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Short-course antibiotics for acute otitis media (Review)

Kozyrskyj AL, Klassen TP, Moffatt M, Harvey K

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[Intervention Review]

Short-course antibiotics for acute otitis media

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ABSTRACT

Background

Acute otitis media (AOM) is a common illness during childhood, for which antibiotics are frequently prescribed.

Objectives

To determine the effectiveness of a short course of antibiotics (less than seven days) in comparison to a long course of antibiotics (seven days or greater) for the treatment of AOM in children.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2009, issue 4) which contains the Acute Respiratory Infections Group's Specialised Register, MEDLINE, EMBASE, MEDLINE In-Process & Other Non-Indexed Citations, CINAHL, BIOSIS Previews, OCLC Papers First and Proceedings First, Proquest Dissertations and Theses (inception to November 2009); International Pharmaceutical Abstracts, the NLM Gateway, ClinicalTrials.gov and Current Controlled Trials (inception to August 2008).

Selection criteria

Trials were included if they met the following criteria: participants aged one month to 18 years; clinical diagnosis of ear infection; no previous antimicrobial therapy; and randomisation to treatment with less than seven days versus seven days or more of antibiotics.

Data collection and analysis

The primary outcome of treatment failure was defined as the absence of clinical resolution, relapse or recurrence of AOM during one month following initiation of therapy. Treatment outcomes were extracted from individual studies and combined in the form of a summary odds ratio (OR). A summary OR of 1.0 indicates that the treatment failure rate following less than seven days of antibiotic treatment was similar to the failure rate following seven days or more of treatment.

Main results

This update included 49 trials containing 12,045 participants. Risk of treatment failure was higher with short courses of antibiotics (OR 1.34, 95% CI 1.15 to 1.55) at one month after initiation of therapy (21% failure with short-course treatment and 18% with long-course; absolute difference of 3% between groups). There were no differences found when examining treatment with ceftriaxone for less than seven days (30% failure in those receiving ceftriaxone and 27% in short-acting antibiotics administered for seven days or more) or azithromycin for less than seven days (18% failure in both those receiving azithromycin and short-acting antibiotics administered for seven days or more) with respect to risk of treatment failure at one month or less. Significant reductions in gastrointestinal adverse events were observed for treatment with short-acting antibiotics and azithromycin.

Authors' conclusions

Clinicians need to evaluate whether the minimal short-term benefit from longer treatment of antibiotics is worth exposing children to a longer course of antibiotics.

PLAIN LANGUAGE SUMMARY

Short course antibiotics for healthy children with uncomplicated acute otitis media

Acute otitis media (AOM), or middle ear infection, is a common childhood illness, with more than half of all children having at least one infection by the time they are seven. Although otitis media often resolves without treatment, it is frequently treated with antibiotics. The length of treatment varies widely. This review of 49 trials found that treating children with a short course (less than seven days) of antibiotics, compared to treatment with a long course (seven days or greater) of antibiotics, increases the likelihood of treatment failure in the short term. No differences are seen one month later. The amount of gastrointestinal adverse events decreased with a shorter course of antibiotics.

Summary of findings for the main comparison. Short-acting antibiotic > 48 hours short-term treatment for acute otitis media

Short-acting antibiotic > 48 hours short-term treatment for acute otitis media

Patient or population: patients with acute otitis media
Settings:
Intervention: Short-acting antibiotic > 48 hours short-term treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Short-acting antibiotic > 48 hours short-term treatment				
Treatment failure at 1 month or less	**Study population**		**OR 1.34** (1.15 to 1.55)	5093 (16)		
	175 per 1000	**221 per 1000** (196 to 247)				
	Medium risk population					
	157 per 1000	**200 per 1000** (176 to 224)				
Treatment failure at 8 to 19 days	**Study population**		**OR 1.37** (1.15 to 1.64)	3932 (11)		
	144 per 1000	**187 per 1000** (162 to 216)				
	Medium risk population					
	117 per 1000	**154 per 1000** (132 to 179)				
Treatment failure at 20 to 30 days	**Study population**		**OR 1.16** (0.94 to 1.42)	2476 (9)		
	203 per 1000	**228 per 1000** (193 to 266)				
	Medium risk population					

	172 per 1000	**194 per 1000** (163 to 228)		
Treatment failure at 3 months or less	**Study population**		**OR 1.18** (0.98 to 1.41)	2068 (7)
	364 per 1000	**403 per 1000** (359 to 447)		
	Medium risk population			
	364 per 1000	**403 per 1000** (359 to 447)		
Treatment failure at 90 days	**Study population**		**OR 1.16** (0.65 to 2.06)	207 (2)
	327 per 1000	**360 per 1000** (240 to 500)		
	Medium risk population			
	311 per 1000	**344 per 1000** (227 to 482)		
Treatment failure at 30 to 45 days	**Study population**		**OR 1.18** (0.97 to 1.43)	1861 (5)
	368 per 1000	**407 per 1000** (361 to 454)		
	Medium risk population			
	364 per 1000	**403 per 1000** (357 to 450)		

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio;

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.

Summary of findings 2. Ceftriaxone for acute otitis media

Ceftriaxone for acute otitis media

Patient or population: patients with acute otitis media
Settings:
Intervention: Ceftriaxone

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Ceftriaxone				
Treatment failure at 1 month or less	**Study population**		**OR 1.07** (0.86 to 1.33)	1709 (8)		
	270 per 1000	**284 per 1000** (241 to 330)				
	Medium risk population					
	254 per 1000	**267 per 1000** (226 to 312)				
Treatment failure at 3 months or less	**Study population**		**OR 0.89** (0.66 to 1.21)	701 (3)		
	402 per 1000	**374 per 1000** (307 to 449)				
	Medium risk population					
	379 per 1000	**352 per 1000** (287 to 425)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio;

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.

Summary of findings 3. Azithromycin 3 to 5 days short-term treatment for acute otitis media

Azithromycin 3 to 5 days short-term treatment for acute otitis media

Patient or population: patients with acute otitis media
Settings:
Intervention: Azithromycin 3 to 5 days short-term treatment

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Azithromycin 3 to 5 days short-term treatment				
Treatment failure at 1 month or less	**Study population**		**OR 1.02** (0.87 to 1.2)	4354 (19)		
	185 per 1000	**188 per 1000** (165 to 214)				
	Medium risk population					
	61 per 1000	**62 per 1000** (53 to 72)				
Treatment failure at 8 to 19 days	**Study population**		**OR 1.27** (1.04 to 1.55)	4347 (18)		
	95 per 1000	**118 per 1000** (98 to 140)				
	Medium risk population					
	56 per 1000	**70 per 1000** (58 to 84)				
Treatment failure at 20 to 30 days	**Study population**		**OR 0.98** (0.82 to 1.17)	2708 (11)		
	265 per 1000	**261 per 1000** (228 to 297)				
	Medium risk population					

	273 per 1000	**269 per 1000** (235 to 305)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **OR:** Odds ratio;

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.

BACKGROUND

Description of the condition

Acute otitis media (AOM) is one of the most common childhood health problems, a leading cause of visits to a physician and the most frequent reason children receive antibiotics or undergo surgery. The cost estimates for AOM in the US are between $3 and $5 billion per year. Most children will have at least one episode of AOM, with the peak incidence period being between 6 and 11 months (Rovers 2004).

AOM is defined as the presence of a middle ear effusion in conjunction with signs and symptoms of inflammation in the middle ear, such as otalgia, otorrhoea, fever or irritability. There is a high rate of spontaneous resolution for AOM, but if left untreated it can occasionally lead to complications, such as acute mastoiditis. Hearing loss can lead to behavioural changes and communication delay (Rovers 2004).

Description of the intervention

The standard duration of therapy in North America is 10 days (Froom 1990). However, the optimal duration of treatment is not known and varies worldwide. Half of the practitioners in Great Britain prescribe a five-day course compared to the majority of practitioners in the Netherlands who prescribe six to seven days of antibiotic therapy. Many opt for no treatment (Froom 1990).

How the intervention might work

The decline during the 1940s and 1950s in suppurative complications of AOM throughout North America and Europe has been attributed to antibiotic therapy (Berman 1995). Evidence suggests that antibiotic-treated and untreated children living in high-income countries have similar long-term outcomes (Burke 1991; Mygind 1981; van Buchem 1981). However, a meta-analysis pooling the results of four studies suggests that although the spontaneous rate of resolution was high with placebo or no drug (81%) (95% confidence interval (CI) 69% to 94%), antimicrobial therapy increased resolution by 13.7% (95% CI 8.2% to 19.2%) (Rosenfeld 1994). A meta-analysis by Del Mar documented that compared to placebo, antibiotics reduce pain at two to seven days after the start of treatment (Del Mar 1997; Sanders 2009). The absolute benefit of this finding is 5.6% fewer children experience pain at two to seven days. Long-term outcomes were similar with and without treatment.

Why it is important to do this review

Practitioners in North America may be hesitant to discontinue prescribing antibiotics, despite findings from the medical literature that support management of AOM without antibiotics. Moreover, the therapy duration for optimal outcome continues to be a question. Expert opinion has recommended five days of antimicrobial treatment for uncomplicated otitis media in children over the age of six years (Paradise 1995; Paradise 1997). The quality of scientific evidence to support a policy for shorter courses of antibiotic treatment has been assessed (Pichichero 1997), but lacks a systematic, quantitative evaluation. Concern regarding resistant bacteria from the overuse of antibiotics (Cohen 1992; Murray 1994) and poor compliance is increasing, as is the cost of health care. Therefore, it is desirable to determine the shortest duration of antibiotic treatment that would result in favorable outcomes. We felt that a systematic review would add some objectivity to this debate.

OBJECTIVES

To determine the effectiveness of a short course of antibiotics (less than seven days) in comparison to a long course (seven days or longer) of antibiotics for the treatment of children with AOM. Subgroup analyses of children less than two years old, children with a perforated ear drum, and children with a history of recurrent otitis media were pursued to address concerns that these groups may have less favorable outcomes.

METHODS

Criteria for considering studies for this review

Types of studies

For inclusion in the review, we considered randomized controlled trials (RCTs) of the empiric treatment of AOM, comparing two antibiotic regimens of different durations, as described in the title or abstract of the clinical trial. When the duration of antibiotic treatment was not specified in the title or abstract, we retrieved the trial to verify the treatment duration in both arms. We placed no language restrictions on the selection of clinical trials (Gregoire 1995).

Types of participants

We included children aged one month to 18 years, with a clinical diagnosis of AOM and no history of immediate antibiotic use, immune deficiency, chronic disease or head and neck abnormalities.

Types of interventions

We compared antibiotic therapy of a treatment arm for less than seven days (defined as the short course), with a treatment arm greater than or equal to seven days (defined as the long course). The antibiotic may be the same or different in the two treatment arms. Studies using the antibiotic ceftibuten were excluded from this 2009 update due to a lack of clinical relevance as the antibiotic is not commonly used by clinicians.

Types of outcome measures

Primary outcomes

Treatment failure, which included lack of clinical resolution, relapse or recurrence of AOM during a one-month period following the initiation of therapy. Clinical resolution meant that the presenting signs or symptoms of AOM had improved or resolved.

Secondary outcomes

The cumulative number of treatment failures, relapses and recurrences reported at time of diagnosis and again at a final evaluation point between one to three months. Middle ear effusion was not classified as a treatment failure because of its documented persistence during the course of the disease, regardless of treatment. We sought data on the number of children with persistent middle ear effusion at both of the evaluation points.

Search methods for identification of studies

Electronic searches

The original search was developed and run in 1997 (see Appendix 1 for details of the search). The search was then updated and run in August 2008 for the years 1997 to 2007 (see search strategies in Appendix 2), and updated again in November 2009.

In this update we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2009, issue 4) which contains the Cochrane Acute Respiratory Infections Group's Specialised Register; MEDLINE (1966 to November Week 1, 2009); EMBASE (1974 to November 2009); MEDLINE In-Process & Other Non-Indexed Citations (1966 to Week 1, 2009); International Pharmaceutical Abstracts (1970 to August Week 1, 2008); BIOSIS Previews (1969 to November 2009); CINAHL (1981 to November 2009); the NLM Gateway (1998 to August 2008); OCLC Papers First and Proceedings First (1997 to November 2009); ClinicalTrials.gov (1998 to August 2008); Proquest Dissertations and Theses (1861 to November 2009); and Current Controlled Trials (1997 to August 2008). We searched the following databases without any date restrictions in September 2007: the National Research Register; CRISP; the TRIP Database; Scirus; and Google Scholar. We imposed no language or publication restrictions.

We ran the following search strategy in MEDLINE and CENTRAL. The MEDLINE search was combined with the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximising version (2008 revision); Ovid version (Lefebvre 2008). The search strategy also incorporated the child search strategy developed by Boluyt (Boluyt 2008). We adapted this search strategy to search the other databases.

MEDLINE (Ovid)

1 exp Otitis Media/
2 otitis media.tw.
3 (OM or OME or AOM).tw.
4 (otorrhea* or otorrhoea*).tw.
5 (ear* adj3 (infect* or acute*)).tw.
6 or/1-5
7 exp treatment outcome/
8 exp Anti-Infective Agents/
9 (antibacter* or anti-bacter* or anti bacter* or antibiotic* or anti-biotic* or anti biotic* or bacteriocid* or antimicrob* or anti-microb* or anti microb*).tw.
10 (amoxicillin* or amoxycillin* or penicillin* or cefprozil* or clarithromycin* or cefpodoxime* or cefaclor* or ceftriaxone* or azthromycin* cefixime*).tw.
11 or/7-10
12 6 and 11

Searching other resources

We retrieved clinical trial references and published reviews on the treatment of AOM in order to identify further trials. We then contacted primary authors for information on such trials.

Data collection and analysis

Selection of studies

In the first publication of this review (Kozyrskyj 2000) clinical trials examining the antibiotic treatment of AOM were retrieved from the medical literature search and evaluated by the review authors according to the selection criteria previously described. Decisions to include the trial were made independently. Interreviewer agreement was assessed by the kappa statistic using PC Agree Software (Stephen Walter, McMaster University, Hamilton, Ontario) and consensus was reached regarding trial inclusion.

In this updated review, two review authors (KH, NH) evaluated for inclusion in the review the clinical trials retrieved during the search update. A third review author (TK) was consulted when consensus could not be reached.

Data extraction and management

At least two review authors (KH, LB) independently performed data extraction, followed by a consensus conference to resolve any differences. We developed a standardized form to facilitate data extraction. Data extracted from each trial included:

- the number of children with no clinical resolution of AOM;
- relapse or recurrence of AOM;
- the number of children with persistent middle ear effusion; and
- the number of withdrawals from each arm of the trial.

We recorded the data as follows:

Primary outcome: evaluation points included time points until one month after initiation of therapy.

Secondary outcome: evaluation point between one to three months after initiation of therapy.

Important subgroups defined a priori for which data were sought are:

1. antibiotic use for two days or less;
2. children aged less than two years; and
3. perforated tympanic membrane (Appelman 1991; Hendrickse 1988; Kaleida 1991; van Buchem 1981).

Descriptive data collected included treatment site, patient baseline characteristics, co-interventions, and inclusion, exclusion and outcome criteria to summarise the generalisability of included studies and to facilitate sensitivity analyses. We also recorded drug dose, route and treatment duration.

Change in statistical methods from original version of review

Two studies (Gooch 1996; Hoberman 1997) in the current review contained two arms comparing long-course versus short-course antibiotics. In the first version of this review (Kozyrskyj 2000) the short-course arm was counted twice against each long-course arm of that study. In this review update, we have modified our methods and combined both long-course arms into a single comparison against the short-course arm, as recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). This prevents overweighing the short-course arm of these trials in the meta-analysis.

Assessment of risk of bias in included studies

We used the Cochrane Collaboration's 'Risk of bias' tool (Higgins 2008) to assess for bias in this updated review. Two review authors (KH, MO) independently evaluated the risk of bias of included trials

and then came to a consensus. When consensus could not be reached a third review author was consulted (TK).

Measures of treatment effect

We compared the treatment failure rate following a short course of antibiotics to the treatment failure rate following a long course of antibiotics using odds ratios (ORs) for individual trial outcomes. We determined a summary OR with 95% CI for trials pooled by antibiotic type using the Peto fixed-effect model.

Unit of analysis issues

We performed analysis on trials grouped by the pharmacokinetic behaviour of the antibiotic used in the short-course treatment arm, as follows.

1. Short-acting oral antibiotics, for example, penicillin, amoxicillin, cefaclor and cefuroxime.
2. Oral azithromycin.
3. Intramuscular ceftriaxone.

We also conducted additional meta-analyses in the short-acting antibiotic group for treatment duration less than 48 hours and more than 48 hours.

Assessment of heterogeneity

We assessed statistical heterogeneity (Higgins 2008; Laupacis 1988). When significant heterogeneity existed, we examined trials for specific potential clinical differences (Thompson 1994). We also calculated summary ORs using the DerSimonian and Laird random-effects model (DerSimonian 1986). We determined the summary risk difference (difference in the failure rate between the short and long-course antibiotics) and a 95% CI for pooled group data.

Sensitivity analysis

We performed a sensitivity analyses to assess whether the results of the primary outcome for all antibiotics was sensitive to blinding, allocation concealment and publication bias. Additionally a sensitivity analysis was undertaken to assess those trials that used the same antibiotic in both the short and long courses of the trial.

RESULTS

Description of studies

See Characteristics of included studies and Characteristics of excluded studies tables.

Results of the search

Updated electronic searches and handsearches from January 2000 through to November 2009 retrieved 4175 additional citations. In this updated review, we included 49 studies containing 12,045 participants. Refer to the Characteristics of included studies for detailed information on individual trials.

Included studies

We included 22 new trials, resulting in 49 eligible trials for this updated review (Adam 2000; Al-Ghamdi 1999; Arguedas 2005; Arrieta 2003; Block 2000; Block 2003; Block 2004; Catania 2004; Cohen 1998; Cohen 1999; Cohen 2000; Dagan 2000a; Dagan 2000b; de Jose 1998; Dunne 2003; Guven 2006; Hoberman 2005; Kara 1998; Oguz 2003; Pessey 1999; Varsano 1997; Wang 2004). Fourty-eight of the included studies were classified as randomized controlled trials (RCTs). Randomisation was not mentioned in one study (Mohs 1993). Included sample sizes ranged from 17 participants (Puczynski 1987) to 868 participants (Hoberman 1997). The median sample size was 215 participants (Dagan 2000b). Studies were primarily conducted in North America, South America, Europe and the Middle East (Israel and Turkey). Single trials were carried out in both Egypt (Mohs 1993) and China (Wang 2004). All trials enrolled children; 39 trials enrolled children less than one year old; eight trials began enrolment at two years of age; and two trials evaluated children three years of age or less. The maximum age of enrolment was 14 years (Kafetzis 1997).

The following antibiotics were evaluated in the included studies (number of studies in brackets): amoxicillin or amoxicillin/clavulanate (32); azithromycin (21); cefaclor (8); cefdinir (2); cefixime (2); cefpodoxime (4); cefprozil (2); cefuroxime (3); ceftriaxone (9); clarithromycin (1); penicillin (3); and trimethoprim-sulfamethoxazole (1). Short-course interventions were primarily a three to five-day regimen. Two studies compared a single dose of azithromycin (Arguedas 2005; Block 2003) and two studies compared a short course of the antibiotic regimen at less than or equal to 48 hours (Meistrup-Larsen 1983; Puczynski 1987).

Short regimens of ceftriaxone or azithromycin were analyzed separately from all other antibiotics. Twenty trials employed tympanocentesis. Of these, four trials (Hendrickse 1988; Pessey 1999; Ploussard 1984; Puczynski 1987) studied short regimens of antibiotics and 15 trials evaluated azithromycin (Arguedas 1996; Arguedas 1997; Arguedas 2005; Aronovitz 1996; Arrieta 2003; Dagan 2000a; Dagan 2000b; Daniel 1993; de Jose 1998; Guven 2006; Hoberman 2005; Khurana 1996; Oguz 2003; Petalozza 1992; Principi 1995).

For the majority of studies, clinical cure or improvement at the end of treatment and at a follow-up period of 10 days to one month after beginning the study were primary outcomes. Please refer to the Characteristics of included studies table for details on individual study outcomes.

Excluded studies

We excluded two short-acting antibiotic trials because outcomes were not reported as treatment failures (Bain 1985; Jones 1986). One study (Jones 1986) reported the number of days symptoms were recorded in diaries and the percentage resolution of ear signs, and the other study (Bain 1985) reported eardrum signs and symptoms. Neither of these studies presented data that could contribute to treatment failure as defined in this review. We excluded an additional two studies because the antibiotic used, ceftibuten, was deemed to be not clinically relevant due to its limited use in clinical practice (Roos 2000; Simon 1997), and excluded one study due to the duration of the antibiotic treatment being the same in both arms (Suzuki 2009).

Risk of bias in included studies

A detailed summary of the risk of bias assessment for each study is available in the Characteristics of included studies table.

Allocation

Adequate sequence generation was performed in 12 studies and was unclear in 37. Allocation concealment was adequate in six studies, inadequate in one study and unclear in 42 studies.

Blinding

Appropriate blinding was employed in 15 studies, there was no blinding in 24 studies and unclear blinding in 10 studies. Allocation concealment was also judged as adequate in only one of the appropriately blinded studies (Green 1993).

Incomplete outcome data

In 33 studies incomplete outcome data were appropriately addressed. Six studies did not address the incomplete outcome data appropriately and in 10 studies it was unclear if the data were appropriately reported.

Selective reporting

Thirty-eight included studies were judged free from a risk of selective reporting bias; five studies had a high risk of selective reporting bias; and six studies were unclear in risk of selective reporting bias.

Other potential sources of bias

Fifteen studies were judged as low risk for other sources of bias. In 31 studies the risk of other sources of bias was unclear, and in three studies the risk was judged as high. Unreported sources of funding were the primary reason for an unclear risk of bias.

Effects of interventions

See: **Summary of findings for the main comparison** Short-acting antibiotic > 48 hours short-term treatment for acute otitis media; **Summary of findings 2** Ceftriaxone for acute otitis media; **Summary of findings 3** Azithromycin 3 to 5 days short-term treatment for acute otitis media

Treatment failure

Treatment failure has been previously defined as lack of clinical resolution, relapse or recurrence of AOM during a one-month period following the initiation of therapy. See summary of findings tables for each intervention (Summary of findings for the main comparison; Summary of findings 2; Summary of findings 3).

Outcome of short-acting antibiotics in the short course (less than seven days)

Two trials were included in the meta-analysis for short-acting antibiotics administered for a period of less than 48 hours, and 17 trials were included in the meta-analysis of short-acting antibiotics administered for more than 48 hours.

i) Short-acting antibiotics given for less than 48 hours

A summary odds ratio (OR) of 2.99 (95% CI 1.04 to 8.54) was found for treatment failures at less than one month (Analysis 1.1). Two trials evaluating a total of 118 children were included in this meta-analysis (Meistrup-Larsen 1983; Puczynski 1987). The trial by Puczynski was prematurely terminated (Puczynski 1987).

ii) Short-acting antibiotics given for more than 48 hours

Risk of treatment failure, defined as lack of clinical resolution, relapse or recurrence of AOM at one month or less, was higher with short courses of antibiotics (OR 1.34, 95% CI 1.15 to 1.55) (Analysis 2.1). Significant results were found when treatment failure was compared at a follow-up period of 19 days or less (OR 1.37, 95% CI 1.15 to 1.64) (Analysis 2.2). At 21 days there was no difference in the risk of treatment failure between short and long-course antibiotics (Analysis 2.3). At one month or less, 22 children needed treatment with short regimens of antibiotics to cause an additional treatment failure compared to longer regimens of antibiotics.

Subgroup analysis examining treatment failure in children less than two years and two years of age or older was performed. Six trials containing 614 children found non-significant results for treatment failure at one month or less in short versus long-course regimens of antibiotics (Analysis 3.1). Significant differences in outcomes between five-day and 10-day treatment among children less than two years old were reported in one trial, but no extractable subgroup data were presented (Hoberman 1997). Non-significant results were repeated in seven trials containing 1183 participants when examining children two years of age or older (Analysis 4.1).

Hendrickse reported outcome data for perforated and non-perforated eardrums (Hendrickse 1988). The OR for treatment failure in children with perforated eardrums (n = 27) was 3.62 (95% CI 0.81 to 16.06) (Analysis 5.1) and 1.06 (95% CI 0.40 to 2.75) (Analysis 6.1) in children with non-perforated eardrums (n = 101).

Outcome of ceftriaxone in the short course (less than seven days)

Eight trials (n = 1709) were included in the meta-analysis for treatment failure at one month or less. No significant results were found (OR 1.07, 95% CI 0.86 to 1.33) (Analysis 17.1), and this lack of significance was repeated when treatment failure at three months or less was examined (Analysis 17.2).

Outcome of azithromycin in the short course (less than seven days)

A comparison of regimens of short-course azithromycin for treatment failure at one month or less yielded an OR of 1.02 (95% CI 0.87 to 1.20). This meta-analysis included 19 trials and 4354 children (Analysis 19.1). Examination of a follow-up period of 8 to 19 days (18 trials, n = 4347) found a significant OR of 1.27 (95% CI 1.04 to 1.55) (Analysis 19.2). Forty-four children needed treatment with short-course azithromycin so that one child may experience an additional treatment failure compared to children treated with longer courses of antibiotics. This significant result was not repeated when 20 to 30-day follow-up periods were examined (Analysis 19.3).

The odds of treatment failure with azithromycin was 1.92 (95% CI 0.73 to 5.04) (Analysis 20.1) in children less than two years (n = 138, 17.4%) and 1.34 (95% CI 0.61 to 2.94) (Analysis 21.1) in older children (n = 656) (Principi 1995; Schaad 1993).

Sensitivity analysis

Assessment of risk of bias

A sensitivity analysis of allocation concealment and blinding from the risk of bias assessment and treatment failure at one month or less was completed. An OR of 1.30 (95% CI 1.09 to 1.54) was found in

short-acting antibiotics for treatment failure in 14 studies (Analysis 12.1) where the risk of bias for allocation concealment was unclear and 1.45 (95% CI 1.08 to 1.93) (Analysis 12.2) in three studies where the risk of bias was low for allocation concealment. Thirteen studies had a high or unclear risk of bias in blinding and an OR of 1.18 (95% CI 1.00 to 1.40) (Analysis 12.3) compared to four studies with a low risk of bias and an OR of 2.03 (95% CI 1.48 to 2.77) (Analysis 12.4).

Due to a lack of difference between the risk of bias assessment for studies examining ceftriaxone, a sensitivity analysis was not completed for this outcome.

Seventeen studies using azithromycin as the antibiotic in the short course were judged to have a high or unclear risk of bias for allocation concealment. The OR was 1.04 (95% CI 0.88 to 1.22) (Analysis 26.1). Two studies had a low risk of bias for allocation concealment and had an OR of 0.13 (95% CI 0.02 to 0.90) (Analysis 26.2). The large difference between these two values should be interpreted with caution given the low number of studies included in the meta-analysis of low risk of bias for allocation concealment. For blinding, 15 studies had a high or unclear risk of bias and an OR of 1.15 (95% CI 0.94 to 1.40) (Analysis 26.3) and four studies with a low risk of bias for blinding and an OR of 0.80 (95% CI 0.60 to 1.07) (Analysis 26.4).

Use of same antibiotic in both arms

A total of 10 studies utilised the same antibiotic in both the short and long courses of therapy. Nine studies including 3321 participants presented data for treatment failure at one month or less; this analysis resulted in an OR of 1.65 (95% CI 1.35 to 2.01) (Analysis 10.1). A sensitivity analysis was also undertaken to compare the two trials that used the same antibiotic (amoxicillin-clavulanate) in both arms. This analysis resulted in an OR of 1.99 (95% CI 1.44 to 2.74) (Analysis 13.1) compared to an OR of 1.20 (95% CI 1.02 to 1.42) when excluding the above trials from the analysis (Analysis 13.2). The effect was larger with amoxicillin-clavulanate, however caution must be used when interpreting these results due to the number of subgroup analyses.

Publication bias

We produced funnel plots for the antibiotic comparisons, short-acting antibiotics (Figure 1), ceftriaxone (Figure 2) and azithromycin (Figure 3). Upon visual inspection, funnel plots suggested publication bias for the azithromycin comparison but not for the other antibiotic groups. Additional statistical tests (Duval 2000; Egger 1997) of significance did not reveal publication bias in any of the groups. A sensitivity analysis of studies declaring industry funding as compared to those not reporting a funding source was not significant (Analysis 27.1 and Analysis 28.1).

Figure 1. Funnel plot of comparison: 2 Short-acting antibiotic > 48 hours short-term treatment, outcome: 2.1 Treatment failure at 1 month or less.

