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Antibiotics for acute otitis media in children (Review)

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[Intervention Review]

Antibiotics for acute otitis media in children

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ABSTRACT

Background

Acute otitis media (AOM) is one of the most common diseases in early infancy and childhood. Antibiotic use for AOM varies from 56% in the Netherlands to 95% in the USA and Australia.

Objectives

To assess the effects of antibiotics for children with AOM.

Search strategy

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, 2008, issue 2) which contains the Acute Respiratory Infections (ARI) Group's Specialized Register; MEDLINE (1966 to June week 4 2008); OLDMEDLINE (1958 to 1965); EMBASE (January 1990 to July 2008); and Current Contents (1966 to July 2008).

Selection criteria

Randomised controlled trials comparing 1) antimicrobial drugs with placebo 2) immediate antibiotic treatment with observational treatment approaches in children with AOM.

Data collection and analysis

Three review authors independently assessed trial quality and extracted data.

Main results

We found 10 trials (2928 children) from high income countries with low risk of bias. Pain was not reduced by antibiotics at 24 hours, but was at two to seven days, (relative risk (RR) 0.72; 95% confidence interval 0.62 to 0.83). However four trials (1271 children) comparing antibiotics prescribed immediately rather than initial observation found no difference at three to seven days. Antibiotics did not reduce tympanometry, perforation or recurrence. The only case of mastoiditis was in an antibiotic treated child. Vomiting, diarrhoea or rash was higher in children taking antibiotics (RR 1.37; 95% CI 1.09 to 1.76). Individual patient data meta-analysis of a subset of the included trials found antibiotics to be most beneficial in children: aged less than two; with bilateral AOM and with both AOM and otorrhoea.

Authors' conclusions

Antibiotics slightly reduce the number of children with acute middle ear infection experiencing pain after a few days. However, most (78%) settle spontaneously in this time, meaning 16 children must be treated to prevent one suffering ear pain. This benefit must be weighed against the possible harms: 1 in 24 children experience symptoms caused by antibiotics. Antibiotics are most useful in children under two years of age, with bilateral AOM, and with both AOM and discharging ears. For most other children with mild disease, an expectant observational approach seems justified. We have no data on populations with higher risks of complications.

PLAIN LANGUAGE SUMMARY

Antibiotics for reducing the pain of middle ear infection (acute otitis media) in children

Acute otitis media (AOM) is common in children, causing pain and deafness. Though AOM usually resolves without treatment, it is often treated with antibiotics. This review found that antibiotics are not very useful for most children with AOM. Antibiotics marginally decreased the number of children with pain at 24 hours (when most children were better), only slightly reduced the number of children with pain in the few days following and did not reduce the number of children with hearing loss (that can last several weeks). However, antibiotics seem to be most beneficial in children younger than two years of age with bilateral AOM (infection in both ears), and in children with both AOM and otorrhoea (discharge from the ear). There was not enough information to know if antibiotics reduced rare complications such as mastoiditis (an infection of the bones around the ear). Some guidelines have recommended a management approach in which certain children are observed and antibiotics taken only if symptoms remain or have worsened after a few days. This review found no difference between immediate antibiotics and observational treatment approaches in the number of children with pain three to seven days after assessment. All of the studies included in this review were from high-income countries. Data from populations in which the incidence of AOM and risk of progression to mastoiditis is much higher are lacking. Antibiotics caused unwanted effects such as diarrhoea, stomach pain and rash, and may also increase resistance to antibiotics in the community. It is difficult to balance the small benefits against the small harms of antibiotics for most children.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Antibiotic versus placebo for acute otitis media in children

Patient or population: patients with acute otitis media in children
Settings:
Intervention: Antibiotic versus placebo

