI)	1.27 [1.04, 1.56]
5 Vomiting - subgroup analysis by macrolide	13	5147	Odds Ratio (M-H, Random, 95% CI)	1.26 [1.00, 1.60]
5.1 Azithromycin	6	2692	Odds Ratio (M-H, Random, 95% CI)	1.06 [0.76, 1.49]
5.2 Erythromycin	7	2455	Odds Ratio (M-H, Random, 95% CI)	1.46 [1.07, 1.98]
6 Vomiting - subgroup analysis by route of administration	15	5328	Odds Ratio (M-H, Random, 95% CI)	1.27 [1.04, 1.56]
6.1 Intravenous	5	2354	Odds Ratio (M-H, Random, 95% CI)	1.21 [0.88, 1.66]
6.2 Peroral	10	2974	Odds Ratio (M-H, Random, 95% CI)	1.32 [0.97, 1.78]
7 Nausea and vomiting	8	1053	Odds Ratio (M-H, Random, 95% CI)	0.92 [0.60, 1.42]
8 Abdominal pain	23	7776	Odds Ratio (M-H, Random, 95% CI)	1.66 [1.22, 2.26]
9 Abdominal pain - subgroup analysis by macrolide	20	7506	Odds Ratio (M-H, Random, 95% CI)	1.68 [1.21, 2.34]
9.1 Azithromycin	14	6072	Odds Ratio (M-H, Random, 95% CI)	1.47 [1.01, 2.13]

9.2 Erythromycin	6	1434	Odds Ratio (M-H, Random, 95% CI)	3.16 [1.14, 8.75]
10 Diarrhoea	37	23754	Odds Ratio (M-H, Random, 95% CI)	1.70 [1.34, 2.16]
11 Diarrhoea - subgroup analysis by macrolide	37	23754	Odds Ratio (M-H, Random, 95% CI)	1.70 [1.34, 2.16]
11.1 Azithromycin	22	15144	Odds Ratio (M-H, Random, 95% CI)	1.96 [1.37, 2.81]
11.2 Clarithromycin	4	4540	Odds Ratio (M-H, Random, 95% CI)	2.09 [1.70, 2.56]
11.3 Erythromycin	8	3711	Odds Ratio (M-H, Random, 95% CI)	1.36 [0.94, 1.98]
11.4 Roxithromycin	3	359	Odds Ratio (M-H, Random, 95% CI)	0.88 [0.38, 2.07]
12 Gastrointestinal disorders not otherwise specified	23	3295	Odds Ratio (M-H, Random, 95% CI)	2.16 [1.56, 3.00]
13 Gastrointestinal disorders not otherwise specified - subgroup analysis by macrolide	22	3238	Odds Ratio (M-H, Random, 95% CI)	2.19 [1.56, 3.09]
13.1 Azithromycin	13	2396	Odds Ratio (M-H, Random, 95% CI)	1.77 [1.30, 2.42]
13.2 Erythromycin	9	842	Odds Ratio (M-H, Random, 95% CI)	4.00 [1.83, 8.74]

Comparison 4. Nervous system disorders

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Dizziness	3	376	Odds Ratio (M-H, Random, 95% CI)	1.83 [0.85, 3.95]
2 Headache	12	1386	Odds Ratio (M-H, Random, 95% CI)	0.81 [0.58, 1.11]
3 Taste disturbance	5	932	Odds Ratio (M-H, Random, 95% CI)	4.95 [1.64, 14.93]

Comparison 5. Skin and subcutaneous tissue disorders

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Itching	4	1388	Odds Ratio (M-H, Random, 95% CI)	1.11 [0.73, 1.67]
2 Rash	8	5314	Odds Ratio (M-H, Random, 95% CI)	1.13 [0.91, 1.41]

Comparison 6. General disorders and administration site conditions

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Fever	7	2451	Odds Ratio (M-H, Random, 95% CI)	0.73 [0.54, 1.00]

Comparison 7. Hepatobiliary disorders

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hepatobiliary disorders	4	443	Odds Ratio (M-H, Random, 95% CI)	1.04 [0.27, 4.09]

Comparison 8. Infections and infestations

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Blood infection	4	356	Odds Ratio (M-H, Random, 95% CI)	0.83 [0.52, 1.34]
2 Respiratory tract infections	11	11062	Odds Ratio (M-H, Random, 95% CI)	0.70 [0.62, 0.80]
3 Skin and soft tissue infections	3	263	Odds Ratio (M-H, Random, 95% CI)	1.57 [0.53, 4.64]

Comparison 9. Investigations

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Change in liver enzymes	6	1187	Odds Ratio (M-H, Random, 95% CI)	1.56 [0.73, 3.37]

Comparison 10. Metabolism and nutrition disorders

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Appetite lost	5	2183	Odds Ratio (M-H, Random, 95% CI)	1.10 [0.84, 1.43]

Comparison 11. Respiratory, thoracic, and mediastinal disorders

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cough	6	1587	Odds Ratio (M-H, Random, 95% CI)	0.57 [0.40, 0.80]
2 Respiratory symptoms not otherwise specified	8	2176	Odds Ratio (M-H, Random, 95% CI)	1.02 [0.82, 1.25]
3 Wheezing	3	484	Odds Ratio (M-H, Random, 95% CI)	2.20 [0.74, 6.52]

Comparison 12. Deaths

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Deaths - overall	52	216246	Odds Ratio (M-H, Random, 95% CI)	0.96 [0.87, 1.06]
2 Deaths - subgroup analysis by type of macrolide	52	216246	Odds Ratio (M-H, Random, 95% CI)	0.96 [0.87, 1.06]
2.1 Azithromycin	24	204719	Odds Ratio (M-H, Random, 95% CI)	0.97 [0.85, 1.10]
2.2 Clarithromycin	8	7216	Odds Ratio (M-H, Random, 95% CI)	0.86 [0.59, 1.24]
2.3 Erythromycin	10	718	Odds Ratio (M-H, Random, 95% CI)	0.73 [0.38, 1.40]
2.4 Roxithromycin	10	3593	Odds Ratio (M-H, Random, 95% CI)	1.03 [0.76, 1.41]
3 Deaths - subgroup analysis by route of administration	51	214875	Odds Ratio (M-H, Random, 95% CI)	0.96 [0.87, 1.06]
3.1 Intravenous	8	1334	Odds Ratio (M-H, Random, 95% CI)	0.83 [0.63, 1.10]
3.2 Peroral	43	213541	Odds Ratio (M-H, Random, 95% CI)	0.98 [0.88, 1.10]

Analysis 1.1. Comparison 1 Cardiac disorders, Outcome 1 Cardiac disorders.

Review: Adverse events in people taking macrolide antibiotics versus placebo for any indication

Comparison: 1 Cardiac disorders

Outcome: 1 Cardiac disorders

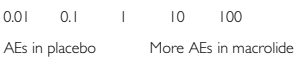
Study or subgroup	Macrolide n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Albert 2011	29/558	33/559		52.5 %	0.87 [0.52, 1.46]
Berkhof 2013	2/42	1/42		3.7 %	2.05 [0.18, 23.51]
Gupta 1997	4/40	2/20		6.7 %	1.00 [0.17, 5.98]
Kim 2004	17/64	14/65		27.5 %	1.32 [0.59, 2.96]
Smith 2000	0/75	4/75		2.6 %	0.11 [0.01, 1.99]
Vammen 2001	0/43	4/49		2.6 %	0.12 [0.01, 2.22]
Vos 2011	1/40	4/43		4.4 %	0.25 [0.03, 2.34]
Total (95% CI)	**862**	**853**		**100.0 %**	**0.87 [0.54, 1.40]**

Total events: 53 (Macrolide), 62 (Placebo)

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 6.60$, df = 6 (P = 0.36); $I^2 = 9\%$

Test for overall effect: Z = 0.59 (P = 0.56)

Test for subgroup differences: Not applicable

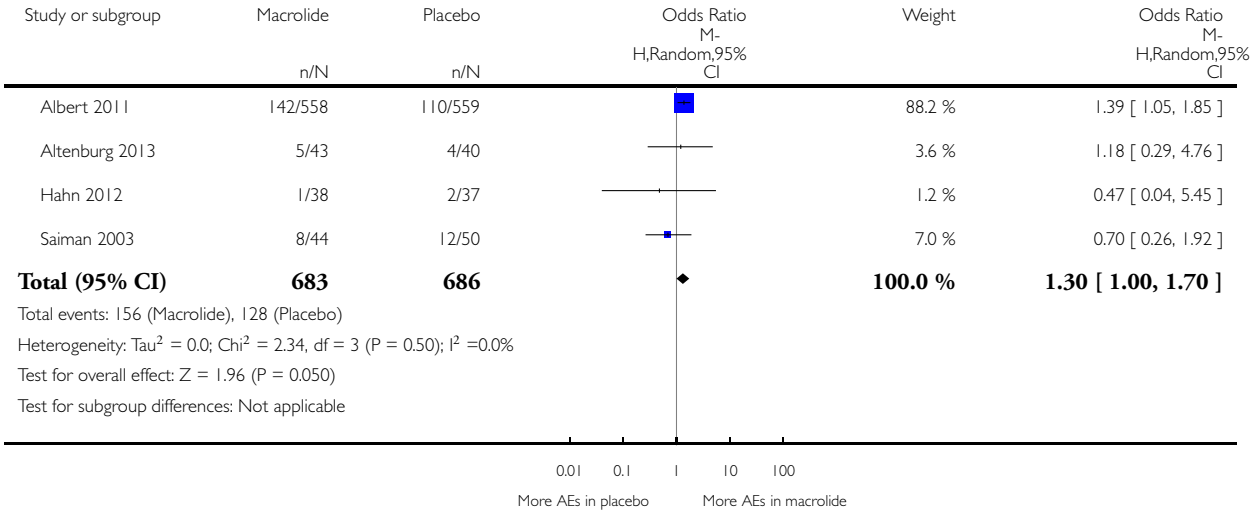


Analysis 2.1. Comparison 2 Ear and labyrinth disorders, Outcome 1 Hearing loss.

Review: Adverse events in people taking macrolide antibiotics versus placebo for any indication

Comparison: 2 Ear and labyrinth disorders

Outcome: 1 Hearing loss



Analysis 3.1. Comparison 3 Gastrointestinal disorders, Outcome 1 Nausea.

Review: Adverse events in people taking macrolide antibiotics versus placebo for any indication

Comparison: 3 Gastrointestinal disorders

Outcome: 1 Nausea

Study or subgroup	Macrolide n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Altenburg 2013	6/43	6/40		1.6 %	0.92 [0.27, 3.12]
Black 2001	13/105	5/114		2.0 %	3.08 [1.06, 8.96]
Branden 2004	5/51	1/52		0.5 %	5.54 [0.62, 49.22]
Brickfield 1986	5/27	9/25		1.5 %	0.40 [0.11, 1.44]
Czarnetzki 2015	15/66	2/66		1.0 %	9.41 [2.06, 43.06]
Eschenbach 1991	194/586	142/548		11.0 %	1.41 [1.09, 1.83]
Gibson 2017	31/213	20/207		4.9 %	1.59 [0.88, 2.90]
Grayston 2005	284/2004	198/2008		12.6 %	1.51 [1.24, 1.83]
Hahn 2012	10/38	3/37		1.2 %	4.05 [1.01, 16.15]
Halperin 1999	18/144	8/166		2.8 %	2.82 [1.19, 6.70]
Haye 1998	7/87	1/82		0.6 %	7.09 [0.85, 58.93]
Hodgson 2016	1/21	1/21		0.3 %	1.00 [0.06, 17.12]
Jackson 1999	4/44	1/44		0.5 %	4.30 [0.46, 40.12]
Jespersen 2006	127/2155	93/2175		10.6 %	1.40 [1.07, 1.84]
Jun 2014	11/56	3/58		1.3 %	4.48 [1.18, 17.05]
Klebanoff 1995	149/466	112/466		10.3 %	1.49 [1.11, 1.98]
Martin 1997	68/205	44/209		7.1 %	1.86 [1.20, 2.90]
McCormack 1987	77/360	75/391		8.8 %	1.15 [0.80, 1.64]
McGregor 1990	32/119	14/110		4.0 %	2.52 [1.26, 5.04]
Ogrendik 2007	5/41	4/40		1.2 %	1.25 [0.31, 5.04]
Ogrendik 2011	6/50	4/50		1.3 %	1.57 [0.41, 5.93]
Petersen 1997	14/93	9/93		2.7 %	1.65 [0.68, 4.04]
Sadreddini 2009	4/51	2/53		0.8 %	2.17 [0.38, 12.40]
Saiman 2003	29/87	16/98		4.0 %	2.56 [1.28, 5.14]
Saiman 2010	11/131	12/129		2.9 %	0.89 [0.38, 2.11]

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Study or subgroup	Macrolide n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Serisier 2013	0/59	3/58		0.3 %	0.13 [0.01, 2.64]
Shafuddin 2015	13/97	1/94		0.6 %	14.39 [1.84, 112.39]
Smith 2000	17/75	18/75		3.5 %	0.93 [0.44, 1.98]
Total (95% CI)	**7474**	**7509**		**100.0 %**	**1.61 [1.37, 1.90]**

Total events: 1156 (Macrolide), 807 (Placebo)

Heterogeneity: $Tau^2 = 0.04$; $Chi^2 = 41.48$, df = 27 (P = 0.04); $I^2 = 35\%$

Test for overall effect: Z = 5.81 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 3.2. Comparison 3 Gastrointestinal disorders, Outcome 2 Nausea - subgroup analysis by macrolide.

Review: Adverse events in people taking macrolide antibiotics versus placebo for any indication

Comparison: 3 Gastrointestinal disorders

Outcome: 2 Nausea - subgroup analysis by macrolide

Study or subgroup	Macrolide n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Azithromycin					
Altenburg 2013	6/43	6/40		2.0 %	0.92 [0.27, 3.12]
Branden 2004	5/51	1/52		0.7 %	5.54 [0.62, 49.22]
Gibson 2017	31/213	20/207		5.8 %	1.59 [0.88, 2.90]
Grayston 2005	284/2004	198/2008		12.9 %	1.51 [1.24, 1.83]
Hahn 2012	10/38	3/37		1.6 %	4.05 [1.01, 16.15]
Haye 1998	7/87	1/82		0.7 %	7.09 [0.85, 58.93]
Hodgson 2016	1/21	1/21		0.4 %	1.00 [0.06, 17.12]
Jackson 1999	4/44	1/44		0.6 %	4.30 [0.46, 40.12]

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Study or subgroup	Macrolide n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Saiman 2003	29/87	16/98		4.7 %	2.56 [1.28, 5.14]
Saiman 2010	11/131	12/129		3.5 %	0.89 [0.38, 2.11]
Subtotal (95% CI)	**2719**	**2718**		**32.9 %**	**1.66 [1.27, 2.16]**
Total events: 388 (Macrolide), 259 (Placebo)					
Heterogeneity: Tau^2 = 0.03; Chi^2 = 10.38, df = 9 (P = 0.32); I^2 =13%					
Test for overall effect: Z = 3.74 (P = 0.00018)					
2 Erythromycin					
Brickfield 1986	5/27	9/25		1.8 %	0.40 [0.11, 1.44]
Czarnetzki 2015	15/66	2/66		1.3 %	9.41 [2.06, 43.06]
Eschenbach 1991	194/586	142/548		11.6 %	1.41 [1.09, 1.83]
Halperin 1999	18/144	8/166		3.5 %	2.82 [1.19, 6.70]
Jun 2014	11/56	3/58		1.7 %	4.48 [1.18, 17.05]
Klebanoff 1995	149/466	112/466		11.0 %	1.49 [1.11, 1.98]
Martin 1997	68/205	44/209		8.0 %	1.86 [1.20, 2.90]
McCormack 1987	77/360	75/391		9.6 %	1.15 [0.80, 1.64]
McGregor 1990	32/119	14/110		4.8 %	2.52 [1.26, 5.04]
Petersen 1997	14/93	9/93		3.3 %	1.65 [0.68, 4.04]
Sadreddini 2009	4/51	2/53		1.0 %	2.17 [0.38, 12.40]
Serisier 2013	0/59	3/58		0.4 %	0.13 [0.01, 2.64]
Smith 2000	17/75	18/75		4.2 %	0.93 [0.44, 1.98]
Subtotal (95% CI)	**2307**	**2318**		**62.2 %**	**1.58 [1.23, 2.04]**
Total events: 604 (Macrolide), 441 (Placebo)					
Heterogeneity: Tau^2 = 0.08; Chi^2 = 24.11, df = 12 (P = 0.02); I^2 =50%					
Test for overall effect: Z = 3.54 (P = 0.00041)					
3 Roxithromycin					
Black 2001	13/105	5/114		2.5 %	3.08 [1.06, 8.96]
Ogrendik 2011	6/50	4/50		1.7 %	1.57 [0.41, 5.93]
Shafuddin 2015	13/97	1/94		0.8 %	14.39 [1.84, 112.39]
Subtotal (95% CI)	**252**	**258**		**4.9 %**	**3.29 [1.15, 9.43]**
Total events: 32 (Macrolide), 10 (Placebo)					
Heterogeneity: Tau^2 = 0.35; Chi^2 = 3.34, df = 2 (P = 0.19); I^2 =40%					
Test for overall effect: Z = 2.22 (P = 0.026)					
Total (95% CI)	**5278**	**5294**		**100.0 %**	**1.67 [1.39, 2.00]**
Total events: 1024 (Macrolide), 710 (Placebo)					
Heterogeneity: Tau^2 = 0.06; Chi^2 = 41.00, df = 25 (P = 0.02); I^2 =39%					
Test for overall effect: Z = 5.45 (P < 0.00001)					

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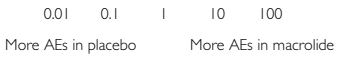
Study or subgroup	Macrolide n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Test for subgroup differences: Chi^2 = 1.76, df = 2 (P = 0.41), I^2 =0.0%					



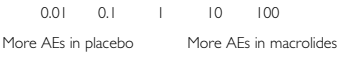
Analysis 3.3. Comparison 3 Gastrointestinal disorders, Outcome 3 Nausea - subgroup analysis by route of administration.