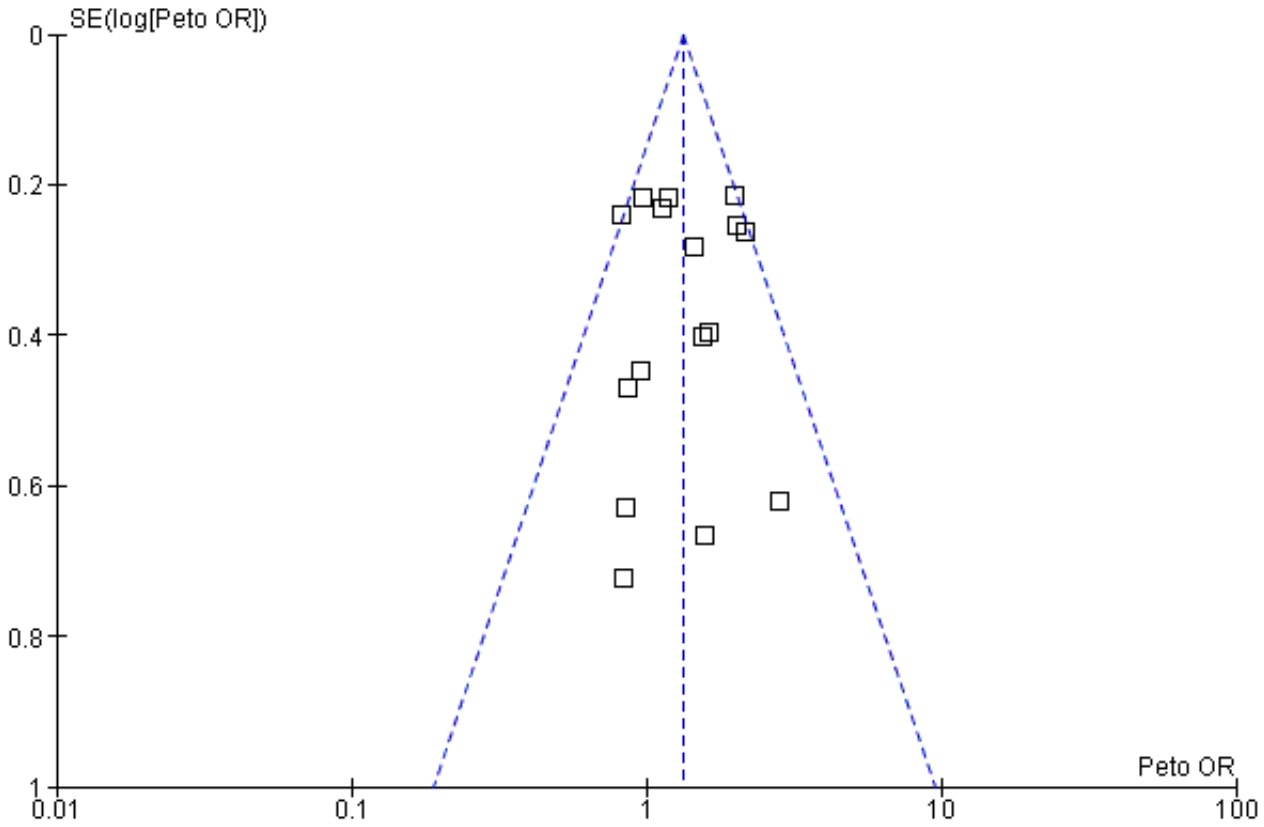


Figure 2. Funnel plot of comparison: 21 Ceftriaxone, outcome: 21.1 Treatment failure at 1 month or less.

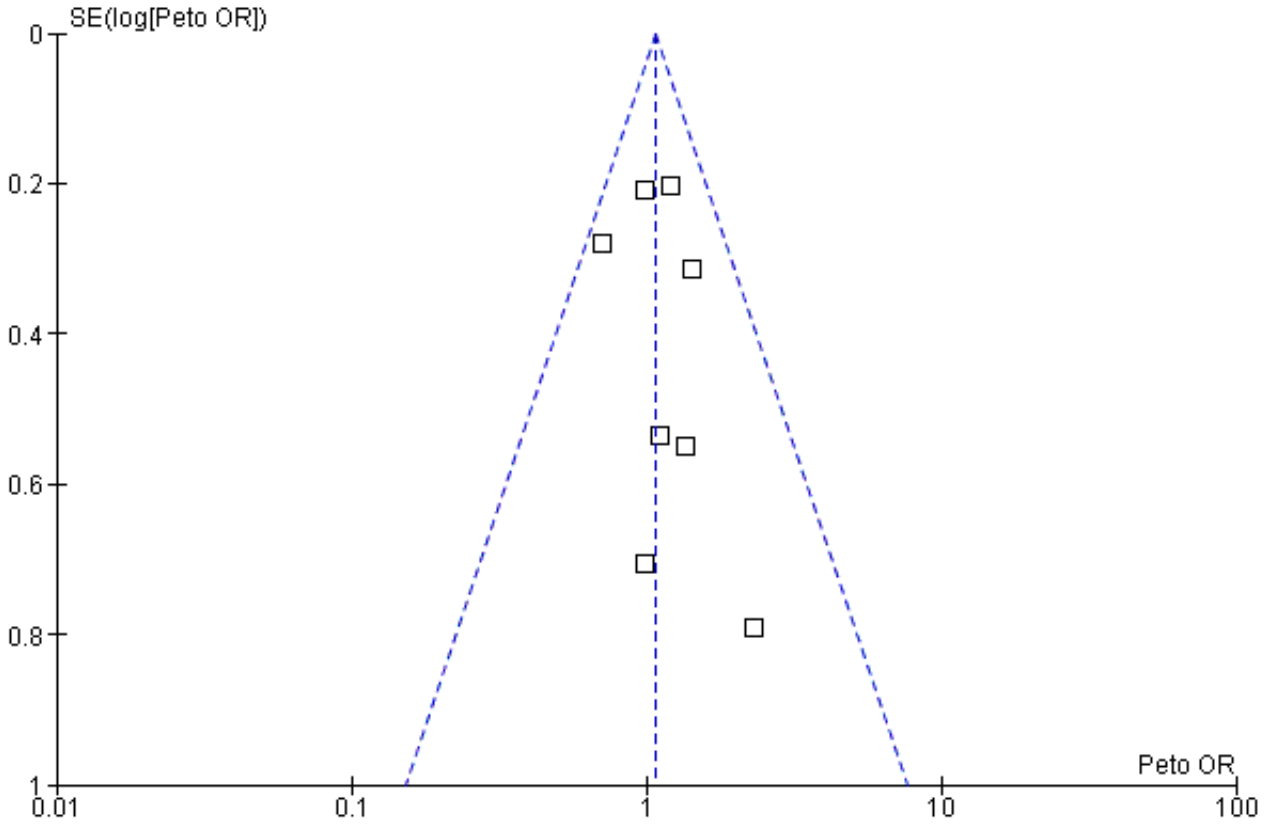
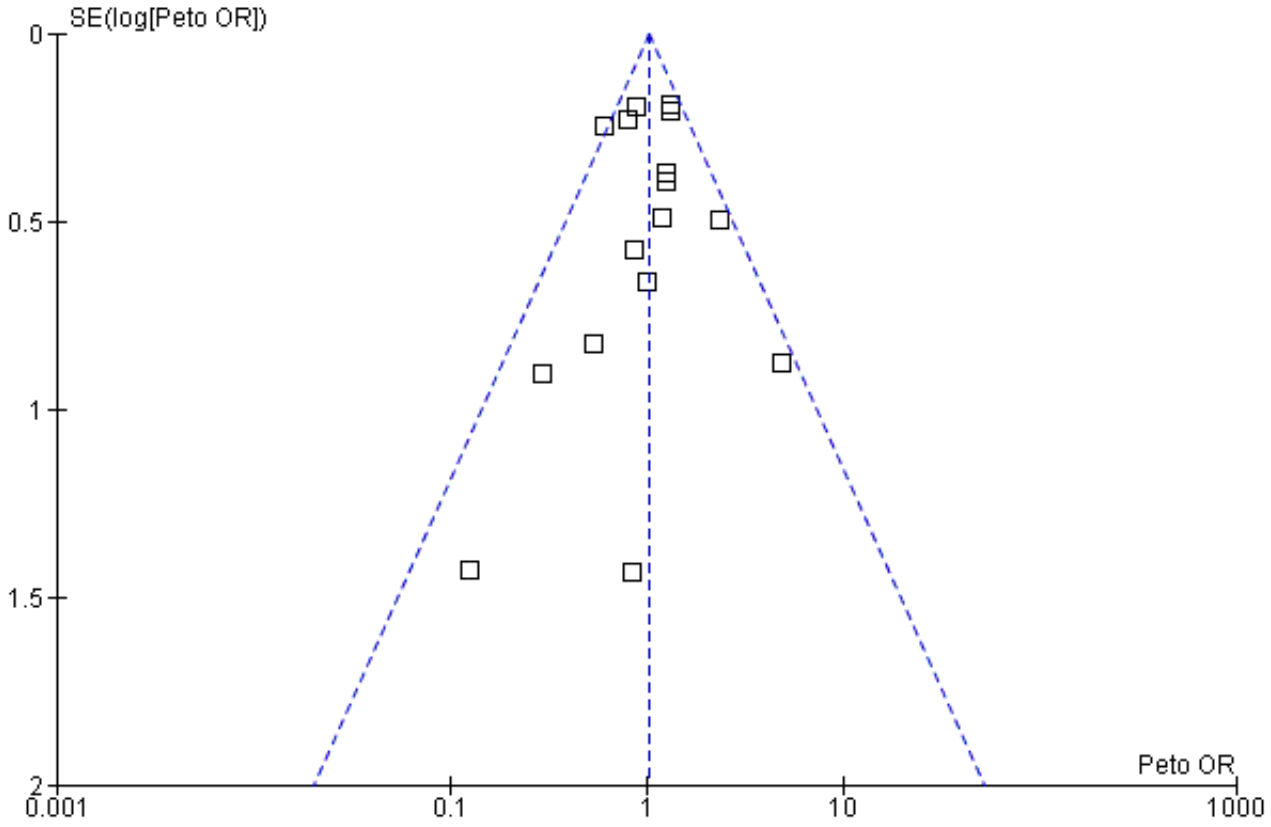


Figure 3. Funnel plot of comparison: 23 Azithromycin 3 to 5 days short-term treatment, outcome: 23.1 Treatment failure at 1 month or less.



Gastrointestinal adverse events

Outcome of short-acting antibiotics in the short course (less than seven days)

In 13 trials containing 4918 children a significant reduction in gastrointestinal adverse events was observed (Analysis 16.1). The OR was found to be 0.72 (95% CI 0.60 to 0.87) which translates to one less child experiencing an adverse event for every 29 children given a short regimen of antibiotics. A sensitivity analysis of the five trials that did not use amoxicillin-clavulanate provided non-significant results (Analysis 11.1).

Outcome of ceftriaxone in the short course (less than seven days)

One trial was included in the analysis of ceftriaxone adverse events (Barnett 1997). In this study (n = 402) more children experienced adverse events in the short course ceftriaxone group (OR 2.89, 95% CI 1.70 to 4.91). This OR translates to an additional child experiencing an adverse gastrointestinal event for every seven to eight children treated compared to long courses of antibiotics (Analysis 17.3).

Outcome of azithromycin in the short course (less than seven days)

In 14 trials containing 3722 children, significantly fewer gastrointestinal events were experienced in the short course of azithromycin comparison group (Analysis 29.1). The OR was 0.36 (95% CI 0.28 to 0.46) which translates to one less child experiencing an adverse event for every 14 children treated compared to longer courses of antibiotics.

DISCUSSION

Summary of main results

A reduction in the treatment of AOM from 10 to five days of short-acting antibiotics may slightly increase the risk of a child experiencing signs and symptoms, relapse or re-infection at eight to 19 days (OR 1.37, 95% CI 1.15 to 1.64). By 30 days following initiation of therapy, a longer course of short-acting antibiotics is comparable to a five-day course in terms of these outcomes (OR 1.17, 95% CI 0.95 to 1.43). When studies comparing the same antibiotics in both arms were analyzed the results favoured the use of longer regimens of therapy (OR 1.65, 95% CI 1.35 to 2.01). Notably 22 studies published after 1998 were added to the updated meta-analysis and brought the 30-day findings closer to equivalence. Studies that had low risk of bias for the component of blinding had significantly higher risks of treatment failure (OR 2.03, 95% CI 1.48 to 2.77) compared to those with high risk of bias for blinding (OR 1.19, 95% CI 1.01 to 1.41). The long-term comparability between a short and long course of antibiotics is biologically plausible, on the basis of: 1) spontaneous resolution of untreated AOM (Del Mar 1997; Rosenfeld 1994); 2) early eradication of pathogens after three to five days of treatment (Howie 1969); 3) poorer penetration of the antibiotic into the ear with continued administration as inflammation decreases (Canafax 1991); and 4) treatment of

children without AOM because of diagnostic uncertainty (Froom 1990).

Overall completeness and applicability of evidence

Appreciating that a shortened course of antibiotics may protect the child from developing resistant microorganisms (Kozyrskyj 1998), we report these results 12 years later when many clinical practice guidelines are proposing no antibiotic treatment or 'watchful waiting' as a first-line approach to treating AOM. The American Academy of Pediatrics recommends reserving antibiotic therapy for children that are less than or equal to two years with severe disease (Pediatric Guidelines 2004). More recently the Canadian Paediatric Society recommended a 'wait and watch' approach for children over six months with uncomplicated, non-severe disease (Forgie 2009). This is consistent with a Cochrane Review examining the effectiveness of antibiotics for AOM (Sanders 2009) and an individual patient meta-analysis (Koopman 2008; Spiro 2008; Vouloumanou 2009). If antibiotics are used, our results indicate that a long course of treatment can minimise the risks of treatment failure or recurrence post-treatment, but may not make a difference in the long term.

This updated review also found no significant differences when examining short courses of ceftriaxone. However, in the one study where adverse effects were examined, they were much higher in the ceftriaxone group. As administering ceftriaxone also requires an injection, this does not seem to be a good option for management of AOM.

Quality of the evidence

Higher risk of treatment failure occurred with three to five days of azithromycin (OR 1.27, 95% CI 1.04 to 1.55) at 8 to 19 days after the initiation of treatment. This significant result was not repeated when examining treatment failure at 20 to 30 days (OR 0.98, 95% CI 0.82 to 1.17). Outcome differences noted between the evaluations at eight to 19 days and 20 to 30 days likely reflects bias in the timing of evaluation. Children treated with a long course of antibiotics had fewer days to experience an outcome than those treated with five days when the time to evaluation was 8 to 19 days, as opposed to 30 days (Pichichero 1997).

Potential biases in the review process

Potential weaknesses of meta-analysis techniques are that they incorporate existing biases and introduce new biases, some of which have predicted discordance of results between meta-analyses and single large RCTs (Borzak 1995; Egger 1997). To minimise bias during study selection, we used pre-determined inclusion criteria, and most trials were assessed in a blinded fashion, although recent evidence suggests that blinded evaluations are not necessary (Berlin 1997). We assessed publication bias in our funnel plot of sample size versus ORs (Higgins 2008) and with additional statistical tests (Duval 2000; Egger 1997) of significance. Publication bias was not evident. The issue of trial heterogeneity was addressed in our grouping of antibiotics according to pharmacokinetic profile (Schentag 1995).

In this review two studies (Gooch 1996; Hoberman 1997) contained two arms comparing longer course versus a short course of antibiotic. In the original review the short-course arm was counted twice against each long-course arm of that study. In the update of this review, we have modified our methods and combined both long-course arms in a single comparison against the short-course arm. In an effort to test whether this new method would change our results we compared the previous meta-analysis against a new analysis where we used the new statistical method but did not add the additional studies which are a part of this update. This new method did not have a great effect on our results.

Agreements and disagreements with other studies or reviews

Most of the 'short-acting' antibiotics in this study are commonly prescribed in primary practice and our sensitivity analyses indicated that comparisons between different short-acting antibiotics did not alter treatment outcomes. Comparability was also demonstrated between ceftriaxone and a longer course of antibiotics, although the sample size of the consolidated trials was smaller. The equivalence observed between a three or five-day course of azithromycin and a 10-day course of other antibiotics was unchanged in sensitivity analyses, but these could not be performed for outcomes at 8 to 19 days. It is difficult to support the use of azithromycin or ceftriaxone based on their cost, and concern over indiscriminate use of broad-spectrum antibiotics (Rosenfeld 1996). Dagan et al documented increasing rates of erythromycin resistance to *Streptococcus pneumoniae (S. pneumoniae)* over the period that azithromycin was prescribed more often to children. The increased prescription of amoxicillin-clavulanate did alter resistance to penicillin (Dagan 2006). Ceftriaxone's intramuscular mode of administration may further limit its role (Eppesl 1997). Incidence of diarrhea and vomiting may be increased with antibiotic use in children with AOM (Del Mar 1997). Findings did not demonstrate that a shortened course of antibiotics decreased the likelihood of gastrointestinal effects, except when compared to a longer course of amoxicillin-clavulanate.

AUTHORS' CONCLUSIONS

Implications for practice

Evidence is increasing for a wait and watch approach to AOM. We believe that this is the most prudent approach for most children who are older than six months or do not have serious or complicated disease. If treatment is warranted, the clinician must decide if treatment for 7 to 10 days is worth the slightly reduced risk of treatment failure in the short term (< 21 days). Shorter courses can also be safely used, resulting in few side effects and, perhaps, a lower risk of antibiotic resistant bacteria. Shorter courses may also be associated with higher levels of compliance.

Implications for research

In light of the increasing use of the wait and watch approach, it would be helpful to have trials that randomise participants to short versus long-course treatment with oral antibiotics after an unsuccessful observation period.

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CHARACTERISTICS OF STUDIES

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

Adam 1996

Methods	RCT
Participants	German multicentre trial of children 3 months to 6 years old
Interventions	Cefpodoxime 40 mg to 60 mg twice daily for 5 days versus cefaclor 40 mg/kg/day 3 times daily for 10 days
Outcomes	Absence or improvement of signs and symptoms at 3 days and no relapse at 3 weeks after study entry
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Blinding (performance bias and detection bias) Treatment failure at 1 month or less	High risk	
Incomplete outcome data (attrition bias) Treatment failure at 1 month or less	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Funding not reported

Adam 2000

Methods	Double-blind RCT
Participants	German children aged 2 to 14 years
Interventions	Cefixime 8 mg/kg/day for 5 days versus same treatment for 10 days
Outcomes	Complete recovery or improvement of symptoms by day 11, clinical response rate at day 6, rate of relapse at day 28
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Blinding (performance bias and detection bias) Treatment failure at 1 month or less	Low risk	
Incomplete outcome data (attrition bias) Treatment failure at 1 month or less	High risk	
Selective reporting (reporting bias)	High risk	
Other bias	Unclear risk	Funding not reported

Al-Ghamdi 1999

Methods	RCT
Participants	Saudi children aged 6 months to 6 years
Interventions	Single intramuscular dose 50 mg/kg ceftriaxone versus 40 mg/kg/day Augmentin 3 times daily for 10 days
Outcomes	Resolution of symptoms at 10 days after study entry; improved otoscopic and tympanometric measurements at 60 days after study entry
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias)	Low risk	

Al-Ghamdi 1999 *(Continued)*

Treatment failure at 1 month or less		
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Did not report baselines or funding

Arguedas 1996

Methods	RCT	
Participants	Children 6 months to 12 years old in an ambulatory unit in Costa Rica	
Interventions	Azithromycin 10 mg/kg once daily for 3 days versus amoxil-clavulanate 40 mg/kg/day 3 times daily for 10 days	
Outcomes	Absence or improvement of signs and symptoms at 11 to 13 days, 28 to 30 days and 55 to 60 days after study entry	
Notes	—	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) Treatment failure at 1 month or less	High risk	
Incomplete outcome data (attrition bias) Treatment failure at 1 month or less	Low risk	
Other bias	Low risk	Industry funding

Arguedas 1997

Methods	RCT
Participants	Children 6 months to 12 years old seen at an ambulatory unit in Costa Rica
Interventions	Azithromyzin 10 mg/kg once daily for 3 days versus

Arguedas 1997 *(Continued)*

	clarithromycin 15 mg/kg/day twice daily for 10 days
Outcomes	Resolution of symptoms with or without the presence of middle ear fluid at 10 to 11 days and 28 to 32 days after study entry
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) Treatment failure at 1 month or less	High risk	
Incomplete outcome data (attrition bias) Treatment failure at 1 month or less	Low risk	
Other bias	Low risk	Industry funding

Arguedas 2005

Methods	Double-blind, double-dummy multinational RCT
Participants	Children 6 to 30 months of age in multiple countries
Interventions	Azithromycin single dose 30 mg/kg versus amoxicillin 90 mg/kg/day for 10 days in 2 divided doses
Outcomes	Absence or improvement of symptoms at 12 to 14 days and at end of study (day 25 to 28)
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Blinding (performance bias and detection bias) Treatment failure at 1 month or less	Low risk	
Incomplete outcome data (attrition bias)	Low risk	

Arguedas 2005 *(Continued)*

Treatment failure at 1 month or less		
Selective reporting (reporting bias)	High risk	
Other bias	High risk	Interim analysis, industry funding

Aronovitz 1996

Methods	RCT	
Participants	US multicentre trial of children 2 to 15 years old	
Interventions	Azithromycin 5 to 10 mg/kg once daily for 5 days versus amoxil-clavulanate 40 mg/kg/day 3 times daily for 10 days	
Outcomes	Absence or improvement of signs and symptoms at 11 days and 30 days after study entry	
Notes	—	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Blinding (performance bias and detection bias) Treatment failure at 1 month or less	High risk	
Incomplete outcome data (attrition bias) Treatment failure at 1 month or less	High risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	No funding declared

Arrieta 2003

Methods	Double-blind, double-dummy, multicentre trial
Participants	US and Latin American children aged 6 months to 6 years
Interventions	Azithromycin 20 mg/kg/day once daily for 3 days versus amoxicillin/clavulanate 45/6.4 mg/kg/day twice daily for 10 days plus additional amoxil 45 mg/kg/day twice daily for 10 days

Arrieta 2003 *(Continued)*

Outcomes	Clinical response (improvement or cure) among clinically evaluated patients at day 28 to 32; clinical response at day 12 to 16
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Blinding (performance bias and detection bias) Treatment failure at 1 month or less	Low risk	
Incomplete outcome data (attrition bias) Treatment failure at 1 month or less	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Corresponding author from Pfizer, unclear independence of authors, industry funding

Barnett 1997

Methods	RCT
Participants	Boston, US multicentre trial of children 3 months to 3 years old
Interventions	Ceftriaxone 50 mg/kg intramuscularly x one dose versus trimethoprim-sulfamethoxazole twice daily for 10 days
Outcomes	Absence of signs and symptoms at 14 days and 28 days after study entry
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Blinding (performance bias and detection bias) Treatment failure at 1 month or less	High risk	Personnel not blinded
Incomplete outcome data (attrition bias) Treatment failure at 1 month or less	High risk	

Barnett 1997 *(Continued)*

Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Industry funding

Block 2000

Methods	Comparative, randomized, investigator blinded multicentre trial
Participants	US children aged 6 months through 12 years
Interventions	Cefdinir 14 mg/kg/day twice daily for 5 days versus cefprozil 30 mg/kg twice daily for 10 days
Outcomes	Cure or failure at end of treatment visit, cure 11 to 16 days post-therapy, long-term follow-up days 38 to 45 after study entry
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Blinding (performance bias and detection bias) Treatment failure at 1 month or less	High risk	Only investigators blinded
Other bias	Low risk	Industry funded

Block 2003

Methods	Double-blind, placebo-controlled, RCT
Participants	US children aged 6 months to 12 years
Interventions	Single dose of 30 mg/kg azithromycin versus amoxicillin/clavulanate 45 mg/kg twice daily for 10 days
Outcomes	Absence or improvement of signs and symptoms on day 12 to 16 and day 28 to 32
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Blinding (performance bias and detection bias)	Low risk	

Block 2003 *(Continued)*

Treatment failure at 1 month or less		
Incomplete outcome data (attrition bias) Treatment failure at 1 month or less	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Industry funding

Block 2004

Methods	Randomised, investigator blinded multicentre study
Participants	US children aged 6 months through 6 years
Interventions	Cefdinir 14 mg/kg twice daily for 5 days versus amoxicillin/clavulanate 45/6.4 mg/kg twice daily for 10 days
Outcomes	Cure at end of treatment (7 to 9 days or 12 to 14 days) and days 25 to 28 of the study
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Blinding (performance bias and detection bias) Treatment failure at 1 month or less	High risk	Only investigator blinded
Selective reporting (reporting bias)	High risk	
Other bias	Low risk	Industry funding

Boulesteix 1995

Methods	RCT
Participants	French multicentre trial of children 6 months to 6 years old
Interventions	Cefpodoxime 4 mg/kg twice daily for 5 days versus cefixime 4 mg/kg twice daily for 8 days
Outcomes	Absence or improvement of signs and symptoms at 8 to 10 days and no recurrence at 30 to 40 days after study entry

Boulesteix 1995 *(Continued)*

Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) Treatment failure at 1 month or less	High risk	
Incomplete outcome data (attrition bias) Treatment failure at 1 month or less	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Funding not declared

Catania 2004

Methods	RCT
Participants	Italian children 2 to 6 years
Interventions	Cefaclor 40 mg/kg/day for 5 days versus cefaclor 40 mg/kg/day for 10 days
Outcomes	Clinical improvement or failure at end of therapy and 15 to 20 days after end of therapy. Relapse at 15 to 20 days after end of therapy
Notes	Italian

Risk of bias

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Treatment failure at 1 month or less	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	No funding declared

Chamberlain 1994

Methods	RCT
Participants	Children 18 months to 6 years old in Washington, DC
Interventions	Ceftriaxone 50 mg/kg intramuscularly x one dose versus cefaclor 40 mg/kg/day for 10 days
Outcomes	Absence or improvement of symptoms, and normal or improved tympanogram at 7 to 10 days and monthly for 90 days after study entry
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Blinding (performance bias and detection bias) Treatment failure at 1 month or less	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	Industry funding

Cohen 1997

Methods	RCT
Participants	French multicentre trial of children 4 months to 3 years old
Interventions	Cefpodoxime 8 mg/kg/day twice daily for 5 days versus amoxil-clavulanate 80 mg/kg/day 3 times daily for 8 days
Outcomes	Absence or improvement of signs and symptoms and no additional antibiotics at 9 to 14 days and 20 to 30 days after study entry
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias)	High risk	

Cohen 1997 *(Continued)*

Treatment failure at 1 month or less		
Incomplete outcome data (attrition bias) Treatment failure at 1 month or less	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Funding not declared

Cohen 1998

Methods	Randomised controlled, double-blind trial	
Participants	French trial of children aged 4 to 30 months	
Interventions	Amoxicillin/clavulanate 80/10 mg/kg/day 3 times daily for 5 days versus same treatment for 10 days	
Outcomes	Resolution or improvement of signs and symptoms at 12 to 14 days and 28 to 42 days after study entry	
Notes	—	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	
Blinding (performance bias and detection bias) Treatment failure at 1 month or less	Low risk	
Selective reporting (reporting bias)	High risk	
Other bias	Unclear risk	The only significant difference at baseline was diarrhea, but GI symptoms are an outcome; industry funding

Cohen 1999

Methods	Randomised open trial	
Participants	French trial of children aged 4 to 30 months	
Interventions	Ceftriaxone 50 mg/kg intramuscularly x one dose versus	

Cohen 1999 *(Continued)*

	amoxicillin/clavulanate 80/10 mg/kg/day 3 times daily for 10 days
Outcomes	Resolution or improvement of signs and symptoms at 12 to 14 days and 28 to 42 days after study entry
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Blinding (performance bias and detection bias) Treatment failure at 1 month or less	High risk	
Incomplete outcome data (attrition bias) Treatment failure at 1 month or less	Low risk	Unclear for the 28 to 42-day follow-up period
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	Industry funding

Cohen 2000

Methods	Randomised controlled, double-blind trial
Participants	French trial of children aged 4 to 30 months
Interventions	Cefpodoxime proxetil 8 mg/kg/day for 5 days versus same regimen for 10 days
Outcomes	Resolution or improvement of signs and symptoms at 12 to 14 days and 28 to 42 days after study entry
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Blinding (performance bias and detection bias) Treatment failure at 1 month or less	Low risk	

Cohen 2000 *(Continued)*

Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	Industry funding

Dagan 2000a

Methods	Single-blind, RCT
Participants	Multicentre trial (Israel, US, Dominican Republic) of children aged 6 to 48 months
Interventions	Azithromycin, 10 mg/kg on day 1 then 5 mg/kg on days 2 to 5 versus amoxicillin/clavulanate 45/6.4 mg/kg in 2 divided doses for 10 days
Outcomes	Resolution of signs and symptoms on day 12 to 14 and day 22 to 28, bacteriologic cure days 4 to 6
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias) Treatment failure at 1 month or less	High risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	Industry funding

Dagan 2000b

Methods	Open label, RCT
Participants	Israeli trial of children aged 3 to 36 months old
Interventions	Azithromycin 10 mg/kg/day for 3 days versus cefaclor 40 mg/kg/day in 3 divided doses for 10 days
Outcomes	Resolution or improvement of signs and symptoms on day 10 and day 17 +/- 2
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Blinding (performance bias and detection bias)	Low risk	

Dagan 2000b *(Continued)*

Treatment failure at 1 month or less		
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	Industry funding

Daniel 1993

Methods	RCT	
Participants	European multicentre trial of children 2 to 8 years old	
Interventions	Azithromycin 10 mg/kg daily for 3 days versus amoxil-clavulanate 3 times daily for 10 days	
Outcomes	Absence or improvement of signs and symptoms at 10 to 12 days after study entry	
Notes	—	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Blinding (performance bias and detection bias) Treatment failure at 1 month or less	High risk	
Incomplete outcome data (attrition bias) Treatment failure at 1 month or less	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	High risk	Potential bias in that in the short course, azithromycin patients were placed on different antibiotics if failing, whereas for co-amoxil they stayed on co-amoxil; industry funding

de Jose 1998

Methods	RCT
Participants	Spanish children 6 months to 12 years old
Interventions	Azithromycin 10 mg/kg/day once daily for 3 days versus amoxicillin/clavulanate 40 mg/kg/day 3 times daily for 10 days
Outcomes	Clinical cure, improvement or failure at end of treatment

de Jose 1998 *(Continued)*

Notes	Spanish

Risk of bias

Bias	Authors' judgement	Support for judgement
Blinding (performance bias and detection bias) Treatment failure at 1 month or less	High risk	Outcome assessors not blinded
Incomplete outcome data (attrition bias) Treatment failure at 1 month or less	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Funding not reported

de Saintongue 1982

Methods	Randomised controlled, double-blind trial
Participants	British multicentre trial of children 2 to 10 years old
Interventions	Amoxicillin 125/250 mg 3 times daily for 3 days + placebo for 7 days versus amoxicillin 125/250 mg 3 times daily for 10 days
Outcomes	Resolution of signs and symptoms at 13 to 16 days after and recurrence within 12 weeks of study entry
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Blinding (performance bias and detection bias) Treatment failure at 1 month or less	Low risk	
Incomplete outcome data (attrition bias) Treatment failure at 1 month or less	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	