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	Antibiotic versus placebo				
Pain - Pain at 24 hours	Medium risk population		RR 0.9 (0.78 to 1.04)	1229 (5)	⊕⊕⊕⊕ high	
	367 per 1000	330 per 1000 (286 to 382)				
Pain - Pain at 2 to 7 days	Medium risk population		RR 0.72 (0.62 to 0.83)	2791 (10)	⊕⊕⊕⊕ high	
	257 per 1000	185 per 1000 (159 to 213)				
Abnormal tympanometry - 1 month	Medium risk population		RR 0.89 (0.75 to 1.07)	927 (4)	⊕⊕⊕⊕ high	
	350 per 1000	311 per 1000 (262 to 375)				
Abnormal tympanometry - 3 months	Medium risk population		RR 0.97 (0.76 to 1.24)	808 (3)	⊕⊕⊕⊕ high	

	234 per 1000	**227 per 1000** (178 to 290)			
Vomiting, diarrhoea, or rash	**Medium risk population**		**RR 1.38** (1.09 to 1.76)	1401 (5)	⊕⊕⊕◯ **moderate**[1]
	113 per 1000	**156 per 1000** (123 to 199)			

*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; RR: Risk ratio;

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

[1] No explanation was provided

BACKGROUND

Description of the condition

Acute otitis media (AOM) is one of the most frequent diseases in early infancy and childhood. It has a high morbidity and low mortality (Stool 1989). Approximately 10% of children have an episode of AOM by three months of age. The peak age-specific incidence is between six and 15 months (Klein 1989).

Description of the intervention

Despite a large number of published clinical trials, there is no consensus on the therapy of AOM; for example, the rates of use of antibiotics for AOM varies from 56% in the Netherlands (Akkerman 2005) to 95% in the USA and Canada (Froom 2001). A meta analysis (Rosenfeld 1994) emphasises that for most children AOM is a disease that resolves spontaneously. However, one semi-randomised trial of 1365 participants in conducted in Sweden 1954 (Rudberg 1954) reported a rate of mastoiditis of 17% in the untreated group versus none in the penicillin treated groups. Recently, prescription strategies in which antibiotic treatment for acute respiratory infection is delayed and instituted only if symptoms persist or worsen after several days have been advocated (AAP 2004).

OBJECTIVES

The aim of this review was to assess the usefulness of antibiotic treatment for AOM in children.

We attempted to determine to what extent antibiotic therapy was more effective than placebo, and what, if any advantages it offered to children in terms of symptom relief, avoidance of complications (such as mastoiditis), and longer term hearing problems from middle ear effusion (as measured by tympanometry or audiogram). We also assess the effect of immediate antibiotic versus observational approaches to AOM and identify subgroups of children with AOM that benefit more or less from antibiotics.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) of antimicrobial drugs versus placebo control. RCTs comparing immediate antibiotic versus observational approaches were also included.

Types of participants

Studies including children (aged from 1 month to 15 years) of either gender without tympanostomy tubes, suffering from AOM irrespective of the setting from which they were recruited.

Types of interventions

Antimicrobial drugs versus placebo control.
Immediate antibiotic versus observational approaches (also known as 'wait and see' or 'watchful waiting' or 'observation therapy'). This includes observational approaches in which prescriptions may or may not be provided.

Types of outcome measures

We focused our data extraction on patient-relevant outcomes, that is, those symptoms or problems that are important to the patients sense of well-being. While other endpoints, such as microbiological cure may enhance medical understanding of the disease process, decisions about treatment should focus on helping the patient. For AOM, we considered the most important outcomes for patients are severity and duration of pain; adverse effects (adverse events related to use of the antibiotic); serious complications of AOM; recurrent attacks; and hearing problems (mid to long term) from the middle ear fluid. Because hearing is notoriously difficult to measure in children, we used the surrogate measure of tympanometry.