Review: Adverse events in people taking macrolide antibiotics versus placebo for any indication

Comparison: 3 Gastrointestinal disorders

Outcome: 3 Nausea - subgroup analysis by route of administration

Study or subgroup	Macrolides n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Intravenous					
Czarnetzki 2015	15/66	2/66		1.0 %	9.41 [2.06, 43.06]
Jun 2014	11/56	3/58		1.3 %	4.48 [1.18, 17.05]
Smith 2000	17/75	18/75		3.5 %	0.93 [0.44, 1.98]
Subtotal (95% CI)	**197**	**199**		**5.9 %**	**3.04 [0.69, 13.51]**
Total events: 43 (Macrolides), 23 (Placebo)					
Heterogeneity: Tau^2 = 1.35; Chi^2 = 9.49, df = 2 (P = 0.01); I^2 =79%					
Test for overall effect: Z = 1.46 (P = 0.14)					
2 Peroral					
Altenburg 2013	6/43	6/40		1.6 %	0.92 [0.27, 3.12]
Black 2001	13/105	5/114		2.0 %	3.08 [1.06, 8.96]
Branden 2004	5/51	1/52		0.5 %	5.54 [0.62, 49.22]
Brickfield 1986	5/27	9/25		1.5 %	0.40 [0.11, 1.44]
Eschenbach 1991	194/586	142/548		11.0 %	1.41 [1.09, 1.83]
Gibson 2017	31/213	20/207		4.9 %	1.59 [0.88, 2.90]
Grayston 2005	284/2004	198/2008		12.6 %	1.51 [1.24, 1.83]



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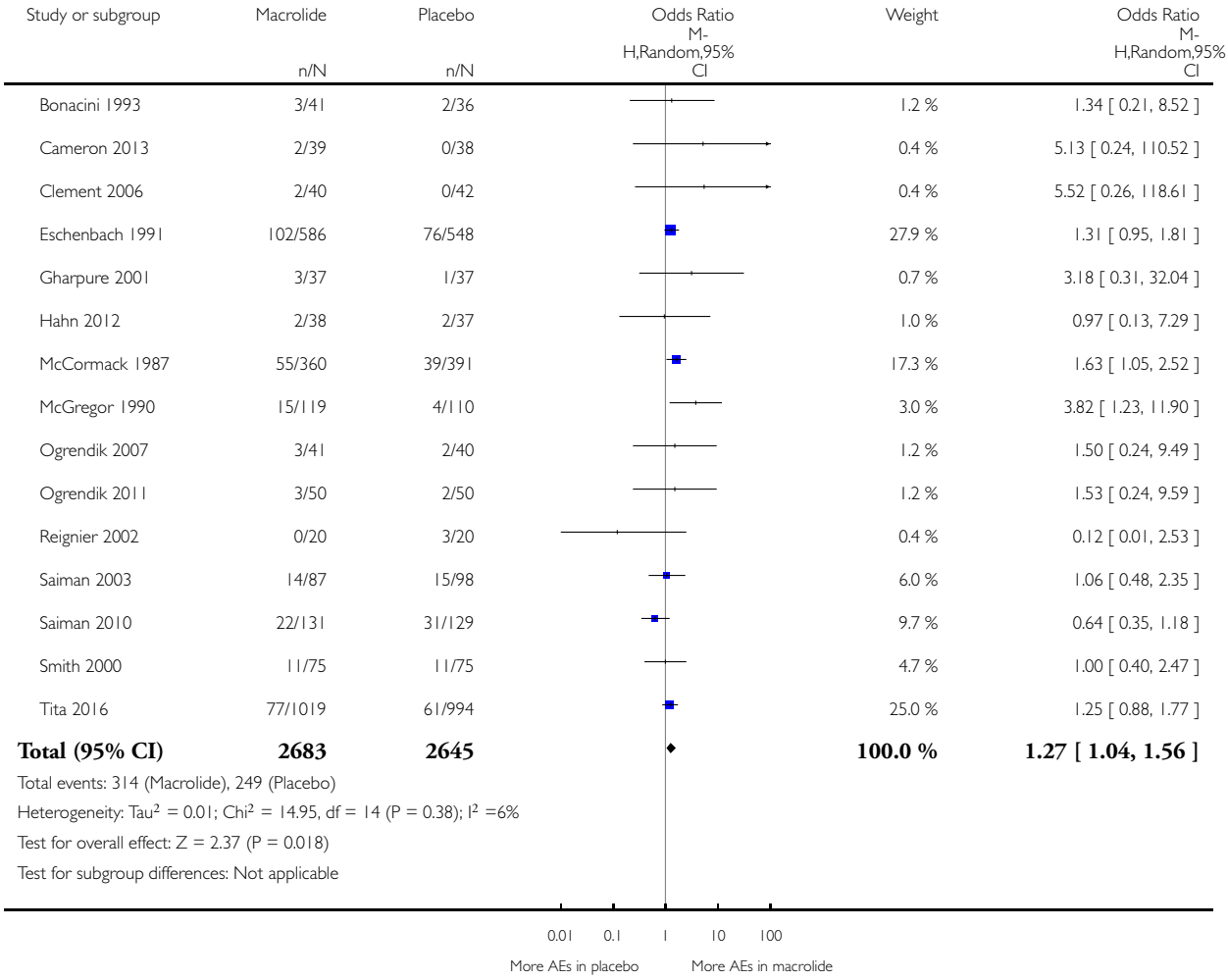
Study or subgroup	Macrolides n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Hahn 2012	10/38	3/37		1.2 %	4.05 [1.01, 16.15]
Halperin 1999	18/144	8/166		2.8 %	2.82 [1.19, 6.70]
Haye 1998	7/87	1/82		0.6 %	7.09 [0.85, 58.93]
Hodgson 2016	1/21	1/21		0.3 %	1.00 [0.06, 17.12]
Jackson 1999	4/44	1/44		0.5 %	4.30 [0.46, 40.12]
Jespersen 2006	127/2155	93/2175		10.6 %	1.40 [1.07, 1.84]
Klebanoff 1995	149/466	112/466		10.3 %	1.49 [1.11, 1.98]
Martin 1997	68/205	44/209		7.1 %	1.86 [1.20, 2.90]
McCormack 1987	77/360	75/391		8.8 %	1.15 [0.80, 1.64]
McGregor 1990	32/119	14/110		4.0 %	2.52 [1.26, 5.04]
Ogrendik 2007	5/41	4/40		1.2 %	1.25 [0.31, 5.04]
Ogrendik 2011	6/50	4/50		1.3 %	1.57 [0.41, 5.93]
Petersen 1997	14/93	9/93		2.7 %	1.65 [0.68, 4.04]
Sadreddini 2009	4/51	2/53		0.8 %	2.17 [0.38, 12.40]
Saiman 2003	29/87	16/98		4.0 %	2.56 [1.28, 5.14]
Saiman 2010	11/131	12/129		2.9 %	0.89 [0.38, 2.11]
Serisier 2013	0/59	3/58		0.3 %	0.13 [0.01, 2.64]
Shafuddin 2015	13/97	1/94		0.6 %	14.39 [1.84, 112.39]
Subtotal (95% CI)	**7277**	**7310**		**94.1 %**	**1.57 [1.35, 1.81]**
Total events: 1113 (Macrolides), 784 (Placebo)					
Heterogeneity: Tau^2 = 0.02; Chi^2 = 31.76, df = 24 (P = 0.13); I^2 =24%					
Test for overall effect: Z = 6.05 (P < 0.00001)					
Total (95% CI)	**7474**	**7509**		**100.0 %**	**1.61 [1.37, 1.90]**
Total events: 1156 (Macrolides), 807 (Placebo)					
Heterogeneity: Tau^2 = 0.04; Chi^2 = 41.48, df = 27 (P = 0.04); I^2 =35%					
Test for overall effect: Z = 5.81 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 0.76, df = 1 (P = 0.38), I^2 =0.0%					

Analysis 3.4. Comparison 3 Gastrointestinal disorders, Outcome 4 Vomiting.

Review: Adverse events in people taking macrolide antibiotics versus placebo for any indication

Comparison: 3 Gastrointestinal disorders

Outcome: 4 Vomiting

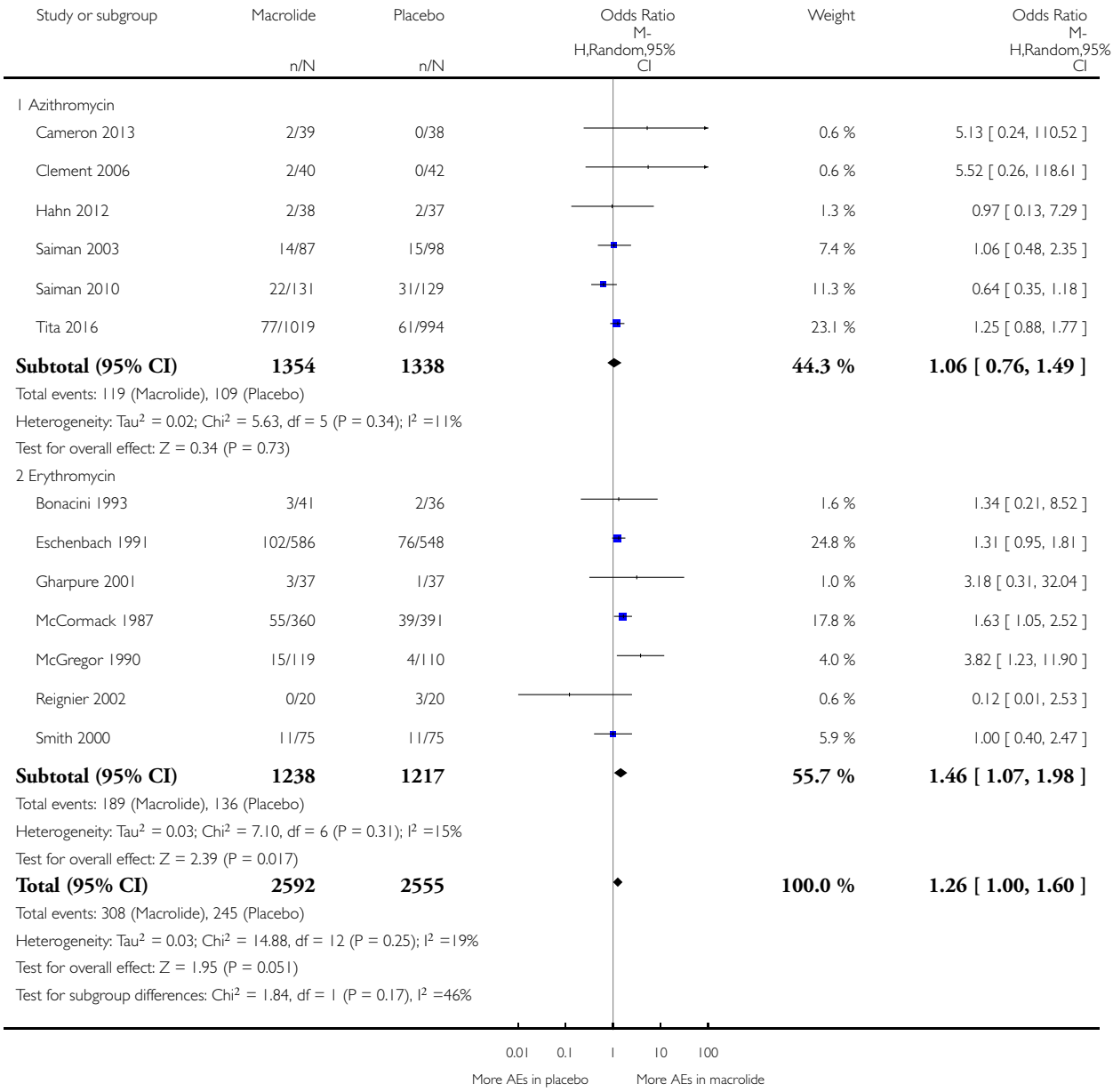


Analysis 3.5. Comparison 3 Gastrointestinal disorders, Outcome 5 Vomiting - subgroup analysis by macrolide.

Review: Adverse events in people taking macrolide antibiotics versus placebo for any indication

Comparison: 3 Gastrointestinal disorders

Outcome: 5 Vomiting - subgroup analysis by macrolide



Analysis 3.6. Comparison 3 Gastrointestinal disorders, Outcome 6 Vomiting - subgroup analysis by route of administration.

Review: Adverse events in people taking macrolide antibiotics versus placebo for any indication

Comparison: 3 Gastrointestinal disorders

Outcome: 6 Vomiting - subgroup analysis by route of administration

Study or subgroup	Macrolides n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Intravenous					
Bonacini 1993	3/41	2/36		1.2 %	1.34 [0.21, 8.52]
Gharpure 2001	3/37	1/37		0.7 %	3.18 [0.31, 32.04]
Reignier 2002	0/20	3/20		0.4 %	0.12 [0.01, 2.53]
Smith 2000	11/75	11/75		4.7 %	1.00 [0.40, 2.47]
Tita 2016	77/1019	61/994		25.0 %	1.25 [0.88, 1.77]
Subtotal (95% CI)	**1192**	**1162**		**32.0 %**	**1.21 [0.88, 1.66]**
Total events: 94 (Macrolides), 78 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 3.10, df = 4 (P = 0.54); I^2 =0.0%					
Test for overall effect: Z = 1.18 (P = 0.24)					
2 Peroral					
Cameron 2013	2/39	0/38		0.4 %	5.13 [0.24, 110.52]
Clement 2006	2/40	0/42		0.4 %	5.52 [0.26, 118.61]
Eschenbach 1991	102/586	76/548		27.9 %	1.31 [0.95, 1.81]
Hahn 2012	2/38	2/37		1.0 %	0.97 [0.13, 7.29]
McCormack 1987	55/360	39/391		17.3 %	1.63 [1.05, 2.52]
McGregor 1990	15/119	4/110		3.0 %	3.82 [1.23, 11.90]
Ogrendik 2007	3/41	2/40		1.2 %	1.50 [0.24, 9.49]
Ogrendik 2011	3/50	2/50		1.2 %	1.53 [0.24, 9.59]
Saiman 2003	14/87	15/98		6.0 %	1.06 [0.48, 2.35]
Saiman 2010	22/131	31/129		9.7 %	0.64 [0.35, 1.18]
Subtotal (95% CI)	**1491**	**1483**		**68.0 %**	**1.32 [0.97, 1.78]**
Total events: 220 (Macrolides), 171 (Placebo)					
Heterogeneity: Tau^2 = 0.05; Chi^2 = 11.71, df = 9 (P = 0.23); I^2 =23%					
Test for overall effect: Z = 1.77 (P = 0.076)					
Total (95% CI)	**2683**	**2645**		**100.0 %**	**1.27 [1.04, 1.56]**
Total events: 314 (Macrolides), 249 (Placebo)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 14.95, df = 14 (P = 0.38); I^2 =6%					
Test for overall effect: Z = 2.37 (P = 0.018)					
Test for subgroup differences: Chi^2 = 0.14, df = 1 (P = 0.70), I^2 =0.0%					

Analysis 3.7. Comparison 3 Gastrointestinal disorders, Outcome 7 Nausea and vomiting.

Review: Adverse events in people taking macrolide antibiotics versus placebo for any indication

Comparison: 3 Gastrointestinal disorders

Outcome: 7 Nausea and vomiting

Study or subgroup	Macrolide n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Heppner 2005	11/170	6/94		17.9 %	1.01 [0.36, 2.84]
Lanza 1998	2/60	2/29		4.7 %	0.47 [0.06, 3.48]
Mandhane 2017	22/140	29/139		50.4 %	0.71 [0.38, 1.30]
McGregor 1991	2/28	0/27		2.0 %	5.19 [0.24, 113.22]
Narchi 1993	2/22	1/22		3.1 %	2.10 [0.18, 25.01]
Peterson 1996	0/55	2/34		2.0 %	0.12 [0.01, 2.52]
Uzun 2014	3/47	2/45		5.6 %	1.47 [0.23, 9.21]
Wong 2012	9/71	5/70		14.4 %	1.89 [0.60, 5.94]
Total (95% CI)	**593**	**460**		**100.0 %**	**0.92 [0.60, 1.42]**

Total events: 51 (Macrolide), 47 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 6.31$, df = 7 (P = 0.50); $I^2 = 0.0\%$

Test for overall effect: Z = 0.37 (P = 0.71)

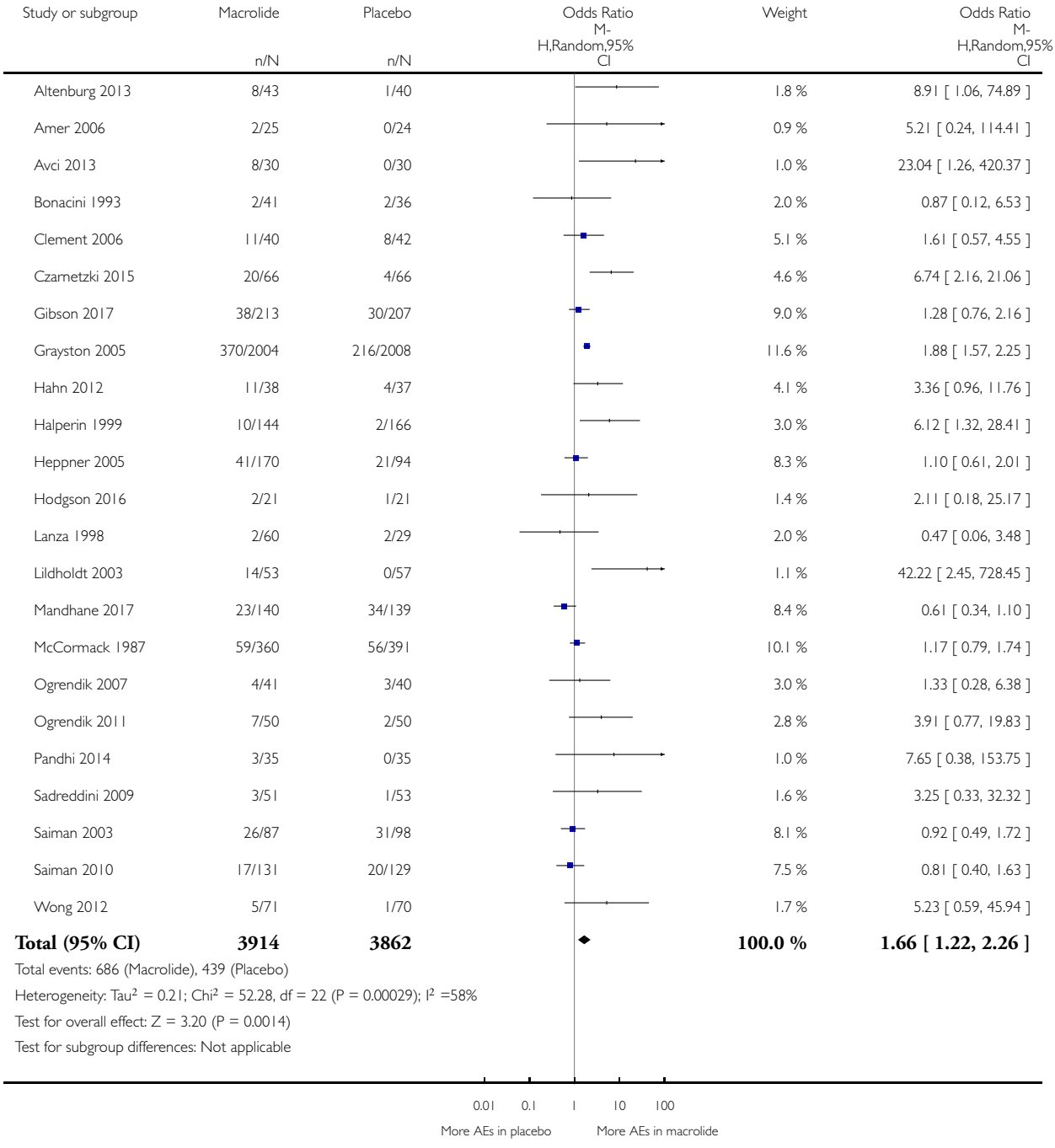
Test for subgroup differences: Not applicable

Analysis 3.8. Comparison 3 Gastrointestinal disorders, Outcome 8 Abdominal pain.