Dunne 2003

Methods	Randomised controlled double-blind trial
Participants	US trial of children 6 months to 12 years
Interventions	Azithromycin 10 mg/kg/day for 3 days versus co-amoxiclav 45 mg/kg/day twice a day for 10 days
Outcomes	Absence of symptoms at day 24 to 28, absence or improvement of symptoms at day 10
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Blinding (performance bias and detection bias) Treatment failure at 1 month or less	Unclear risk	Method not described
Incomplete outcome data (attrition bias) Treatment failure at 1 month or less	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Industry funding, first author from Pfizer

Gooch 1996

Methods	Randomised controlled, double-blind trial
Participants	US multicentre trial of children 3 months to 12 years old
Interventions	Cefuroxime 30 mg/kg/day twice daily for 5 days + placebo twice daily for 5 days versus cefuroxime 30 mg/kg/day twice daily for 10 days
Outcomes	Absence or improvement of signs and symptoms at 14 to 18 days after study entry
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Incomplete outcome data (attrition bias)	High risk	

Gooch 1996 *(Continued)*

Treatment failure at 1 month or less		
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	Industry funding

Green 1993

Methods	Randomised controlled, double-blind trial	
Participants	Children 5 months to 5 years old seen in emergency departments or medical centres in California, North Carolina, US	
Interventions	Ceftriaxone 50 mg/kg intramuscularly x 1 dose + placebo 3 times daily for 10 days versus placebo intramuscularly x 1 dose + amoxicillin 40 mg/kg 3 times daily for 10 days	
Outcomes	Absence of symptoms at 10 days and no recurrence at 11 to 30 days and 31 to 90 days after study entry	
Notes	—	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) Treatment failure at 1 month or less	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	Industry funding

Guven 2006

Methods	RCT
Participants	Turkish children between 6 months and 12 years
Interventions	Azithromycin (10 mg/kg/24 hours, per oral) once daily for 3 days versus amoxicillin-clavulanate (45 mg/kg/24 hours to 6.4 mg/kg/24 hours, peroral in 2 divided doses) for 10 days
Outcomes	Clinical cure, failure or improvement at the end of treatment and clinical cure, failure, improvement, relapse or re-infection at 26 to 28 days following study entry
Notes	—

Guven 2006 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Blinding (performance bias and detection bias) Treatment failure at 1 month or less	Unclear risk	Regimen was not equivalent
Incomplete outcome data (attrition bias) Treatment failure at 1 month or less	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	Funding not declared

Hendrickse 1988

Methods	Randomised controlled, double-blind trial
Participants	Children 1 month to 12 years old seen at a medical centre in Dallas, US
Interventions	Cefaclor 40 mg/kg/day twice daily for 5 days + placebo for 5 days versus cefaclor 40 mg/kg/day twice daily for 10 days
Outcomes	Resolution of middle ear fluid, or healing of tympanic membrane with resolution of signs and symptoms at 10 days, 30 days, 60 days and 90 days after study entry
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Blinding (performance bias and detection bias) Treatment failure at 1 month or less	Low risk	
Incomplete outcome data (attrition bias) Treatment failure at 1 month or less	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	Industry funding

Hoberman 1997

Methods	RCT
Participants	US and Canadian multicentre trial of children 2 months to 12 years old
Interventions	Amoxil-clavulanate (new formulation) twice daily for 5 days versus amoxil-clavulanate (new formulation) twice daily for 10 days or amoxil-clavulanate (old formulation) 3 times daily for 10 days
Outcomes	Absence or improvement of signs and symptoms with or without middle ear effusion at 12 to 14 days and 32 to 38 days after study entry
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) Treatment failure at 1 month or less	Unclear risk	Only investigators blinded
Incomplete outcome data (attrition bias) Treatment failure at 1 month or less	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Industry funding and authors from SmithKline Beecham, baseline differences in exposure to cigarette smoke

Hoberman 2005

Methods	Investigator blinded, randomized controlled multicentre trial
Participants	Multicentre trial of children 6 to 30 months of age in various countries
Interventions	Azithromycin 10 mg/kg for 1 day followed by 5 mg/kg/d for 5 days versus amoxicillin/clavulanate 90/6.4 mg/kg/d in 2 divided doses for 10 days
Outcomes	Absence or improvement of signs and symptoms at day 4 to 6, 12 to 14 and 21 to 25 days after study entry
Notes	—

Risk of bias

Hoberman 2005 *(Continued)*

Bias	Authors' judgement	Support for judgement
Blinding (performance bias and detection bias) Treatment failure at 1 month or less	Unclear risk	Investigator blinded
Selective reporting (reporting bias)	Low risk	
Other bias	Low risk	Industry funding

Ingvarsson 1982

Methods	RCT
Participants	Swedish children 6 months to 7 years old
Interventions	Penicillin-V 25 mg/kg twice daily for 5 days versus penicillin-V 25 mg/kg twice daily for 10 days
Outcomes	Improved signs and symptoms at 10 to 12 days and normal eardrum at 28 to 30 days after study entry
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Blinding (performance bias and detection bias) Treatment failure at 1 month or less	High risk	Not mentioned and no placebo
Incomplete outcome data (attrition bias) Treatment failure at 1 month or less	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Funding not reported

Kafetzis 1997

Methods	RCT
Participants	Greek multicentre trial of children 2 to 172 months old
Interventions	Cefprozil 30 mg/kg/day twice daily for 5 days versus

Kafetzis 1997 *(Continued)*

	cefprozil 30 mg/kg/day twice daily for 10 days	
Outcomes	Absence or improvement of signs and symptoms at 7 to 14 days and 28 to 32 days after study entry	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Blinding (performance bias and detection bias) Treatment failure at 1 month or less	High risk	
Incomplete outcome data (attrition bias) Treatment failure at 1 month or less	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Funding not reported

Kara 1998

Methods	RCT	
Participants	Turkish children aged 6 months to 6 years	
Interventions	Ceftriaxone 50 mg/kg single intramuscular dose versus cefuroxime axetil 30 mg/kg 3 times daily for 10 days versus amoxicillin 40 mg/kg 3 times daily for 10 days	
Outcomes	Clinical cure rate at 10 days after study entry	
Notes	—	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Other bias	Unclear risk	Funding not reported, baseline characteristics not reported

Khurana 1996

Methods	RCT
Participants	US multicentre trial of children 6 months to 12 years old

Khurana 1996 *(Continued)*

Interventions	Azithromycin 5 to 10 mg/kg once daily for 5 days versus amoxil-clavulanate 40 mg/kg/day 3 times daily for 10 days
Outcomes	Absence or improvement of signs and symptoms at 45 days after study entry
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Blinding (performance bias and detection bias) Treatment failure at 1 month or less	High risk	
Incomplete outcome data (attrition bias) Treatment failure at 1 month or less	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Funding not reported

McLinn 1996

Methods	Randomised controlled, double-blind trial
Participants	US multicentre trial of children 1 to 15 years old
Interventions	Azithromycin 5 to 10 mg/kg once daily/placebo twice daily for 5 days + placebo 3 times daily for 5 days versus amoxil-clavulanate 40 mg/kg/day 3 times daily for 10 days
Outcomes	Absence or improvement of signs and symptoms at 11 days and 30 days after study entry
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Blinding (performance bias and detection bias) Treatment failure at 1 month or less	Low risk	
Incomplete outcome data (attrition bias) Treatment failure at 1 month or less	High risk	

McLinn 1996 *(Continued)*

Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Funding not reported

Meistrup-Larsen 1983

Methods	Randomised controlled, double-blind trial	
Participants	Children 1 to 10 years old in Copenhagen	
Interventions	Penicillin-V 55 mg/kg twice daily for 2 days + placebo for 5 days versus penicillin-V 55 mg/kg twice daily for 7 days	
Outcomes	Absence of symptoms and no otorrhoea or contralateral otitis at 6 to 7 days after study entry	
Notes	—	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Blinding (performance bias and detection bias) Treatment failure at 1 month or less	Low risk	
Incomplete outcome data (attrition bias) Treatment failure at 1 month or less	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Funding not reported, doses prepared in the home

Mohs 1993

Methods	Comparative, open trial (randomisation not mentioned)
Participants	Multicentre trial (South America and Egypt) of children 2 to 12 years old
Interventions	Azithromycin 10 mg/kg once daily for 3 days versus amoxicillin 10 mg/kg 3 times daily for 10 days
Outcomes	Absence or improvement of signs and symptoms at 11 to 13 days after study entry
Notes	—

Mohs 1993 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Blinding (performance bias and detection bias) Treatment failure at 1 month or less	High risk	
Incomplete outcome data (attrition bias) Treatment failure at 1 month or less	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Funding not reported

Oguz 2003

Methods	Randomised, single-blind, open study
Participants	Turkish children aged 6 months to 12 years
Interventions	Azithromycin 10 mg/kg/day for 3 days versus cefaclor 40 mg/kg/day in 3 divided doses for 10 days
Outcomes	Resolution of all clinical and otoscopic findings at 3 to 5, 10 and 30 days after study entry; relapse at 10 and 30 days
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Blinding (performance bias and detection bias) Treatment failure at 1 month or less	Low risk	
Incomplete outcome data (attrition bias) Treatment failure at 1 month or less	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Funding not reported

Pessey 1999

Methods	Randomised, open, multinational study
Participants	Children aged 6 to 36 months
Interventions	Cefuroxime axetil 30 mg/kg/day twice daily for 5 days versus amoxicillin/clavulanate 40 mg/kg/day 3 times daily for 10 days versus amoxicillin/clavulanate 80 mg/kg/day 3 times daily for 8 days
Outcomes	Absence of symptoms 1 to 4 days after therapy completion; no relapse 21 to 28 days after therapy completion
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Blinding (performance bias and detection bias) Treatment failure at 1 month or less	High risk	Open study
Incomplete outcome data (attrition bias) Treatment failure at 1 month or less	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Corresponding author from Glaxo, funding not reported

Petalozza 1992

Methods	RCT
Participants	Italian children 11 months to 9 years old
Interventions	Azithromycin 10 mg/kg once daily for 3 days versus amoxil-clavulanate 50 mg/kg/day twice daily for 10 days
Outcomes	Absence or improvement of signs and symptoms at 12 to 14 days and 30 days after study entry
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	High risk	Openly randomized

Petalozza 1992 *(Continued)*

Blinding (performance bias and detection bias) Treatment failure at 1 month or less	High risk	
Incomplete outcome data (attrition bias) Treatment failure at 1 month or less	Low risk	
Other bias	Unclear risk	Funding not reported

Ploussard 1984

Methods	RCT
Participants	Children 5 months to 5 years old in Alabama, US
Interventions	Cefaclor 40 mg/kg 3 times daily for 5 days versus amoxicillin 40 mg/kg 3 times daily for 10 days
Outcomes	Absence or improvement of signs and symptoms at 10 to 16 days after study entry
Notes	—

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	
Blinding (performance bias and detection bias) Treatment failure at 1 month or less	High risk	
Incomplete outcome data (attrition bias) Treatment failure at 1 month or less	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Funding not reported

Principi 1995

Methods	RCT
Participants	Multicentre trial (Europe, South America) of children 6 months to 12 years old

Principi 1995 *(Continued)*

Interventions	Azithromycin 10 mg/kg once daily for 3 days versus amoxil-clavulanate 40 mg/kg 3 times daily for 10 days
Outcomes	Absence or improvement of signs and symptoms at 10 to 14 days after study entry
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Blinding (performance bias and detection bias) Treatment failure at 1 month or less	High risk	
Incomplete outcome data (attrition bias) Treatment failure at 1 month or less	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Funding not reported

Puczynski 1987

Methods	Randomised controlled, double-blind trial
Participants	Children > 2 years old enrolled May 1984 to February 1985 in Illinois, US
Interventions	Amoxicillin 100 mg x 1 dose followed by placebo 3 times daily for 10 days versus placebo x 1 dose followed by amoxicillin 40 mg/kg 3 times daily for 10 days
Outcomes	Absence of fever and otalgia, decreased irritability and improved appearance of tympanic membrane at 48 to 72 hours and 10 to 14 days after study entry
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Blinding (performance bias and detection bias) Treatment failure at 1 month or less	Low risk	
Incomplete outcome data (attrition bias) Treatment failure at 1 month or less	Low risk	

Puczynski 1987 *(Continued)*

Selective reporting (reporting bias)	Low risk	
Other bias	High risk	Stopped early with small sample size due to treatment failures in experimental group, funding not reported

Rodriguez 1996

Methods	RCT	
Participants	Multicentre trial of children 6 months to 12 years old in Guatemala	
Interventions	Azithromycin 10 mg/kg once daily for 3 days versus cefaclor 40 mg/kg 3 times daily for 10 days	
Outcomes	Absence or improvement of signs and symptoms at 10 to 14 days after study entry	
Notes	—	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Blinding (performance bias and detection bias) Treatment failure at 1 month or less	High risk	
Incomplete outcome data (attrition bias) Treatment failure at 1 month or less	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Funding not reported

Schaad 1993

Methods	RCT
Participants	Swiss multicentre trial of children 2 to 12 years old
Interventions	Azithromycin 10 mg/kg once daily for 3 days versus amoxil-clavulanate 40 mg/kg 3 times daily for 10 days
Outcomes	Absence or improvement of signs and symptoms at 12 to 16 days after study entry
Notes	—

Schaad 1993 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Blinding (performance bias and detection bias) Treatment failure at 1 month or less	High risk	
Incomplete outcome data (attrition bias) Treatment failure at 1 month or less	Low risk	
Selective reporting (reporting bias)	Low risk	
Other bias	Unclear risk	Funding not reported

Varsano 1988

Methods	Randomised controlled, double-blind trial
Participants	Children 6 months to 8 years old seen at a medical clinic in Israel
Interventions	Ceftriaxone 50 mg/kg intramuscularly x 1 dose + placebo 3 times daily for 7 days versus placebo intramuscularly x 1 dose + amoxicillin 12.5 mg/kg 3 times daily for 7 days
Outcomes	Absence of signs and symptoms with or without middle ear effusion at 7 to 10 days and no recurrence at 30 days after study entry
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Other bias	Unclear risk	Industry funded

Varsano 1997

Methods	RCT
Participants	Israeli children aged 4 months to 6 years
Interventions	Ceftriaxone 50 mg/kg single intramuscular dose versus 37.5/9.4 mg/kg/day amoxicillin/clavulanate for 10 days
Outcomes	Resolution of symptoms and no recurrence at 11 days, no relapse at 30, 60 and 90 days after study entry

Varsano 1997 *(Continued)*

Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	
Blinding (performance bias and detection bias) Treatment failure at 1 month or less	High risk	
Incomplete outcome data (attrition bias) Treatment failure at 1 month or less	Low risk	
Selective reporting (reporting bias)	High risk	Separate analysis performed for simple and recurrent AOM. Findings only reported in cases where differences reached statistical significance
Other bias	Unclear risk	Industry funded

Wang 2004

Methods	Prospective comparative randomized trial
Participants	Chinese children between 3 months and 6 years of age
Interventions	Ceftriaxone 50 mg/kg single intramuscular dose versus amoxicillin/clavulanate 45 mg/kg/day 3 times daily for 10 days
Outcomes	Absence or improvement of signs and symptoms at day 11 and day 28 after study entry
Notes	—

Risk of bias

Bias	Authors' judgement	Support for judgement
Blinding (performance bias and detection bias) Treatment failure at 1 month or less	High risk	
Incomplete outcome data (attrition bias) Treatment failure at 1 month or less	Low risk	
Selective reporting (reporting bias)	Low risk	

Wang 2004 *(Continued)*

Other bias	Unclear risk	Funding not reported

d: day; GI: gastrointestinal; RCT: randomized controlled trial

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

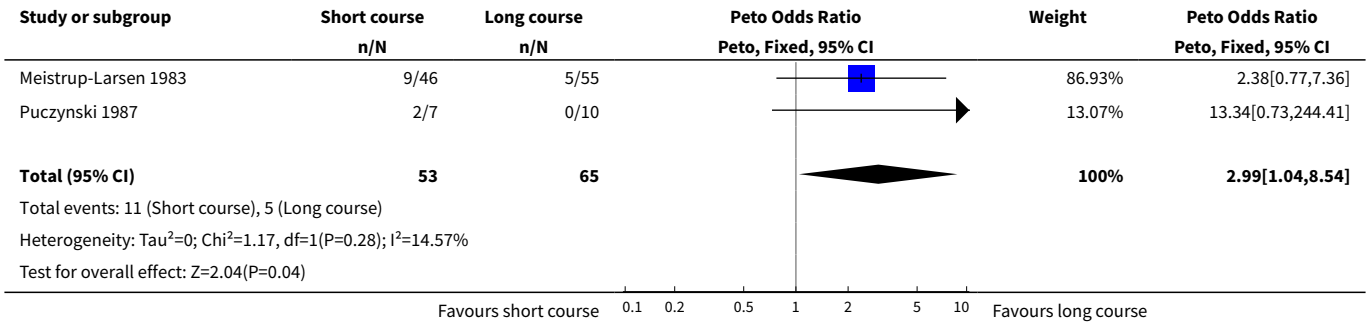
Study	Reason for exclusion
Bain 1985	Outcomes not reported as treatment failures
Gehanno 1990	Duration of antibiotic in both treatment arms was less than 7 days
Harrison 1993	Duration of antibiotic therapy equivalent in both arms
Jacobson 1979	Duration of antibiotic therapy equivalent in both arms
Jenner 1987	Duration of antibiotic in both treatment arms was less than 7 days
Johnson 1991	Duration of antibiotic therapy equivalent in both arms
Jones 1986	Outcomes not reported as treatment failures
MacLouglin 1996	Duration of antibiotic therapy equivalent in both arms
Mandel 1995	Duration of antibiotic in both treatment arms 7 days or greater
Murph 1993	Duration of antibiotic therapy equivalent in both arms
O'Doherty 1996	Trial participants predominantly adults
Roos 2000	Antibiotic ceftibuten was deemed to be not clinically relevant
Rubenstein 1965	Antibiotic therapy no longer current
Scott 1990	No comparison of different durations of antibiotic
Simon 1997	Antibiotic ceftibuten was deemed to be not clinically relevant
Spencer 1993	Duration of antibiotic therapy equivalent in both arms
Stickler 1964	Antibiotic therapy no longer current
Stickler 1967	Antibiotic therapy no longer current
Suzuki 2009	Duration of antibiotic therapy equivalent in both arms
Varsano 1994	Insufficient data reported in abstract

DATA AND ANALYSES

Comparison 1. Short-acting antibiotic =< 48 hours in short treatment arm

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure at 1 month or less	2	118	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.99 [1.04, 8.54]

Analysis 1.1. Comparison 1 Short-acting antibiotic =< 48 hours in short treatment arm, Outcome 1 Treatment failure at 1 month or less.

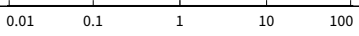


Comparison 2. Short-acting antibiotic > 48 hours short-term treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure at 1 month or less	16	5093	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.34 [1.15, 1.55]
2 Treatment failure at 8 to 19 days	11	3932	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.37 [1.15, 1.64]
3 Treatment failure at 20 to 30 days	9	2476	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.16 [0.94, 1.42]
4 Treatment failure at 3 months or less	7	2068	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.18 [0.98, 1.41]
5 Treatment failure at 90 days	2	207	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.16 [0.65, 2.06]
6 Treatment failure at 30 to 45 days	5	1861	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.18 [0.97, 1.43]

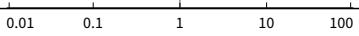
Analysis 2.1. Comparison 2 Short-acting antibiotic > 48 hours short-term treatment, Outcome 1 Treatment failure at 1 month or less.

Study or subgroup	Short course n/N	Long course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Adam 1996	6/48	4/48		1.29%	1.56[0.42,5.72]
Adam 2000	8/102	3/110		1.49%	2.82[0.84,9.46]
Block 2000	66/190	65/183		12.17%	0.97[0.63,1.48]
Block 2004	36/164	26/160		7.18%	1.44[0.83,2.51]
Boulesteix 1995	11/124	11/118		2.87%	0.95[0.39,2.27]
Catania 2004	9/204	10/196		2.59%	0.86[0.34,2.16]
Cohen 1997	60/166	56/168		10.85%	1.13[0.72,1.77]
Cohen 1998	51/192	28/186		8.95%	2[1.22,3.29]
Cohen 2000	46/226	23/222		8.36%	2.15[1.29,3.59]
Gooch 1996	46/147	98/350		12.2%	1.17[0.77,1.79]
Hendrickse 1988	20/62	15/66		3.66%	1.61[0.74,3.49]
Hoberman 1997	57/197	64/367		12.36%	1.98[1.3,3.01]
Ingvarsson 1982	5/66	6/68		1.45%	0.85[0.25,2.9]
Kafetzis 1997	16/286	10/274		3.55%	1.55[0.71,3.4]
Pessey 1999	45/175	51/172		9.95%	0.82[0.51,1.31]
Ploussard 1984	4/27	5/29		1.1%	0.84[0.2,3.45]
Total (95% CI)	**2376**	**2717**		**100%**	**1.34[1.15,1.55]**
Total events: 486 (Short course), 475 (Long course)					
Heterogeneity: Tau^2=0; Chi^2=20.78, df=15(P=0.14); I^2=27.8%					
Test for overall effect: Z=3.84(P=0)					



Analysis 2.2. Comparison 2 Short-acting antibiotic > 48 hours short-term treatment, Outcome 2 Treatment failure at 8 to 19 days.

Study or subgroup	Short course n/N	Long course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Adam 2000	8/102	3/110		2.1%	2.82[0.84,9.46]
Block 2000	66/190	65/183		17.11%	0.97[0.63,1.48]
Block 2004	24/194	28/192		9.06%	0.83[0.46,1.48]
Boulesteix 1995	11/124	11/118		4.03%	0.95[0.39,2.27]
Catania 2004	9/204	10/196		3.64%	0.86[0.34,2.16]
Cohen 1997	26/186	31/184		9.71%	0.8[0.46,1.41]
Cohen 1998	51/192	28/186		12.58%	2[1.22,3.29]
Cohen 2000	46/226	23/222		11.75%	2.15[1.29,3.59]
Hendrickse 1988	14/74	6/77		3.51%	2.62[1.02,6.69]
Hoberman 1997	57/197	64/367		17.38%	1.98[1.3,3.01]
Pessey 1999	28/203	24/205		9.13%	1.21[0.67,2.16]
Total (95% CI)	**1892**	**2040**		**100%**	**1.37[1.15,1.64]**
Total events: 340 (Short course), 293 (Long course)					
Heterogeneity: Tau^2=0; Chi^2=22.08, df=10(P=0.01); I^2=54.71%					
Test for overall effect: Z=3.53(P=0)					



Analysis 2.3. Comparison 2 Short-acting antibiotic > 48 hours short-term treatment, Outcome 3 Treatment failure at 20 to 30 days.

Study or subgroup	Short course n/N	Long course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Adam 1996	6/48	4/48		2.52%	1.56[0.42,5.72]
Block 2004	36/164	26/160		14.02%	1.44[0.83,2.51]
Cohen 1997	60/166	56/168		21.18%	1.13[0.72,1.77]
Gooch 1996	46/147	98/350		23.81%	1.17[0.77,1.79]
Hendrickse 1988	20/62	15/66		7.14%	1.61[0.74,3.49]
Ingvarsson 1982	5/66	6/68		2.84%	0.85[0.25,2.9]
Kafetzis 1997	16/286	10/274		6.92%	1.55[0.71,3.4]
Pessey 1999	45/175	51/172		19.42%	0.82[0.51,1.31]
Ploussard 1984	4/27	5/29		2.14%	0.84[0.2,3.45]
Total (95% CI)	**1141**	**1335**		**100%**	**1.16[0.94,1.42]**
Total events: 238 (Short course), 271 (Long course)					
Heterogeneity: Tau²=0; Chi²=4.54, df=8(P=0.81); I²=0%					
Test for overall effect: Z=1.37(P=0.17)					

Favours short course — Favours long course

Analysis 2.4. Comparison 2 Short-acting antibiotic > 48 hours short-term treatment, Outcome 4 Treatment failure at 3 months or less.

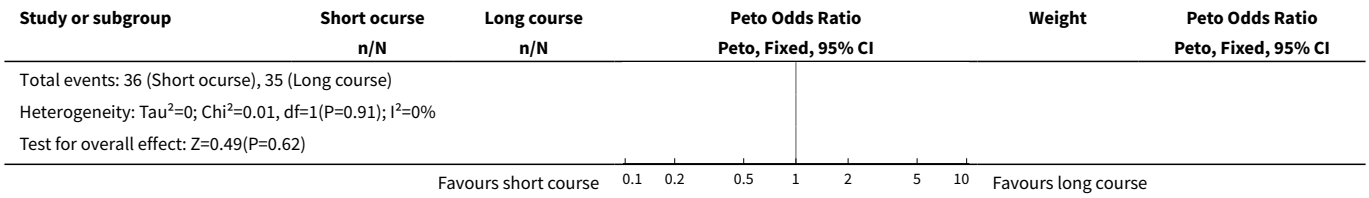
Study or subgroup	Short course n/N	Long course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Block 2000	91/179	80/169		18.69%	1.15[0.76,1.75]
Boulesteix 1995	23/117	26/111		8.28%	0.8[0.43,1.5]
Cohen 1998	88/190	77/185		19.86%	1.21[0.8,1.82]
Cohen 2000	85/226	73/226		22.08%	1.26[0.86,1.86]
de Saintongue 1982	10/38	10/41		3.24%	1.11[0.4,3.03]
Hendrickse 1988	26/62	25/66		6.62%	1.18[0.58,2.39]
Hoberman 1997	68/161	108/297		21.23%	1.28[0.86,1.9]
Total (95% CI)	**973**	**1095**		**100%**	**1.18[0.98,1.41]**
Total events: 391 (Short course), 399 (Long course)					
Heterogeneity: Tau²=0; Chi²=1.78, df=6(P=0.94); I²=0%					
Test for overall effect: Z=1.77(P=0.08)					

Favours short course — Favours long course

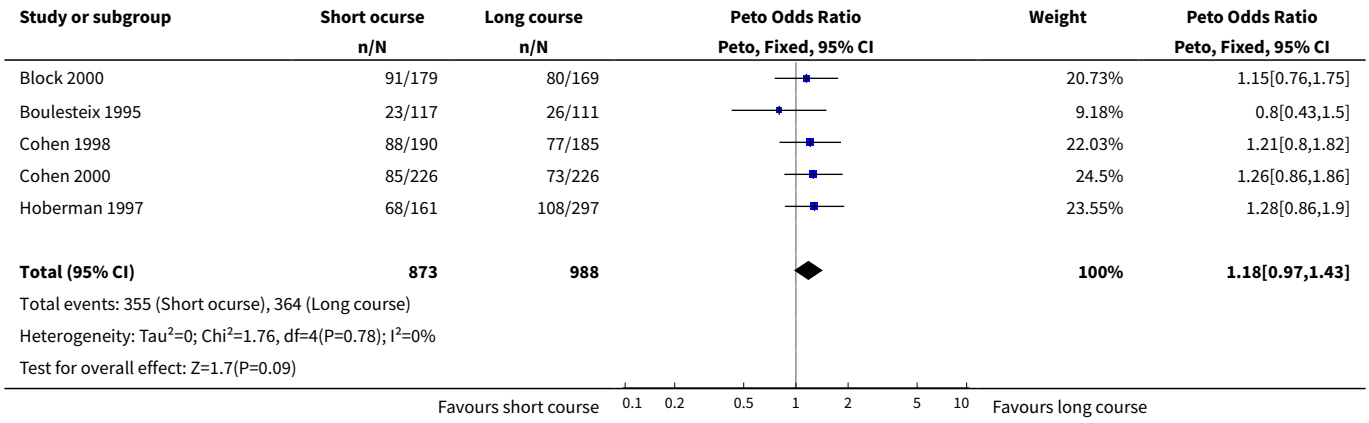
Analysis 2.5. Comparison 2 Short-acting antibiotic > 48 hours short-term treatment, Outcome 5 Treatment failure at 90 days.

Study or subgroup	Short ocurse n/N	Long course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
de Saintongue 1982	10/38	10/41		32.84%	1.11[0.4,3.03]
Hendrickse 1988	26/62	25/66		67.16%	1.18[0.58,2.39]
Total (95% CI)	**100**	**107**		**100%**	**1.16[0.65,2.06]**

Favours short course — Favours long course



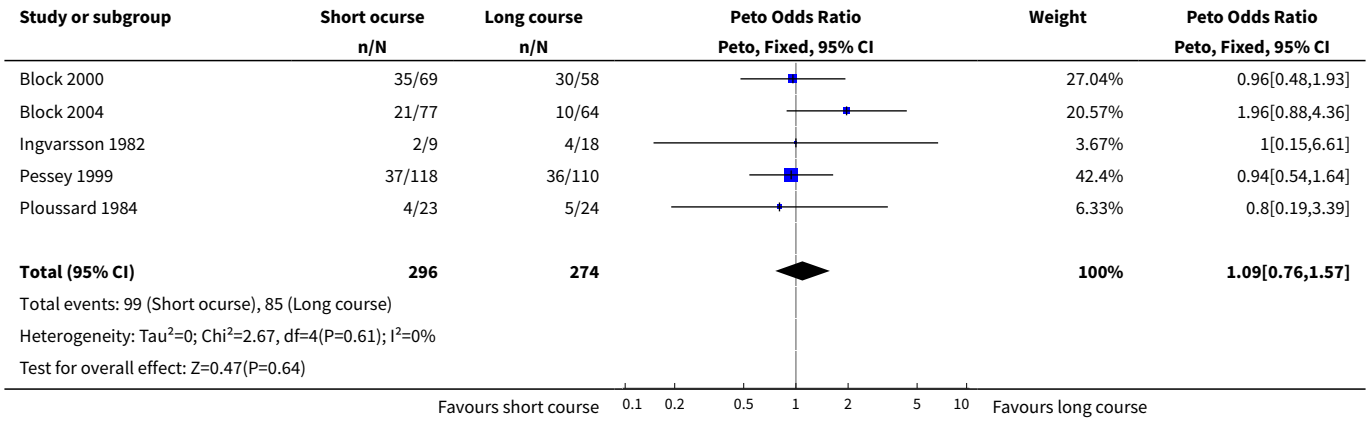
Analysis 2.6. Comparison 2 Short-acting antibiotic > 48 hours short-term treatment, Outcome 6 Treatment failure at 30 to 45 days.