Search methods for identification of studies

Electronic searches

Several electronic databases were used to compile relevant published RCTs of antibiotic treatment of AOM in children. The Cochrane Controlled Trials Register, MEDLINE and Current Contents were searched from 1966 to January 2000 by an expert librarian in conjunction with one researcher, using combinations of "OTITIS MEDIA" and a search strategy described by (Dickersin 1994) for optimally identifying controlled trials. In addition, titles in Index Medicus were checked from 1958 to 1965. The references of all relevant retrieved trials were checked to identify other articles.
The search was updated in March 2003, and again in July 2008. We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library*, 2008, issue 2) which contains the ARI Group's Specialized Register; MEDLINE (1966 to June week 4 2008); OLDMEDLINE (1958 to 1965); EMBASE (January 1990 to July 2008); and Current Contents (1966 to July 2008). The bibliographies of relevant articles were checked. A forward search of relevant articles was conducted in Web of Science®. The following search strategy was run on MEDLINE (Ovid) combined with terms from Phase 1 and 2 of the Cochrane highly

sensitive search strategy for identifying reports of RCTs (Lefebvre 2008). Modified terms were used to search the other databases:

MEDLINE (Ovid)

#1 exp Otitis Media/
#2 exp Otitis Media with Effusion/
#3 exp Otitis Media, Suppurative/
#4 glue ear.mp.
#5 otitis media.mp.
#6 OME.mp.
#7 AOM.mp.
#8 #1 or #2 or #3 or #4 or #5 or #6 or #7
#9 exp Anti-Bacterial Agents/
#10 exp Drug Therapy/
#11 exp Anti-Infective Agents/
#12 antibiotic$.mp.
#13 #9 or #10 or #11 or #12
#14 #8 and #13
There were no language or publication restrictions.

Searching other resources

The WHO International Clinical Trials Registry Platform was checked for ongoing trials (1st Sept 2008)

Data collection and analysis

Selection of studies

One review author screened titles and abstracts obtained from the database searches. Three review authors reviewed the full text of the potentially relevant titles and abstracts against the inclusion criteria.

Data extraction and management

Data were extracted from the included studies by two review authors and disagreements were resolved by discussion.

Assessment of risk of bias in included studies

We used a modification of a published method to assess the methodological quality (Chalmers 1990). The items were assessed for the following four characteristics:
1. Method of treatment assignment
a. Correct, blinded, randomisation method described OR
randomised, double-blind stated AND group similarity documented
b. Blinding and randomisation stated, but method not described OR
suspect technique, for example, envelope
c. Randomisation claimed but not described, and investigator not blinded
d. Randomisation not mentioned
2. Control of selection bias after treatment assignment
a. Intention to treat analysis AND full follow-up
b. Intention to treat analysis AND < 15% loss to follow-up
c. Analysis by treatment received only OR no mention of withdrawals
d. Analysis by treatment received AND no mention of withdrawals OR
more than 15% withdrawals/loss-to-follow-up/post-randomisation exclusions
3. Blinding
a. Blinding of (i) outcome assessor AND (ii) patient AND (iii) care giver
b. Blinding of (i) outcome assessor OR (patient AND care giver)
d. Blinding not done
4. Outcome assessment
a. All patients had standardised assessment
b. No standardised assessment OR not mentioned

The quality of all the study trials that met the inclusion criteria were assessed by each review author. Assessment of the trials included in the first version of the review was done "blind", (i.e. without the knowledge of the study results, nor the names of the authors, institutions, journal of publication). The review authors met after their study assessments in order to resolve any disagreements, still blinded to results. Trials included after the first version of the review were not assessed 'blind'. If necessary and possible, intention to treat analyses were reconstructed. The worst case scenario was used to impute ouctome data to those lost to follow-up. A sensitivity analysis found that imputation of a small amount of data did not significantly affect the outcomes of the review.

Assessment of heterogeneity

Heterogeneity was assessed the chi^2 test, the I^2 statistic and with visual inspection of the forest plots. When heterogeneity was present ($P < 0.1$) the data was re-analysed using the random-effects model. For the outcome of pain the magnitude of baseline risk and heterogeneity was explored using a L'Abbé plot (graph of the proportion of participants with an outcome by the proportion of participants without an outcome).

Data synthesis

Treatment differences were analysed as risk ratios (RR) with a 95% confidence interval (CI) calculated by the Mantel-Haenszel method using a fixed-effect model.