Review: Adverse events in people taking macrolide antibiotics versus placebo for any indication

Comparison: 3 Gastrointestinal disorders

Outcome: 8 Abdominal pain

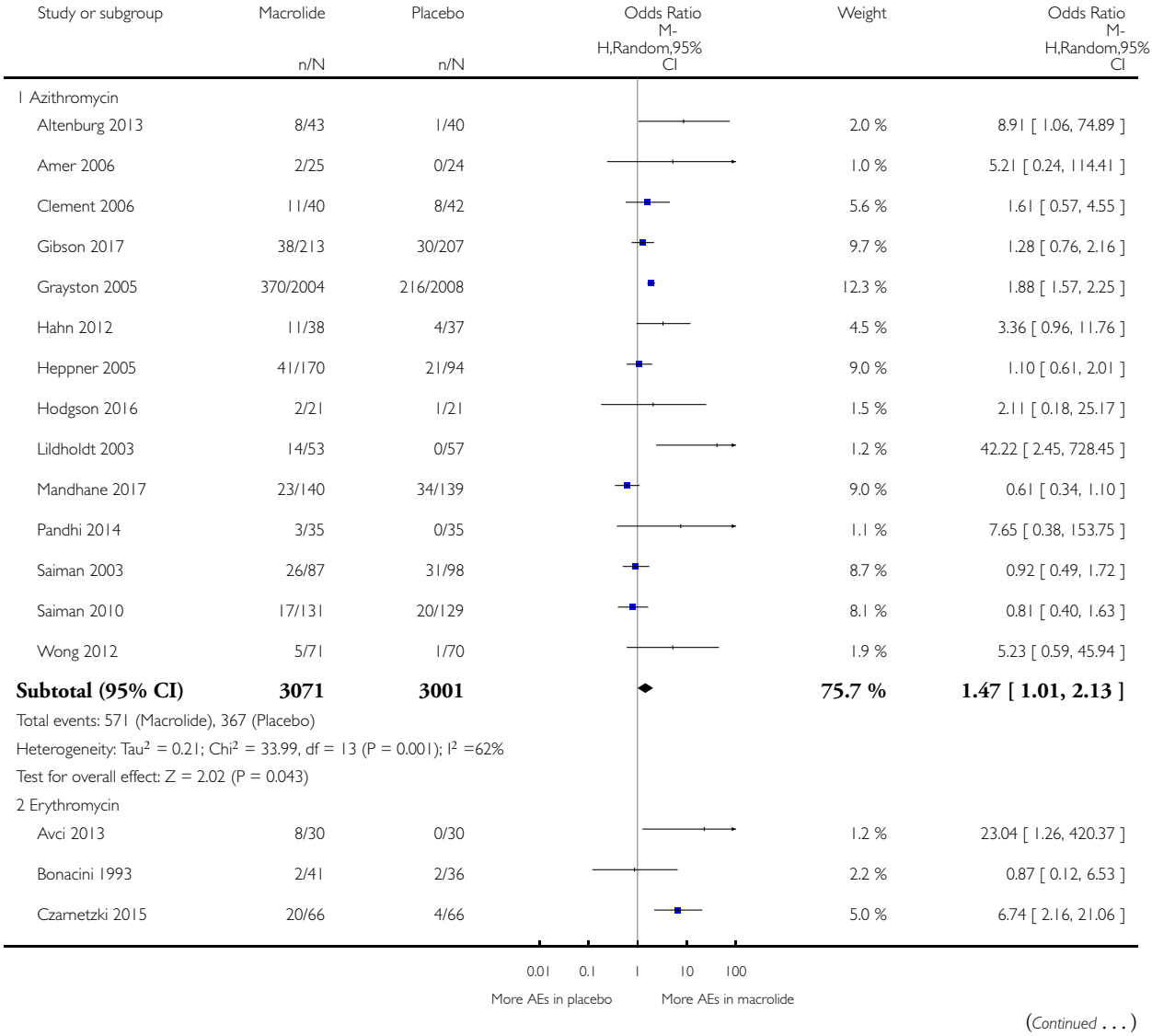


Analysis 3.9. Comparison 3 Gastrointestinal disorders, Outcome 9 Abdominal pain - subgroup analysis by macrolide.

Review: Adverse events in people taking macrolide antibiotics versus placebo for any indication

Comparison: 3 Gastrointestinal disorders

Outcome: 9 Abdominal pain - subgroup analysis by macrolide



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Study or subgroup	Macrolide n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Halperin 1999	10/144	2/166		3.4 %	6.12 [1.32, 28.41]
McCormack 1987	59/360	56/391		10.8 %	1.17 [0.79, 1.74]
Sadreddini 2009	3/51	1/53		1.8 %	3.25 [0.33, 32.32]
Subtotal (95% CI)	**692**	**742**		**24.3 %**	**3.16 [1.14, 8.75]**
Total events: 102 (Macrolide), 65 (Placebo)					
Heterogeneity: Tau^2 = 0.93; Chi^2 = 15.80, df = 5 (P = 0.01); I^2 =68%					
Test for overall effect: Z = 2.22 (P = 0.026)					
Total (95% CI)	**3763**	**3743**		**100.0 %**	**1.68 [1.21, 2.34]**
Total events: 673 (Macrolide), 432 (Placebo)					
Heterogeneity: Tau^2 = 0.22; Chi^2 = 49.61, df = 19 (P = 0.00015); I^2 =62%					
Test for overall effect: Z = 3.12 (P = 0.0018)					
Test for subgroup differences: Chi^2 = 1.94, df = 1 (P = 0.16), I^2 =48%					

Analysis 3.10. Comparison 3 Gastrointestinal disorders, Outcome 10 Diarrhoea.

Review: Adverse events in people taking macrolide antibiotics versus placebo for any indication

Comparison: 3 Gastrointestinal disorders

Outcome: 10 Diarrhoea

Study or subgroup	Macrolide n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Altenburg 2013	9/43	1/40		1.0 %	10.32 [1.24, 85.71]
Amer 2006	2/25	0/24		0.5 %	5.21 [0.24, 114.41]
Andere 2017	2/20	0/20		0.5 %	5.54 [0.25, 123.08]
Black 2001	6/105	10/114		2.8 %	0.63 [0.22, 1.80]
Branden 2004	16/51	2/52		1.7 %	11.43 [2.47, 52.89]
Cameron 2013	4/39	3/38		1.7 %	1.33 [0.28, 6.40]
Clement 2006	3/40	4/42		1.7 %	0.77 [0.16, 3.68]
Eschenbach 1991	94/586	64/548		5.4 %	1.44 [1.03, 2.03]
Gibson 2017	72/213	39/207		5.0 %	2.20 [1.40, 3.45]
Grassly 2016	92/376	63/378		5.3 %	1.62 [1.13, 2.32]
Grayston 2005	724/2004	446/2008		5.9 %	1.98 [1.72, 2.28]
Hahn 2012	12/38	5/37		2.5 %	2.95 [0.92, 9.47]
Halperin 1999	29/144	14/166		4.0 %	2.74 [1.38, 5.42]
Haye 1998	11/87	5/82		2.6 %	2.23 [0.74, 6.72]
Heppner 2005	14/170	17/94		3.8 %	0.41 [0.19, 0.87]
Hodgson 2016	4/21	2/21		1.3 %	2.24 [0.36, 13.78]
Hyde 2001	6/73	5/74		2.3 %	1.24 [0.36, 4.24]
Jackson 1999	8/44	8/44		2.7 %	1.00 [0.34, 2.95]
Jespersen 2006	292/2155	151/2175		5.8 %	2.10 [1.71, 2.58]
Klebanoff 1995	60/466	42/466		5.1 %	1.49 [0.98, 2.26]
Lanza 1998	4/60	2/29		1.4 %	0.96 [0.17, 5.60]
Mandhane 2017	42/140	44/139		4.7 %	0.93 [0.56, 1.54]
McCormack 1987	23/360	23/391		4.4 %	1.09 [0.60, 1.98]
McGregor 1990	6/119	0/110		0.6 %	12.66 [0.70, 227.35]
O'Connor 2003	313/3866	54/3856		5.5 %	6.20 [4.63, 8.31]

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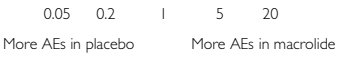
Study or subgroup	Macrolide n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Ogrendik 2007	2/41	1/40		0.8 %	2.00 [0.17, 22.97]
Ogrendik 2011	3/50	2/50		1.3 %	1.53 [0.24, 9.59]
Petersen 1997	4/93	11/93		2.4 %	0.34 [0.10, 1.09]
Saiman 2003	20/87	8/98		3.3 %	3.36 [1.39, 8.09]
Saiman 2010	6/131	11/129		2.9 %	0.51 [0.18, 1.44]
Sampaio 2011	2/20	0/20		0.5 %	5.54 [0.25, 123.08]
Uzun 2014	9/47	1/45		1.1 %	10.42 [1.26, 86.05]
Videler 2011	2/29	2/31		1.1 %	1.07 [0.14, 8.17]
Wiesli 2002	2/20	1/20		0.8 %	2.11 [0.18, 25.35]
Wilson 1977	9/26	5/25		2.2 %	2.12 [0.59, 7.54]
Wong 2012	13/71	4/70		2.5 %	3.70 [1.14, 11.97]
Yeo 1993	6/58	9/60		2.6 %	0.65 [0.22, 1.97]
Total (95% CI)	**11918**	**11836**		**100.0 %**	**1.70 [1.34, 2.16]**

Total events: 1926 (Macrolide), 1059 (Placebo)

Heterogeneity: $Tau^2 = 0.25$; $Chi^2 = 140.51$, df = 36 (P<0.00001); $I^2 = 74\%$

Test for overall effect: Z = 4.37 (P = 0.000012)

Test for subgroup differences: Not applicable



Analysis 3.11. Comparison 3 Gastrointestinal disorders, Outcome 11 Diarrhoea - subgroup analysis by macrolide.

Review: Adverse events in people taking macrolide antibiotics versus placebo for any indication

Comparison: 3 Gastrointestinal disorders

Outcome: 11 Diarrhoea - subgroup analysis by macrolide

Study or subgroup	Macrolide n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Azithromycin					
Altenburg 2013	9/43	1/40		1.0 %	10.32 [1.24, 85.71]
Amer 2006	2/25	0/24		0.5 %	5.21 [0.24, 114.41]
Branden 2004	16/51	2/52		1.7 %	11.43 [2.47, 52.89]
Cameron 2013	4/39	3/38		1.7 %	1.33 [0.28, 6.40]
Clement 2006	3/40	4/42		1.7 %	0.77 [0.16, 3.68]
Gibson 2017	72/213	39/207		5.0 %	2.20 [1.40, 3.45]
Grassly 2016	92/376	63/378		5.3 %	1.62 [1.13, 2.32]
Grayston 2005	724/2004	446/2008		5.9 %	1.98 [1.72, 2.28]
Hahn 2012	12/38	5/37		2.5 %	2.95 [0.92, 9.47]
Haye 1998	11/87	5/82		2.6 %	2.23 [0.74, 6.72]
Heppner 2005	14/170	17/94		3.8 %	0.41 [0.19, 0.87]
Hodgson 2016	4/21	2/21		1.3 %	2.24 [0.36, 13.78]
Hyde 2001	6/73	5/74		2.3 %	1.24 [0.36, 4.24]
Jackson 1999	8/44	8/44		2.7 %	1.00 [0.34, 2.95]
Mandhane 2017	42/140	44/139		4.7 %	0.93 [0.56, 1.54]
O'Connor 2003	313/3866	54/3856		5.5 %	6.20 [4.63, 8.31]
Saiman 2003	20/87	8/98		3.3 %	3.36 [1.39, 8.09]
Saiman 2010	6/131	11/129		2.9 %	0.51 [0.18, 1.44]
Sampaio 2011	2/20	0/20		0.5 %	5.54 [0.25, 123.08]
Uzun 2014	9/47	1/45		1.1 %	10.42 [1.26, 86.05]
Videler 2011	2/29	2/31		1.1 %	1.07 [0.14, 8.17]
Wong 2012	13/71	4/70		2.5 %	3.70 [1.14, 11.97]
Subtotal (95% CI)	**7615**	**7529**		**59.7 %**	**1.96 [1.37, 2.81]**
Total events: 1384 (Macrolide), 724 (Placebo)					

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Study or subgroup	Macrolide n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Heterogeneity: Tau² = 0.39; Chi² = 108.72, df = 21 (P<0.00001); I² =81%					
Test for overall effect: Z = 3.68 (P = 0.00024)					
2 Clarithromycin					
Andere 2017	2/20	0/20		0.5 %	5.54 [0.25, 123.08]
Jespersen 2006	292/2155	151/2175		5.8 %	2.10 [1.71, 2.58]
Lanza 1998	4/60	2/29		1.4 %	0.96 [0.17, 5.60]
Ogrendik 2007	2/41	1/40		0.8 %	2.00 [0.17, 22.97]
Subtotal (95% CI)	**2276**	**2264**		**8.6 %**	**2.09 [1.70, 2.56]**
Total events: 300 (Macrolide), 154 (Placebo)					
Heterogeneity: Tau² = 0.0; Chi² = 1.13, df = 3 (P = 0.77); I² =0.0%					
Test for overall effect: Z = 7.08 (P < 0.00001)					
3 Erythromycin					
Eschenbach 1991	94/586	64/548		5.4 %	1.44 [1.03, 2.03]
Halperin 1999	29/144	14/166		4.0 %	2.74 [1.38, 5.42]
Klebanoff 1995	60/466	42/466		5.1 %	1.49 [0.98, 2.26]
McCormack 1987	23/360	23/391		4.4 %	1.09 [0.60, 1.98]
McGregor 1990	6/119	0/110		0.6 %	12.66 [0.70, 227.35]
Petersen 1997	4/93	11/93		2.4 %	0.34 [0.10, 1.09]
Wilson 1977	9/26	5/25		2.2 %	2.12 [0.59, 7.54]
Yeo 1993	6/58	9/60		2.6 %	0.65 [0.22, 1.97]
Subtotal (95% CI)	**1852**	**1859**		**26.8 %**	**1.36 [0.94, 1.98]**
Total events: 231 (Macrolide), 168 (Placebo)					
Heterogeneity: Tau² = 0.12; Chi² = 14.58, df = 7 (P = 0.04); I² =52%					
Test for overall effect: Z = 1.63 (P = 0.10)					
4 Roxithromycin					
Black 2001	6/105	10/114		2.8 %	0.63 [0.22, 1.80]
Ogrendik 2011	3/50	2/50		1.3 %	1.53 [0.24, 9.59]
Wiesli 2002	2/20	1/20		0.8 %	2.11 [0.18, 25.35]
Subtotal (95% CI)	**175**	**184**		**4.9 %**	**0.88 [0.38, 2.07]**
Total events: 11 (Macrolide), 13 (Placebo)					
Heterogeneity: Tau² = 0.0; Chi² = 1.22, df = 2 (P = 0.54); I² =0.0%					
Test for overall effect: Z = 0.29 (P = 0.77)					
Total (95% CI)	**11918**	**11836**		**100.0 %**	**1.70 [1.34, 2.16]**
Total events: 1926 (Macrolide), 1059 (Placebo)					
Heterogeneity: Tau² = 0.25; Chi² = 140.51, df = 36 (P<0.00001); I² =74%					
Test for overall effect: Z = 4.37 (P = 0.000012)					
Test for subgroup differences: Chi² = 6.93, df = 3 (P = 0.07), I² =57%					

Analysis 3.12. Comparison 3 Gastrointestinal disorders, Outcome 12 Gastrointestinal disorders not otherwise specified.

Review: Adverse events in people taking macrolide antibiotics versus placebo for any indication

Comparison: 3 Gastrointestinal disorders

Outcome: 12 Gastrointestinal disorders not otherwise specified

Study or subgroup	Macrolide n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Alger 1991	9/39	1/44		2.0 %	12.90 [1.55, 107.25]
Anderson 1999	31/150	12/152		7.7 %	3.04 [1.49, 6.18]
Anthony 2014	3/39	1/39		1.7 %	3.17 [0.31, 31.86]
Beigelman 2015	7/19	8/20		4.2 %	0.88 [0.24, 3.18]
Berkhof 2013	5/42	6/42		4.3 %	0.81 [0.23, 2.89]
Dunlay 1987	4/32	0/31		1.1 %	9.95 [0.51, 192.99]
Hahn 2006	5/24	2/21		2.7 %	2.50 [0.43, 14.51]
Haxel 2015	5/29	0/29		1.1 %	13.24 [0.70, 251.60]
Hooton 1990	18/34	3/35		3.9 %	12.00 [3.07, 46.83]
Ikeoka 2007	5/42	0/40		1.1 %	11.88 [0.64, 222.25]
Johnston 2016	25/97	20/102		8.1 %	1.42 [0.73, 2.78]
Kaiser 2001	32/133	14/132		8.0 %	2.67 [1.35, 5.28]
Kaul 2004	22/230	18/236		8.2 %	1.28 [0.67, 2.46]
King 1996	13/49	2/42		3.2 %	7.22 [1.52, 34.21]
Kvien 2004	30/81	12/71		7.3 %	2.89 [1.34, 6.23]
Mercer 1992	7/106	8/114		5.4 %	0.94 [0.33, 2.68]
Pradeep 2011	1/20	0/20		0.9 %	3.15 [0.12, 82.16]
Seemungal 2008	8/53	8/56		5.3 %	1.07 [0.37, 3.08]
Shanson 1985	29/56	10/53		6.6 %	4.62 [1.94, 10.97]
Uzun 2014	4/47	7/45		4.2 %	0.50 [0.14, 1.86]
Vainas 2005	15/257	10/252		6.9 %	1.50 [0.66, 3.40]
Vos 2011	3/40	1/43		1.7 %	3.41 [0.34, 34.17]

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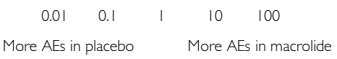
Study or subgroup	Macrolide n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Wilson 1979	7/27	5/30		4.2 %	1.75 [0.48, 6.35]
Total (95% CI)	**1646**	**1649**		**100.0 %**	**2.16 [1.56, 3.00]**
Total events: 288 (Macrolide), 148 (Placebo)					
Heterogeneity: $Tau^2 = 0.23$; $Chi^2 = 38.05$, df = 22 (P = 0.02); $I^2 = 42\%$					
Test for overall effect: Z = 4.62 (P < 0.00001)					
Test for subgroup differences: Not applicable					



Analysis 3.13. Comparison 3 Gastrointestinal disorders, Outcome 13 Gastrointestinal disorders not otherwise specified - subgroup analysis by macrolide.