Comparison 3. Short-acting antibiotic > 48 hours short-term treatment, < 2 yrs old

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure at 1 month or less	5	570	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.09 [0.76, 1.57]

Analysis 3.1. Comparison 3 Short-acting antibiotic > 48 hours short-term treatment, < 2 yrs old, Outcome 1 Treatment failure at 1 month or less.



Comparison 4. Short-acting antibiotic > 48 hours short-term treatment, => 2 yrs old

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure at 1 month or less	6	1064	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.85 [0.60, 1.21]

Analysis 4.1. Comparison 4 Short-acting antibiotic > 48 hours short-term treatment, => 2 yrs old, Outcome 1 Treatment failure at 1 month or less.

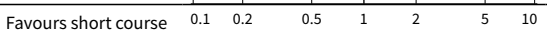
Study or subgroup	Short ocurse n/N	Long course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Block 2000	31/121	35/125		37.85%	0.89[0.5,1.56]
Block 2004	15/87	16/96		20.16%	1.04[0.48,2.25]
Catania 2004	9/204	10/196		14.16%	0.86[0.34,2.16]
Ingvarsson 1982	11/57	10/50		13.25%	0.96[0.37,2.48]
Pessey 1999	8/57	15/62		14.58%	0.52[0.21,1.3]
Ploussard 1984	0/4	0/5			Not estimable
Total (95% CI)	**530**	**534**		**100%**	**0.85[0.6,1.21]**
Total events: 74 (Short ocurse), 86 (Long course)					
Heterogeneity: Tau^2=0; Chi^2=1.44, df=4(P=0.84); I^2=0%					
Test for overall effect: Z=0.9(P=0.37)					

Comparison 5. Short-acting antibiotic > 48 hours short-term treatment, perforated eardrum

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure at 1 month or less	1	27	Peto Odds Ratio (Peto, Fixed, 95% CI)	3.62 [0.81, 16.06]

Analysis 5.1. Comparison 5 Short-acting antibiotic > 48 hours short-term treatment, perforated eardrum, Outcome 1 Treatment failure at 1 month or less.

Study or subgroup	Short ocurse n/N	Long course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Hendrickse 1988	10/15	4/12		100%	3.62[0.81,16.06]
Total (95% CI)	**15**	**12**		**100%**	**3.62[0.81,16.06]**
Total events: 10 (Short ocurse), 4 (Long course)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.69(P=0.09)					



Comparison 6. Short-acting antibiotic > 48 hours short-term treatment, non-perforated eardrum

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure at 1 month or less	1	101	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.06 [0.40, 2.75]

Analysis 6.1. Comparison 6 Short-acting antibiotic > 48 hours short-term treatment, non-perforated eardrum, Outcome 1 Treatment failure at 1 month or less.

Study or subgroup	Short course n/N	Long course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Hendrickse 1988	10/47	11/54		100%	1.06[0.4,2.75]
Total (95% CI)	**47**	**54**		**100%**	**1.06[0.4,2.75]**
Total events: 10 (Short course), 11 (Long course)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.11(P=0.91)					

Favours short course — Favours long course

Comparison 7. Short-acting antibiotic > 48 hours short-term treatment; Sensitivity Analysis: include chronic OM

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure at 1 month or less	6	1713	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.37 [1.09, 1.72]
2 Treatment failure at 20 to 30 days	5	1149	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.17 [0.89, 1.54]

Analysis 7.1. Comparison 7 Short-acting antibiotic > 48 hours short-term treatment; Sensitivity Analysis: include chronic OM, Outcome 1 Treatment failure at 1 month or less.

Study or subgroup	Short course n/N	Long course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Cohen 1997	60/166	56/168		26.06%	1.13[0.72,1.77]
Gooch 1996	46/147	98/350		29.31%	1.17[0.77,1.79]
Hendrickse 1988	20/62	15/66		8.79%	1.61[0.74,3.49]
Hoberman 1997	57/197	64/367		29.71%	1.98[1.3,3.01]
Ingvarsson 1982	5/66	6/68		3.49%	0.85[0.25,2.9]
Ploussard 1984	4/27	5/29		2.64%	0.84[0.2,3.45]
Total (95% CI)	**665**	**1048**		**100%**	**1.37[1.09,1.72]**
Total events: 192 (Short course), 244 (Long course)					
Heterogeneity: Tau^2=0; Chi^2=5.32, df=5(P=0.38); I^2=6.06%					
Test for overall effect: Z=2.67(P=0.01)					

Favours short course — Favours long course

Analysis 7.2. Comparison 7 Short-acting antibiotic > 48 hours short-term treatment; Sensitivity Analysis: include chronic OM, Outcome 2 Treatment failure at 20 to 30 days.

Study or subgroup	Short cours n/N	Long course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Cohen 1997	60/166	56/168		37.08%	1.13[0.72,1.77]
Gooch 1996	46/147	98/350		41.7%	1.17[0.77,1.79]
Hendrickse 1988	20/62	15/66		12.5%	1.61[0.74,3.49]
Ingvarsson 1982	5/66	6/68		4.97%	0.85[0.25,2.9]
Ploussard 1984	4/27	5/29		3.75%	0.84[0.2,3.45]
Total (95% CI)	**468**	**681**		**100%**	**1.17[0.89,1.54]**
Total events: 135 (Short cours), 180 (Long course)					
Heterogeneity: Tau^2=0; Chi^2=1.15, df=4(P=0.89); I^2=0%					
Test for overall effect: Z=1.12(P=0.26)					

Favours short course — Favours long course

Comparison 8. Short-acting antibiotic > 48 hours short-term treatment; Sensitivity Analysis: exclude chronic OM

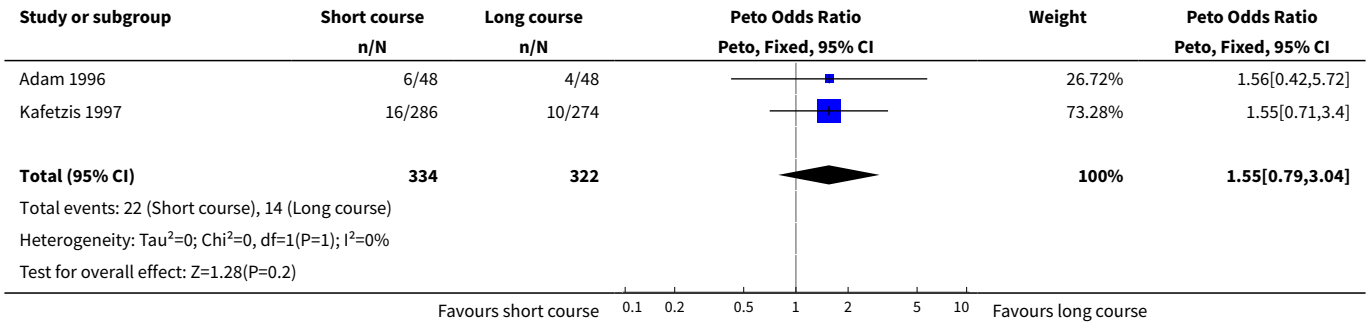
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Treatment failure at 1 month or less	4	1298	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.17 [0.73, 1.85]
2 Treatment failure at 20 to 30 days	2	656	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.55 [0.79, 3.04]

Analysis 8.1. Comparison 8 Short-acting antibiotic > 48 hours short-term treatment; Sensitivity Analysis: exclude chronic OM, Outcome 1 Treatment failure at 1 month or less.

Study or subgroup	Short course n/N	Long course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Adam 1996	6/48	4/48		12.56%	1.56[0.42,5.72]
Boulesteix 1995	11/124	11/118		27.84%	0.95[0.39,2.27]
Catania 2004	9/204	10/196		25.16%	0.86[0.34,2.16]
Kafetzis 1997	16/286	10/274		34.44%	1.55[0.71,3.4]
Total (95% CI)	**662**	**636**		**100%**	**1.17[0.73,1.85]**
Total events: 42 (Short course), 35 (Long course)					
Heterogeneity: Tau^2=0; Chi^2=1.33, df=3(P=0.72); I^2=0%					
Test for overall effect: Z=0.65(P=0.52)					

Favours short course — Favours Long course

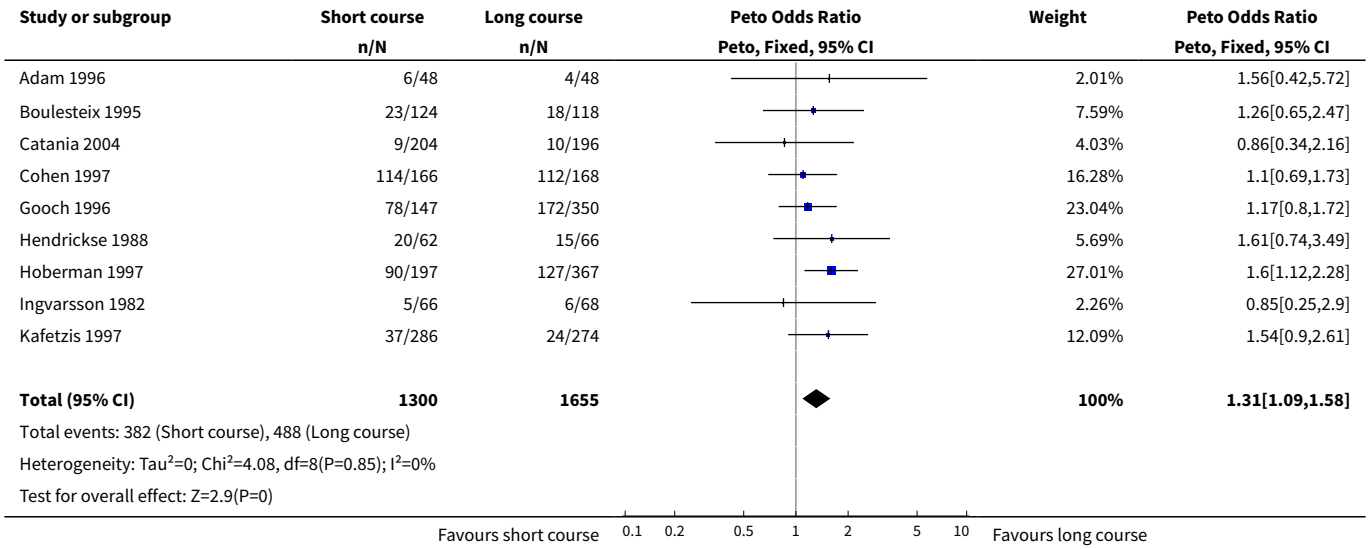
Analysis 8.2. Comparison 8 Short-acting antibiotic > 48 hours short-term treatment; Sensitivity Analysis: exclude chronic OM, Outcome 2 Treatment failure at 20 to 30 days.



Comparison 9. Short-acting antibiotic > 48 hours short-term treatment; Sensitivity analysis: outcome only if "cured"

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Treatment failure at 1 month or less	9	2955	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.31 [1.09, 1.58]
2 Treatment failure at 20 to 30 days	6	1749	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.25 [0.98, 1.58]

Analysis 9.1. Comparison 9 Short-acting antibiotic > 48 hours short-term treatment; Sensitivity analysis: outcome only if "cured", Outcome 1 Treatment failure at 1 month or less.



Analysis 9.2. Comparison 9 Short-acting antibiotic > 48 hours short-term treatment; Sensitivity analysis: outcome only if "cured", Outcome 2 Treatment failure at 20 to 30 days.

Study or subgroup	Short course n/N	Long course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Adam 1996	6/48	4/48		3.28%	1.56[0.42,5.72]
Cohen 1997	114/166	112/168		26.53%	1.1[0.69,1.73]
Gooch 1996	78/147	172/350		37.54%	1.17[0.8,1.72]
Hendrickse 1988	20/62	15/66		9.27%	1.61[0.74,3.49]
Ingvarsson 1982	5/66	6/68		3.68%	0.85[0.25,2.9]
Kafetzis 1997	37/286	24/274		19.7%	1.54[0.9,2.61]
Total (95% CI)	**775**	**974**		**100%**	**1.25[0.98,1.58]**
Total events: 260 (Short course), 333 (Long course)					
Heterogeneity: Tau^2=0; Chi^2=1.91, df=5(P=0.86); I^2=0%					
Test for overall effect: Z=1.83(P=0.07)					

Favours short course — Favours long course

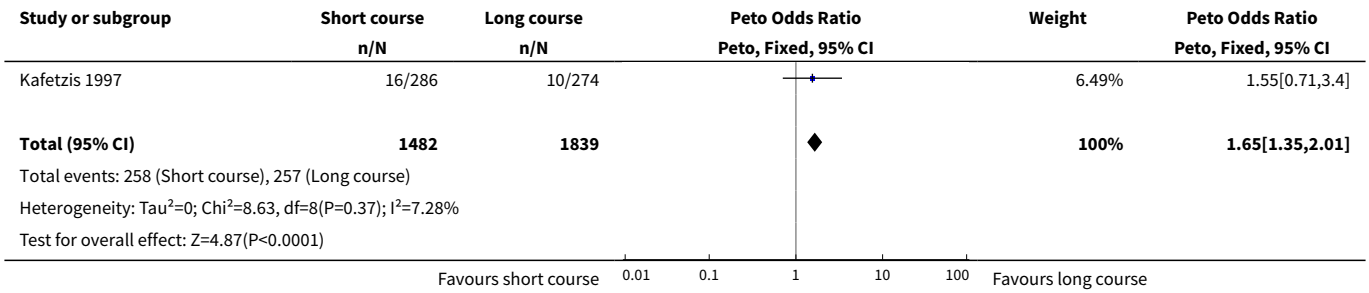
Comparison 10. Short-acting antibiotic > 48 hours short-term treatment; Sensitivity analysis: same antibiotic in treatment arms

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure at 1 month or less	9	3321	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.65 [1.35, 2.01]
2 Treatment failure at 8 to 19 days	6	2153	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.97 [1.54, 2.52]
3 Treatment failure at 20 to 30 days	4	1319	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.27 [0.92, 1.76]
4 Treatment failure at 3 months or less	5	1492	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.24 [1.00, 1.53]
5 Treatment failure at 90 days	2	207	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.16 [0.65, 2.06]
6 Treatment failure at 30 to 45 days	3	1285	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.25 [1.00, 1.57]

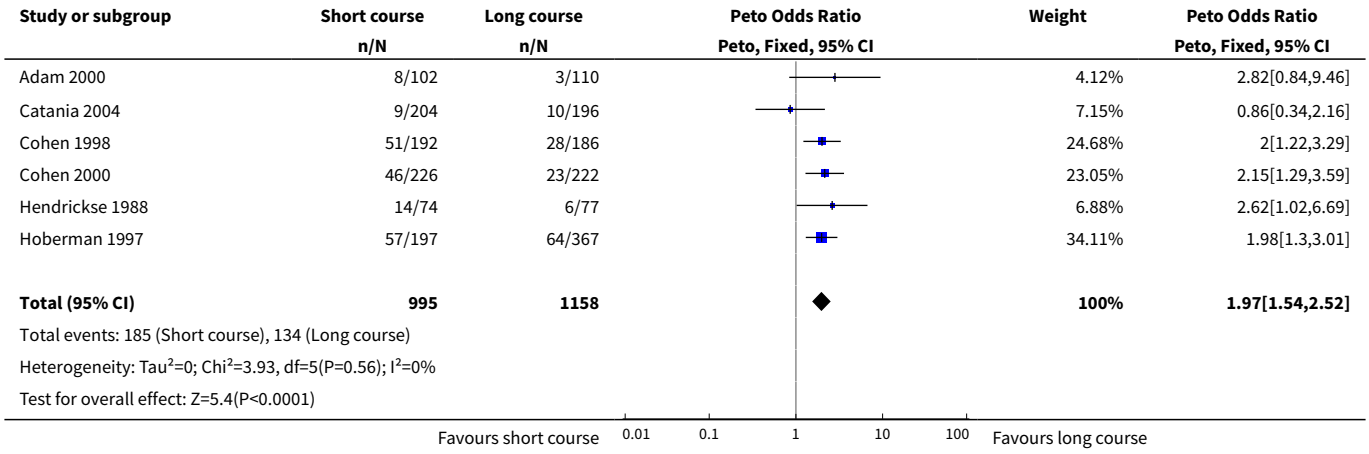
Analysis 10.1. Comparison 10 Short-acting antibiotic > 48 hours short-term treatment; Sensitivity analysis: same antibiotic in treatment arms, Outcome 1 Treatment failure at 1 month or less.

Study or subgroup	Short course n/N	Long course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Adam 2000	8/102	3/110		2.74%	2.82[0.84,9.46]
Catania 2004	9/204	10/196		4.74%	0.86[0.34,2.16]
Cohen 1998	51/192	28/186		16.39%	2[1.22,3.29]
Cohen 2000	46/226	23/222		15.3%	2.15[1.29,3.59]
Gooch 1996	46/147	98/350		22.34%	1.17[0.77,1.79]
Hendrickse 1988	20/62	15/66		6.7%	1.61[0.74,3.49]
Hoberman 1997	57/197	64/367		22.64%	1.98[1.3,3.01]
Ingvarsson 1982	5/66	6/68		2.66%	0.85[0.25,2.9]

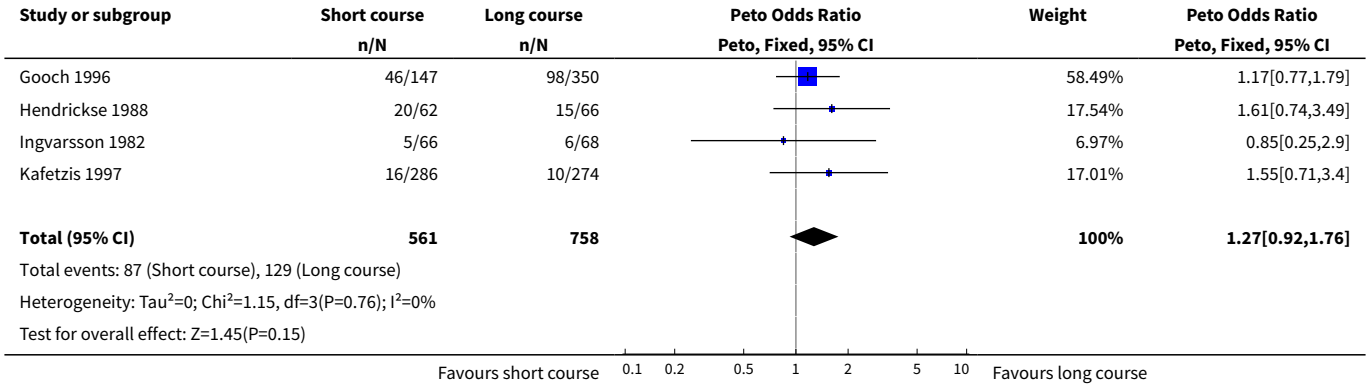
Favours short course — Favours long course



Analysis 10.2. Comparison 10 Short-acting antibiotic > 48 hours short-term treatment; Sensitivity analysis: same antibiotic in treatment arms, Outcome 2 Treatment failure at 8 to 19 days.

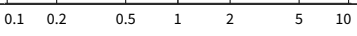


Analysis 10.3. Comparison 10 Short-acting antibiotic > 48 hours short-term treatment; Sensitivity analysis: same antibiotic in treatment arms, Outcome 3 Treatment failure at 20 to 30 days.



Analysis 10.4. Comparison 10 Short-acting antibiotic > 48 hours short-term treatment; Sensitivity analysis: same antibiotic in treatment arms, Outcome 4 Treatment failure at 3 months or less.

Study or subgroup	Short course n/N	Long course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Cohen 1998	88/190	77/185		27.19%	1.21[0.8,1.82]
Cohen 2000	85/226	73/226		30.24%	1.26[0.86,1.86]
de Saintongue 1982	10/38	10/41		4.43%	1.11[0.4,3.03]
Hendrickse 1988	26/62	25/66		9.07%	1.18[0.58,2.39]
Hoberman 1997	68/161	108/297		29.07%	1.28[0.86,1.9]
Total (95% CI)	**677**	**815**		**100%**	**1.24[1,1.53]**
Total events: 277 (Short course), 293 (Long course)					
Heterogeneity: Tau^2=0; Chi^2=0.12, df=4(P=1); I^2=0%					
Test for overall effect: Z=1.97(P=0.05)					



Analysis 10.5. Comparison 10 Short-acting antibiotic > 48 hours short-term treatment; Sensitivity analysis: same antibiotic in treatment arms, Outcome 5 Treatment failure at 90 days.

Study or subgroup	Short ocurse n/N	Long course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
de Saintongue 1982	10/38	10/41		32.84%	1.11[0.4,3.03]
Hendrickse 1988	26/62	25/66		67.16%	1.18[0.58,2.39]
Total (95% CI)	**100**	**107**		**100%**	**1.16[0.65,2.06]**
Total events: 36 (Short ocurse), 35 (Long course)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.91); I^2=0%					
Test for overall effect: Z=0.49(P=0.62)					

Analysis 10.6. Comparison 10 Short-acting antibiotic > 48 hours short-term treatment; Sensitivity analysis: same antibiotic in treatment arms, Outcome 6 Treatment failure at 30 to 45 days.

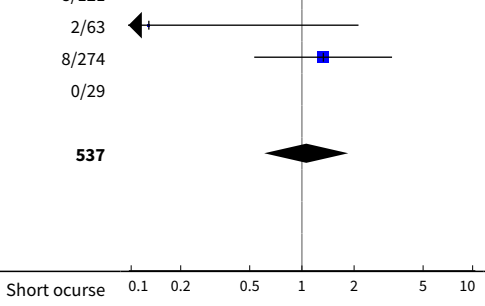
Study or subgroup	Short ocurse n/N	Long course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Cohen 1998	88/190	77/185		31.44%	1.21[0.8,1.82]
Cohen 2000	85/226	73/226		34.96%	1.26[0.86,1.86]
Hoberman 1997	68/161	108/297		33.61%	1.28[0.86,1.9]
Total (95% CI)	**577**	**708**		**100%**	**1.25[1,1.57]**
Total events: 241 (Short ocurse), 258 (Long course)					
Heterogeneity: Tau^2=0; Chi^2=0.04, df=2(P=0.98); I^2=0%					
Test for overall effect: Z=1.93(P=0.05)					

Comparison 11. Short-acting antibiotic > 48 hours short-term treatment, excluding amoxicillin-clavulanate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Gastrointestinal adverse effects	5	1088	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.06 [0.61, 1.85]

Analysis 11.1. Comparison 11 Short-acting antibiotic > 48 hours short-term treatment, excluding amoxicillin-clavulanate, Outcome 1 Gastrointestinal adverse effects.

Study or subgroup	Short course n/N	Long course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Adam 1996	10/50	8/50		30.17%	1.31[0.47,3.61]
Boulesteix 1995	7/124	8/121		28.61%	0.85[0.3,2.4]
Hendrickse 1988	0/64	2/63		4.02%	0.13[0.01,2.12]
Kafetzis 1997	11/286	8/274		37.2%	1.33[0.53,3.31]
Ploussard 1984	0/27	0/29			Not estimable
Total (95% CI)	**551**	**537**		**100%**	**1.06[0.61,1.85]**
Total events: 28 (Short course), 26 (Long course)					
Heterogeneity: Tau^2=0; Chi^2=2.74, df=3(P=0.43); I^2=0%					
Test for overall effect: Z=0.2(P=0.84)					



Comparison 12. Short-acting antibiotic > 48 hours short-term treatment; Sensitivity analysis: treatment failure at 1 month or less and risk of bias

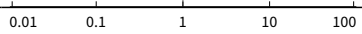
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Sensitivity analysis: allocation concealment unclear risk of bias	13	3953	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.30 [1.09, 1.54]
2 Sensitivity analysis: allocation concealment low risk of bias	3	1140	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.45 [1.08, 1.93]
3 Sensitivity analysis: blinding high and unclear risk of bias	12	3927	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.18 [1.00, 1.40]
4 Sensitivity analysis: blinding low risk of bias	4	1166	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.03 [1.48, 2.77]

Analysis 12.1. Comparison 12 Short-acting antibiotic > 48 hours short-term treatment; Sensitivity analysis: treatment failure at 1 month or less and risk of bias, Outcome 1 Sensitivity analysis: allocation concealment unclear risk of bias.

Study or subgroup	Short Course n/N	Long Course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Adam 1996	6/48	4/48		1.75%	1.56[0.42,5.72]
Adam 2000	8/102	3/110		2.02%	2.82[0.84,9.46]
Block 2000	66/190	65/183		16.46%	0.97[0.63,1.48]
Block 2004	36/164	26/160		9.72%	1.44[0.83,2.51]
Catania 2004	9/204	10/196		3.5%	0.86[0.34,2.16]
Cohen 1998	51/192	28/186		12.1%	2[1.22,3.29]
Cohen 2000	46/226	23/222		11.3%	2.15[1.29,3.59]
Gooch 1996	46/147	98/350		16.5%	1.17[0.77,1.79]
Hendrickse 1988	20/62	15/66		4.95%	1.61[0.74,3.49]
Ingvarsson 1982	5/66	6/68		1.97%	0.85[0.25,2.9]
Kafetzis 1997	16/286	10/274		4.8%	1.55[0.71,3.4]
Pessey 1999	45/175	51/172		13.45%	0.82[0.51,1.31]
Ploussard 1984	4/27	5/29		1.48%	0.84[0.2,3.45]
Total (95% CI)	**1889**	**2064**		**100%**	**1.3[1.09,1.54]**
Total events: 358 (Short Course), 344 (Long Course)					
Heterogeneity: Tau^2=0; Chi^2=16.25, df=12(P=0.18); I^2=26.15%					
Test for overall effect: Z=2.99(P=0)					

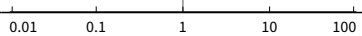
Analysis 12.2. Comparison 12 Short-acting antibiotic > 48 hours short-term treatment; Sensitivity analysis: treatment failure at 1 month or less and risk of bias, Outcome 2 Sensitivity analysis: allocation concealment low risk of bias.

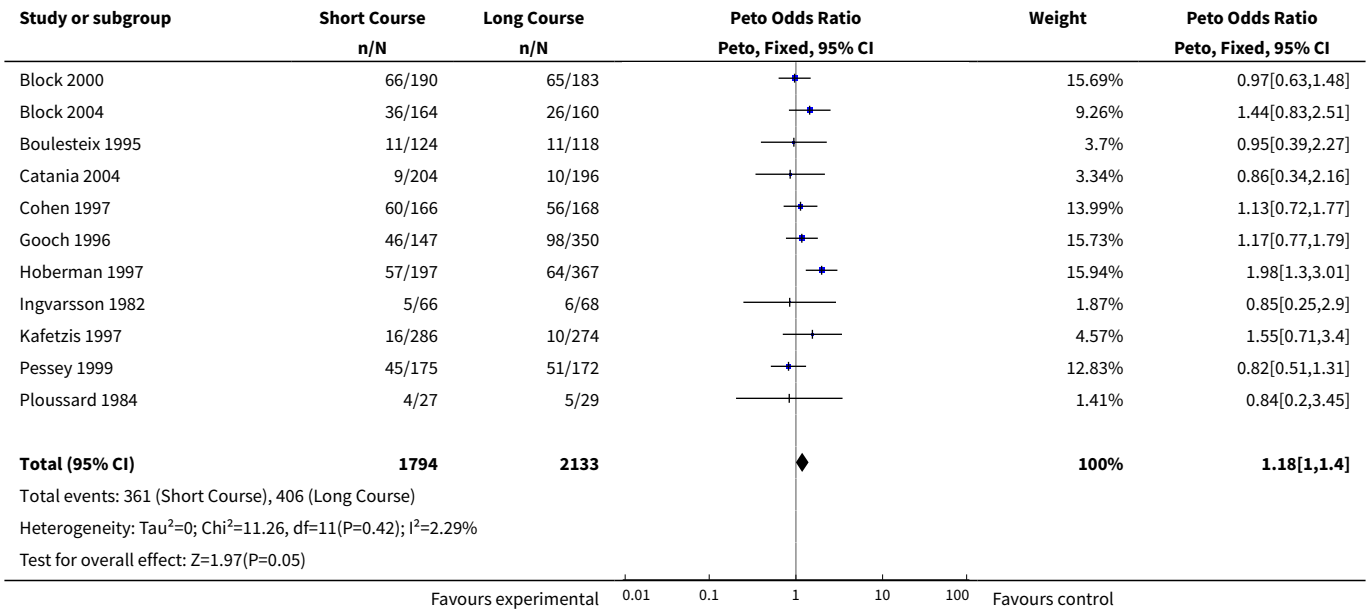
Study or subgroup	Short Course n/N	Long Course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Boulesteix 1995	11/124	11/118		10.99%	0.95[0.39,2.27]
Cohen 1997	60/166	56/168		41.59%	1.13[0.72,1.77]
Hoberman 1997	57/197	64/367		47.41%	1.98[1.3,3.01]
Total (95% CI)	**487**	**653**		**100%**	**1.45[1.08,1.93]**
Total events: 128 (Short Course), 131 (Long Course)					
Heterogeneity: Tau^2=0; Chi^2=4.15, df=2(P=0.13); I^2=51.78%					
Test for overall effect: Z=2.49(P=0.01)					



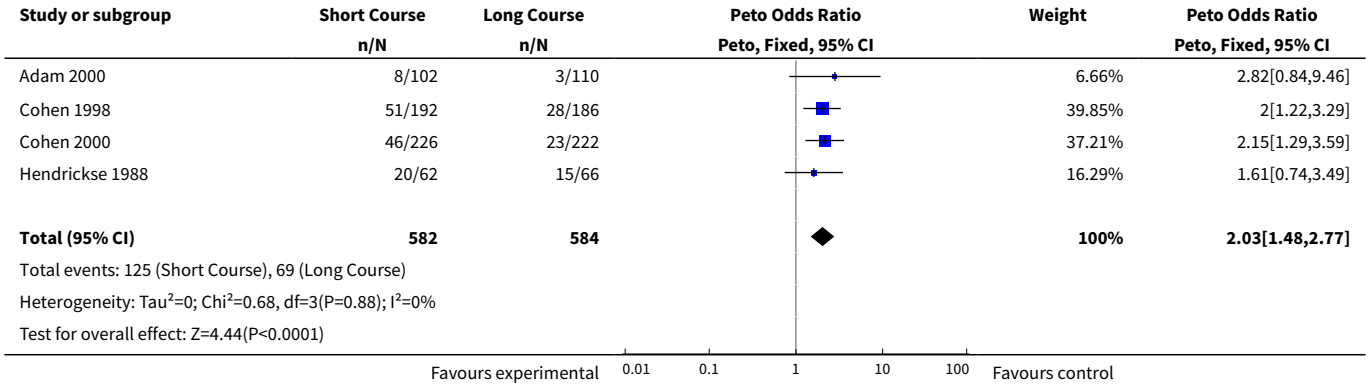
Analysis 12.3. Comparison 12 Short-acting antibiotic > 48 hours short-term treatment; Sensitivity analysis: treatment failure at 1 month or less and risk of bias, Outcome 3 Sensitivity analysis: blinding high and unclear risk of bias.