Subgroup analysis and investigation of heterogeneity

In an individual patient data (IPD) meta-analysis on a subset of trials included in this review (six trials including 1643 children aged 6 months to 12 years with AOM) Rovers (Rovers 2006), performed subgroup analysis to identify children with acute otitis media who might benefit more than others from treatment with antibiotics. The primary outcome was a prolonged course of acute otitis media which was defined as having either residual pain or fever (> 38 ºC) at three to seven days. Potential subgroups were selected on the basis of a multivariable prediction tool. The independent baseline predictors, that is, age (< 2 years versus > 2 years), fever and bilateral acute otitis media (yes versus no), were used to study whether those at risk of a prolonged course also benefit more from treatment with antibiotics. In addition, otorrhoea (yes versus no) at baseline was studied as this appears to be a clinically relevant outcome that occurs too infrequently to be identified as an independent predictor.

To assess whether the effect of antibiotics was modified by age, bilateral disease and/or otorrhoea, a fixed-effect logistic regression analysis was performed. In this model antibiotics (yes versus no), the potential effect modifier (age, bilateral disease and/or otorrhoea), a dummy for the particular study, and an interaction term (antibiotics * potential effect modifier) were included as independent variables, and a prolonged course at three to seven days was the dependent variable. If a significant interaction effect was found, stratified analysis were performed to study the rate ratios and rate differences within each stratum of the subgroups.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Included studies

Eleven trials including a total of 2928 children were eligible for the review of antibiotics against placebo. The children were aged 2 months and 15 years and between 50 to 60% of included children were male. One trial (vanBuchem 1981a) had a factorial design (myringotomy, antibiotics, both or neither): we used all arms of the trial (vanBuchem 1981b includes the myringotomy only and myringotomy plus antibiotic arms). Ten trials included patient relevant outcomes; Howie (Howie 1972) did not report on patient-relevant outcomes such as symptoms or hearing problems.

Four trials (Little 2001; McCormick 2005; Neumark 2007; Spiro 2006) including a total of 1271 children aged between 6 months and 16 years compared different treatment approaches. In two of these trials (Little 2001; Spiro 2006) provision of an immediate antibiotic script was compared with an antibiotic script with instructions not to commence antibiotic treatment unless the child was not better or was worse at 48 hours (Spiro 2006) or 72 hours (Little 2001). In these trials 24% (36/150) and 38% (50/132) of children in the delayed arms reported using antibiotics at some stage during the illness. The third trial (McCormick 2005) compared immediate antibiotics with a 'watchful waiting' approach. In the watchful waiting arm, a prescription was not provided. Antibiotics were administered to the watchful waiting group if a child returned to the office with a treatment failure or recurrence (four children in the watchful waiting arm had received antibiotics by day 4). Data on pain at four to six days was provided in two of these trials (Little 2001; Spiro 2006) and provided by the author in the third trial (McCormick 2005). The fourth trial (Neumark 2007) also compared immediate antibiotics with a watchful waiting approach. In this trial 5% (4/87) of children randomised to the watchful waiting arm received antibiotics due to treatment failure. This trial reported on the number of children with moderate or severe pain between days three and seven.

Risk of bias in included studies

The methodological quality of the included studies was generally high. Eight of the 10 trials comparing antibiotics with placebo that reported patient-relevant outcomes used adequately concealed allocation and outcome assessments. Two studies failed to include all children in follow-up assessments, but exclusions were less than 10% (Halsted 1968; Howie 1972).