Review: Adverse events in people taking macrolide antibiotics versus placebo for any indication

Comparison: 3 Gastrointestinal disorders

Outcome: 13 Gastrointestinal disorders not otherwise specified - subgroup analysis by macrolide

Study or subgroup	Macrolide n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Azithromycin					
Anderson 1999	31/150	12/152		8.0 %	3.04 [1.49, 6.18]
Anthony 2014	3/39	1/39		1.9 %	3.17 [0.31, 31.86]
Beigelman 2015	7/19	8/20		4.4 %	0.88 [0.24, 3.18]
Berkhof 2013	5/42	6/42		4.5 %	0.81 [0.23, 2.89]
Hahn 2006	5/24	2/21		2.9 %	2.50 [0.43, 14.51]
Ikeoka 2007	5/42	0/40		1.2 %	11.88 [0.64, 222.25]
Johnston 2016	25/97	20/102		8.3 %	1.42 [0.73, 2.78]
Kaiser 2001	32/133	14/132		8.2 %	2.67 [1.35, 5.28]
Kaul 2004	22/230	18/236		8.4 %	1.28 [0.67, 2.46]

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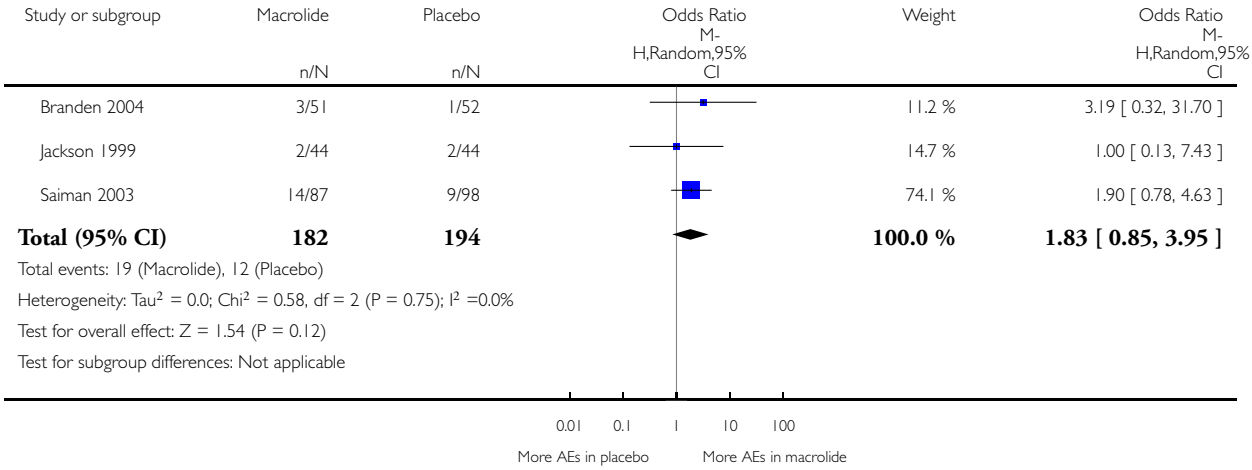
Study or subgroup	Macrolide n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Kvien 2004	30/81	12/71		7.5 %	2.89 [1.34, 6.23]
Uzun 2014	4/47	7/45		4.4 %	0.50 [0.14, 1.86]
Vainas 2005	15/257	10/252		7.1 %	1.50 [0.66, 3.40]
Vos 2011	3/40	1/43		1.9 %	3.41 [0.34, 34.17]
Subtotal (95% CI)	**1201**	**1195**		**68.7 %**	**1.77 [1.30, 2.42]**
Total events: 187 (Macrolide), 111 (Placebo)					
Heterogeneity: Tau^2 = 0.07; Chi^2 = 15.19, df = 12 (P = 0.23); I^2 =21%					
Test for overall effect: Z = 3.60 (P = 0.00032)					
2 Erythromycin					
Alger 1991	9/39	1/44		2.1 %	12.90 [1.55, 107.25]
Dunlay 1987	4/32	0/31		1.2 %	9.95 [0.51, 192.99]
Haxel 2015	5/29	0/29		1.2 %	13.24 [0.70, 251.60]
Hooton 1990	18/34	3/35		4.1 %	12.00 [3.07, 46.83]
King 1996	13/49	2/42		3.5 %	7.22 [1.52, 34.21]
Mercer 1992	7/106	8/114		5.7 %	0.94 [0.33, 2.68]
Seemungal 2008	1/20	0/20		1.0 %	3.15 [0.12, 82.16]
Shanson 1985	8/53	8/56		5.6 %	1.07 [0.37, 3.08]
Wilson 1979	29/56	10/53		6.8 %	4.62 [1.94, 10.97]
Subtotal (95% CI)	**418**	**424**		**31.3 %**	**4.00 [1.83, 8.74]**
Total events: 94 (Macrolide), 32 (Placebo)					
Heterogeneity: Tau^2 = 0.69; Chi^2 = 18.04, df = 8 (P = 0.02); I^2 =56%					
Test for overall effect: Z = 3.47 (P = 0.00052)					
Total (95% CI)	**1619**	**1619**		**100.0 %**	**2.19 [1.56, 3.09]**
Total events: 281 (Macrolide), 143 (Placebo)					
Heterogeneity: Tau^2 = 0.25; Chi^2 = 37.99, df = 21 (P = 0.01); I^2 =45%					
Test for overall effect: Z = 4.50 (P < 0.00001)					
Test for subgroup differences: Chi^2 = 3.57, df = 1 (P = 0.06), I^2 =72%					

Analysis 4.1. Comparison 4 Nervous system disorders, Outcome 1 Dizziness.

Review: Adverse events in people taking macrolide antibiotics versus placebo for any indication

Comparison: 4 Nervous system disorders

Outcome: 1 Dizziness

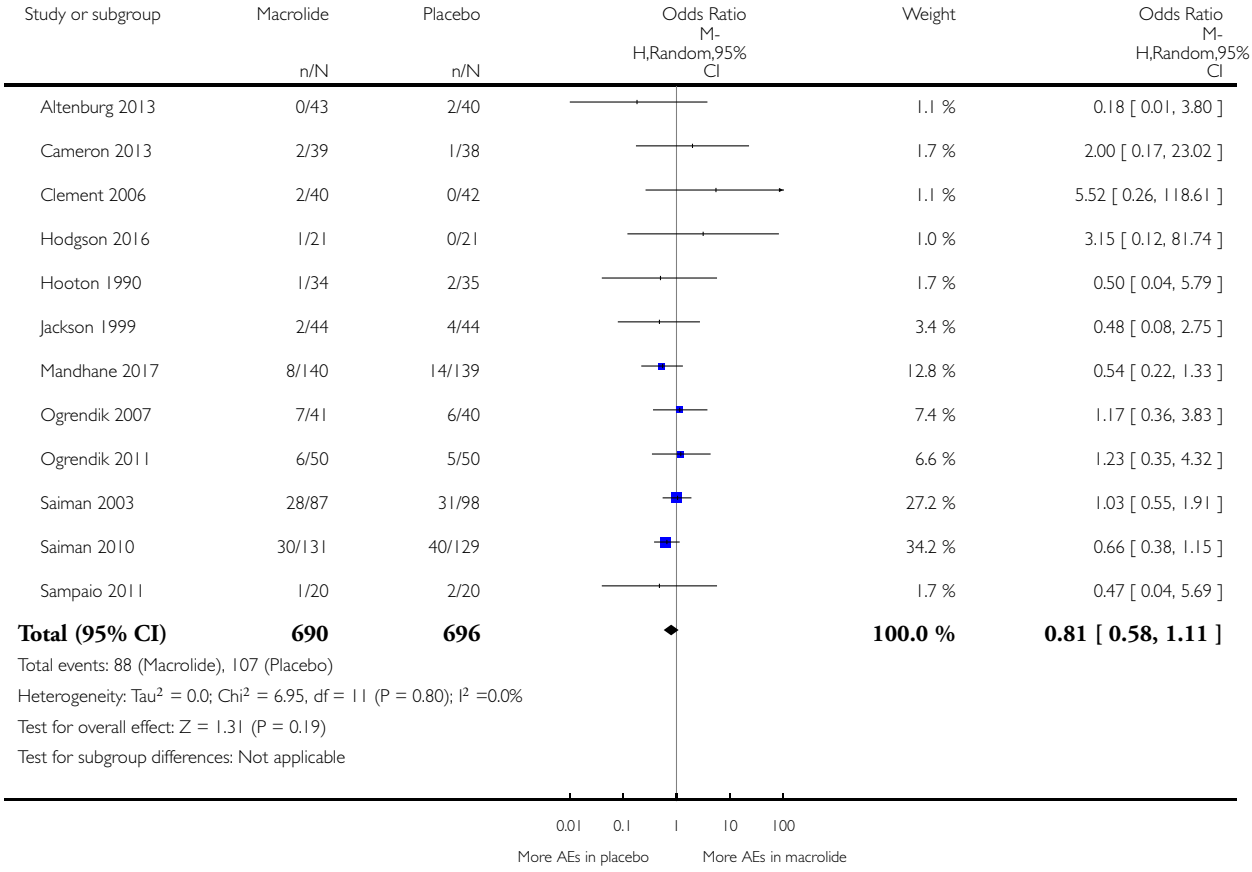


Analysis 4.2. Comparison 4 Nervous system disorders, Outcome 2 Headache.

Review: Adverse events in people taking macrolide antibiotics versus placebo for any indication

Comparison: 4 Nervous system disorders

Outcome: 2 Headache

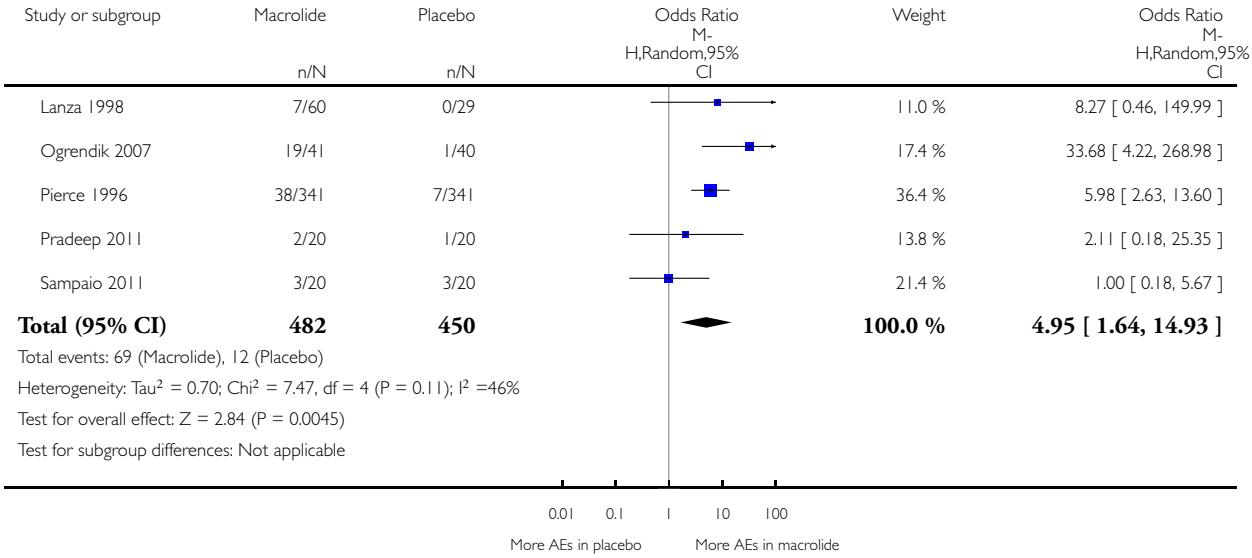


Analysis 4.3. Comparison 4 Nervous system disorders, Outcome 3 Taste disturbance.

Review: Adverse events in people taking macrolide antibiotics versus placebo for any indication

Comparison: 4 Nervous system disorders

Outcome: 3 Taste disturbance



Analysis 5.1. Comparison 5 Skin and subcutaneous tissue disorders, Outcome 1 Itching.

Review: Adverse events in people taking macrolide antibiotics versus placebo for any indication

Comparison: 5 Skin and subcutaneous tissue disorders

Outcome: 1 Itching

Study or subgroup	Macrolide n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Altenburg 2013	2/43	3/40		5.0 %	0.60 [0.10, 3.80]
Heppner 2005	9/170	5/94		13.5 %	1.00 [0.32, 3.06]
McCormack 1987	27/360	26/399		54.7 %	1.16 [0.67, 2.03]
Rozman 1984	15/146	12/136		26.8 %	1.18 [0.53, 2.63]
Total (95% CI)	**719**	**669**		**100.0 %**	**1.11 [0.73, 1.67]**

Total events: 53 (Macrolide), 46 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.51$, df = 3 (P = 0.92); $I^2 = 0.0\%$

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

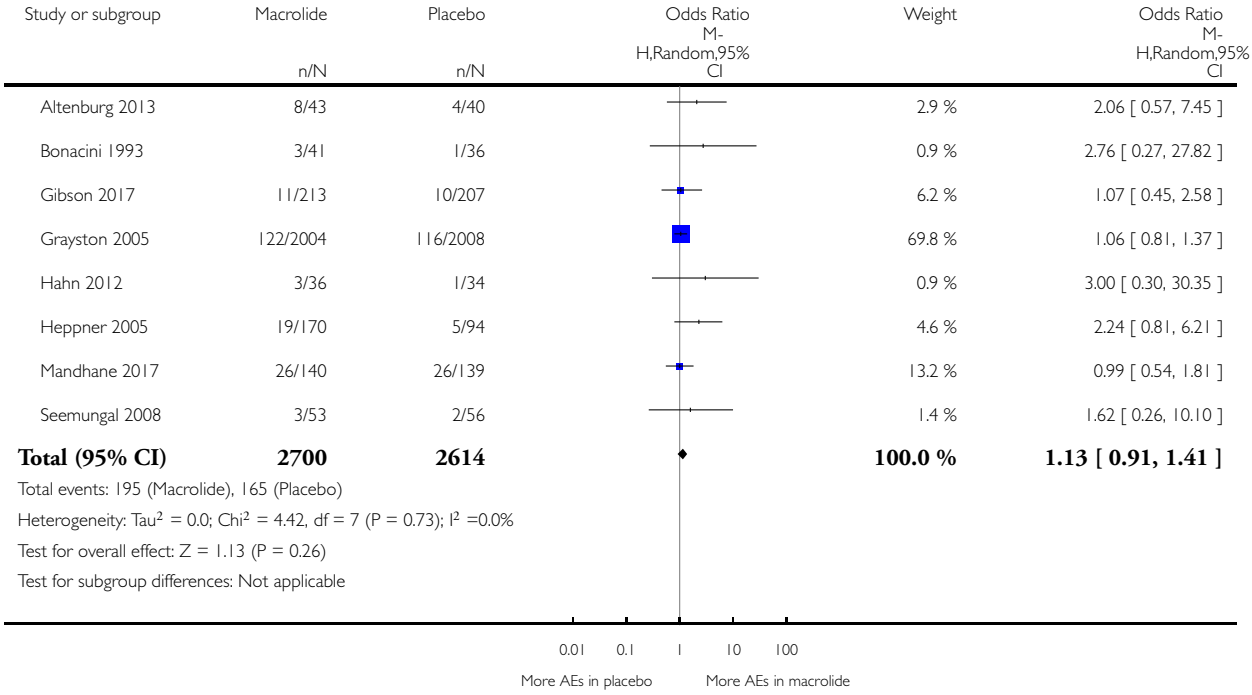
Test for subgroup differences: Not applicable

Analysis 5.2. Comparison 5 Skin and subcutaneous tissue disorders, Outcome 2 Rash.

Review: Adverse events in people taking macrolide antibiotics versus placebo for any indication

Comparison: 5 Skin and subcutaneous tissue disorders

Outcome: 2 Rash



Analysis 6.1. Comparison 6 General disorders and administration site conditions, Outcome 1 Fever.

Review: Adverse events in people taking macrolide antibiotics versus placebo for any indication

Comparison: 6 General disorders and administration site conditions

Outcome: 1 Fever

Study or subgroup	Macrolide n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Bonacini 1993	1/41	3/36		1.7 %	0.28 [0.03, 2.77]
Clement 2006	2/40	3/42		2.6 %	0.68 [0.11, 4.33]
Grassly 2016	100/376	107/378		30.6 %	0.92 [0.67, 1.26]
Heppner 2005	63/170	32/94		19.5 %	1.14 [0.67, 1.93]
Roca 2016a	8/414	24/415		11.0 %	0.32 [0.14, 0.72]
Saiman 2003	24/87	36/98		15.9 %	0.66 [0.35, 1.22]
Saiman 2010	30/131	41/129		18.6 %	0.64 [0.37, 1.11]
Total (95% CI)	**1259**	**1192**		**100.0 %**	**0.73 [0.54, 1.00]**

Total events: 228 (Macrolide), 246 (Placebo)

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 9.19$, df = 6 (P = 0.16); $I^2 = 35\%$

Test for overall effect: Z = 1.96 (P = 0.050)

Test for subgroup differences: Not applicable

Analysis 7.1. Comparison 7 Hepatobiliary disorders, Outcome 1 Hepatobiliary disorders.

Review: Adverse events in people taking macrolide antibiotics versus placebo for any indication

Comparison: 7 Hepatobiliary disorders

Outcome: 1 Hepatobiliary disorders

Study or subgroup	Macrolide n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Aly 2007	2/30	4/30		28.1 %	0.46 [0.08, 2.75]
Black 2001	6/105	1/114		23.2 %	6.85 [0.81, 57.87]
Nuntnarumit 2006	3/23	2/23		26.5 %	1.58 [0.24, 10.44]
Yeo 1993	1/58	4/60		22.2 %	0.25 [0.03, 2.27]
Total (95% CI)	**216**	**227**		**100.0 %**	**1.04 [0.27, 4.09]**

Total events: 12 (Macrolide), 11 (Placebo)

Heterogeneity: $Tau^2 = 0.91$; $Chi^2 = 5.63$, df = 3 (P = 0.13); $I^2 = 47\%$

Test for overall effect: Z = 0.06 (P = 0.95)

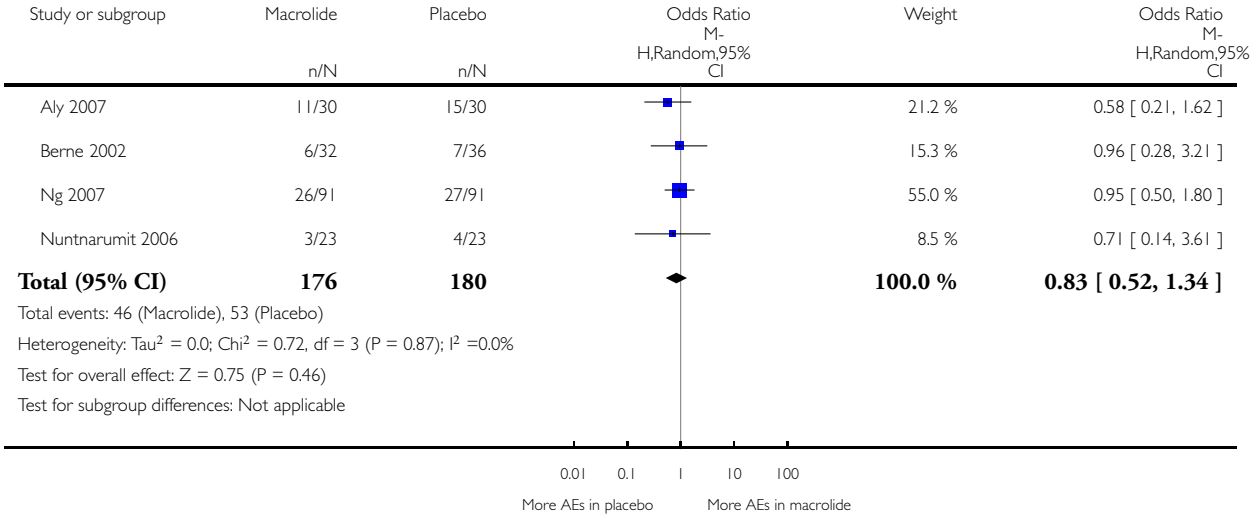
Test for subgroup differences: Not applicable

Analysis 8.1. Comparison 8 Infections and infestations, Outcome 1 Blood infection.