Study or subgroup	Short Course n/N	Long Course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Adam 1996	6/48	4/48		1.67%	1.56[0.42,5.72]





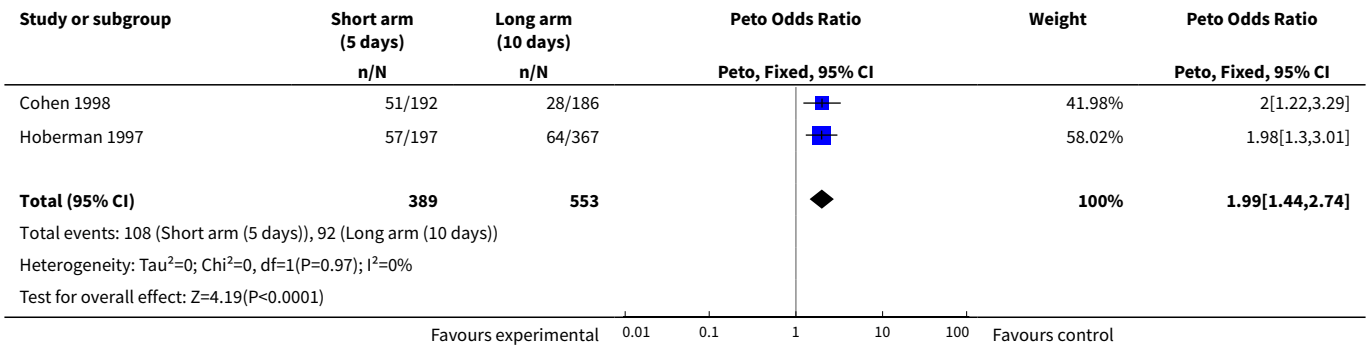
Analysis 12.4. Comparison 12 Short-acting antibiotic > 48 hours short-term treatment; Sensitivity analysis: treatment failure at 1 month or less and risk of bias, Outcome 4 Sensitivity analysis: blinding low risk of bias.



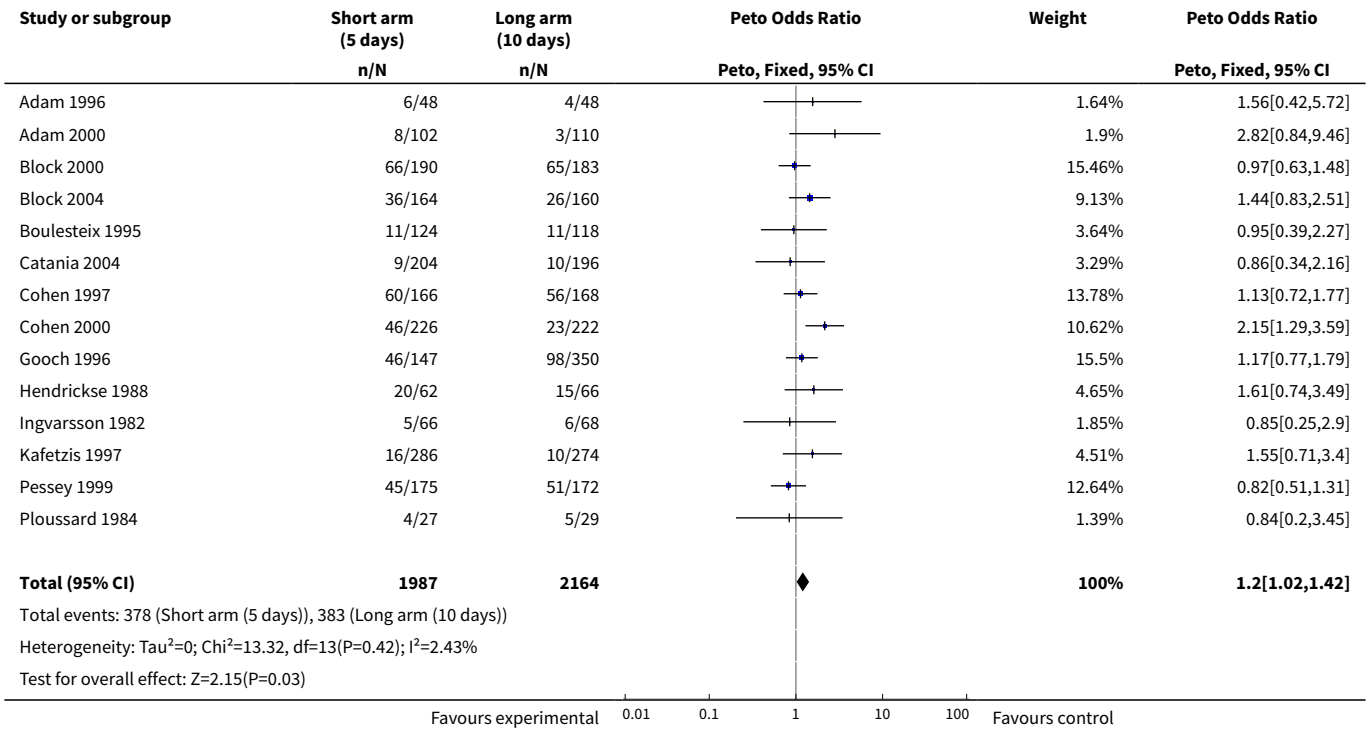
Comparison 13. Short-acting antibiotic > 48 hours short-term treatment; Sensitivity analysis amoxil-clav. both arms

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Amoxil-clav. 5 versus 10 days, treatment failure 1 month or less	2	942	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.99 [1.44, 2.74]
2 Excluding amoxil-clav. 5 versus 10 days, treatment failure 1 month or less	14	4151	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.20 [1.02, 1.42]

Analysis 13.1. Comparison 13 Short-acting antibiotic > 48 hours short-term treatment; Sensitivity analysis amoxil-clav. both arms, Outcome 1 Amoxil-clav. 5 versus 10 days, treatment failure 1 month or less.



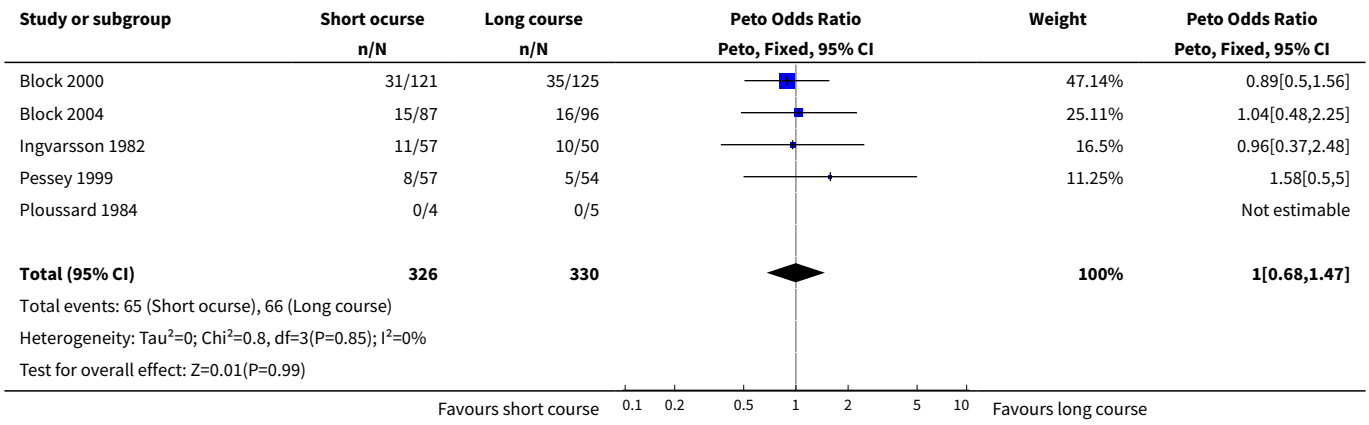
Analysis 13.2. Comparison 13 Short-acting antibiotic > 48 hours short-term treatment; Sensitivity analysis amoxil-clav. both arms, Outcome 2 Excluding amoxil-clav. 5 versus 10 days, treatment failure 1 month or less.



Comparison 14. Short-acting antibiotic > 48 hours short-term treatment, => 2 yrs old; Sensitivity analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure at 1 month or less	5	656	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.00 [0.68, 1.47]

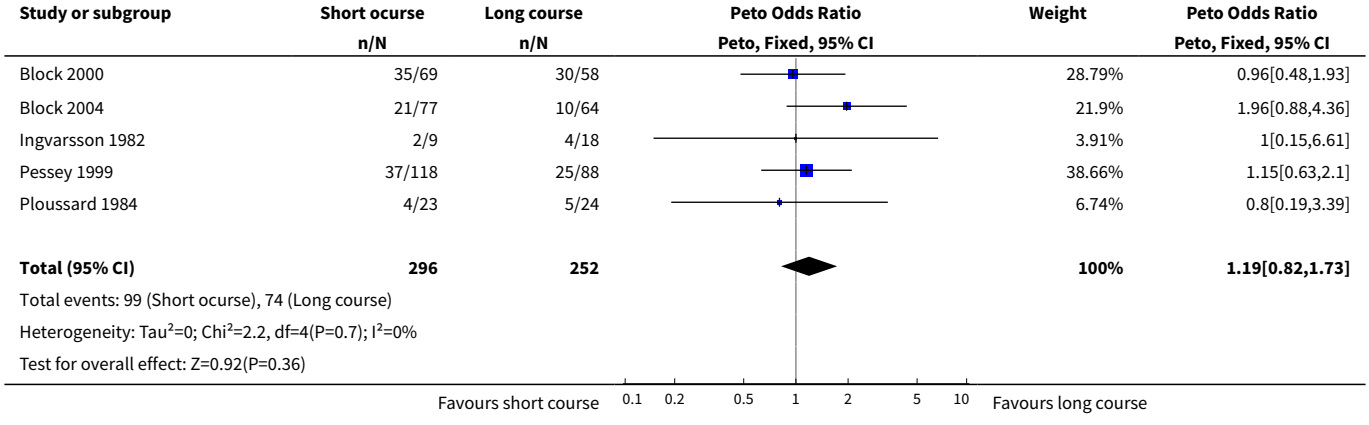
Analysis 14.1. Comparison 14 Short-acting antibiotic > 48 hours short-term treatment, => 2 yrs old; Sensitivity analysis, Outcome 1 Treatment failure at 1 month or less.



Comparison 15. Short-acting antibiotic > 48 hours short-term treatment, < 2 yrs old; Sensitivity analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure at 1 month or less	5	548	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.19 [0.82, 1.73]

Analysis 15.1. Comparison 15 Short-acting antibiotic > 48 hours short-term treatment, < 2 yrs old; Sensitivity analysis, Outcome 1 Treatment failure at 1 month or less.

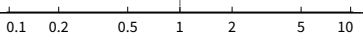


Comparison 16. Short-acting antibiotic, > 48 hours short-term treatment, adverse GI effects

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Gastrointestinal adverse effects	13	4918	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.72 [0.60, 0.87]

Analysis 16.1. Comparison 16 Short-acting antibiotic, > 48 hours short-term treatment, adverse GI effects, Outcome 1 Gastrointestinal adverse effects.

Study or subgroup	Short course n/N	Long course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Adam 1996	10/50	8/50		3.21%	1.31[0.47,3.61]
Adam 2000	5/115	4/113		1.87%	1.24[0.33,4.68]
Block 2000	17/219	9/216		5.28%	1.89[0.86,4.18]
Block 2004	17/211	32/214		9.36%	0.51[0.28,0.92]
Boulesteix 1995	7/124	8/121		3.05%	0.85[0.3,2.4]
Catania 2004	13/204	17/196		5.99%	0.72[0.34,1.51]
Cohen 1997	16/199	36/199		9.76%	0.41[0.23,0.74]
Cohen 1998	44/194	33/188		13.28%	1.37[0.83,2.26]
Gooch 1996	41/242	111/477		23.1%	0.68[0.47,1]
Hendrickse 1988	0/64	2/63		0.43%	0.13[0.01,2.12]
Hoberman 1997	25/286	101/557		20.72%	0.48[0.32,0.71]
Kafetzis 1997	11/286	8/274		3.96%	1.33[0.53,3.31]
Ploussard 1984	0/27	0/29			Not estimable
Total (95% CI)	**2221**	**2697**		**100%**	**0.72[0.6,0.87]**
Total events: 206 (Short course), 369 (Long course)					
Heterogeneity: Tau^2=0; Chi^2=26.24, df=11(P=0.01); I^2=58.08%					
Test for overall effect: Z=3.49(P=0)					



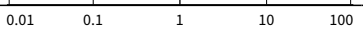
Short course — Long course

Comparison 17. Ceftriaxone

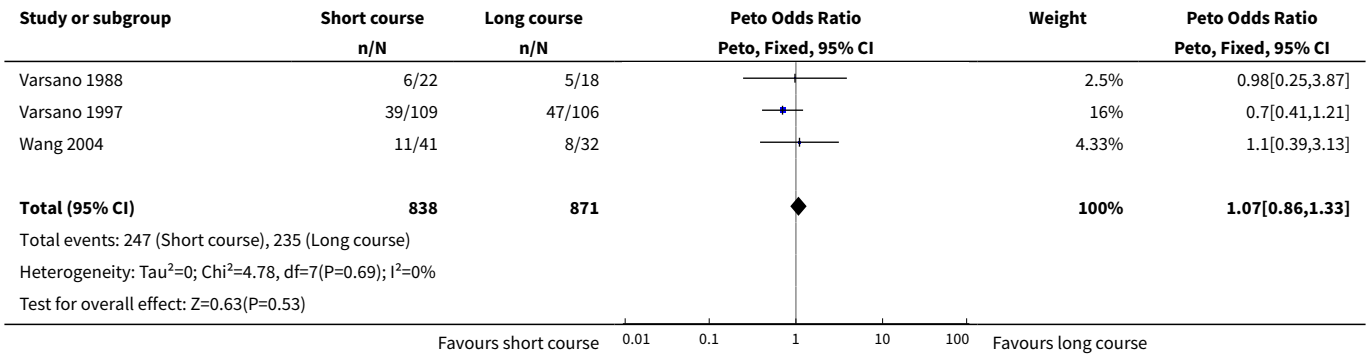
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure at 1 month or less	8	1709	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.07 [0.86, 1.33]
2 Treatment failure at 3 months or less	3	701	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.89 [0.66, 1.21]
3 Gastrointestinal adverse effects	1	402	Peto Odds Ratio (Peto, Fixed, 95% CI)	2.89 [1.70, 4.91]

Analysis 17.1. Comparison 17 Ceftriaxone, Outcome 1 Treatment failure at 1 month or less.

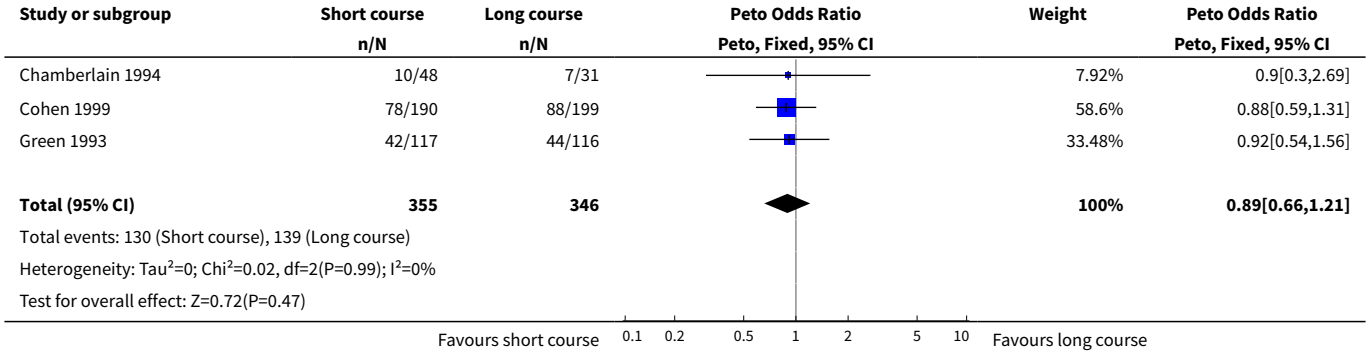
Study or subgroup	Short course n/N	Long course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Al-Ghamdi 1999	7/77	8/115		4.12%	1.34[0.46,3.93]
Barnett 1997	85/193	81/205		29.93%	1.2[0.81,1.79]
Cohen 1999	65/255	59/228		28.43%	0.98[0.65,1.47]
Green 1993	30/116	23/117		12.7%	1.42[0.77,2.62]
Kara 1998	4/25	4/50		1.99%	2.29[0.49,10.73]



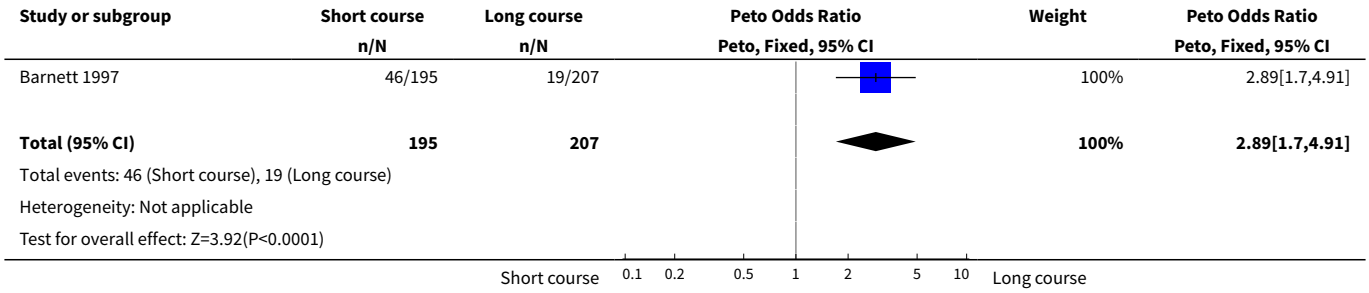
Favours short course — Favours long course



Analysis 17.2. Comparison 17 Ceftriaxone, Outcome 2 Treatment failure at 3 months or less.



Analysis 17.3. Comparison 17 Ceftriaxone, Outcome 3 Gastrointestinal adverse effects.



Comparison 18. Azithromycin single-dose short-term treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure at 25 to 32 days	2	608	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.01 [0.69, 1.47]
2 Treatment failure at 25 to 32 days, =< 2 yrs old	2	368	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.68 [0.43, 1.09]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
3 Treatment failure at 25 to 32 days, > 2 yrs old	2	240	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.08 [0.53, 2.20]
4 Gastrointestinal adverse effects	2	658	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.66 [0.45, 0.96]

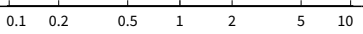
Analysis 18.1. Comparison 18 Azithromycin single-dose short-term treatment, Outcome 1 Treatment failure at 25 to 32 days.

Study or subgroup	Short course n/N	Long course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Arguedas 2005	35/152	34/151		48.51%	1.03[0.6,1.76]
Block 2003	37/151	38/154		51.49%	0.99[0.59,1.67]
Total (95% CI)	**303**	**305**		**100%**	**1.01[0.69,1.47]**
Total events: 72 (Short course), 72 (Long course)					
Heterogeneity: Tau^2=0; Chi^2=0.01, df=1(P=0.92); I^2=0%					
Test for overall effect: Z=0.05(P=0.96)					

Favours short course — Favours long course

Analysis 18.2. Comparison 18 Azithromycin single-dose short-term treatment, Outcome 2 Treatment failure at 25 to 32 days, =< 2 yrs old.

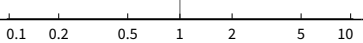
Study or subgroup	Short course n/N	Long course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Arguedas 2005	32/130	30/121		65.26%	0.99[0.56,1.76]
Block 2003	13/64	23/53		34.74%	0.34[0.16,0.75]
Total (95% CI)	**194**	**174**		**100%**	**0.68[0.43,1.09]**
Total events: 45 (Short course), 53 (Long course)					
Heterogeneity: Tau^2=0; Chi^2=4.61, df=1(P=0.03); I^2=78.31%					
Test for overall effect: Z=1.61(P=0.11)					



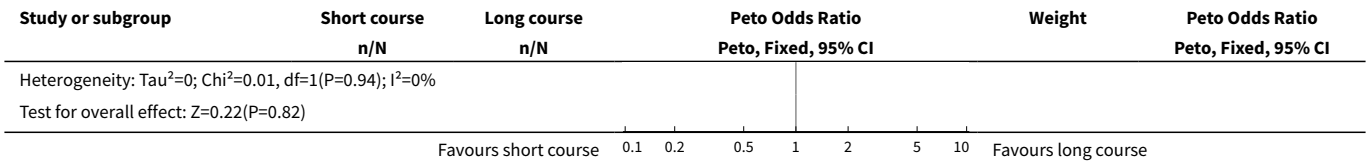
Favours short course — Favours long course

Analysis 18.3. Comparison 18 Azithromycin single-dose short-term treatment, Outcome 3 Treatment failure at 25 to 32 days, > 2 yrs old.

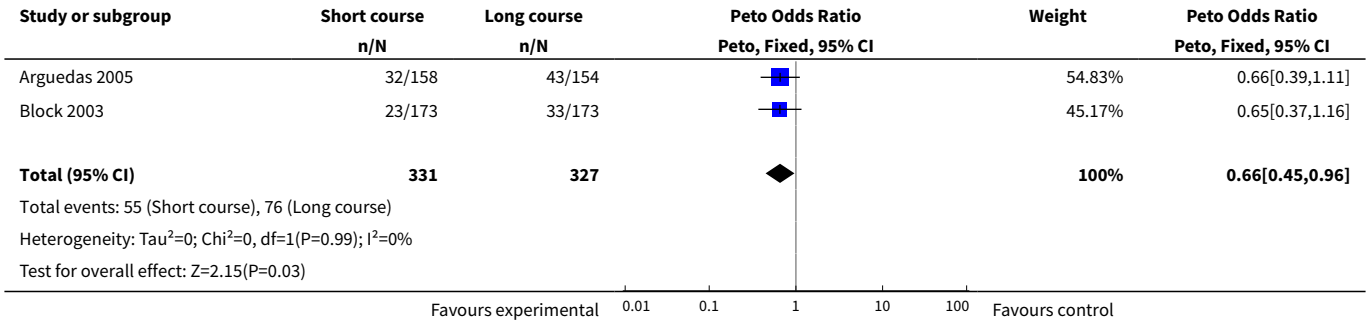
Study or subgroup	Short course n/N	Long course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Arguedas 2005	3/22	4/30		19.74%	1.03[0.21,5.06]
Block 2003	14/87	15/101		80.26%	1.1[0.5,2.43]
Total (95% CI)	**109**	**131**		**100%**	**1.08[0.53,2.2]**
Total events: 17 (Short course), 19 (Long course)					



Favours short course — Favours long course



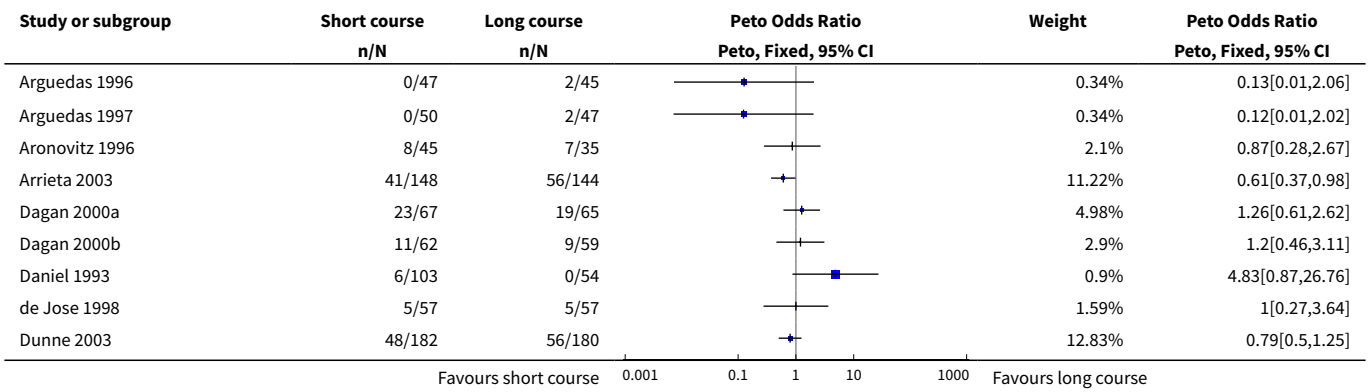
Analysis 18.4. Comparison 18 Azithromycin single-dose short-term treatment, Outcome 4 Gastrointestinal adverse effects.