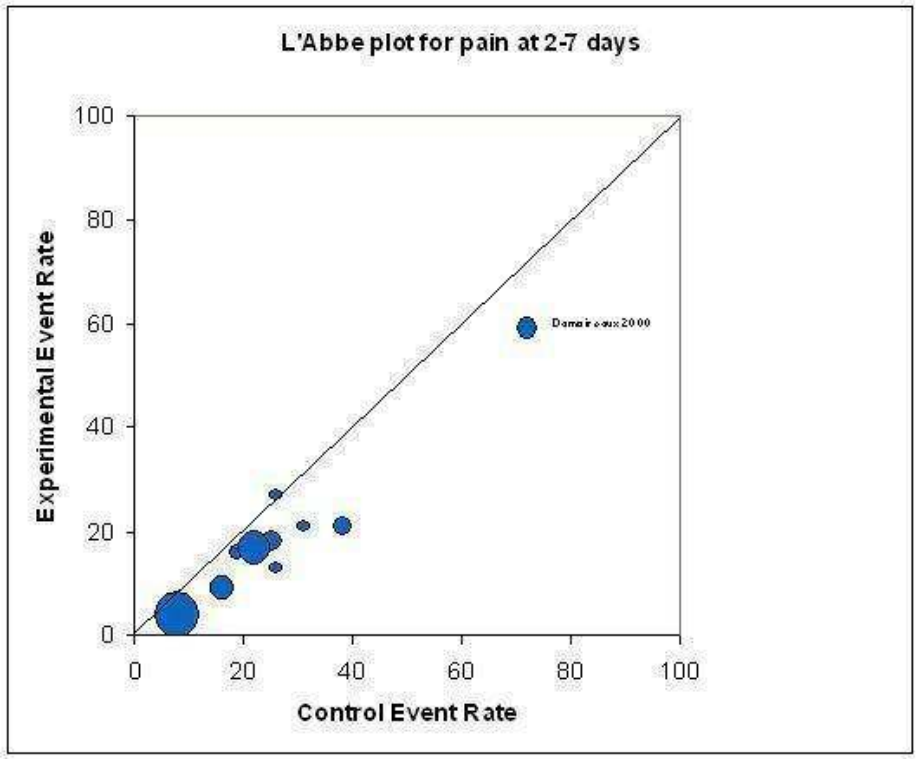
Effects of interventions

See: **Summary of findings for the main comparison**

Pain

The combined results of the trials showed that by 24 hours from the start of treatment, almost two thirds of children had recovered whether or not they had placebo or antibiotics. At two to seven days, 78% of children had spontaneously recovered (pooled control groups). Antibiotics achieved a further 28% relative reduction in the risk of pain at two to seven days (95% CI 0.15 to 0.41). This means overall 6% (95% CI 0.04 to 0.09) fewer children had pain after two to seven days: about 16 (95% CI 0.11 to 0.31) children needed to be treated to prevent one child experiencing pain after two to seven days (1/(relative risk reduction*control event rate [0.22])). Compared with delayed treatment, immediate antibiotic treatment was associated with decreased ear pain at day four (RR 0.77, 95% CI 0.50 to 1.17). A plot of the event rate (pain at two to seven days) in the treatment and control groups for each study is shown in Figure 1.

Figure 1. L'Abbe plot of the rates of pain at 2 to 7 days for the placebo versus treatment group



Hearing (as measured by tympanometry)

In the four trials that measured tympanometry there were no clinically or statistically significant difference in tympanometry results at one or three months after the acute episode, suggesting no effects on hearing. However, audiometry was done in only two studies and incompletely reported. The two studies that used audiograms were: (i) van Buchem (vanBuchem 1981a), who reported that, "After one month, 31% of the patients showed an air/bone gap of more than 20 dB. After two months, this was still the case with 19% of the patients. Here again, there were no significant differences between the groups". (ii) Kaleida 1991, states that "Analysis of hearing acuity in children two years of age and older indicated that elevated hearing thresholds ... bore no apparent relationship ... to mode of treatment (amoxicillin versus placebo)".

Progression of symptoms (contralateral otitis or late recurrence)

Antibiotics appear to reduce the development of contralateral otitis, though the difference is not statistically significant. Relapse was common. Burke (Burke 1991) states "The mean number of recorded recurrences of otitis media or acute red ear was 0.70 (range 0 to 4) in the antibiotic group and 0.63 (range 0 to 7) in the placebo group and this difference was not significant (difference 0.06; 95% CI -0.22 to 0.339)." Six other trials reported the proportions who relapsed; combined these give RR 0.93, 95% CI 0.79 to 1.10, which is consistent with Burke's findings.