Review: Adverse events in people taking macrolide antibiotics versus placebo for any indication

Comparison: 8 Infections and infestations

Outcome: 1 Blood infection

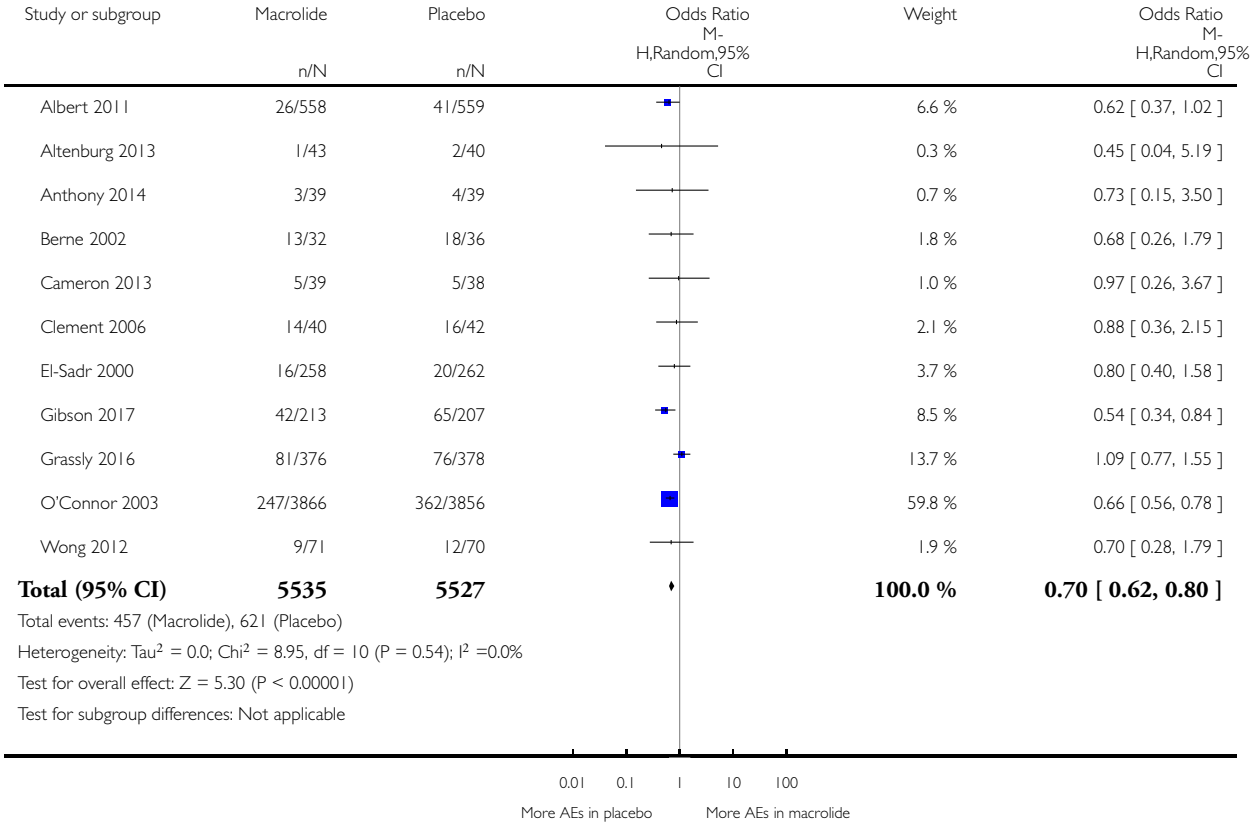


Analysis 8.2. Comparison 8 Infections and infestations, Outcome 2 Respiratory tract infections.

Review: Adverse events in people taking macrolide antibiotics versus placebo for any indication

Comparison: 8 Infections and infestations

Outcome: 2 Respiratory tract infections



Total events: 457 (Macrolide), 621 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 8.95$, df = 10 (P = 0.54); $I^2 = 0.0\%$

Test for overall effect: Z = 5.30 (P < 0.00001)

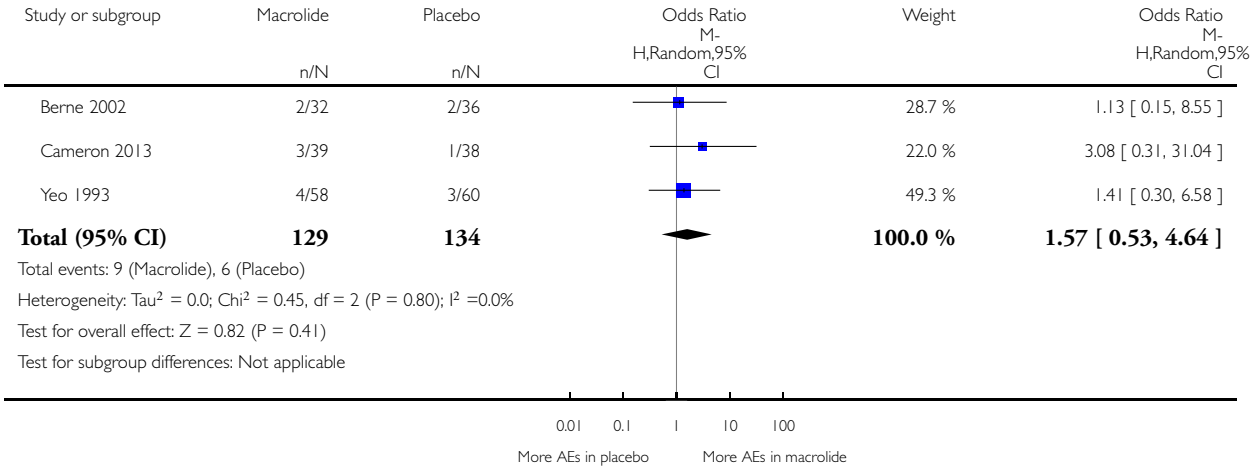
Test for subgroup differences: Not applicable

Analysis 8.3. Comparison 8 Infections and infestations, Outcome 3 Skin and soft tissue infections.

Review: Adverse events in people taking macrolide antibiotics versus placebo for any indication

Comparison: 8 Infections and infestations

Outcome: 3 Skin and soft tissue infections

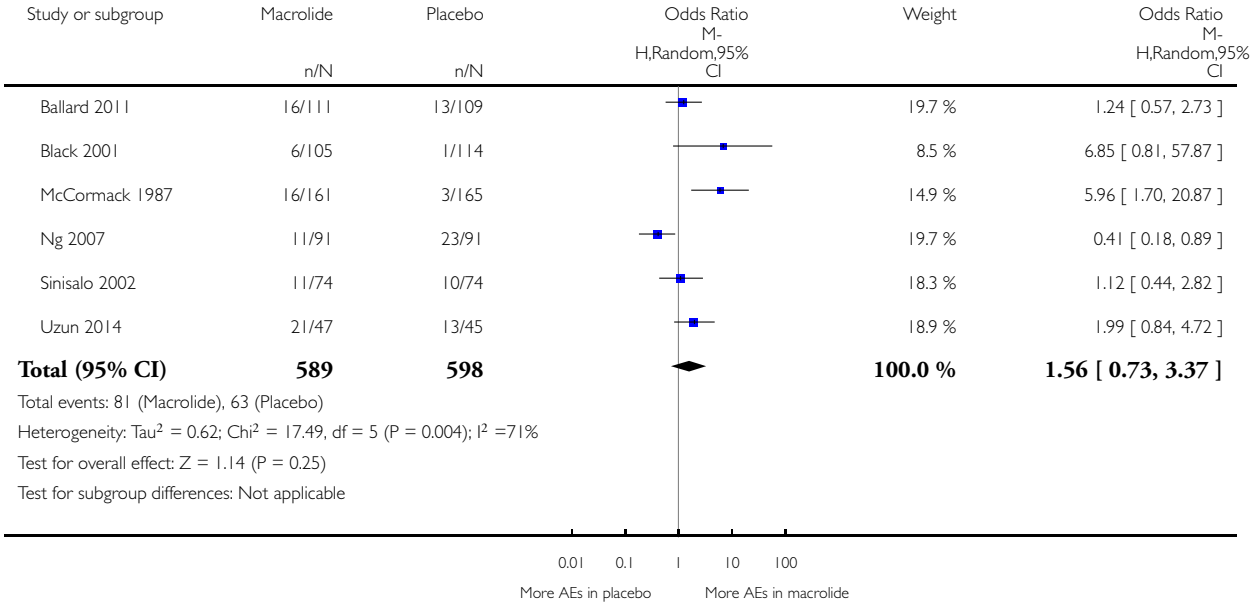


Analysis 9.1. Comparison 9 Investigations, Outcome 1 Change in liver enzymes.

Review: Adverse events in people taking macrolide antibiotics versus placebo for any indication

Comparison: 9 Investigations

Outcome: 1 Change in liver enzymes



Analysis 10.1. Comparison 10 Metabolism and nutrition disorders, Outcome 1 Appetite lost.

Review: Adverse events in people taking macrolide antibiotics versus placebo for any indication

Comparison: 10 Metabolism and nutrition disorders

Outcome: 1 Appetite lost

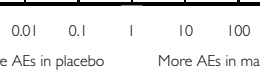
Study or subgroup	Macrolide n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Eschenbach 1991	91/586	79/548		42.8 %	1.09 [0.79, 1.51]
Heppner 2005	15/170	13/94		10.4 %	0.60 [0.27, 1.33]
Martin 1997	43/205	29/209		21.8 %	1.65 [0.98, 2.76]
Petersen 1997	25/93	25/93		14.9 %	1.00 [0.52, 1.91]
Saiman 2003	13/87	15/98		10.0 %	0.97 [0.43, 2.18]
Total (95% CI)	**1141**	**1042**		**100.0 %**	**1.10 [0.84, 1.43]**

Total events: 187 (Macrolide), 161 (Placebo)

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 4.75$, df = 4 (P = 0.31); $I^2 = 16\%$

Test for overall effect: Z = 0.67 (P = 0.50)

Test for subgroup differences: Not applicable



Analysis 11.1. Comparison 11 Respiratory, thoracic, and mediastinal disorders, Outcome 1 Cough.

Review: Adverse events in people taking macrolide antibiotics versus placebo for any indication

Comparison: 11 Respiratory, thoracic, and mediastinal disorders

Outcome: 1 Cough

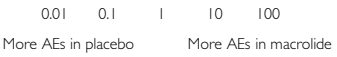
Study or subgroup	Macrolide n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Clement 2006	0/40	2/42		1.2 %	0.20 [0.01, 4.30]
Grassly 2016	15/376	19/378		20.3 %	0.79 [0.39, 1.57]
Heppner 2005	30/170	20/94		23.6 %	0.79 [0.42, 1.49]
Hodgson 2016	1/21	5/21		2.3 %	0.16 [0.02, 1.51]
Saiman 2003	64/87	80/98		20.0 %	0.63 [0.31, 1.26]
Saiman 2010	63/131	91/129		32.6 %	0.39 [0.23, 0.64]
Total (95% CI)	**825**	**762**		**100.0 %**	**0.57 [0.40, 0.80]**

Total events: 173 (Macrolide), 217 (Placebo)

Heterogeneity: $Tau^2 = 0.03$; $Chi^2 = 5.82$, df = 5 (P = 0.32); $I^2 = 14\%$

Test for overall effect: Z = 3.24 (P = 0.0012)

Test for subgroup differences: Not applicable



Analysis 11.2. Comparison 11 Respiratory, thoracic, and mediastinal disorders, Outcome 2 Respiratory symptoms not otherwise specified.

Review: Adverse events in people taking macrolide antibiotics versus placebo for any indication

Comparison: 11 Respiratory, thoracic, and mediastinal disorders

Outcome: 2 Respiratory symptoms not otherwise specified

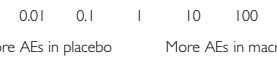
Study or subgroup	Macrolide n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Bergeron 2017	27/234	31/231		14.7 %	0.84 [0.48, 1.46]
Berkhof 2013	7/42	8/42		3.6 %	0.85 [0.28, 2.60]
Bonacini 1993	2/41	1/36		0.7 %	1.79 [0.16, 20.66]
Grassly 2016	81/376	76/378		36.1 %	1.09 [0.77, 1.55]
Johnston 2016	20/97	28/102		10.4 %	0.69 [0.36, 1.32]
Kvien 2004	10/81	9/71		4.8 %	0.97 [0.37, 2.54]
Saiman 2003	38/87	36/98		12.8 %	1.34 [0.74, 2.41]
Saiman 2010	45/131	42/129		16.8 %	1.08 [0.65, 1.81]
Total (95% CI)	**1089**	**1087**		**100.0 %**	**1.02 [0.82, 1.25]**

Total events: 230 (Macrolide), 231 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 3.18$, df = 7 (P = 0.87); $I^2 = 0.0\%$

Test for overall effect: Z = 0.14 (P = 0.89)

Test for subgroup differences: Not applicable

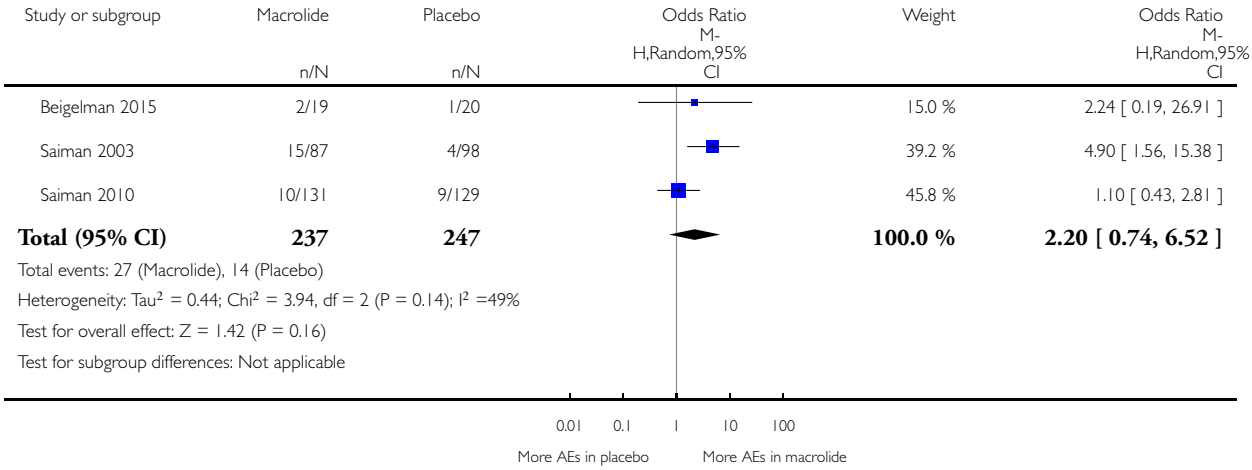


Analysis 11.3. Comparison 11 Respiratory, thoracic, and mediastinal disorders, Outcome 3 Wheezing.

Review: Adverse events in people taking macrolide antibiotics versus placebo for any indication

Comparison: 11 Respiratory, thoracic, and mediastinal disorders

Outcome: 3 Wheezing

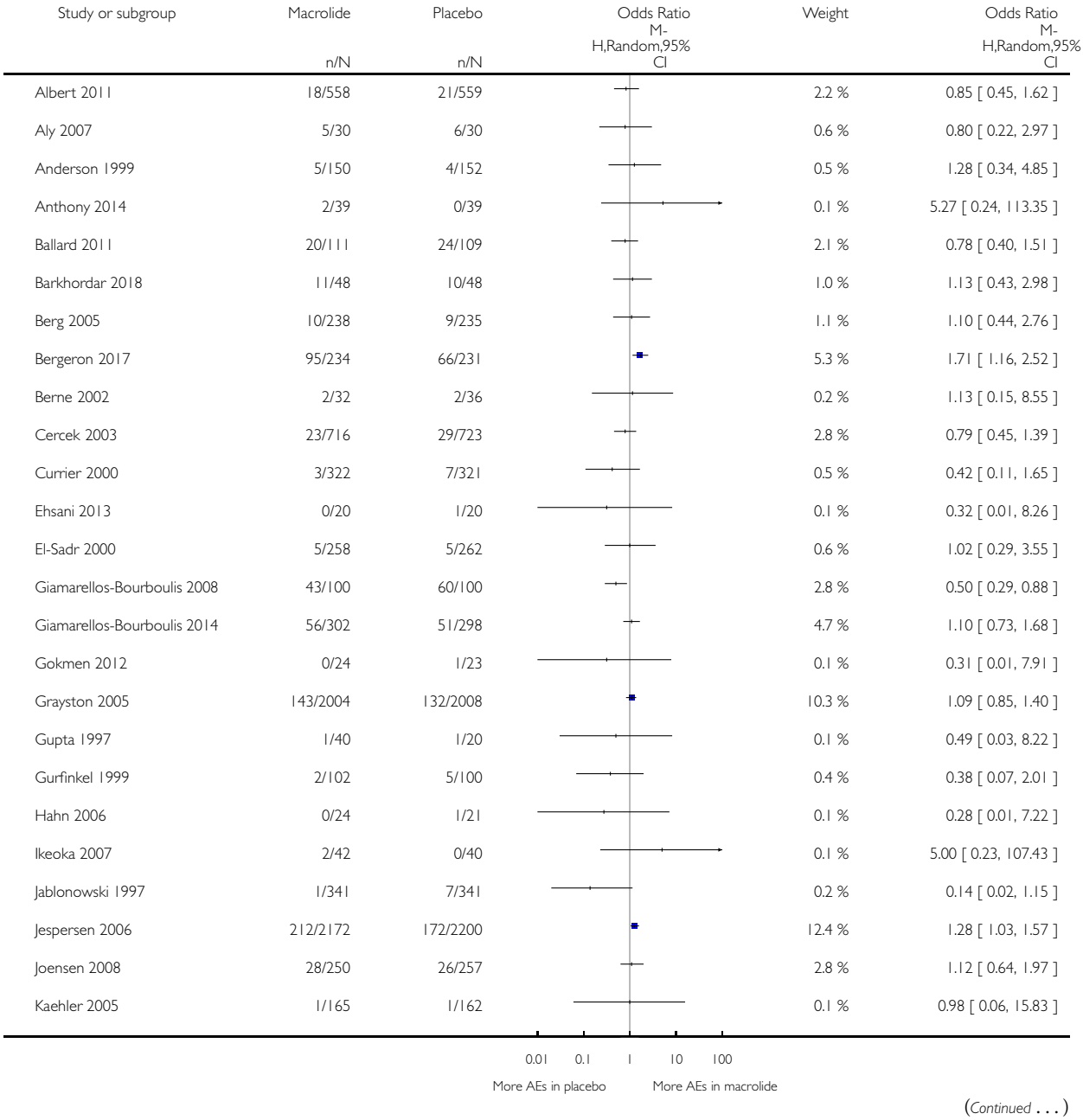


Analysis 12.1. Comparison 12 Deaths, Outcome 1 Deaths - overall.