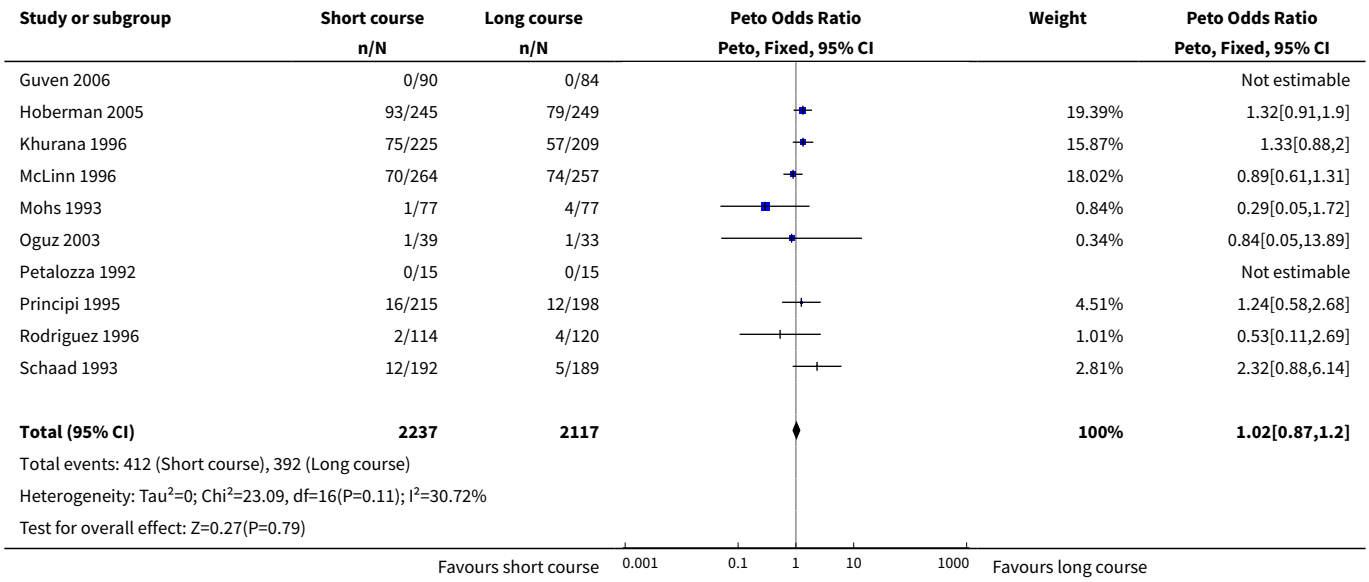


Comparison 19. Azithromycin 3 to 5 days short-term treatment

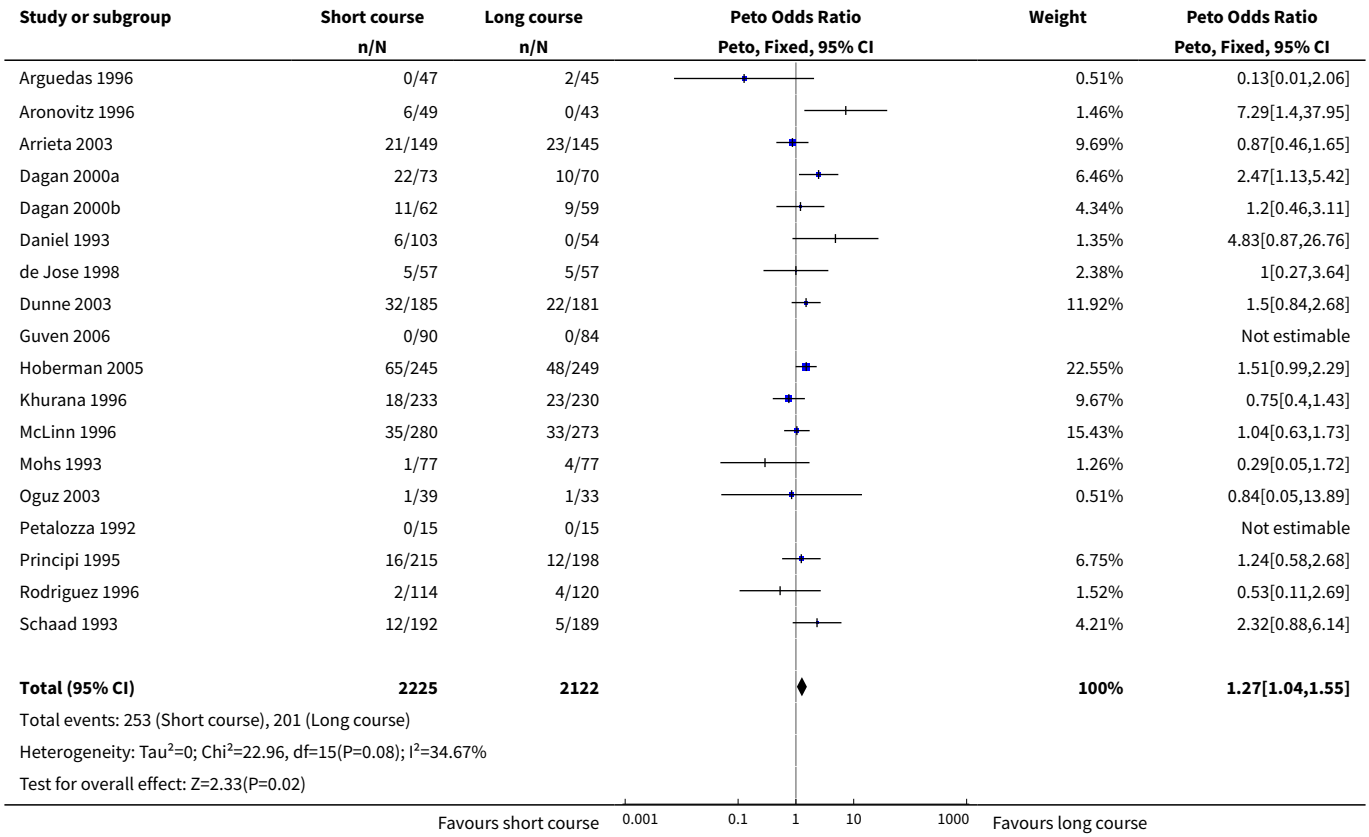
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure at 1 month or less	19	4354	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.02 [0.87, 1.20]
2 Treatment failure at 8 to 19 days	18	4347	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.27 [1.04, 1.55]
3 Treatment failure at 20 to 30 days	11	2708	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.82, 1.17]

Analysis 19.1. Comparison 19 Azithromycin 3 to 5 days short-term treatment, Outcome 1 Treatment failure at 1 month or less.



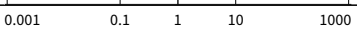


Analysis 19.2. Comparison 19 Azithromycin 3 to 5 days short-term treatment, Outcome 2 Treatment failure at 8 to 19 days.



Analysis 19.3. Comparison 19 Azithromycin 3 to 5 days short-term treatment, Outcome 3 Treatment failure at 20 to 30 days.

Study or subgroup	Short course n/N	Long course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Arguedas 1996	0/47	2/45		0.4%	0.13[0.01,2.06]
Arguedas 1997	0/50	2/47		0.4%	0.12[0.01,2.02]
Aronovitz 1996	8/45	7/35		2.46%	0.87[0.28,2.67]
Arrieta 2003	41/148	56/144		13.18%	0.61[0.37,0.98]
Dagan 2000a	23/67	19/65		5.85%	1.26[0.61,2.62]
Dunne 2003	48/182	56/180		15.08%	0.79[0.5,1.25]
Guven 2006	0/90	0/84			Not estimable
Hoberman 2005	93/245	79/249		22.79%	1.32[0.91,1.9]
Khurana 1996	75/225	57/209		18.65%	1.33[0.88,2]
McLinn 1996	70/264	74/257		21.18%	0.89[0.61,1.31]
Petalozza 1992	0/15	0/15			Not estimable
Total (95% CI)	**1378**	**1330**		**100%**	**0.98[0.82,1.17]**
Total events: 358 (Short course), 352 (Long course)					
Heterogeneity: Tau^2=0; Chi^2=14.1, df=8(P=0.08); I^2=43.27%					
Test for overall effect: Z=0.18(P=0.86)					



Comparison 20. Azithromycin 3 to 5 days short-term treatment, < 2 years old

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure at 1 month or less	2	138	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.92 [0.73, 5.04]

Analysis 20.1. Comparison 20 Azithromycin 3 to 5 days short-term treatment, < 2 years old, Outcome 1 Treatment failure at 1 month or less.

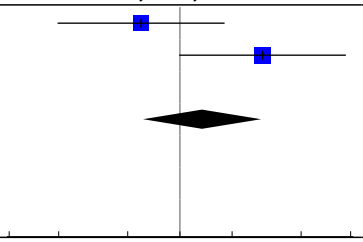
Study or subgroup	Short course n/N	Long course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Principi 1995	11/61	4/49		78.42%	2.29[0.77,6.83]
Schaad 1993	2/14	2/14		21.58%	1[0.13,8]
Total (95% CI)	**75**	**63**		**100%**	**1.92[0.73,5.04]**
Total events: 13 (Short course), 6 (Long course)					
Heterogeneity: Tau^2=0; Chi^2=0.48, df=1(P=0.49); I^2=0%					
Test for overall effect: Z=1.32(P=0.19)					

Comparison 21. Azithromycin 3 to 5 days short-term treatment, => 2 years old

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure at 1 month or less	2	656	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.34 [0.61, 2.94]

Analysis 21.1. Comparison 21 Azithromycin 3 to 5 days short-term treatment, => 2 years old, Outcome 1 Treatment failure at 1 month or less.

Study or subgroup	Short course n/N	Long course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Principi 1995	5/154	8/149		49.85%	0.6[0.2,1.81]
Schaad 1993	10/178	3/175		50.15%	3[0.99,9.06]
Total (95% CI)	**332**	**324**		**100%**	**1.34[0.61,2.94]**
Total events: 15 (Short course), 11 (Long course)					
Heterogeneity: Tau^2=0; Chi^2=4.07, df=1(P=0.04); I^2=75.42%					
Test for overall effect: Z=0.73(P=0.46)					

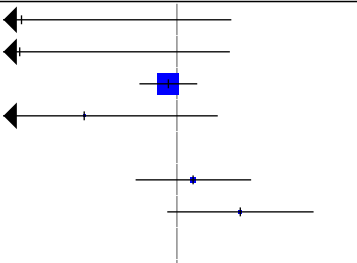


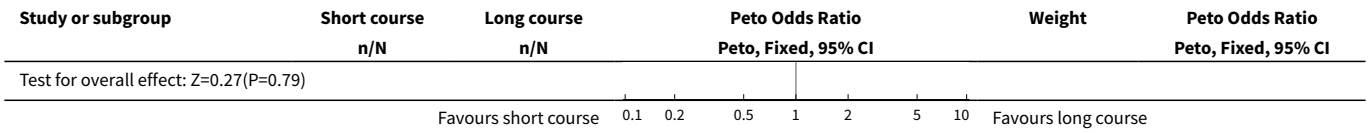
Comparison 22. Azithromycin 3-5 days short-term treatment; Sensitivity analysis: include chronic OM

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure at 1 month or less	7	1688	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.96 [0.70, 1.31]
2 Treatment failure at 20 to 30 days	4	740	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.83 [0.57, 1.21]

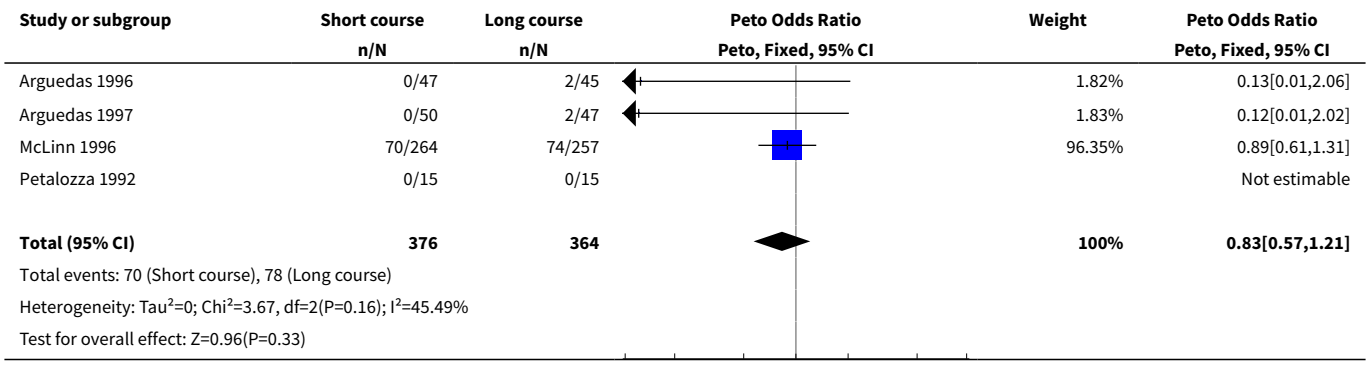
Analysis 22.1. Comparison 22 Azithromycin 3-5 days short-term treatment; Sensitivity analysis: include chronic OM, Outcome 1 Treatment failure at 1 month or less.

Study or subgroup	Short course n/N	Long course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Arguedas 1996	0/47	2/45		1.27%	0.13[0.01,2.06]
Arguedas 1997	0/50	2/47		1.27%	0.12[0.01,2.02]
McLinn 1996	70/264	74/257		67.08%	0.89[0.61,1.31]
Mohs 1993	1/77	4/77		3.13%	0.29[0.05,1.72]
Petalozza 1992	0/15	0/15			Not estimable
Principi 1995	16/215	12/198		16.79%	1.24[0.58,2.68]
Schaad 1993	12/192	5/189		10.46%	2.32[0.88,6.14]
Total (95% CI)	**860**	**828**		**100%**	**0.96[0.7,1.31]**
Total events: 99 (Short course), 99 (Long course)					
Heterogeneity: Tau^2=0; Chi^2=9.58, df=5(P=0.09); I^2=47.82%					





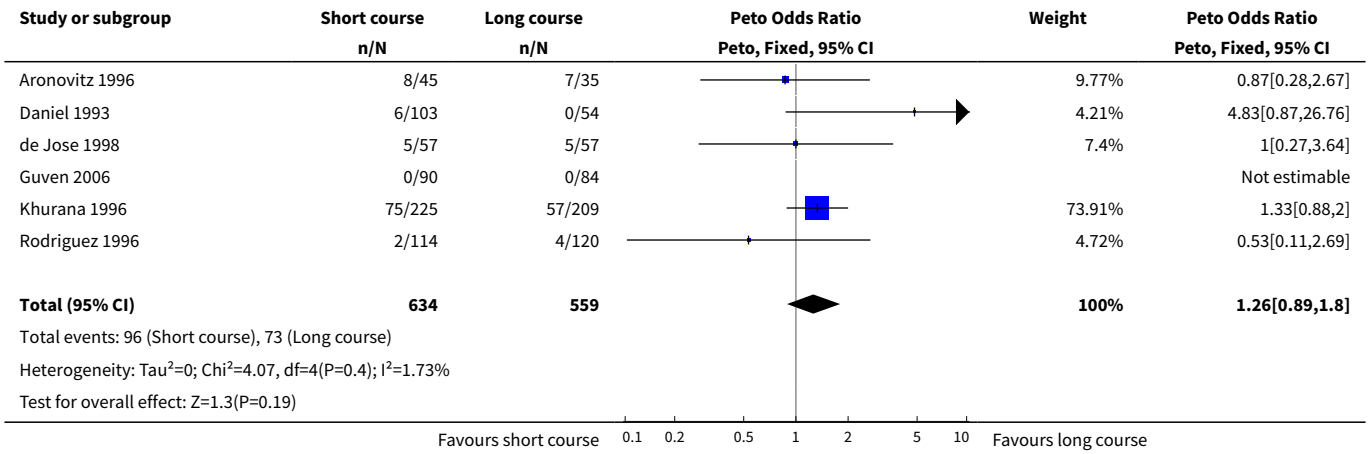
Analysis 22.2. Comparison 22 Azithromycin 3-5 days short-term treatment; Sensitivity analysis: include chronic OM, Outcome 2 Treatment failure at 20 to 30 days.



Comparison 23. Azithromycin 3 to 5 days short-term treatment; Sensitivity analysis: exclude chronic OM

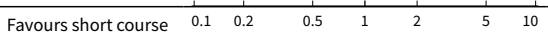
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Treatment failure at 1 month or less	6	1193	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.26 [0.89, 1.80]
2 Treatment failure at 20 to 30 days	3	688	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.27 [0.86, 1.86]

Analysis 23.1. Comparison 23 Azithromycin 3 to 5 days short-term treatment; Sensitivity analysis: exclude chronic OM, Outcome 1 Treatment failure at 1 month or less.



Analysis 23.2. Comparison 23 Azithromycin 3 to 5 days short-term treatment; Sensitivity analysis: exclude chronic OM, Outcome 2 Treatment failure at 20 to 30 days.

Study or subgroup	Short course n/N	Long course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Aronovitz 1996	8/45	7/35		11.67%	0.87[0.28,2.67]
Guven 2006	0/90	0/84			Not estimable
Khurana 1996	75/225	57/209		88.33%	1.33[0.88,2]
Total (95% CI)	**360**	**328**		**100%**	**1.27[0.86,1.86]**
Total events: 83 (Short course), 64 (Long course)					
Heterogeneity: Tau^2=0; Chi^2=0.5, df=1(P=0.48); I^2=0%					
Test for overall effect: Z=1.2(P=0.23)					

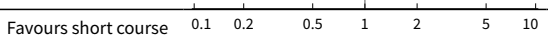


Comparison 24. Azithromycin 3 to 5 days short-term treatment; Sensitivity analysis: outcome only if "cured"

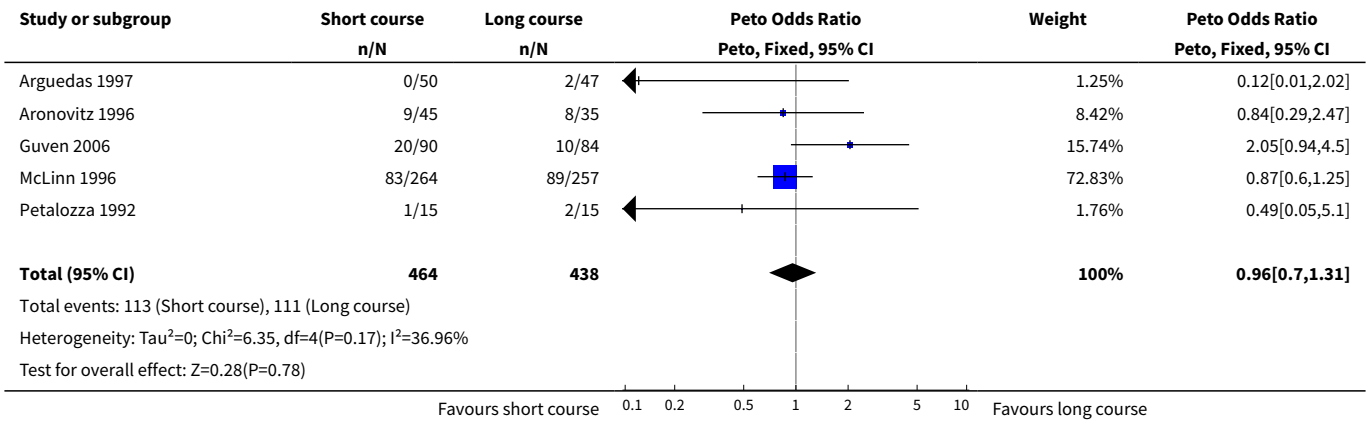
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Treatment failure at 1 month or less	11	2355	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.74 [0.61, 0.90]
2 Treatment failure at 20 to 30 days	5	902	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.96 [0.70, 1.31]

Analysis 24.1. Comparison 24 Azithromycin 3 to 5 days short-term treatment; Sensitivity analysis: outcome only if "cured", Outcome 1 Treatment failure at 1 month or less.

Study or subgroup	Short course n/N	Long course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Arguedas 1997	0/50	2/47		0.48%	0.12[0.01,2.02]
Aronovitz 1996	9/45	8/35		3.27%	0.84[0.29,2.47]
Daniel 1993	17/103	9/54		4.83%	0.99[0.41,2.39]
de Jose 1998	11/57	17/57		5.22%	0.57[0.24,1.33]
Guven 2006	20/90	10/84		6.11%	2.05[0.94,4.5]
McLinn 1996	83/264	89/257		28.28%	0.87[0.6,1.25]
Mohs 1993	16/77	32/77		8.15%	0.38[0.19,0.75]
Petalozza 1992	1/15	2/15		0.68%	0.49[0.05,5.1]
Principi 1995	32/215	53/198		16.55%	0.48[0.3,0.78]
Rodriguez 1996	17/114	34/120		9.81%	0.46[0.25,0.85]
Schaad 1993	47/192	41/189		16.62%	1.17[0.73,1.88]
Total (95% CI)	**1222**	**1133**		**100%**	**0.74[0.61,0.9]**
Total events: 253 (Short course), 297 (Long course)					
Heterogeneity: Tau^2=0; Chi^2=22.29, df=10(P=0.01); I^2=55.13%					
Test for overall effect: Z=3(P=0)					



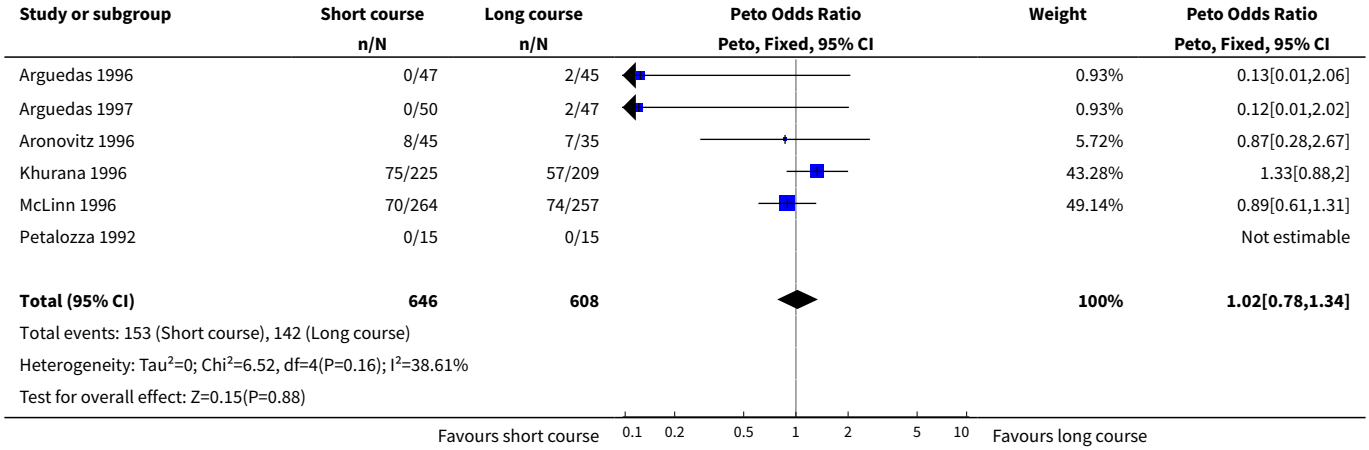
Analysis 24.2. Comparison 24 Azithromycin 3 to 5 days short-term treatment; Sensitivity analysis: outcome only if "cured", Outcome 2 Treatment failure at 20 to 30 days.



Comparison 25. Azithromycin 3 to 5 days short-term treatment; Sensitivity analysis: similar spectrum antibiotic in treatment arms

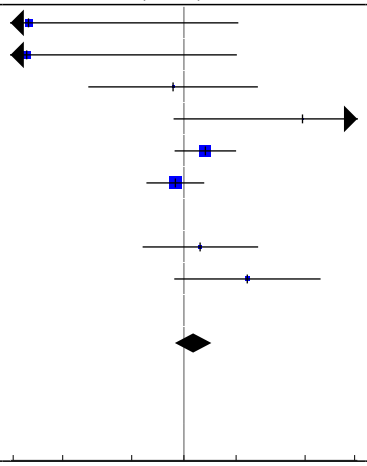
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Treatment failure at 20 to 30 days	6	1254	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.02 [0.78, 1.34]
2 Treatment failure at 1 month or less	9	2205	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.13 [0.89, 1.44]

Analysis 25.1. Comparison 25 Azithromycin 3 to 5 days short-term treatment; Sensitivity analysis: similar spectrum antibiotic in treatment arms, Outcome 1 Treatment failure at 20 to 30 days.



Analysis 25.2. Comparison 25 Azithromycin 3 to 5 days short-term treatment; Sensitivity analysis: similar spectrum antibiotic in treatment arms, Outcome 2 Treatment failure at 1 month or less.

Study or subgroup	Short course n/N	Long course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Arguedas 1996	0/47	2/45		0.76%	0.13[0.01,2.06]
Arguedas 1997	0/50	2/47		0.76%	0.12[0.01,2.02]
Aronovitz 1996	8/45	7/35		4.67%	0.87[0.28,2.67]
Daniel 1993	6/103	0/54		2.02%	4.83[0.87,26.76]
Khurana 1996	75/225	57/209		35.35%	1.33[0.88,2]
McLinn 1996	70/264	74/257		40.14%	0.89[0.61,1.31]
Petalozza 1992	0/15	0/15			Not estimable
Principi 1995	16/215	12/198		10.04%	1.24[0.58,2.68]
Schaad 1993	12/192	5/189		6.26%	2.32[0.88,6.14]
Total (95% CI)	**1156**	**1049**		**100%**	**1.13[0.89,1.44]**
Total events: 187 (Short course), 159 (Long course)					
Heterogeneity: Tau^2=0; Chi^2=12, df=7(P=0.1); I^2=41.68%					
Test for overall effect: Z=1(P=0.32)					

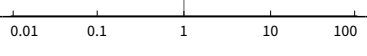


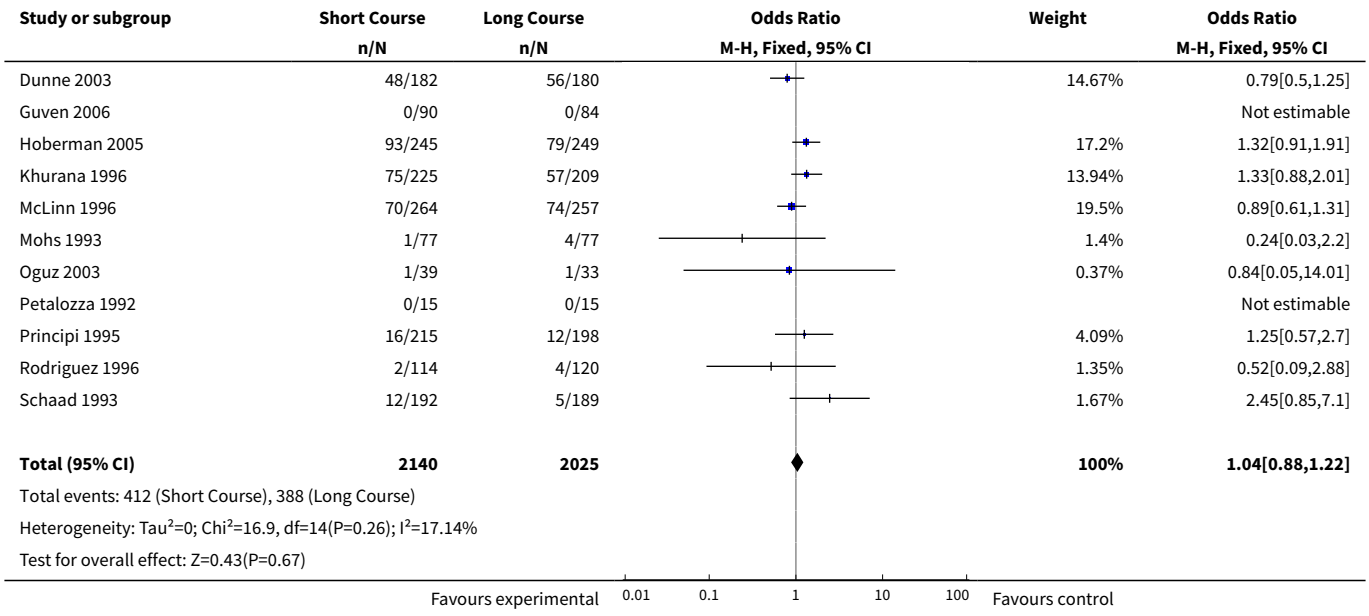
Comparison 26. Azithromycin 3 to 5 days short-term treatment; Sensitivity analysis: risk of bias

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Sensitivity analysis: allocation concealment unclear or high risk of bias	17	4165	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.88, 1.22]
2 Sensitivity analysis: allocation concealment low risk of bias	2	189	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.13 [0.02, 0.90]
3 Sensitivity analysis: blinding high and unclear risk of bias	15	3348	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.15 [0.94, 1.40]
4 Sensitivity analysis: blinding low risk of bias	4	1006	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.80 [0.60, 1.07]

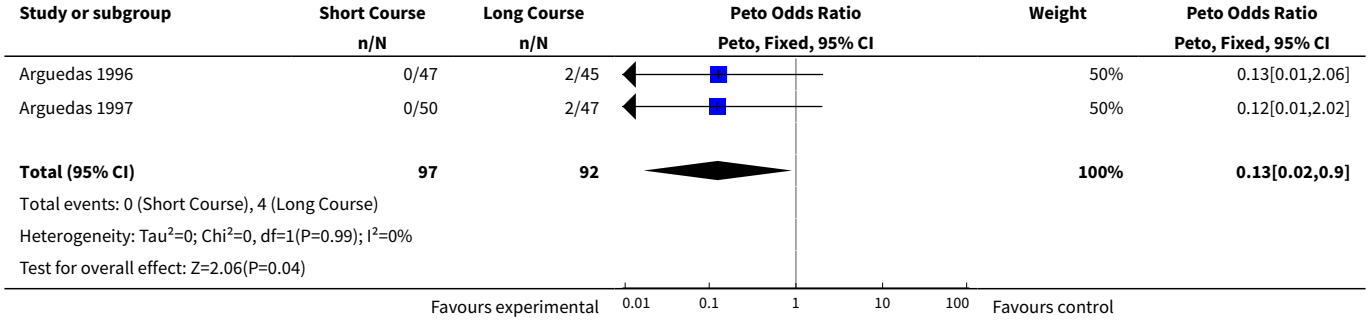
Analysis 26.1. Comparison 26 Azithromycin 3 to 5 days short-term treatment; Sensitivity analysis: risk of bias, Outcome 1 Sensitivity analysis: allocation concealment unclear or high risk of bias.