Serious complications

Few serious complications occurred in either the antibiotic treated group or the controls. In just over two thousand children studied, only one case of mastoiditis occurred (in a penicillin treated group (Mygind 1981)). Hence the applicability of these findings

to groups in whom mastoiditis is common is uncertain. One of the excluded studies (Rudberg 1954) did report high rates of mastoiditis. This was an open, semi-randomised study conducted in Sweden in 1954. Patients were randomised by case-sheet number, but a proportion (about 30 of 220) requested, and were granted, entry to the penicillin group. The rate of mastoiditis was 17% in the untreated group versus 1.5% in the sulphonamide group and 0% in the penicillin treated group. The biases of this study (semi-randomisation and unblinded outcome assessment) are unlikely to explain such a large difference.

Adverse events (vomiting, diarrhoea or rash)

The occurrence of vomiting, diarrhoea or rash was reported in five trials. Antibiotics resulted in a 37% (95% CI 0.05 to 0.67) relative increase in risk of adverse events (16% [110/690] of children treated with antibiotics versus 11% [83/711] of children treated with placebo experienced vomiting, diarrhoea or rash). The number needed to treat for an additional harmful outcome is 24.

Immediate antibiotics versus observational approaches

At three to seven days, there was no difference in pain between children receiving an immediate antibiotic prescription and those randomised to observation with or without an antibiotic prescription (RR 0.77, 95% CI 0.50 to 1.17).

Individual patient data meta-analysis to identify children most likely to benefit from antibiotic treatment

In children aged less than two years with bilateral AOM, 55% of the control group and 30% of the antibiotics group still had pain, fever or both at three to seven days (risk difference (RD) = 25% and NNT of 4). In children two years or older with bilateral AOM the RD was 12%. Among children with otorrhoea, 60% of those in the control group had pain, fever or both at three to seven days. In the antibiotics group, 25% had pain, fever or both at three to seven days giving a RD of about 36%. The RD between the control and antibiotics group among those without otorrhoea was 14%. No differences were identified for age alone.

DISCUSSION

This review shows that antibiotics have no early impact, and a modest overall impact on the clinical course of AOM. However, in applying these results, there are a number of issues to consider, including the individual potential for serious complications and subgroups of children in whom there may be greater benefits.

What are the potential consequences of not using antibiotics?Besides the immediate pain of AOM, there are some more serious complications. Though none of the trials reported cases of mastoiditis occurring in the placebo group (one case occurred in a penicillin group), a semi-randomised trial in Sweden in 1954 (Rudberg 1954) reported a rate of 17% in the untreated group versus none in the penicillin treated groups. In populations or subpopulations where mastoiditis is still judged a frequent problem, such as in some low-income countries (Berman 1995), antibiotic treatment would be strongly advised.