Review: Adverse events in people taking macrolide antibiotics versus placebo for any indication

Comparison: 12 Deaths

Outcome: 1 Deaths - overall



Study or subgroup	Macrolide n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Albert 2011	18/558	21/559		2.2 %	0.85 [0.45, 1.62]
Aly 2007	5/30	6/30		0.6 %	0.80 [0.22, 2.97]
Anderson 1999	5/150	4/152		0.5 %	1.28 [0.34, 4.85]
Anthony 2014	2/39	0/39		0.1 %	5.27 [0.24, 113.35]
Ballard 2011	20/111	24/109		2.1 %	0.78 [0.40, 1.51]
Barkhordar 2018	11/48	10/48		1.0 %	1.13 [0.43, 2.98]
Berg 2005	10/238	9/235		1.1 %	1.10 [0.44, 2.76]
Bergeron 2017	95/234	66/231		5.3 %	1.71 [1.16, 2.52]
Berne 2002	2/32	2/36		0.2 %	1.13 [0.15, 8.55]
Cercek 2003	23/716	29/723		2.8 %	0.79 [0.45, 1.39]
Currier 2000	3/322	7/321		0.5 %	0.42 [0.11, 1.65]
Ehsani 2013	0/20	1/20		0.1 %	0.32 [0.01, 8.26]
El-Sadr 2000	5/258	5/262		0.6 %	1.02 [0.29, 3.55]
Giamarellos-Bourboulis 2008	43/100	60/100		2.8 %	0.50 [0.29, 0.88]
Giamarellos-Bourboulis 2014	56/302	51/298		4.7 %	1.10 [0.73, 1.68]
Gokmen 2012	0/24	1/23		0.1 %	0.31 [0.01, 7.91]
Grayston 2005	143/2004	132/2008		10.3 %	1.09 [0.85, 1.40]
Gupta 1997	1/40	1/20		0.1 %	0.49 [0.03, 8.22]
Gurfinkel 1999	2/102	5/100		0.4 %	0.38 [0.07, 2.01]
Hahn 2006	0/24	1/21		0.1 %	0.28 [0.01, 7.22]
Ikeoka 2007	2/42	0/40		0.1 %	5.00 [0.23, 107.43]
Jablonowski 1997	1/341	7/341		0.2 %	0.14 [0.02, 1.15]
Jespersen 2006	212/2172	172/2200		12.4 %	1.28 [1.03, 1.57]
Joensen 2008	28/250	26/257		2.8 %	1.12 [0.64, 1.97]
Kaehler 2005	1/165	1/162		0.1 %	0.98 [0.06, 15.83]

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Study or subgroup	Macrolide n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Karlsson 2009	5/122	8/125		0.7 %	0.63 [0.20, 1.97]
Kaul 2004	1/230	2/236		0.2 %	0.51 [0.05, 5.67]
Keenan 2018	2404/97047	2616/93191		25.7 %	0.88 [0.83, 0.93]
Kim 2004	2/64	2/65		0.2 %	1.02 [0.14, 7.44]
Leowattana 2001	1/43	1/41		0.1 %	0.95 [0.06, 15.75]
Neumann 2001	16/506	13/504		1.7 %	1.23 [0.59, 2.59]
Ng 2007	2/91	4/91		0.3 %	0.49 [0.09, 2.74]
Nuntnarumit 2006	2/23	0/23		0.1 %	5.47 [0.25, 120.37]
Oei 2001	1/24	1/24		0.1 %	1.00 [0.06, 16.97]
Oldfield 1998	38/85	38/86		2.5 %	1.02 [0.56, 1.87]
Ozdemir 2011	2/37	4/37		0.3 %	0.47 [0.08, 2.75]
Pierce 1996	107/333	137/334		7.2 %	0.68 [0.50, 0.93]
Reignier 2002	6/20	8/20		0.6 %	0.64 [0.17, 2.38]
Robins-Browne 1983	1/39	1/39		0.1 %	1.00 [0.06, 16.58]
Sander 2002	4/136	5/136		0.5 %	0.79 [0.21, 3.02]
Schwameis 2017	0/685	1/686		0.1 %	0.33 [0.01, 8.20]
Seemungal 2008	0/53	1/56		0.1 %	0.35 [0.01, 8.68]
Shafuddin 2015	3/97	5/94		0.5 %	0.57 [0.13, 2.45]
Sinisalo 2002	4/74	1/74		0.2 %	4.17 [0.46, 38.24]
Uzun 2014	0/47	2/45		0.1 %	0.18 [0.01, 3.92]
Vainas 2005	20/257	25/252		2.4 %	0.77 [0.41, 1.42]
Vammen 2001	3/43	2/49		0.3 %	1.76 [0.28, 11.08]
Van Delden 2012	9/47	6/45		0.8 %	1.54 [0.50, 4.74]
Van den Broek 2009	7/1149	3/1148		0.5 %	2.34 [0.60, 9.07]
Vos 2011	5/15	8/13		0.4 %	0.31 [0.07, 1.47]
Wiesli 2002	1/20	2/20		0.2 %	0.47 [0.04, 5.69]
Zahn 2003	28/431	26/437		2.9 %	1.10 [0.63, 1.91]
Total (95% CI)	**110040**	**106206**		**100.0 %**	**0.96 [0.87, 1.06]**

Total events: 3360 (Macrolide), 3563 (Placebo)

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 57.03$, df = 51 (P = 0.26); $I^2 = 11\%$

Test for overall effect: Z = 0.81 (P = 0.42)

Test for subgroup differences: Not applicable

Analysis 12.2. Comparison 12 Deaths, Outcome 2 Deaths - subgroup analysis by type of macrolide.

Review: Adverse events in people taking macrolide antibiotics versus placebo for any indication

Comparison: 12 Deaths

Outcome: 2 Deaths - subgroup analysis by type of macrolide

Study or subgroup	Macrolide n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Azithromycin					
Albert 2011	18/558	21/559		2.2 %	0.85 [0.45, 1.62]
Anderson 1999	5/150	4/152		0.5 %	1.28 [0.34, 4.85]
Anthony 2014	2/39	0/39		0.1 %	5.27 [0.24, 113.35]
Ballard 2011	20/111	24/109		2.1 %	0.78 [0.40, 1.51]
Barkhordar 2018	11/48	10/48		1.0 %	1.13 [0.43, 2.98]
Bergeron 2017	95/234	66/231		5.3 %	1.71 [1.16, 2.52]
Cercek 2003	23/716	29/723		2.8 %	0.79 [0.45, 1.39]
Currier 2000	3/322	7/321		0.5 %	0.42 [0.11, 1.65]
El-Sadr 2000	5/258	5/262		0.6 %	1.02 [0.29, 3.55]
Grayston 2005	143/2004	132/2008		10.3 %	1.09 [0.85, 1.40]
Gupta 1997	1/40	1/20		0.1 %	0.49 [0.03, 8.22]
Hahn 2006	0/24	1/21		0.1 %	0.28 [0.01, 7.22]
Ikeoka 2007	2/42	0/40		0.1 %	5.00 [0.23, 107.43]
Karlsson 2009	5/122	8/125		0.7 %	0.63 [0.20, 1.97]
Kaul 2004	1/230	2/236		0.2 %	0.51 [0.05, 5.67]
Keenan 2018	2404/97047	2616/93191		25.7 %	0.88 [0.83, 0.93]
Kim 2004	2/64	2/65		0.2 %	1.02 [0.14, 7.44]
Oldfield 1998	38/85	38/86		2.5 %	1.02 [0.56, 1.87]
Schwameis 2017	0/685	1/686		0.1 %	0.33 [0.01, 8.20]
Uzun 2014	0/47	2/45		0.1 %	0.18 [0.01, 3.92]
Vainas 2005	20/257	25/252		2.4 %	0.77 [0.41, 1.42]

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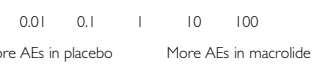
Study or subgroup	Macrolide n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Van Delden 2012	9/47	6/45		0.8 %	1.54 [0.50, 4.74]
Van den Broek 2009	7/1149	3/1148		0.5 %	2.34 [0.60, 9.07]
Vos 2011	5/15	8/13		0.4 %	0.31 [0.07, 1.47]
Subtotal (95% CI)	**104294**	**100425**		**59.4 %**	**0.97 [0.85, 1.10]**
Total events: 2819 (Macrolide), 3011 (Placebo)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 25.88, df = 23 (P = 0.31); I^2 =11%					
Test for overall effect: Z = 0.53 (P = 0.59)					
2 Clarithromycin					
Berg 2005	10/238	9/235		1.1 %	1.10 [0.44, 2.76]
Giamarellos-Bourboulis 2008	43/100	60/100		2.8 %	0.50 [0.29, 0.88]
Giamarellos-Bourboulis 2014	56/302	51/298		4.7 %	1.10 [0.73, 1.68]
Jablonowski 1997	1/341	7/341		0.2 %	0.14 [0.02, 1.15]
Jespersen 2006	212/2172	172/2200		12.4 %	1.28 [1.03, 1.57]
Ozdemir 2011	2/37	4/37		0.3 %	0.47 [0.08, 2.75]
Pierce 1996	107/333	137/334		7.2 %	0.68 [0.50, 0.93]
Sinisalo 2002	4/74	1/74		0.2 %	4.17 [0.46, 38.24]
Subtotal (95% CI)	**3597**	**3619**		**28.9 %**	**0.86 [0.59, 1.24]**
Total events: 435 (Macrolide), 441 (Placebo)					
Heterogeneity: Tau^2 = 0.14; Chi^2 = 22.42, df = 7 (P = 0.002); I^2 =69%					
Test for overall effect: Z = 0.82 (P = 0.41)					
3 Erythromycin					
Aly 2007	5/30	6/30		0.6 %	0.80 [0.22, 2.97]
Berne 2002	2/32	2/36		0.2 %	1.13 [0.15, 8.55]
Ehsani 2013	0/20	1/20		0.1 %	0.32 [0.01, 8.26]
Gokmen 2012	0/24	1/23		0.1 %	0.31 [0.01, 7.91]
Ng 2007	2/91	4/91		0.3 %	0.49 [0.09, 2.74]
Nuntnarumit 2006	2/23	0/23		0.1 %	5.47 [0.25, 120.37]
Oei 2001	1/24	1/24		0.1 %	1.00 [0.06, 16.97]
Reignier 2002	6/20	8/20		0.6 %	0.64 [0.17, 2.38]
Robins-Browne 1983	1/39	1/39		0.1 %	1.00 [0.06, 16.58]
Seemungal 2008	0/53	1/56		0.1 %	0.35 [0.01, 8.68]
Subtotal (95% CI)	**356**	**362**		**2.3 %**	**0.73 [0.38, 1.40]**
Total events: 19 (Macrolide), 25 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 2.91, df = 9 (P = 0.97); I^2 =0.0%					
Test for overall effect: Z = 0.94 (P = 0.35)					



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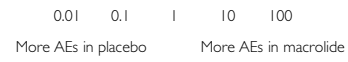
Study or subgroup	Macrolide n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
4 Roxithromycin					
Gurfinkel 1999	2/102	5/100		0.4 %	0.38 [0.07, 2.01]
Joensen 2008	28/250	26/257		2.8 %	1.12 [0.64, 1.97]
Kaehler 2005	1/165	1/162		0.1 %	0.98 [0.06, 15.83]
Leowattana 2001	1/43	1/41		0.1 %	0.95 [0.06, 15.75]
Neumann 2001	16/506	13/504		1.7 %	1.23 [0.59, 2.59]
Sander 2002	4/136	5/136		0.5 %	0.79 [0.21, 3.02]
Shafuddin 2015	3/97	5/94		0.5 %	0.57 [0.13, 2.45]
Vammen 2001	3/43	2/49		0.3 %	1.76 [0.28, 11.08]
Wiesli 2002	1/20	2/20		0.2 %	0.47 [0.04, 5.69]
Zahn 2003	28/431	26/437		2.9 %	1.10 [0.63, 1.91]
Subtotal (95% CI)	**1793**	**1800**		**9.4 %**	**1.03 [0.76, 1.41]**
Total events: 87 (Macrolide), 86 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 3.24, df = 9 (P = 0.95); I^2 =0.0%					
Test for overall effect: Z = 0.21 (P = 0.84)					
Total (95% CI)	**110040**	**106206**		**100.0 %**	**0.96 [0.87, 1.06]**
Total events: 3360 (Macrolide), 3563 (Placebo)					
Heterogeneity: Tau^2 = 0.01; Chi^2 = 57.03, df = 51 (P = 0.26); I^2 =11%					
Test for overall effect: Z = 0.81 (P = 0.42)					
Test for subgroup differences: Chi^2 = 1.25, df = 3 (P = 0.74), I^2 =0.0%					



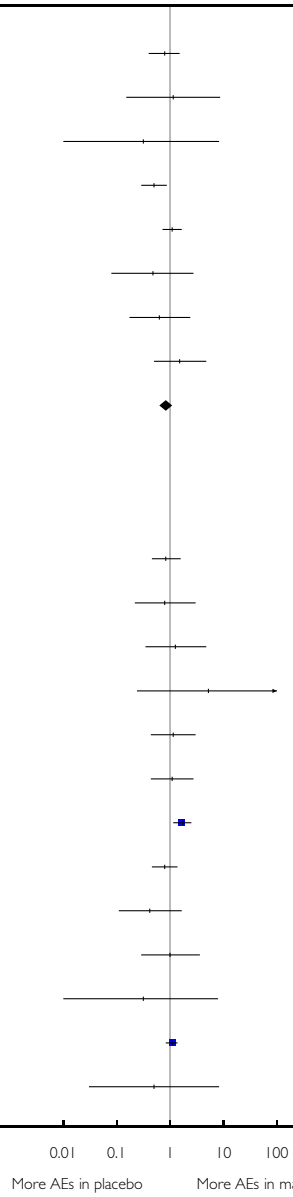
Analysis 12.3. Comparison 12 Deaths, Outcome 3 Deaths - subgroup analysis by route of administration.

Review: Adverse events in people taking macrolide antibiotics versus placebo for any indication

Comparison: 12 Deaths

Outcome: 3 Deaths - subgroup analysis by route of administration

Study or subgroup	Macrolide n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
1 Intravenous					
Ballard 2011	20/111	24/109		2.1 %	0.78 [0.40, 1.51]
Berne 2002	2/32	2/36		0.2 %	1.13 [0.15, 8.55]
Ehsani 2013	0/20	1/20		0.1 %	0.32 [0.01, 8.26]
Giamarellos-Bourboulis 2008	43/100	60/100		2.9 %	0.50 [0.29, 0.88]
Giamarellos-Bourboulis 2014	56/302	51/298		4.8 %	1.10 [0.73, 1.68]
Ozdemir 2011	2/37	4/37		0.3 %	0.47 [0.08, 2.75]
Reignier 2002	6/20	8/20		0.6 %	0.64 [0.17, 2.38]
Van Delden 2012	9/47	6/45		0.8 %	1.54 [0.50, 4.74]
Subtotal (95% CI)	**669**	**665**		**11.8 %**	**0.83 [0.63, 1.10]**
Total events: 138 (Macrolide), 156 (Placebo)					
Heterogeneity: Tau^2 = 0.0; Chi^2 = 6.97, df = 7 (P = 0.43); I^2 =0.0%					
Test for overall effect: Z = 1.31 (P = 0.19)					
2 Peroral					
Albert 2011	18/558	21/559		2.3 %	0.85 [0.45, 1.62]
Aly 2007	5/30	6/30		0.6 %	0.80 [0.22, 2.97]
Anderson 1999	5/150	4/152		0.6 %	1.28 [0.34, 4.85]
Anthony 2014	2/39	0/39		0.1 %	5.27 [0.24, 113.35]
Barkhordar 2018	11/48	10/48		1.0 %	1.13 [0.43, 2.98]
Berg 2005	10/238	9/235		1.2 %	1.10 [0.44, 2.76]
Bergeron 2017	95/234	66/231		5.4 %	1.71 [1.16, 2.52]
Cercek 2003	23/716	29/723		2.9 %	0.79 [0.45, 1.39]
Currier 2000	3/322	7/321		0.5 %	0.42 [0.11, 1.65]
El-Sadr 2000	5/258	5/262		0.6 %	1.02 [0.29, 3.55]
Gokmen 2012	0/24	1/23		0.1 %	0.31 [0.01, 7.91]
Grayston 2005	143/2004	132/2008		10.3 %	1.09 [0.85, 1.40]
Gupta 1997	1/40	1/20		0.1 %	0.49 [0.03, 8.22]



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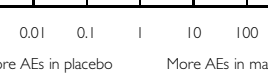
Study or subgroup	Macrolide n/N	Placebo n/N	Odds Ratio M-H,Random,95% CI	Weight	Odds Ratio M-H,Random,95% CI
Gurfinkel 1999	2/102	5/100		0.4 %	0.38 [0.07, 2.01]
Hahn 2006	0/24	1/21		0.1 %	0.28 [0.01, 7.22]
Ikeoka 2007	2/42	0/40		0.1 %	5.00 [0.23, 107.43]
Jablonowski 1997	1/341	7/341		0.2 %	0.14 [0.02, 1.15]
Jespersen 2006	212/2172	172/2200		12.3 %	1.28 [1.03, 1.57]
Joensen 2008	28/250	26/257		2.9 %	1.12 [0.64, 1.97]
Kaehler 2005	1/165	1/162		0.1 %	0.98 [0.06, 15.83]
Karlsson 2009	5/122	8/125		0.8 %	0.63 [0.20, 1.97]
Kaul 2004	1/230	2/236		0.2 %	0.51 [0.05, 5.67]
Keenan 2018	2404/97047	2616/93191		24.4 %	0.88 [0.83, 0.93]
Kim 2004	2/64	2/65		0.3 %	1.02 [0.14, 7.44]
Leowattana 2001	1/43	1/41		0.1 %	0.95 [0.06, 15.75]
Neumann 2001	16/506	13/504		1.7 %	1.23 [0.59, 2.59]
Ng 2007	2/91	4/91		0.3 %	0.49 [0.09, 2.74]
Nuntnarumit 2006	2/23	0/23		0.1 %	5.47 [0.25, 120.37]
Oei 2001	1/24	1/24		0.1 %	1.00 [0.06, 16.97]
Oldfield 1998	38/85	38/86		2.5 %	1.02 [0.56, 1.87]
Pierce 1996	107/333	137/334		7.3 %	0.68 [0.50, 0.93]
Robins-Browne 1983	1/39	1/39		0.1 %	1.00 [0.06, 16.58]
Sander 2002	4/136	5/136		0.6 %	0.79 [0.21, 3.02]
Seemungal 2008	0/53	1/56		0.1 %	0.35 [0.01, 8.68]
Shafuddin 2015	3/97	5/94		0.5 %	0.57 [0.13, 2.45]
Sinisalo 2002	4/74	1/74		0.2 %	4.17 [0.46, 38.24]
Uzun 2014	0/47	2/45		0.1 %	0.18 [0.01, 3.92]
Vainas 2005	20/257	25/252		2.4 %	0.77 [0.41, 1.42]
Vammen 2001	3/43	2/49		0.3 %	1.76 [0.28, 11.08]
Van den Broek 2009	7/1149	3/1148		0.5 %	2.34 [0.60, 9.07]
Vos 2011	5/15	8/13		0.4 %	0.31 [0.07, 1.47]
Wiesli 2002	1/20	2/20		0.2 %	0.47 [0.04, 5.69]
Zahn 2003	28/431	26/437		3.0 %	1.10 [0.63, 1.91]
Subtotal (95% CI)	**108686**	**104855**		**88.2 %**	**0.98 [0.88, 1.10]**