Study or subgroup	Short Course n/N	Long Course n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Arguedas 1996	8/45	7/35		2.29%	0.86[0.28,2.67]
Arrieta 2003	41/148	56/144		14.52%	0.6[0.37,0.98]
Dagan 2000a	23/67	19/65		4.48%	1.27[0.61,2.64]
Dagan 2000b	11/62	9/59		2.68%	1.2[0.46,3.14]
Daniel 1993	6/103	0/54		0.22%	7.27[0.4,131.47]
de Jose 1998	5/57	5/57		1.61%	1[0.27,3.66]

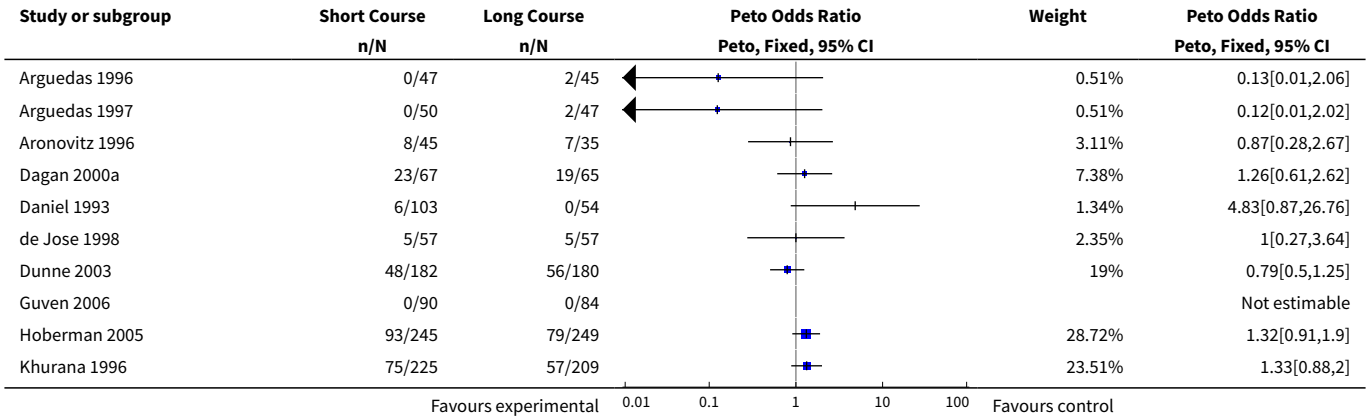


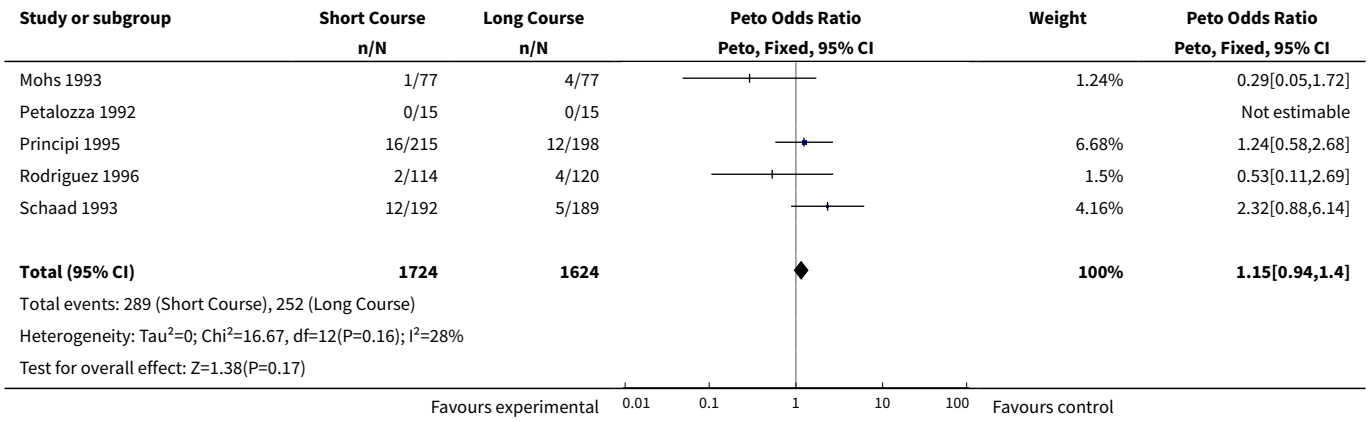


Analysis 26.2. Comparison 26 Azithromycin 3 to 5 days short-term treatment; Sensitivity analysis: risk of bias, Outcome 2 Sensitivity analysis: allocation concealment low risk of bias.

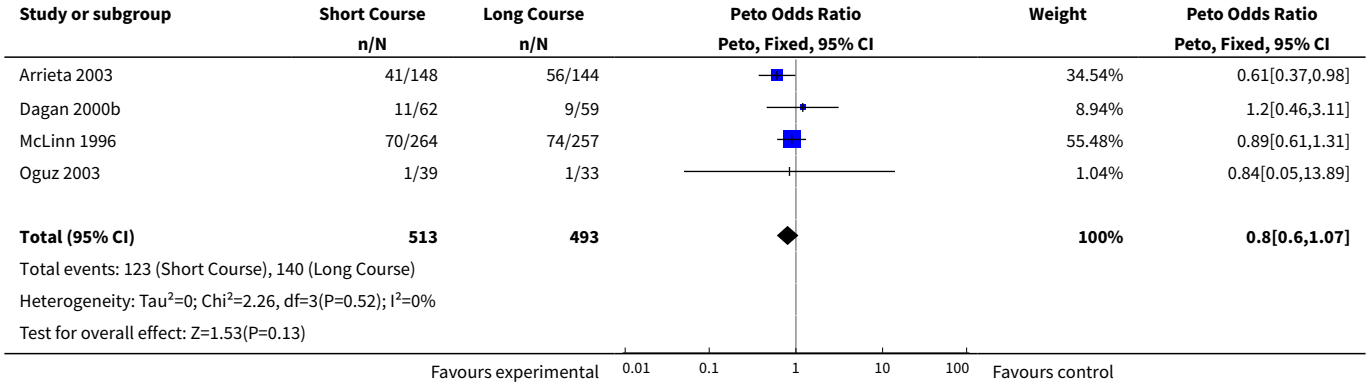


Analysis 26.3. Comparison 26 Azithromycin 3 to 5 days short-term treatment; Sensitivity analysis: risk of bias, Outcome 3 Sensitivity analysis: blinding high and unclear risk of bias.





Analysis 26.4. Comparison 26 Azithromycin 3 to 5 days short-term treatment; Sensitivity analysis: risk of bias, Outcome 4 Sensitivity analysis: blinding low risk of bias.

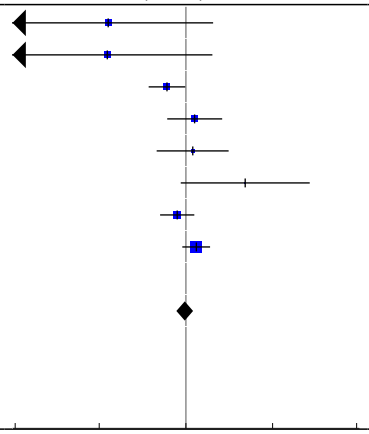


Comparison 27. Azithromycin 3 to 5 days short-term treatment; Sensitivity analysis: industry funding

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Treatment failure 1 month or less	8	1747	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.97 [0.78, 1.21]
2 Treatment failure at 8 to 19	7	1667	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.43 [1.10, 1.87]
3 Treatment failure at 20 to 30 days	6	1469	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.93 [0.74, 1.17]

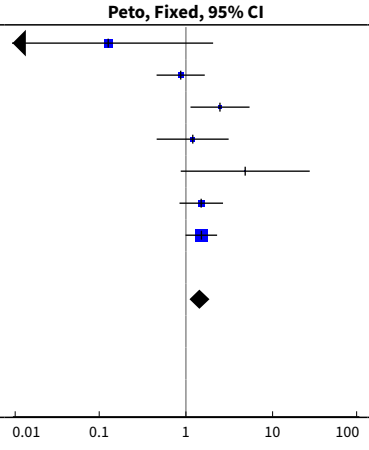
Analysis 27.1. Comparison 27 Azithromycin 3 to 5 days short-term treatment; Sensitivity analysis: industry funding, Outcome 1 Treatment failure 1 month or less.

Study or subgroup	Short course n/N	Long course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Arguedas 1996	0/47	2/45		0.65%	0.13[0.01,2.06]
Arguedas 1997	0/50	2/47		0.65%	0.12[0.01,2.02]
Arrieta 2003	41/148	56/144		21.2%	0.61[0.37,0.98]
Dagan 2000a	23/67	19/65		9.41%	1.26[0.61,2.62]
Dagan 2000b	11/62	9/59		5.49%	1.2[0.46,3.11]
Daniel 1993	6/103	0/54		1.71%	4.83[0.87,26.76]
Dunne 2003	48/182	56/180		24.25%	0.79[0.5,1.25]
Hoberman 2005	93/245	79/249		36.65%	1.32[0.91,1.9]
Total (95% CI)	**904**	**843**		**100%**	**0.97[0.78,1.21]**
Total events: 222 (Short course), 223 (Long course)					
Heterogeneity: Tau^2=0; Chi^2=15.17, df=7(P=0.03); I^2=53.86%					
Test for overall effect: Z=0.26(P=0.79)					



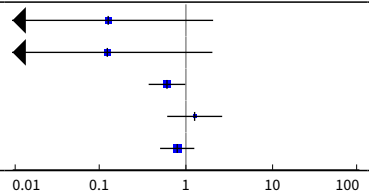
Analysis 27.2. Comparison 27 Azithromycin 3 to 5 days short-term treatment; Sensitivity analysis: industry funding, Outcome 2 Treatment failure at 8 to 19.

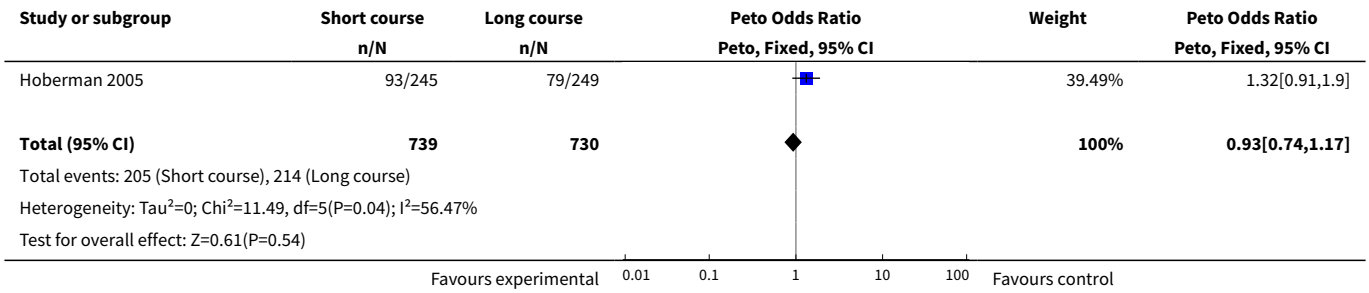
Study or subgroup	Short course n/N	Long course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Arguedas 1996	0/47	2/45		0.9%	0.13[0.01,2.06]
Arrieta 2003	21/149	23/145		17.06%	0.87[0.46,1.65]
Dagan 2000a	22/73	10/70		11.36%	2.47[1.13,5.42]
Dagan 2000b	11/62	9/59		7.64%	1.2[0.46,3.11]
Daniel 1993	6/103	0/54		2.38%	4.83[0.87,26.76]
Dunne 2003	32/185	22/181		20.97%	1.5[0.84,2.68]
Hoberman 2005	65/245	48/249		39.68%	1.51[0.99,2.29]
Total (95% CI)	**864**	**803**		**100%**	**1.43[1.1,1.87]**
Total events: 157 (Short course), 114 (Long course)					
Heterogeneity: Tau^2=0; Chi^2=9.26, df=6(P=0.16); I^2=35.22%					
Test for overall effect: Z=2.67(P=0.01)					



Analysis 27.3. Comparison 27 Azithromycin 3 to 5 days short-term treatment; Sensitivity analysis: industry funding, Outcome 3 Treatment failure at 20 to 30 days.

Study or subgroup	Short course n/N	Long course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Arguedas 1996	0/47	2/45		0.7%	0.13[0.01,2.06]
Arguedas 1997	0/50	2/47		0.7%	0.12[0.01,2.02]
Arrieta 2003	41/148	56/144		22.85%	0.61[0.37,0.98]
Dagan 2000a	23/67	19/65		10.14%	1.26[0.61,2.62]
Dunne 2003	48/182	56/180		26.13%	0.79[0.5,1.25]

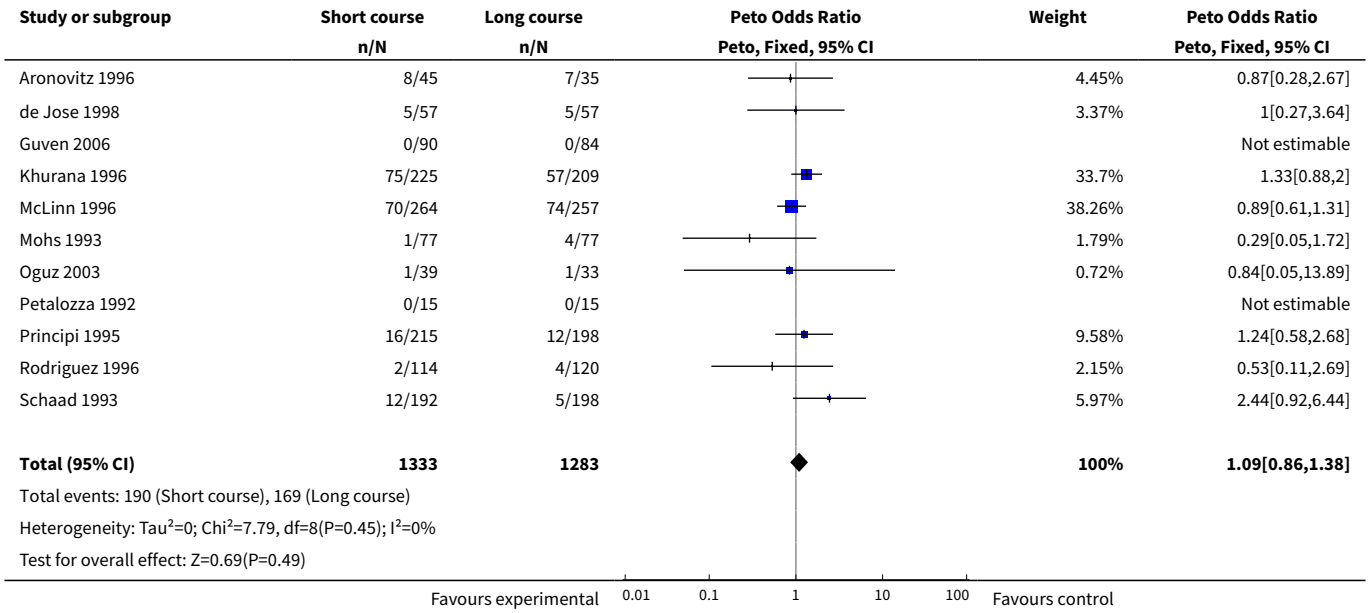




Comparison 28. Azithromycin 3 to 5 days short-term treatment; Sensitivity analysis: funding not reported

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure 1 month or less	11	2616	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.09 [0.86, 1.38]
2 Treatment failure at 8 to 19 days	11	2680	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.08 [0.80, 1.46]
3 Treatment failure at 20 to 30 days	5	1239	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.06 [0.81, 1.39]

Analysis 28.1. Comparison 28 Azithromycin 3 to 5 days short-term treatment; Sensitivity analysis: funding not reported, Outcome 1 Treatment failure 1 month or less.



Analysis 28.2. Comparison 28 Azithromycin 3 to 5 days short-term treatment; Sensitivity analysis: funding not reported, Outcome 2 Treatment failure at 8 to 19 days.

Study or subgroup	Short course n/N	Long course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Aronovitz 1996	6/49	0/43		3.38%	7.29[1.4,37.95]
de Jose 1998	5/57	5/57		5.51%	1[0.27,3.64]
Guven 2006	0/90	0/84			Not estimable
Khurana 1996	18/233	23/230		22.41%	0.75[0.4,1.43]
McLinn 1996	35/280	33/273		35.74%	1.04[0.63,1.73]
Mohs 1993	1/77	4/77		2.91%	0.29[0.05,1.72]
Oguz 2003	1/39	1/33		1.17%	0.84[0.05,13.89]
Petalozza 1992	0/15	0/15			Not estimable
Principi 1995	16/215	12/198		15.63%	1.24[0.58,2.68]
Rodriguez 1996	2/114	4/120		3.51%	0.53[0.11,2.69]
Schaad 1993	12/192	5/189		9.74%	2.32[0.88,6.14]
Total (95% CI)	**1361**	**1319**		**100%**	**1.08[0.8,1.46]**
Total events: 96 (Short course), 87 (Long course)					
Heterogeneity: Tau^2=0; Chi^2=11.75, df=8(P=0.16); I^2=31.94%					
Test for overall effect: Z=0.48(P=0.63)					

Analysis 28.3. Comparison 28 Azithromycin 3 to 5 days short-term treatment; Sensitivity analysis: funding not reported, Outcome 3 Treatment failure at 20 to 30 days.

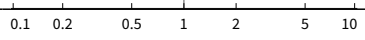
Study or subgroup	Short course n/N	Long course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Aronovitz 1996	8/45	7/35		5.83%	0.87[0.28,2.67]
Guven 2006	0/90	0/84			Not estimable
Khurana 1996	75/225	57/209		44.1%	1.33[0.88,2]
McLinn 1996	70/264	74/257		50.07%	0.89[0.61,1.31]
Petalozza 1992	0/15	0/15			Not estimable
Total (95% CI)	**639**	**600**		**100%**	**1.06[0.81,1.39]**
Total events: 153 (Short course), 138 (Long course)					
Heterogeneity: Tau^2=0; Chi^2=2.08, df=2(P=0.35); I^2=4.07%					
Test for overall effect: Z=0.44(P=0.66)					

Comparison 29. Azithromycin 3 to 5 days short-term treatment, adverse GI effects

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Gastrointestinal adverse effects	14	3722	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.36 [0.28, 0.46]

Analysis 29.1. Comparison 29 Azithromycin 3 to 5 days short-term treatment, adverse GI effects, Outcome 1 Gastrointestinal adverse effects.

Study or subgroup	Short course n/N	Long course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Arguedas 1996	3/47	14/45		5.67%	0.2[0.07,0.56]
Arrieta 2003	44/153	59/147		27.46%	0.6[0.38,0.97]
Dagan 2000a	5/120	19/118		8.77%	0.27[0.12,0.63]
Daniel 1993	9/157	0/54		2.67%	4.04[0.88,18.61]
de Jose 1998	5/57	9/57		5.01%	0.52[0.17,1.6]
Guven 2006	4/90	4/84		3.1%	0.93[0.23,3.83]
Khurana 1996	3/263	25/263		10.75%	0.19[0.09,0.41]
McLinn 1996	8/340	54/334		22.82%	0.19[0.11,0.32]
Mohs 1993	0/77	3/77		1.2%	0.13[0.01,1.29]
Oguz 2003	1/41	1/37		0.8%	0.9[0.06,14.72]
Petalozza 1992	0/15	0/15			Not estimable
Principi 1995	6/243	13/240		7.4%	0.46[0.18,1.15]
Rodriguez 1996	1/125	7/134		3.15%	0.23[0.06,0.94]
Schaad 1993	2/197	1/192		1.21%	1.9[0.2,18.42]
Total (95% CI)	**1925**	**1797**		**100%**	**0.36[0.28,0.46]**
Total events: 91 (Short course), 209 (Long course)					
Heterogeneity: Tau^2=0; Chi^2=30.26, df=12(P=0); I^2=60.34%					
Test for overall effect: Z=8.01(P<0.0001)					



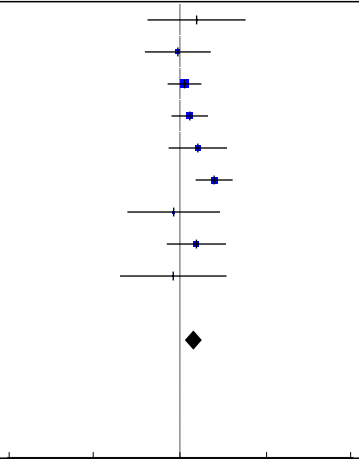
Comparison 30. Methods - combined control group versus twice counting tx

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Twice counting - short-acting antibiotic > 48 hours short-term treatment, treatment failure at 1 month or less	9	2249	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.43 [1.14, 1.79]
2 Combined control groups - short-acting antibiotic > 48 hours short-term treatment, treatment failure 1 month or less	9	2611	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.36 [1.10, 1.67]
3 Twice counting - short-acting antibiotic > 48 hours short-term treatment, treatment failure at 1 to 19 days	4	1138	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.52 [1.11, 2.10]
4 Combined control groups - short-acting antibiotic > 48 hours short-term treatment, treatment failure 1 to 19 days	4	1327	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.45 [1.08, 1.95]
5 Twice counting - short-acting antibiotic > 48 hours short-term treatment, treatment failure 20 to 30 days	7	1632	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.26 [0.97, 1.64]
6 Combined control groups - short-acting antibiotic > 48 hours short-term treatment, treatment failure at 20 to 30 days	7	1805	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.22 [0.95, 1.57]
7 Twice counting - short-acting antibiotic > 48 hours short-term treatment, treatment failure at 30 to 40 days	2	538	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.07 [0.74, 1.55]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
8 Combined control groups - short-acting antibiotic > 48 hours short-term treatment, treatment failure 30 to 40 days	2	686	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.12 [0.80, 1.57]
9 Twice counting - short-acting antibiotic > 48 hours short-term treatment, treatment failure at 3 months or less	4	745	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.10 [0.80, 1.50]
10 Combined control groups - short-acting antibiotic > 48 hours short-term treatment, treatment failure at 3 months or less	4	893	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.13 [0.85, 1.51]

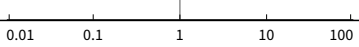
Analysis 30.1. Comparison 30 Methods - combined control group versus twice counting tx, Outcome 1 Twice counting - short-acting antibiotic > 48 hours short-term treatment, treatment failure at 1 month or less.

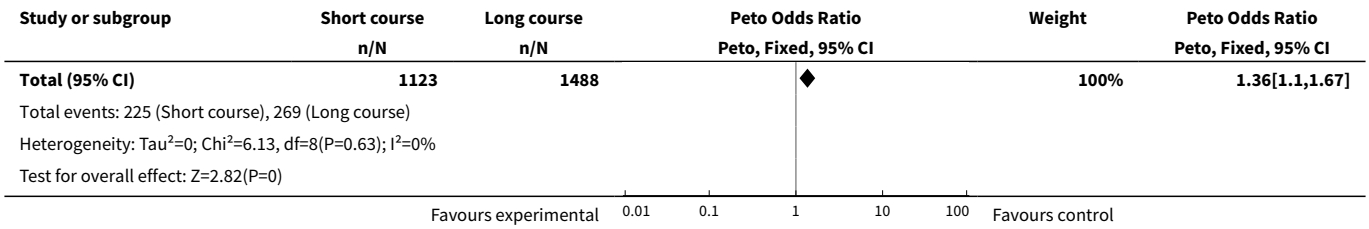
Study or subgroup	Short course n/N	Long course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Adam 1996	6/48	4/48		2.99%	1.56[0.42,5.72]
Boulesteix 1995	11/124	11/118		6.64%	0.95[0.39,2.27]
Cohen 1997	60/166	56/168		25.11%	1.13[0.72,1.77]
Gooch 1996	46/147	46/177		21.67%	1.3[0.8,2.11]
Hendrickse 1988	20/62	15/66		8.47%	1.61[0.74,3.49]
Hoberman 1997	57/197	24/178		21%	2.48[1.52,4.06]
Ingvarsson 1982	5/66	6/68		3.36%	0.85[0.25,2.9]
Kafetzis 1997	16/286	10/274		8.21%	1.55[0.71,3.4]
Ploussard 1984	4/27	5/29		2.54%	0.84[0.2,3.45]
Total (95% CI)	**1123**	**1126**		**100%**	**1.43[1.14,1.79]**
Total events: 225 (Short course), 177 (Long course)					
Heterogeneity: Tau^2=0; Chi^2=8.28, df=8(P=0.41); I^2=3.35%					
Test for overall effect: Z=3.08(P=0)					



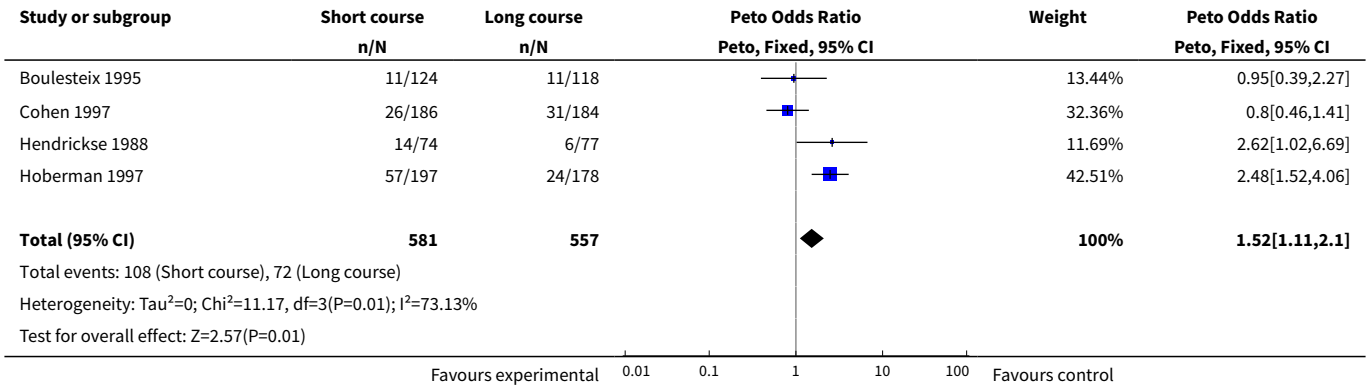
Analysis 30.2. Comparison 30 Methods - combined control group versus twice counting tx, Outcome 2 Combined control groups - short-acting antibiotic > 48 hours short-term treatment, treatment failure 1 month or less.

Study or subgroup	Short course n/N	Long course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Adam 1996	6/48	4/48		2.62%	1.56[0.42,5.72]
Boulesteix 1995	11/124	11/118		5.81%	0.95[0.39,2.27]
Cohen 1997	60/166	56/168		21.99%	1.13[0.72,1.77]
Gooch 1996	46/147	98/350		24.73%	1.17[0.77,1.79]
Hendrickse 1988	20/62	15/66		7.42%	1.61[0.74,3.49]
Hoberman 1997	57/197	64/367		25.07%	1.98[1.3,3.01]
Ingvarsson 1982	5/66	6/68		2.95%	0.85[0.25,2.9]
Kafetzis 1997	16/286	10/274		7.19%	1.55[0.71,3.4]
Ploussard 1984	4/27	5/29		2.22%	0.84[0.2,3.45]

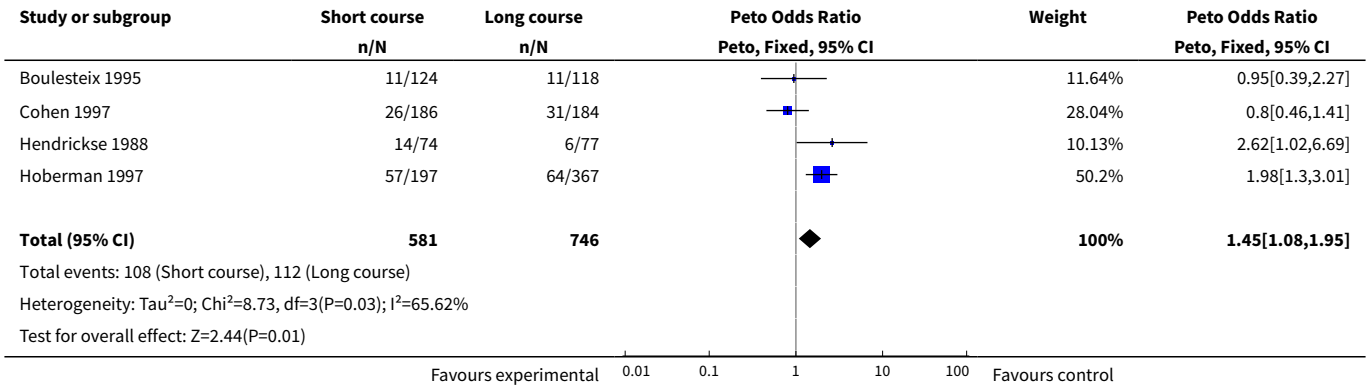




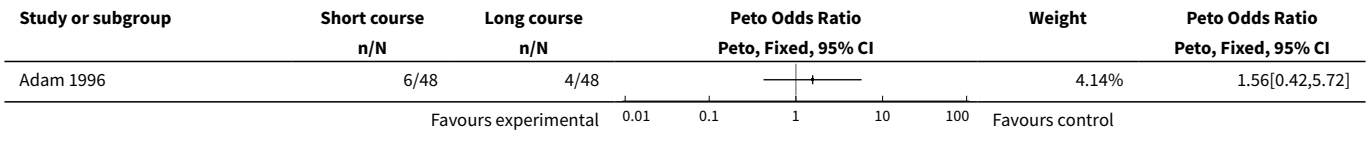
Analysis 30.3. Comparison 30 Methods - combined control group versus twice counting tx, Outcome 3 Twice counting - short-acting antibiotic > 48 hours short-term treatment, treatment failure at 1 to 19 days.

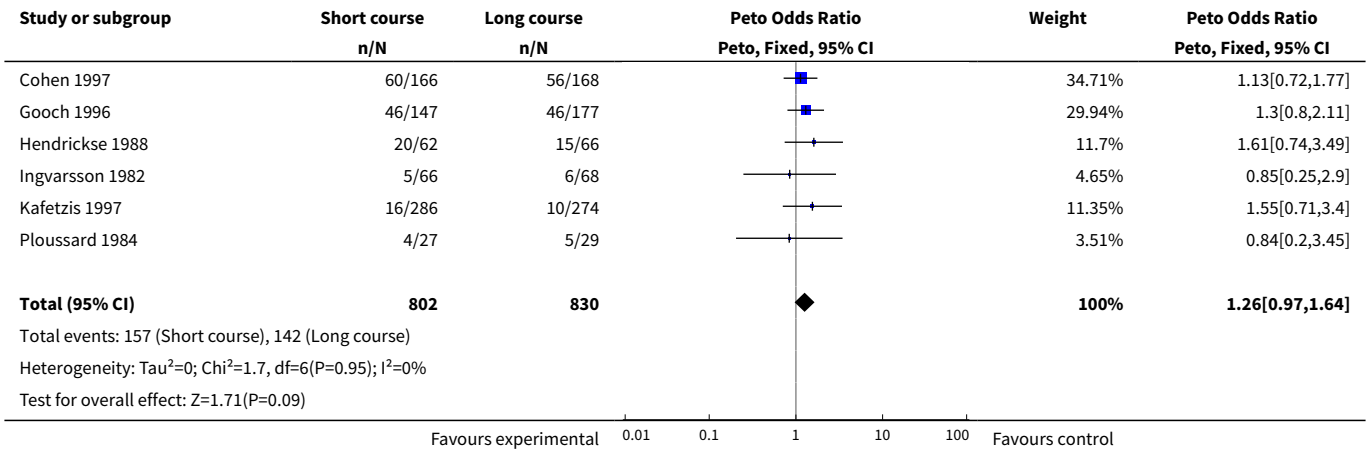


Analysis 30.4. Comparison 30 Methods - combined control group versus twice counting tx, Outcome 4 Combined control groups - short-acting antibiotic > 48 hours short-term treatment, treatment failure 1 to 19 days.