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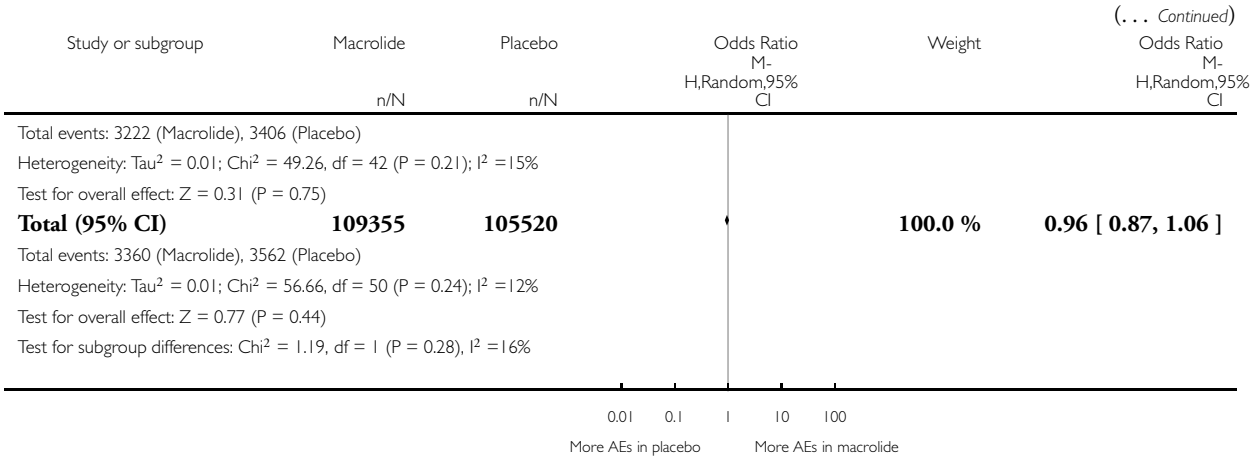

ADDITIONAL TABLES

Table 1. Rarely reported adverse events classified according to System Organ Classes

System Organ Class[1]	Adverse event[2]	Participants with an event		P value
		Macrolide N (%)	Placebo N (%)	
Blood and lymphatic system disorders	Anaemia (Garcia-Burguillo 1996)	2 (7)	3 (10)	0.640
Gastrointestinal disorders	Dental disorder NOS (Cameron 2013)	0	2 (5)	0.147
	Rectal disorder (Pierce 1996)	27 (8)	10 (3)	**0.004**
	Dry mouth (Ogrendik 2011)	3 (6)	2 (4)	0.646
	Dyspepsia (Lanza 1998)	0	2 (7)	**0.040**
	Flatulence (Jespersen 2006)	99 (5)	29 (1)	**0.000**
	Frequent bowel movement (Frossard 2002)	3 (6)	0	0.071
	Upset stomach (Jespersen 2006)	232 (11)	146 (7)	**0.000**

Table 1. Rarely reported adverse events classified according to System Organ Classes (*Continued*)

	Haemorrhoids (Cameron 2013)	0	2 (5)	0.147
	Heartburn (Hodgson 2016)	1 (5)	1 (5)	1.000
	Necrotising enterocolitis (Aly 2007)	3 (10)	4 (13)	0.688
	Necrotising enterocolitis (Nuntnarumit 2006)	1 (4)	3 (13)	0.295
	Pancreatic fistula[3] (Yeo 1993)	5 (9)	10 (17)	0.190
General disorders and administration site conditions	Infusion site pain (Giamarellos-Bourboulis 2014)	26 (9)	1 (0)	**0.000**
	Swelling (Hahn 2012)	0	2 (5)	0.146
	General disorders (Johnston 2016)	16 (16)	19 (19)	0.693
	Generally unwell (Saiman 2003)	1 (5)	1 (5)	1.000
	Malaise (Cameron 2013)	1 (3)	2 (5)	0.541
	Fatigue (Saiman 2003)	24 (28)	36 (37)	0.185
	Fatigue (Saiman 2010)	9 (7)	13 (10)	0.353
Immune system disorders	Allergic reaction (Hyde 2001)	4 (5)	0	**0.041**
Infections and infestations	Puerperal pyrexia (Tita 2016)	51 (5)	81 (8)	**0.001**
	Gastroenteritis (Cameron 2013)	7 (18)	0 (0)	**0.006**
	Bacterial infection (Haxel 2015)	13 (45)	9 (31)	0.279
	Infection NOS (Roca 2016a)	15 (4)	38 (9)	**0.001**

Table 1. Rarely reported adverse events classified according to System Organ Classes (*Continued*)

	Viral infection (Cameron 2013)	0 (0)	2 (5)	0.147
	Chorioamnionitis (Garcia-Burguillo 1996)	3 (10)	1 (3)	0.301
	Endometritis (Garcia-Burguillo 1996)	3 (10)	2 (7)	0.640
	Urinary tract infection (Berne 2002)	4 (13)	8 (22)	0.294
	Vaginal candidiasis (Hahn 2012)	4 (11)	3 (8)	0.719
	Otitis (Cameron 2013)	0 (0)	7 (18)	**0.005**
Injury, poisoning, and procedural complications	Accident[4] (Valery 2013)	2 (4)	2 (5)	0.982
	Drug dosage error (Valery 2013)	3 (7)	1 (2)	0.317
	Fall (Hodgson 2016)	0 (0)	1 (5)	0.312
Investigations	Blood urea nitrogen increased (Uzun 2014)	4 (9)	10 (22)	0.067
	Gastric residuals (Reignier 2002)	7 (35)	11 (55)	0.204
	Decreased lung function (Saiman 2003)	13 (15)	7 (7)	0.088
	Decreased lung function (Saiman 2010)	8 (6)	16 (12)	0.080
	Hearing test abnormal (Ballard 2011)	20 (18)	24 (22)	0.458
	Heart rate irregular (Mandhane 2017)	10 (7)	4 (3)	0.103
	Laboratory test abnormalities[5] (Currier 2000)	82 (25)	104 (32)	0.053
Metabolism and nutrition disorders	Hypochloraemia (Uzun 2014)	6 (13)	5 (11)	0.807

Table 1. Rarely reported adverse events classified according to System Organ Classes (*Continued*)

Musculoskeletal and connective tissue disorders	Back pain (Cameron 2013)	2 (5)	6 (16)	0.125
	Back pain (Hodgson 2016)	0	1 (5)	0.312
	Knee pain (Cameron 2013)	2 (5)	0	0.157
	Myalgia (Heppner 2005)	51 (30)	30 (32)	0.747
	Rib pain (Hodgson 2016)	0	1 (5)	0.312
Nervous system disorders	Nervous system disorder NOS (Johnston 2016)	14 (14)	13 (13)	0.728
	Impaired concentration (Peterson 1996)	0 (0)	2 (6)	0.069
	Sleepiness (Sampaio 2011)	3 (15)	3 (15)	1.000
Psychiatric disorders	Psychiatric symptom NOS (Cameron 2013)	4 (10)	2 (5)	0.414
Renal and urinary disorders	Urine colour abnormal[6] (McCormack 1987)	21 (6)	23 (6)	0.977
Reproductive system and breast disorders	Vaginal itching[7] (Eschenbach 1991)	55 (9)	48 (9)	0.714
Skin and subcutaneous tissues disorders	Allergic skin reaction[8] (Petersen 1997)	7 (8)	7 (8)	1.000
	Cutaneous symptom (Kvien 2004)	5 (6)	3 (4)	0.592
	Dermatitis (Cameron 2013)	1 (3)	2 (5)	0.541
	Hives (Mandhane 2017)	10 (7)	16 (12)	0.210
	Skin ulcer (Heppner 2005)	13 (8)	14 (15)	0.063
Surgical and medical procedures	Sinus operation NOS (Altenburg 2013)	1 (2)	2 (5)	0.514

Table 1. Rarely reported adverse events classified according to System Organ Classes (*Continued*)

	Surgery[9] (Valery 2013)	3 (7)	3 (7)	0.977

Abbreviations:
MedDRA: Medical Dictionary for Regulatory Activities.
NOS: not otherwise specified.
[1]System Organ Classes are groupings by aetiology, manifestation site, or purpose defined by MedDRA 2018.
[2]Best matching term identified in MedDRA 2018.

[3]Reported as a postoperative complication.
[4]Reported as accident, fracture, or foreign body.
[5]Participants who developed a severe or life-threatening laboratory toxicity.
[6]Treated with erythromycin estolate or erythromycin stearate.
[7]Reported as "vaginal or rectal itching" - coded as vaginal itching.
[8]Adverse events reported at day 3.
[9]Type of surgery not specified.

Table 2. Deaths

Indication for treatment	Study ID	Follow-up period (days)	Participants who died		P value
			Macrolide N (%)	Placebo N (%)	
Acute respiratory tract infection	Van Delden 2012	7[1]	9 (19)	6 (13)	0.450
Cancer	Barkhordar 2018[2]	n/a	11 (23)	10 (21)	0.804
	Bergeron 2017[3]	730	95 (41)	66 (29)	**0.006**
Cardiovascular disease	Anderson 1999[4]	730	5 (3)	4 (3)	0.720
	Berg 2005	730	10 (4)	9 (4)	0.837
	Cercek 2003	n/a	23 (3)	29 (4)	0.417
	Grayston 2005	1424	143 (7)	132 (7)	0.481
	Gupta 1997[5]	n/a	1 (3)	1 (5)	0.611
	Gurfinkel 1999	30	0	2 (2)	0.151
	Gurfinkel 1999	90	0	4 (4)	**0.041**
	Gurfinkel 1999	180	2 (2)	5 (5)	0.238
	Ikeoka 2007[6]	183	2 (5)	0	0.162

Table 2. Deaths (*Continued*)

	Jespersen 2006[7]	949	212 (10)	172 (8)	**0.023**
	Jespersen 2006[8]	2190	497 (23)	426 (19)	**0.004**
	Jespersen 2006[9]	3650	866 (40)	815 (37)	0.055
	Joensen 2008	767	28 (11)	26 (10)	0.693
	Kaehler 2005	365	1 (1)	1 (1)	0.990
	Karlsson 2009	548	5 (4)	8 (6)	0.418
	Kim 2004[10]	365	2 (3)	2 (3)	0.987
	Leowattana 2001[11]	90	1 (2)	1 (2)	0.973
	Neumann 2001	365	16 (3)	13 (3)	0.579
	Sander 2002[12]	730	4 (3)	5 (4)	0.735
	Sinisalo 2002[13]	555	4 (5)	1 (1)	0.172
	Vainas 2005	730	20 (8)	25 (10)	0.396
	Vammen 2001	767	3 (7)	2 (4)	0.541
	Wiesli 2002	986	1 (5)	2 (10)	0.548
	Zahn 2003	365	28 (6)	26 (6)	0.739
Chronic respiratory disease	Albert 2011[14]	344	18 (3)	21 (4)	0.629
	Anthony 2014[15]	168	2 (5)	0	0.152
	Ballard 2011[16]	n/a[17]	20 (18)	24 (22)	0.458
	Hahn 2006[18]	n/a	0	1 (5)	0.280
	Ozdemir 2011[19]	n/a	2 (5)	4 (11)	0.394
	Seemungal 2008	365	0	1 (2)	0.328
	Shafuddin 2015	420	3 (3)	5 (5)	0.443
	Uzun 2014[20]	365	0	2 (4)	0.144
	Vos 2011[21]	2555	5 (33)	8 (62)	0.136

Table 2. Deaths (*Continued*)

Gastrointestinal condition	Aly 2007	n/a	5 (17)	6 (20)	0.739
	Berne 2002	n/a	2 (6)	2 (6)	0.903
	Ehsani 2013	n/a	0	1 (5)	0.311
	Gokmen 2012	14	0	1 (4)	0.302
	Ng 2007	n/a	2 (2)	4 (4)	0.406
	Nuntnarumit 2006[22]	n/a	2 (9)	0	0.148
	Oei 2001[23]	n/a	1 (4)	1 (4)	1.000
	Reignier 2002	n/a	6 (30)	8 (40)	0.507
	Robins-Browne 1983	7	1 (3)	1 (3)	1.000
HIV	Currier 2000	483	3 (1)	7 (2)	0.201
	El-Sadr 2000[24]	386	5 (2)	5 (2)	0.980
	Jablonowski 1997	n/a	1 (< 1)	7 (2)	**0.033**
	Oldfield 1998	n/a	38 (45)	38 (44)	0.946
	Pierce 1996	427/402[25]	107 (32)	137 (41)	**0.017**
Prevention of childhood mortality	Keenan 2018	7[26]	4 (< 1)	1 (< 1)	0.195
	Keenan 2018	621[27]	2404 (2)	2616 (3)	**0.000**
Sepsis	Giamarellos-Bourboulis 2008	28	31 (31)	28 (28)	0.642
	Giamarellos-Bourboulis 2008	90	43 (43)	60 (60)	**0.016**
	Giamarellos-Bourboulis 2014	28	56 (19)	51 (17)	0.648
Skin and soft tissue complaints	Schwameis 2017	30	0	1 (< 1)	0.318
Urogynaecological conditions	Kaul 2004[28]	801/764[29]	1 (< 1)	2 (1)	0.578

Table 2. Deaths (*Continued*)

	Van den Broek 2009	n/a[30]	1 (< 1)	2 (< 1)	0.563
	Van den Broek 2009	42[31]	7 (1)	3 (< 1)	0.205

Abbreviation:
HIV: human immunodeficiency virus.
n/a: not available.
[1]Post-treatment.
[2]Death caused by relapse, infection, and other reasons. Relapse caused five and seven deaths in the macrolide and placebo groups, respectively.
[3]Relapse caused 52 and 23 deaths in the macrolide and placebo groups, respectively.
[4]Cardiovascular death.
[5]Cardiovascular death.
[6]Death caused by respiratory complications of chronic obstructive pulmonary disease or sepsis after limb revascularising surgery.
[7]All-cause mortality.
[8]All-cause mortality.
[9]All-cause mortality. Data obtained by e-mail correspondence with authors (Winkel 2017 [pers comm]).
[10]Cardiac death.
[11]Cardiac death.
[12]Incomplete reporting of death at 4-year follow-up. We contacted the authors but received no reply.
[13]Death caused by ischaemic heart disease or cancer.
[14]Death caused by chronic obstructive pulmonary disease, cardiovascular attacks, neoplasm, or other/unknown causes. Report on data from Sadatsafavi 2016, a secondary study of Albert 2011.
[15]Death caused by bronchopneumonia with underlying coronary artery disease.
[16]Death caused by hypoxic respiratory failure, confirmed sepsis and/or necrotising enterocolitis, pulmonary haemorrhage, or withdrawal of life support due to intraventricular haemorrhage.
[17]Data collected at days 3, 5, 7, then weekly for the duration of the study, and at discharge.
[18]Death caused by asthma-related cause.
[19]Death caused by sepsis or necrotising enterocolitis.
[20]Death caused by respiratory failure due to exacerbation in chronic obstructive pulmonary disease.
[21]Report on patients that never received open-label azithromycin. Report on data from Ruttens 2015, a secondary study of Vos 2011.
[22]Death caused by severe bronchopulmonary dysplasia or from necrotising enterocolitis.
[23]Death caused by necrotising enterocolitis and septicaemia.
[24]Death caused by liver failure, cardiovascular disease, cancer, an overdose of methadone, or wasting.
[25]Follow-up reported separately for clarithromycin and placebo group.
[26]Deaths reported within one week of study drug administration.
[27]Follow-up period estimated as person-years (N = 323,302)/total number of children randomised (N = 190,238).
[28]Deaths caused by trauma.
[29]Follow-up period reported separately for azithromycin and placebo groups.
[30]During pregnancy.
[31]During six weeks after delivery.

Table 3. Participants with macrolide-resistant bacteria

Participants with macrolide-resistant bacteria[1]: 13 studies								
Study ID	**Type of macrolide (days of treatment)**	**Time for follow-up swabs**	**Macrolide-resistant bacteria at baseline N (%)**		**Macrolide-resistant bacteria after treatment [2]N (%)**		**Absolute increase in resistance with antibiotic (%)**	**Relative increase in resistance with antibiotic (%)**
			Macrolide	**Placebo**	**Macrolide**	**Placebo**		
Bacharier 2015[3]	AZM (5)	≥ 14 days postintervention	5 (12)	4 (9)	8 (20)	7 (17)	0	1
Berg 2005[4]	CLM (16*)	Week 2	50 (34)	50 (34)	102 (69)	46 (31)	38	N/A
		Week 8			96 (65)	55 (37)	28	N/A
Berkhof 2013[5]	AZM (84)	Week 12	0	1 (2)	1 (3)	0	1	-2
Brusselle 2013[6]	AZM (182)	Week 26	11 (48)	9 (39)	20 (87)	8 (35)	43	6
Gibson 2017[7]	AZM (336)	Week 48	14 (22)	18 (26)	20 (51)	17 (41)	6	-3
McCallum 2015[7,8]	AZM (21)	Day 23	8 (8)	13 (12)	7 (7)	13 (12)	1	1
Pierce 1996[8,9]	CLM (315*)	Not specified	N/A	N/A	11 (58)	0	N/A	N/A
Roca 2016a[9,10]	AZM (1)	Day 3	12 (3)	11 (3)	19 (5)	9 (2)	3	N/A
		Day 6			25 (6)	17 (4)	2	N/A
		Day 14			41 (11)	15 (4)	7	N/A
		Day 28			56 (15)	13 (3)	12	N/A
Saiman 2010[10,11]	AZM (168)	Day 168	38 (29)	50 (39)	43 (N/A)	9 (N/A)	N/A	N/A
Sirinavin 2003[11,12]	AZM (5)	Day 7	5 (5)	4 (4)	1 (33)	5 (24)	8	9
		Day 30			3 (18)	0	17	18
		Day 60			1 (4)	3 (14)	9	-10

Table 3. Participants with macrolide-resistant bacteria (*Continued*)

		Day 90			10 (42)	7 (37)	4	5
Uzun 2014 [12,13]	AZM (365)	1 year	5 (23)	4 (20)	3 (12)	11 (41)	26	-10
Valery 2013 [13,14]	AZM (621*)	End of study	10 (24)	8 (22)	19 (46)	4 (11)	33	18
		> 30 days and ≤ 12 months postintervention[14,15]			6 (17)	3 (12)	3	3
Wilson 1977	ERY (7)	Post-treatment	0	1 (4)	0	1 (4)	0	1

Brill 2016 [pers comm] reported via email correspondence on both number of participants with resistant bacteria and the number of resistant isolates (unpublished data). We contacted the author again for information on what type of resistant bacteria they report on (macrolide-resistant or 'others'), and are awaiting author reply.

Smith 2002 present the mean number of colony forming units of azithromycin-resistant streptococci per sample, and state that the number of streptococci resistant to 2 mg/L azithromycin was significantly higher in people who had taken azithromycin compared to placebo even at 22 weeks (data from Sefton 1996, a secondary study of Smith 2002). We contacted the author, but did not receive any reply.

Wallwork 2006 report on nasal swabs from participants treated with roxithromycin and state that no macrolide-resistant organisms were noted to have developed. Data not given for placebo group.

Wong 2012 state that macrolide resistance testing was not routinely undertaken, but two (4%) participants in the azithromycin group developed macrolide-resistant *Streptococcus pneumoniae* at six months.

Abbreviations:

AZM: azithromycin.

CLM: clarithromycin.

ERY: erythromycin.

N/A: not available.

*Mean duration of treatment.

[1]Bacterial isolates tested vary between studies. The most common ones were: *Streptococcus pneumoniae*,*Haemophilus influenza*,*Moraxella catarrhalis*,*Pseudomonas aeruginosa*, and *Staphylococcus aureus.*

[2]Some studies report on macrolide-resistant bacteria during treatment.

[3]A subsample of participants (14%) was tested for resistant bacteria. The authors also report on the number of participants acquiring azithromycin-resistant bacteria (6 in AZM group versus 4 in placebo group).

[4]Data from Figure 2 in Berg 2005. Only the percentages of participants with macrolide-resistant bacteria are reported. We used the number of participants randomised and screened for culture of pathogens (N = 148 in both groups) to calculate the number of participants in each group.

[5]Data from Table 4 in Berkhof 2013.

[6]A subsample of participants (42%) was tested for resistant bacteria.

[7]Data from Table S8 and Table S9 in Gibson 2017. We only present data from nose swabs, as the same bacteria may be identified in the various samples (sputum, throat, nose). A subsample of participants was tested for resistant bacteria.

[8]Data from Table 3 in McCallum 2015. We have reported on any of the macrolide-resistant bacteria.

[9]Report on people who contracted *Mycobacterium avium* complex infections.

[10]Data on mothers from Table 3 in Roca 2016a. We only present data from mothers' nasopharyngeal swabs, as the same bacteria may be identified in the various samples (nasopharynx, milk, vagina).

[11]Data from Table 4 in Saiman 2010. Report on treatment-emergent bacteria at day 168. Not possible to calculate the percentage of resistant bacteria at day 168, as the given denominator varies for each reported micro-organism.
[12]Data from Table 4 in Sirinavin 2003. Report on participants with a *Salmonella* isolate. The denominator (number with available data) varied significantly (range 3 to 98) at days 7, 30, 60, and 90.
[13]Data from supplementary Table 2 in Uzun 2014. Number of participants with sputum samples used as denominator.
[14]Data from Table 4 in Valery 2013.
[15]Data on post-intervention macrolide-resistant bacteria are from Table 3 in Hare 2015, a secondary study of Valery 2013.

Table 4. Isolates with macrolide-resistant bacteria

Isolates with macrolide-resistant bacteria[1]: 8 studies								
Study ID	**Type of macrolide (days of treatment)**	**Time for follow-up swabs**	**Macrolide-resistant bacteria at baseline N (%)**		**Macrolide-resistant bacteria after treatment [2]N (%)**		**Absolute increase in resistance with antibiotic (%)**	**Relative increase in resistance with antibiotic (%)**
			Macrolide	**Placebo**	**Macrolide**	**Placebo**		
Albert 2011[3]	AZM (365)	At enrolment and every 3 months	23 (52)	28 (57)	38 (81)	44 (41)	35	-8
Altenburg 2013[4]	AZM (365)	Week 12 and 64 + exacerbations	7 (35)	8 (28)	53 (88)	29 (26)	55	9
Berg 2005[5]	CLM (16*)	"After therapy"	27 (35)	33 (38)	51 (66)	40 (45)	18	-7
Lildholdt 2003[6]	AZM (183)	Week 26	1 (2)	0	2 (14)	0	12	7
		Week 43			1 (6)	0	6	3
		Week 60			1 (9)	0	9	5
		Week 78			0	0	0	0
Seemungal 2008[7]	ERY (365)	12 months	0	0	1 (4)	0	4	N/A
Tita 2016	AZM (1)	Postpartum	N/A	N/A	3	4	N/A	N/A
Videler 2011	AZM (84)	Day 84	2 (4)	1 (2)	1 (2)	3 (7)	3	-3
Wilson 1979	ERY (7)	"Post-treatment"	0	0	0	0	0	N/A

Brill 2016 [pers comm] report via email correspondence on both the number of participants with resistant bacteria and the number of resistant isolates (unpublished data). We contacted the author again for information on what type of resistant bacteria they report on (macrolide-resistant or 'others'), and are awaiting author reply.

Van Delden 2012 state that azithromycin exposure did not lead to an MIC increase comparing the initial and last *Pseudomonas aeruginosa* isolates. Data not shown.

Abbreviations:

AZM: azithromycin.

CLM: clarithromycin.

ERY: erythromycin.

MIC: minimum inhibitory concentration.

N/A: not available.

*Mean duration of treatment.

[1]Bacterial isolates tested vary between studies. The most common ones were: *Staphylococcus aureus*,*Streptococcus pneumoniae*,*Moraxella catarrhalis*, and*Haemophilus influenzae.*

[2]Some studies report on macrolide-resistant bacteria during treatment.

[3]The denominator varies. At baseline: cultures from participants who had selected respiratory pathogens cultured at enrolment. During course: cultures from participants who became colonised with selected respiratory pathogens during the course of the study. Note: a much larger number of participants were colonised in the placebo group compared to the azithromycin group during the course of treatment (range: 44 to 108).

[4]Data from supplementary online content, eResults from Altenburg 2013. Number of pathogens tested is used as denominator.

[5]Data from Table 3 in Berg 2005. Denominator: total number of oropharyngeal *Haemophilus parainfluenzae* strains (sensitive, intermediate, resistant).

[6]Data from Table 2 in Lildholdt 2003. Denominator: number of positive cultures (range: 6 to 47).

[7]Report on one resistant *Streptococcus pneumoniae*, and state that all *Haemophilus influenzae* were resistant or assumed constitutionally resistant to erythromycin.

Table 5. Proportion of macrolide-resistant streptococci

Proportion of macrolide-resistant streptococci[1] isolates: 3 studies								
Study ID	**Type of macrolide (days of treatment)**	**Time for follow-up swabs**	**Proportion of resistant streptococci at baseline**		**Proportion of resistant streptococci after treatment**		**Absolute increase in resistance with antibiotic (%)**	**Relative increase in resistance with antibiotic (%)**
			Macrolide	**Placebo**	**Macrolide**	**Placebo**		
Brusselle 2013[2]	AZM (182)	Day 30	18	11	52	10	35	6
		Day 180			74	18	49	8
		Day 210			44	12	25	5
Malhotra-Kumar 2007a[3]	AZM (3)	Day 4	26	28	87	33	52	-27
		Day 8			83	34	47	-25
		Day 14			83	34	47	-25
		Day 28			80	33	45	-24

Table 5. Proportion of macrolide-resistant streptococci (*Continued*)

		Day 42			67	36	29	-16
		Day 180			46	23	21	-12
Malhotra-Kumar 2007b[4]	CLM (7)	Day 8	30	25	81	31	45	10
		Day 14			71	31	35	8
		Day 28			63	30	28	7
		Day 42			59	28	26	6
		Day 180			43	21	17	4
Serisier 2013[5]	ERY (336)	Week 48	N/A	N/A	29	0	N/A	N/A

Abbreviations:
AZM: azithromycin.
CLM: clarithromycin.
ERY: erythromycin.
N/A: not available.
[1]Denominator: number of streptococci.
[2]Data from Figure S3 in Brusselle 2013. A subsample of participants (42%) was tested for resistant bacteria.
[3]Data from Figure 2 in Malhotra-Kumar 2007a. Note that only about 47% of participants attended follow-up on day 180.
[4]Data from Figure 2 in Malhotra-Kumar 2007b. Note that only about 47% of participants attended follow-up on day 180.
[5]Data from eTable 2 in Serisier 2013. Results are presented for the intention-to-treat population. Report on median change in the proportion of macrolide-resistant streptococci.

APPENDICES

Appendix 1. MEDLINE (Ovid) and Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

1 exp Macrolides/
2 macrolide*.tw,nm,ot.
3 (azithromycin* or clarithromycin* or erythromycin* or roxithromycin*).tw,nm,ot.
4 or/1-3
5 exp Placebos/
6 placebo*.tw,nm,ot.
7 5 or 6
8 4 and 7

Appendix 2. Embase (Elsevier) search strategy

#13 #8 AND #11 AND [1-1-2010]/sd NOT [22-8-2015]/sd (690)
#12 #8 AND #11 (2,267)
#11 #9 OR #10 (1,401,271)
#10 random*:ab,ti OR placebo*:ab,ti OR crossover*:ab,ti OR 'cross-over':ab,ti OR factorial:ab,ti OR volunteer*:ab,ti OR allocat*:ab,ti OR assign*:ab,ti OR ((singl* OR doubl*) NEAR/2 blind*):ab,ti AND [embase]/lim (1,246,381)
#9 'single blind procedure'/de OR 'double blind procedure'/de OR 'crossover procedure'/exp OR 'randomized controlled trial'/de (421,654)
#8 #4 AND #7 (5,008)
#7 #5 OR #6 (328,717)
#6 placebo*:ab,ti AND [embase]/lim (204,119)
#5 'placebo'/de AND [embase]/lim (263,844)
#4 #1 OR #2 OR #3 (129,809)
#3 azithromycin*:ab,ti OR clarithromycin*:ab,ti OR erythromycin*:ab,ti OR roxithromycin*:ab,ti AND [embase]/lim (31,108)
#2 macrolide*:ab,ti AND [embase]/lim (14,020)
#1 'macrolide'/exp AND [embase]/lim (126,714)

Appendix 3. CINAHL (EBSCO) search strategy

S19	S8 AND S18
S18	S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17
S17	(MH "Quantitative Studies")
S16	TI placebo* OR AB placebo*
S15	(MH "Placebos")
S14	(MH "Random Assignment")
S13	TI random* OR AB random*
S12	TI ((singl* or doubl* or tripl* or trebl*) W1 (blind* or mask*)) OR AB ((singl* or doubl* or tripl* or trebl*) W1 (blind* or mask*))
S11	TI clinic* trial* OR AB clinic* trial*
S10	PT clinical trial
S9	(MH "Clinical Trials+")
S8	S4 AND S7
S7	S5 OR S6
S6	TI placebo* OR AB placebo*

(*Continued*)

S5	(MH "Placebos")
S4	S1 OR S2 OR S3
S3	TI (azithromycin* or clarithromycin* or erythromycin* or roxithromycin*) OR AB (azithromycin* or clarithromycin* or erythromycin* or roxithromycin*)
S2	TI macrolide* OR AB macrolide*
S1	(MH "Antibiotics, Macrolide+")

Appendix 4. LILACS (BIREME) search strategy

(mh:macrolides OR macrolide* OR macrólidos OR macrolídeos or mh:d02.540.505* OR mh:d02.540.576.500* OR mh:d04.345.674.500* OR mh:azithromycin OR azithromycin* OR azitromicina OR mh:d02.540.505.250.050* OR mh:clarithromycin OR clarithromycin* OR mh:claritromicina* OR mh:d02.540.505.250.100* OR mh:erythromycin OR erythromycin* OR eritromicina or mh:d02.540.505.250* OR mh:roxithromycin OR roxithromycin* OR roxitromicina OR mh:d02.540.505.250.630*) AND (mh:placebos OR placebo*)

Appendix 5. Web of Science (Clarivate Analytics) search strategy

#6	**71**	#4 AND #3 **Refined by**: publication years**:** (2015 OR 2016) Indexes = SCI-EXPANDED, SSCI,A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan = 1985-2016
#5	**1254**	#4 AND #3 Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan = 1985-2016
#4	**1,797,642**	**TOPIC:** (random* or placebo* or crossover* or "cross over" or allocat* or ((doubl* or singl*) NEAR/1 blind*)) *OR* **TITLE:** (trial) Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan = 1985-2016
#3	**1254**	#2 AND #1 Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan = 1985-2016
#2	**198,122**	**TOPIC:** (placebo*) Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan = 1985-2016

(*Continued*)

#1	**40,012**	**TOPIC:** (macrolide* or azithromycin* or clarithromycin* or erythromycin* or roxithromycin*) Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC Timespan = 1985-2016

CONTRIBUTIONS OF AUTHORS

Malene Plejdrup Hansen (MPH) contributed to the selection of studies, data extraction, 'Risk of bias' assessment, data analysis, and was responsible for drafting the review.

Anna M Scott (AMS) contributed to the selection of studies, data extraction, 'Risk of bias' assessment, data analysis, and the drafting of the review.

Amanda McCullough (AMcC) contributed to the selection of studies, data extraction, 'Risk of bias' assessment, and contributed to the final version of the review.

Sarah Thorning (ST) and Justin Clark (JC) performed the searches. ST contributed to the selection of studies, and both ST and JC contributed to the final version of the review.

Jeffrey K Aronson (JKA) provided methodological expertise on dealing with adverse events, and contributed to the final version of the review.

Elaine M Beller (EMB) provided statistical expertise and contributed to the final version of the review.

Paul P Glasziou (PG) and Tammy C Hoffmann (TH) contributed to the final version of the review.

Chris B Del Mar (CDM) conceived the original idea for this review. CDM resolved disagreements at any stage in the review process and contributed to the writing of the review.

DECLARATIONS OF INTEREST

Malene Plejdrup Hansen: senior research fellow at the Research Unit for General Practice in Aalborg funded by the Research Foundation of General Practice in Denmark. From 2014 to 2016 she was a postdoctoral fellow at the Centre for Research Excellence in Minimising Antibiotic Resistance from Acute Respiratory Infections (CREMARA) funded by the National Health and Medical Research Council (NHMRC), Australia (1044904).

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Sarah Thorning: none known.

Jeffrey K Aronson: is a President Emeritus of the British Pharmacological Society and a member of the Advisory Board of the British National Formulary; was until recently a member of a Technology Appraisal Committee of the UK's National Institute for Health and Care Excellence (NICE); and is editor of textbooks on adverse drug reactions, including *Meyler's Side Effects of Drugs: The International Encyclopedia of Adverse Drug Reactions and Interactions.* He has published in peer-reviewed journals on different aspects of adverse drug reactions.

Elaine M Beller: co-investigator on the National Health and Medical Research Council (NHMRC)-funded Centre for Research Excellence grant on Antibiotic Resistance.

Paul P Glasziou: co-investigator on the National Health and Medical Research Council (NHMRC)-funded Centre for Research Excellence grant on Antibiotic Resistance.

Tammy C Hoffmann: co-investigator on the National Health and Medical Research Council (NHMRC)-funded Centre for Research Excellence grant on Antibiotic Resistance.

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Chris B Del Mar: Co-ordinating Editor of the Cochrane Acute Respiratory Infections Group and chief investigator at the Centre for Research Excellence in Minimising Antibiotic Resistance from Acute Respiratory Infections (CREMARA), both funded by the National Health and Medical Research Council (NHMRC), Australia. He has received royalties from BMJ Books and Elsevier for activities unrelated to this submitted work.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The review differs from the protocol, Hansen 2015, in the following ways.

Objectives and Types of outcome measures: while conducting this review we realised that it would be most appropriate to present each of the specific reported adverse events separately. Consequently, instead of handling the adverse events as adverse effects, adverse reactions, and serious adverse events, as stated in the protocol, we have presented each of the adverse events separately. We have reported on adverse events that occurred in ≥ 5% in any of the groups (macrolide or placebo) (Zarin 2016). However, all reported adverse events are available: adverse events by System Organ Classes: threshold ≥ 5%, Hansen 2018a, and adverse events by System Organ Classes < 5%, Hansen 2018b.

Trial authors very seldom referred to a specific definition of how they classified severe adverse events, and consequently we did not find it appropriate to report these as a composite outcome labelled 'severe adverse events'. However, every single adverse event reported in all of the included studies, regardless of how it was labelled by the trial authors, was extracted, and data are available (Hansen 2018a; Hansen 2018b).

'Subsequent carriage of resistant bacteria' has been refined to 'subsequent carriage of macrolide-resistant bacteria'.

Types of studies: we clarified that we included trials with more than two intervention arms, if it was possible to identify a macrolide arm and a placebo arm. After the protocol was published, we decided to exclude purely pharmacodynamic and pharmacokinetic studies, unless they also reported clinical parameters. We also excluded studies with fewer than 20 participants randomised to each arm. We made these decisions after starting the title and abstract screening, when we realised that many of these small pharmacodynamic or pharmacokinetic studies posed a high risk of reporting drug-drug interactions of macrolides or non-macrolide-related adverse events.

Searching other resources and Dealing with missing data: in the protocol we stated that we would contact authors of trials if adverse events data were not published. However, as this evolved into an unexpectedly large review with generally very poor reporting of adverse events, we contacted only trial authors if adverse events were incompletely reported and an e-mail address was available in the publication.

Data collection and analysis: we stated in the protocol that MPH and ST would assess all studies identified by the searches, extract data, and assess risk of bias for each of the included studies. However, the size of the review necessitated involvement of additional authors.

ST participated in the process of selecting studies, while both AMcC and AMS participated in the selection of studies, data extraction, and 'Risk of bias' assessments. Uniform data collection was ensured by the participation of MPH at all stages and by having CDM as the third review author in resolving any discrepancies.

Measures of treatment effect: in the protocol we planned to express all outcomes as Peto odds ratios (OR) as we expected that the included trials would report on few adverse events. However, Peto OR mandates fixed-effect models, which would not be appropriate to apply to our data as several sources of heterogeneity that might undermine the use of a fixed-effect approach exist in this review.

Unit of analysis issues: we deviated from the protocol by including both participants and bacterial isolates as units of analysis when reporting subsequent carriage of macrolide-resistant bacteria.

Data synthesis: as trial authors used a wide range of terms when reporting adverse events, we categorised the reported adverse events using a clinically validated, standardised medical classification system, the Medical Dictionary for Regulatory Activities (MedDRA). We added a section describing the classification system to the review and how we analysed adverse events. To deal with an enormous long tail of (mostly irrelevant) adverse events described in tiny numbers, we decided that we would undertake a meta-analysis when $\geq$ 3 studies reported a specific adverse event.

Subgroup analysis and investigation of heterogeneity: as in the case of meta-analyses of the primary outcomes, at least three studies were required for subgroup analyses.