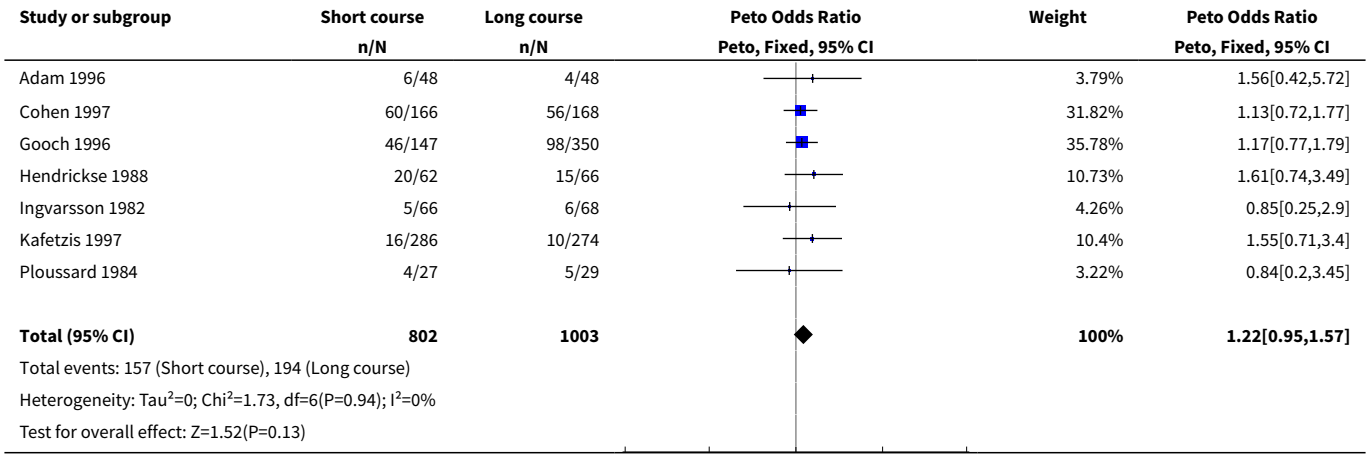


Analysis 30.5. Comparison 30 Methods - combined control group versus twice counting tx, Outcome 5 Twice counting - short-acting antibiotic > 48 hours short-term treatment, treatment failure 20 to 30 days.

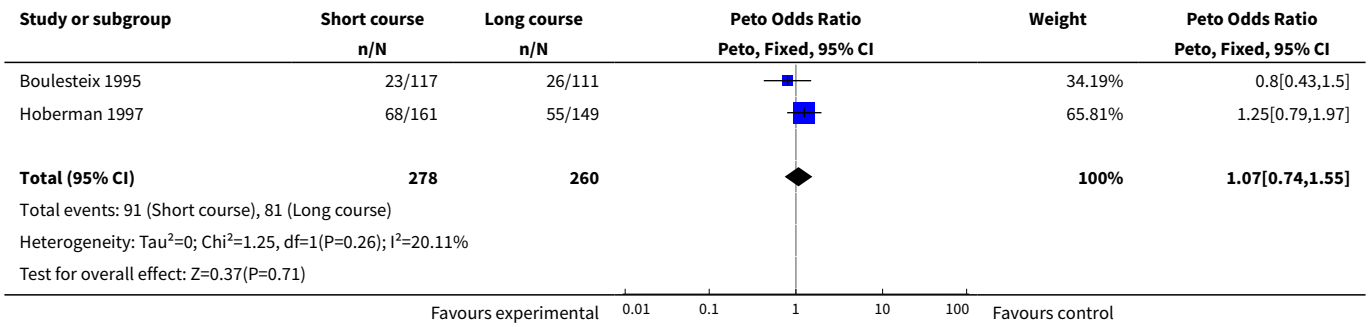




Analysis 30.6. Comparison 30 Methods - combined control group versus twice counting tx, Outcome 6 Combined control groups - short-acting antibiotic > 48 hours short-term treatment, treatment failure at 20 to 30 days.

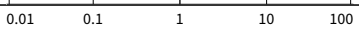


Analysis 30.7. Comparison 30 Methods - combined control group versus twice counting tx, Outcome 7 Twice counting - short-acting antibiotic > 48 hours short-term treatment, treatment failure at 30 to 40 days.



Analysis 30.8. Comparison 30 Methods - combined control group versus twice counting tx, Outcome 8 Combined control groups - short-acting antibiotic > 48 hours short-term treatment, treatment failure 30 to 40 days.

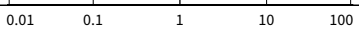
Study or subgroup	Short course n/N	Long course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Boulesteix 1995	23/117	26/111		28.05%	0.8[0.43,1.5]
Hoberman 1997	68/161	108/297		71.95%	1.28[0.86,1.9]
Total (95% CI)	**278**	**408**		**100%**	**1.12[0.8,1.57]**
Total events: 91 (Short course), 134 (Long course)					
Heterogeneity: Tau^2=0; Chi^2=1.53, df=1(P=0.22); I^2=34.77%					
Test for overall effect: Z=0.68(P=0.5)					



Favours experimental — Favours control

Analysis 30.9. Comparison 30 Methods - combined control group versus twice counting tx, Outcome 9 Twice counting - short-acting antibiotic > 48 hours short-term treatment, treatment failure at 3 months or less.

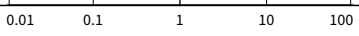
Study or subgroup	Short course n/N	Long course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Boulesteix 1995	23/117	26/111		24.29%	0.8[0.43,1.5]
de Saintongue 1982	10/38	10/41		9.5%	1.11[0.4,3.03]
Hendrickse 1988	26/62	25/66		19.44%	1.18[0.58,2.39]
Hoberman 1997	68/161	55/149		46.76%	1.25[0.79,1.97]
Total (95% CI)	**378**	**367**		**100%**	**1.1[0.8,1.5]**
Total events: 127 (Short course), 116 (Long course)					
Heterogeneity: Tau^2=0; Chi^2=1.31, df=3(P=0.73); I^2=0%					
Test for overall effect: Z=0.58(P=0.56)					



Favours experimental — Favours control

Analysis 30.10. Comparison 30 Methods - combined control group versus twice counting tx, Outcome 10 Combined control groups - short-acting antibiotic > 48 hours short-term treatment, treatment failure at 3 months or less.

Study or subgroup	Short course n/N	Long course n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Boulesteix 1995	23/117	26/111		21.03%	0.8[0.43,1.5]
de Saintongue 1982	10/38	10/41		8.23%	1.11[0.4,3.03]
Hendrickse 1988	26/62	25/66		16.82%	1.18[0.58,2.39]
Hoberman 1997	68/161	108/297		53.93%	1.28[0.86,1.9]
Total (95% CI)	**378**	**515**		**100%**	**1.13[0.85,1.51]**
Total events: 127 (Short course), 169 (Long course)					
Heterogeneity: Tau^2=0; Chi^2=1.55, df=3(P=0.67); I^2=0%					
Test for overall effect: Z=0.84(P=0.4)					



Favours experimental — Favours control

APPENDICES

Appendix 1. Previous searches

The research librarian, in collaboration with the research team, developed and implemented search strategies designed to identify the highest quality of evidence for this review. The English and non-English language medical literature was searched using the MEDLINE and EMBASE databases to identify published clinical trials of AOM during the time period, January 1966 to July 1997. The Science Citation Index was utilised to identify additional trials which had cited relevant papers. The Current Contents/Life Sciences Index was searched for recently published AOM trials, not yet abstracted in MEDLINE.

Search updates were conducted with a modified search strategy using the following electronic resources for the years 1997 to August 2008 (exceptions stated in brackets) and no language restriction: MEDLINE, EMBASE, MEDLINE In-Process & Other Non-Indexed Citations, Cochrane Central Register of Controlled Trials (which contains the Cochrane Acute Respiratory Infections Group; this group handsearches journals pertinent to their content area and adds relevant trials to the registry), and International Pharmaceutical Abstracts, BIOSIS Previews (ISI Web of Knowledge^{SM} [3.0]), CINAHL Full Text (via EBSCOhost). The NLM (National Library of Medicine) Gateway, BioMed Central and OCLC PapersFirst and ProceedingsFirst were searched for identification of meeting abstracts. Additionally, trials registers such as Current Controlled Trials, ClinicalTrials.gov, the National Research Register, CRISP (Computer Retrieval of Information on Scientific Projects), the TRIP Database (Turning Research Into Practice), Scirus, Proquest Dissertations and Theses - Full Text (1861 to 2008), and Google Scholar were searched for additional unpublished controlled trials and reports. The reference lists of relevant reviews and included studies were reviewed, and authors of included studies were contacted, as required (e.g. to clarify the source of population in cases of multiple publications or to seek additional data).

For the search strategies, a combination of subject headings and keywords were adapted for each electronic resource using the following terms: ‘otitis media’, ‘acute otitis media’, ‘ear infection’, ‘otorrhea’, ‘anti-infective agents’, ‘treatment outcome’, ‘antibacterial’, ‘antibiotic’, ‘bacteriocide’ and ‘antimicrobial’.

Appendix 2. Search strategies for 1997-2008 update

Electronic databases	Search strategies
MEDLINE OVID Version: rel10.5.2 1950 to August Week 2008 Searched: 1 August 2008 Results: 1892 Limits: Date: 1997 to 2008	1. exp Otitis Media/ 2. (acute adj5 (OM or otitis media or ear or infection?)).mp. 3. (OM or OME or AOM).ti,ab. 4. otorrh?ea.ti,ab. 5. or/1-4 6. exp Anti-Infective Agents/ 7. exp treatment outcome/ 8. (antibacter$ or anti-bacter$ or "anti bacter$" or antibiotic$ or anti-biotic$ or "anti biotic$" or bacteriocid$ or antimicrob$ or anti-microb$ or "anti microb$").mp. 9. or/6-8 10. clinical trial.pt. 11. randomized controlled trial.pt. 12. randomi?ed.ti,ab. 13. placebo.ti,ab. 14. dt.fs. 15. randomly.ti,ab. 16. trial.ti,ab. 17. groups.ti,ab. 18. or/10-17 19. animals/ 20. humans/ 21. 19 not (19 and 20) 22. 18 not 21 23. and/5,9,22 24. exp Infant/ 25. exp Child/ 26. Adolescent/ 27. Minors/ 28. exp Puberty/ 29. exp Pediatrics/

(Continued)

	30. infant$.mp. 31. infancy.mp. 32. newborn$.mp. 33. baby.mp. 34. babies.mp. 35. neonat$.mp. 36. preterm$.mp. 37. prematur$.mp. 38. postmatur$.mp. 39. child$.mp. 40. kid.mp. 41. kids.mp. 42. toddler$.mp. 43. adolescen$.mp. 44. teen$.mp. 45. boy$.mp. 46. girl.mp. 47. minor$.mp. 48. pubert$.mp. 49. pubescen$.mp. 50. prepubescen$.mp. 51. pediatric$.mp. 52. paediatric$.mp. 53. peadiatric$.mp. 54. or/24-52 55. and/5,9,22,54 56. limit 55 to yr="1997 - 2007"
Ovid MEDLINE In-Process & Other Non-Indexed Citations OVID Version: rel10.5.2 1 August 2008 Searched: 1 August 2008 Results: 6 Limits: Date: 1997 to 2008	1. (acute adj5 (OM or otitis media or ear or infection?)).mp. 2. (OM or OME or AOM).ti,ab. 3. otorrh?ea.ti,ab. 4. or/1-3 5. (antibacter$ or anti-bacter$ or "anti bacter$" or antibiotic$ or anti-biotic$ or "anti biotic$" or bacteriocid$ or antimicrob$ or anti-microb$ or "anti microb$").mp. 6. (treatment adj5 outcome?).mp. [mp=title, original title, abstract, name of substance word, subject heading word] 7. or/5-6 8. "controlled clinical trial$".mp. 9. "randomi?ed controlled trial$".mp. 10. "research design$".mp. 11. "clinical research".mp. 12. "random allocation".mp. 13. randomi?ed.ti,ab. 14. ("double blind" adj3 method$).mp. 15. ("single blind" adj3 method$).mp. 16. ((clin$ or control$) adj25 trial$).mp. 17. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. 18. placebo$.ti,ab. 19. randomly.ti,ab. 20. or/8-19 21. infant$.mp. 22. infancy.mp. 23. newborn$.mp. 24. baby.mp. 25. babies.mp. 26. neonat$.mp. 27. preterm$.mp. 28. prematur$.mp. 29. postmatur$.mp. 30. child$.mp. 31. kid.mp.

(Continued)

	32. kids.mp. 33. toddler$.mp. 34. adolescen$.mp. 35. teen$.mp. 36. boy$.mp. 37. girl.mp. 38. minor$.mp. 39. pubert$.mp. 40. pubescen$.mp. 41. prepubescen$.mp. 42. pediatric$.mp. 43. paediatric$.mp. 44. peadiatric$.mp. 45. or/21-44 46. and/4,7,20,45 47. limit 46 to yr="1997 - 2007"
EMBASE OVID Version: rel10.5.2 1996 to 2008 Searched: 1 August 2008 Results: 2993 Limits: Date: 1997 to 2008	1. exp Otitis Media/ 2. (acute adj5 (OM or otitis media or ear or infection?)).mp. 3. (OM or OME or AOM).ti,ab. 4. otorrh?ea.ti,ab. 5. or/1-4 6. exp Antiinfective Agent/ 7. exp treatment outcome/ 8. (antibacter$ or anti-bacter$ or "anti bacter$" or antibiotic$ or anti-biotic$ or "anti biotic$" or bacteriocid$ or antimicrob$ or anti-microb$ or "anti microb$").mp. 9. or/6-8 10. exp clinical trial/ 11. randomi?ed.ti,ab. 12. placebo.ti,ab. 13. dt.fs. 14. randomly.ti,ab. 15. trial.ti,ab. 16. groups.ti,ab. 17. or/10-16 18. exp child/ 19. exp newborn/ 20. exp adolescent/ 21. exp puberty/ 22. exp pediatrics/ 23. infant$.mp. 24. infancy.mp. 25. newborn$.mp. 26. baby.mp. 27. babies.mp. 28. neonat$.mp. 29. preterm$.mp. 30. prematur$.mp. 31. postmatur$.mp. 32. child$.mp. 33. kid.mp. 34. kids.mp. 35. toddler$.mp. 36. adolescen$.mp. 37. teen$.mp. 38. boy$.mp. 39. girl.mp. 40. minor$.mp. 41. pubert$.mp. 42. pubescen$.mp. 43. prepubescen$.mp.

(Continued)

	44. pediatric$.mp. 45. paediatric$.mp. 46. peadiatric$.mp. 47. or/18-46 48. and/5,9,17,47 49. limit 48 to yr="1997 - 2007"
International Pharmaceutical Abstracts OVID Version: rel10.5.2 1970 to August 2008 Searched: 1 August 2008 Results: 45 Limits: Date: 1997 to 2008	1. (acute adj5 (OM or otitis media or ear or infection?)).mp. 2. (OM or OME or AOM).ti,ab. 3. otorrh?ea.ti,ab. 4. or/1-3 5. (antibacter$ or anti-bacter$ or "anti bacter$" or antibiotic$ or anti-biotic$ or "anti biotic$" or bacteriocid$ or antimicrob$ or anti-microb$ or "anti microb$").mp. 6. (treatment adj5 outcome?).mp. [mp=title, original title, abstract, name of substance word, subject heading word] 7. or/5-6 8. "controlled clinical trial$".mp. 9. "randomi?ed controlled trial$".mp. 10. "research design$".mp. 11. "clinical research".mp. 12. "random allocation".mp. 13. randomi?ed.ti,ab. 14. ("double blind" adj3 method$).mp. 15. ("single blind" adj3 method$).mp. 16. ((clin$ or control$) adj25 trial$).mp. 17. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. 18. placebo$.ti,ab. 19. randomly.ti,ab. 20. or/8-19 21. infant$.mp. 22. infancy.mp. 23. newborn$.mp. 24. baby.mp. 25. babies.mp. 26. neonat$.mp. 27. preterm$.mp. 28. prematur$.mp. 29. postmatur$.mp. 30. child$.mp. 31. kid.mp. 32. kids.mp. 33. toddler$.mp. 34. adolescen$.mp. 35. teen$.mp. 36. boy$.mp. 37. girl.mp. 38. minor$.mp. 39. pubert$.mp. 40. pubescen$.mp. 41. prepubescen$.mp. 42. pediatric$.mp. 43. paediatric$.mp. 44. peadiatric$.mp. 45. or/21-44 46. and/4,7,20,45 47. limit 46 to yr="1997 - 2007"
EBM Reviews Cochrane Central Register of Controlled Trials 2nd Quarter 2008	1. exp Otitis Media/ 2. (acute adj5 (OM or otitis media or ear or infection?)).mp. 3. (OM or OME or AOM).ti,ab.

(Continued)

OVID Version: rel10.5.2 Searched: 1 August 2008 Results: 425 Limits: Date: 1997 to 2008	4. otorrh?ea.ti,ab. 5. or/1-4 6. exp Anti-Infective Agents/ 7. exp treatment outcome/ 8. (antibacter$ or anti-bacter$ or "anti bacter$" or antibiotic$ or anti-biotic$ or "anti biotic$" or bacteriocid$ or antimicrob$ or anti-microb$ or "anti microb$").mp. 9. or/6-8 10. exp Infant/ 11. exp Child/ 12. Adolescent/ 13. Minors/ 14. exp Puberty/ 15. exp Pediatrics/ 16. infant$.mp. 17. infancy.mp. 18. newborn$.mp. 19. baby.mp. 20. babies.mp. 21. neonat$.mp. 22. preterm$.mp. 23. prematur$.mp. 24. postmatur$.mp. 25. child$.mp. 26. kid.mp. 27. kids.mp. 28. toddler$.mp. 29. adolescen$.mp. 30. teen$.mp. 31. boy$.mp. 32. girl.mp. 33. minor$.mp. 34. pubert$.mp. 35. pubescen$.mp. 36. prepubescen$.mp. 37. pediatric$.mp. 38. paediatric$.mp. 39. peadiatric$.mp. 40. or/10-38 41. and/5,9,40 limit 41 to yr="1997 - 2007"
CINAHL Plus with Full Text (EBSCOhost) 1981-present Searched: 1 August 2008 Results: 532 Limits: Date: 1997 to 2008 Age Groups: Infant, Newborn 0-1 month, Infant, 1-23 months, Child, Preschool 2-5 years, Child, 6-12 years, Adolescence, 13-18 years	# Query S7(S5 and S1) S6(S5 and S1) S5(S4 or S3 or S2) S4(antibacter* or anti-bacter* or "anti bacter*" or antibiotic* or anti-biotic* or "anti biotic*" or bacteriocid* or antimicrob* or anti-microb* or "anti microb*") S3(MH "Treatment Outcomes+") S2(MH "Antiinfective Agents+") S1(MH "Otitis Media+") or (acute w5 OM OR acute w5 "otitis media" OR actue w5 ear OR acute w5 infection) or (ottorrh?ea or OM or OME or AOM)
BIOSIS Previews® (ISI Web of Knowledge℠ [3.0]) 1969 to present	Sets History #6 #5 AND #4

(Continued)

Searched: 1 August 2008 Results: 1161 Limits: 1997 to 2008	#5 TS=clinical trial* OR TS=research design OR TS=comparative stud* OR TS=evaluation stud* OR TS=controlled trial* OR TS=follow-up stud* OR TS=prospective stud* OR TS=random* OR TS=placebo* OR TS=(single blind*) OR TS=(double blind*) #4#3 OR #2 OR #1 #3 TS=ottorrhea #2 TS=(OM OR OME OR OME OR AOM) #1 TS="otitis media" OR TS=(acute SAME OM OR acute SAME "otitis media" OR acute SAME "ear infection")
OCLC PapersFirst (OCLC FirstSearch) Searched: 1 August 2008 Results: 25 + 3 Limits: 1997 to 2008	(kw: otitis w media) and (kw: antibiotic* OR kw: antibacter* OR kw: bacteriocid* OR kw: antimicrob*)
OCLC ProceedingsFirst (OCLC FirstSearch) Searched: 1 August 2008 Results: 1 Limits: 1997 to 2008	(kw: otitis w media) and (kw: antibiotic* OR kw: antibacter* OR kw: bacteriocid* OR kw: antimicrob*)
ProQuest® Dissertations & Theses Full Text 1861 to present Searched: 1 August 2008 Results: 62 = 3	(("otitis media" OR "ear infection" or ottorrhea) AND (acute))

OVID databases:
RCT filter adapted from:
Cochrane Highly Sensitive Search Strategy (2005) Revision from
Glanville JM, Lefebvre C, Miles JNV, Camosso-Stefinovic J. How to identify randomized controlled trials in Medline: ten years on. J Med Libr Assoc 2006; 94(2):130-6

Appendix 3. Search Strategies 2009 Update

Database: **Ovid MEDLINE(R)** In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1950 to Present>
Search strategy:
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1 otitis media.tw.
2 (OM or OME or AOM).tw.
3 (ear* adj3 (infect* or acute)).tw.
4 (otorrhea or otorrhoea).tw.
5 or/1-4
6 (antibacter* or anti-bacter* or anti bacter* or antibiotic* or anti-biotic* or anti biotic* or bacteriocid* or antimicrob* or anti-microb* or anti microb*).tw.
7 (amoxicillin* or amoxycillin* or penicillin* or cefprozil* or clarithromycin* or cefpodoxime* or cefaclor* or ceftriaxone* or azithromycin* or cefixime*).tw.
8 (treatment* adj5 outcome*).tw.
9 or/6-8
10 5 and 9
11 (infant* or infancy or newborn* or baby* or babies or neonat* or preterm* or prematur* or child* or kid or kids or toddler* or adolescen* or teen* or boy* or girl* or minor* or pubert* or pubescen* or prepubescen* or pediatric* or paediatric* or schoolchild* or school age* or preschool* or kindergar* or nursery school* or primary school* or secondary school* or elementary school* or high school* or highschool*).tw. (1599556)

12 10 and 11
13 (random* or placebo* or clinical trial* or research design* or doubl* blind* or singl* blind*).tw. (692296)
14 12 and 13

EMBASE.com
23. #18 AND #22
22. #19 OR #20 OR #21
21. ((singl* OR doubl*) NEAR/2 blind*):ab,ti
20. random*:ab,ti OR placebo*:ab,ti OR factorial*:ab,ti OR crossover*:ab,ti OR 'cross-over':ab,ti OR 'cross over':ab,ti OR assign*:ab,ti OR allocat*:ab,ti OR volunteer*:ab,ti
19. 'randomized controlled trial'/exp OR 'single blind procedure'/exp OR 'double blind procedure'/exp OR 'crossover procedure'/exp
18. #12 AND #17
17. #13 OR #14 OR #15 OR #16
16. ((age* OR nursery OR primary OR secondary OR elementary OR high) NEAR/2 school*):ti,ab
15. schoolchild*:ab,ti OR preschool*:ab,ti OR kindergar*:ab,ti OR highschool*:ab,ti
14. infant*:ab,ti OR infancy:ab,ti OR newborn*:ab,ti OR baby*:ab,ti OR babies*:ab,ti OR neonat*:ab,ti
OR preterm*:ab,ti OR prematur*:ab,ti OR postmatur*:ab,ti OR child*:ab,ti OR kid:ab,ti OR kids:ab,ti OR toddler*:ab,ti OR adolescen*:ab,ti OR teen*:ab,ti OR boy*:ab,ti OR girl*:ab,ti OR minor*:ab,ti OR pubert*:ab,ti OR pubescen*:ab,ti OR prepubescen*:ab,ti OR pediatric*:ab,ti OR paediatric*:ab,ti
13. 'child'/exp OR 'newborn'/exp OR 'adolescent'/exp OR 'puberty'/exp OR 'pediatrics'/exp
12. #6 AND #11
11. #7 OR #8 OR #9 OR #10
10. amoxicillin*:ab,ti OR amoxycillin*:ab,ti OR penicillin*:ab,ti OR cefprozil*:ab,ti OR clarithromycin*:ab,ti OR cefpodoxime*:ab,ti OR cefaclor*:ab,ti OR ceftriaxone*:ab,ti OR azithromycin*:ab,ti OR cefixime*:ab,ti
9. antibacter*:ab,ti OR 'anti-bacterial':ab,ti OR 'anti-bacterials':ab,ti OR 'anti bacterial':ab,ti
OR 'anti bacterials':ab,ti OR antibiotic*:ab,ti OR 'anti-biotic':ab,ti OR 'anti-biotics':ab,ti OR 'anti biotic':ab,ti OR bacteriocid*:ab,ti OR antimicrob*:ab,ti OR 'anti-microbial':ab,ti OR 'anti-microbials':ab,ti OR
'anti microbial':ab,ti OR 'anti microbials':ab,ti
8. 'antiinfective agent'/exp
7. 'treatment outcome'/exp
6. #1 OR #2 OR #3 OR #4 OR #5
5. otorrhoea:ab,ti OR otorrhea:ab,ti
4. om:ab,ti OR ome:ab,ti OR aom:ab,ti
3. ((infect* OR acute*) NEAR/5 ear*):ab,ti
2. 'otitis media':ab,ti
1. 'otitis media'/exp

F E E D B A C K

'Short course antibiotics for acute otitis media' has severe errors of analysis and procedure and needs to be withdrawn, 29 November 2006

Summary

1. Data are counted twice as follows
Study Short course Long course
Boulesteix, 1995 11/124 11/118
Cohen, 1997 26/186 31/184
Hendrickse, 1988 14/74 6/77
Hoberman, 1997a 57/197 24/178
Hoberman, 1997b 57/197 40/189

Hoberman 1997a and b are the same study and so the short course data have been counted twice.

2. For both the Hoberman and Boulesteix studies the treatments being compared differ not only in terms of duration (short versus long) but also in terms of other aspects (for example, formulation, dose and dosing schedule). Thus as regards the comparison of short versus long they are biased.

Reply

1. Two studies (Gooch 1996; Hoberman 1997) in the current review contained two arms comparing long course versus short course of antibiotics. In the original review the short arm was counted twice against each long arm of that study. In the update of this review, we have modified our methods and combined both long-course arms in a single comparison against the short-course arm, as recommended in the *Cochrane Handbook* (Higgins 2008).

The remaining articles (Boulesteix 1995; Cohen 1997; Hendrickse 1988) were checked to ensure that all patients enrolled in the study were accounted for only once. These three trials clearly indicate that each patient is only accounted for in one of the groups (short or long-course).

Hoberman 1997b has been removed from the updated review.

2. These minor differences were considered but were not deemed clinically important to the current question, and we don't believe this introduces any bias to the comparison.

Reply approved and added to review September 2009 by: Anita Kozyrskyj, Terry P Klassen, and Michael Moffatt

Contributors

Stephen Senn
Comment submitted 30 November 2006. Added to review 22 Decemer 2008.

WHAT'S NEW

Date	Event	Description
19 June 2012	Review declared as stable	As of 19 June 2012, this Cochrane Review is no longer being updated, as there is high-quality evidence that treating children with acute otitis media with a short course (less than seven days) of antibiotics, compared to treatment with a long course (seven days or greater) of antibiotics, increases the likelihood of treatment failure in the short term, meaning further research is unlikely to change our confidence in the estimate of effect in our primary outcome. The review authors recommend that it is no longer necessary to update this review.

HISTORY

Protocol first published: Issue 2, 1998
Review first published: Issue 2, 2000

Date	Event	Description
9 September 2010	Amended	Contact details updated.
18 November 2009	New citation required but conclusions have not changed	The searches were conducted in November 2009, with a total of 22 new trials added since the original review in 2000 (Adam 2000; Al-Ghamdi 1999; Arguedas 2005; Arrieta 2003; Block 2000; Block 2003; Block 2004; Catania 2004; Cohen 1998; Cohen 1999; Cohen 2000; Dagan 2000a; Dagan 2000b; de Jose 1998; Dunne 2003; Guven 2006; Hoberman 2005; Kara 1998; Oguz 2003; Pessey 1999; Varsano 1997; Wang 2004). Two of the studies included in the first version of this review (Kozyrskyj 2000) were excluded due to the outcome not being reported as a treatment failure (Bain 1985; Jones 1986) and an additional three studies have been excluded; two were excluded due to use of ceftibuten which has been deemed not to be clinically relevant (Roos 2000; Simon 1997); and one for the duration of antibiotic therapy being equivalent in both arms (Suzuki 2009). The 22 studies that were included in this updated review brought the 30-day findings closer to equivalence (primary outcome). This would suggest that any new studies would not change the current outcomes and the review authors recommend that it is no longer necessary to update this review.

Date	Event	Description
11 November 2009	New search has been performed	Searches conducted.
22 December 2008	Feedback has been incorporated	Feedback added.
12 March 2008	Amended	Converted to new review format.
30 January 2000	New search has been performed	Searches conducted.

CONTRIBUTIONS OF AUTHORS

Anita Kozyrskyj (AK), Terry Klassen (TK) and Michael Moffatt (MM) first conceived the review, presenting it as a meta-analysis in a journal (Kozyrskyj 1998). It was updated for *The Cochrane Library* with assistance from Krystal Harvey (KH) and Liza Bialy (LB).

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- Alberta Research Centre for Health Evidence, Canada.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Age Factors; Anti-Bacterial Agents [adverse effects] [*therapeutic use]; Azithromycin [therapeutic use]; Ceftriaxone [adverse effects] [therapeutic use]; Drug Administration Schedule; Otitis Media [*drug therapy]; Time Factors

MeSH check words

Child; Humans