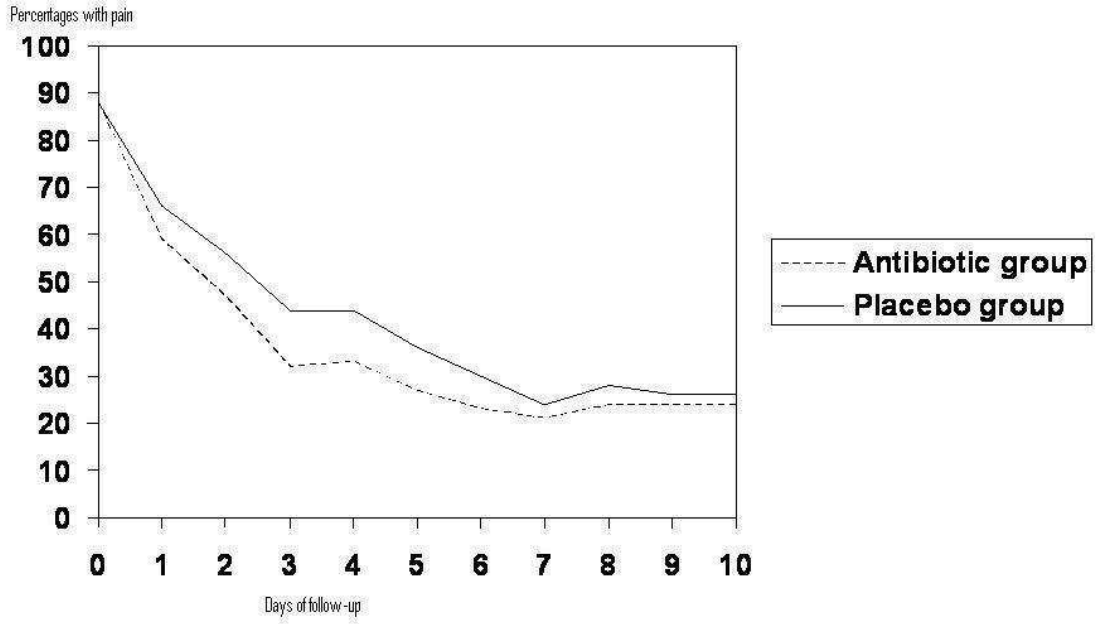
Does the effect vary in different clinical groups? Our NNT of 16 at two to seven days is for the 'average' case, and may vary in subgroups. Some studies (Appelman 1991; Burke 1991; Damoiseaux 2000) have reported higher rates of failure of placebo treatment among children less than two years and those with bilateral disease and another (Little 2001) has suggested that most benefit is seen in children with high fevers or vomiting. The recent meta-analysis of individual patient data (Rovers 2006) however, showed that the relative effects of antibiotics were not significantly modified by either age or bilateral disease alone, but the absolute differences were larger in the younger patients (< 2 years) with bilateral disease and in children with both AOM and otorrhoea. Further analysis of this data has shown that age younger than two years is an independent predictor of the development of asymptomatic middle ear effusion (Koopman 2008). This analysis also found that antibiotic therapy has a marginal effect on the development of asymptomatic middle ear effusion in children with AOM.

This review showed that at 24 hours two thirds of children had recovered spontaneously and that the majority had recovered in the following two to seven days regardless of whether they had received placebo or antibiotics. The independent patient data meta-analysis that included six of the trials included in this review however, showed a slower rate of recovery (Figure 2) with only 22% of children experiencing spontaneous recovery at 24 hours (Rovers 2006). There are a number of possible explanations for this. Firstly data from older trials was not included in the individual patient data meta-analysis and consequently the study population may reflect a higher threshold of doctor visitation for example, the children may be 'sicker' or presenting to the doctor later in the course of their illness. Variation in the definitions of pain/no pain cutoffs among the trials included in the reviews may also explain some of this variation. From the individual patient data meta-analysis survival curve (Figure 2) it can be seen that antibiotics had greatest effect compared to placebo at day three.

Does the impact vary by duration of antibiotics?Most trials use seven days of antibiotic treatment. A recent meta-analysis of short (< 7 days) versus long course antibiotics found the longer course of short acting antibiotics was comparable to the five day course in terms of signs, symptoms, relapse or reinfection at 30 days after

initiation of therapy (Kozyrskyj 2000).

Figure 2. Percentage with pain based on the subset of 6 studies included in the IPD Meta-analysis (Rovers et al 2006)



A previous meta-analysis had examined the question of whether antibiotics were indicated for AOM in children and concluded that the answer is a qualified "yes" (Rosenfeld 1994). It estimated a NNT of seven for 'primary control' (complete clinical resolution), compared with our NNT of 15 for symptom relief. The difference may be the consequence of our focus on patient-oriented outcomes, such as pain, rather than clinical signs, such as eardrum appearance. This systematic review suggest that where mastoiditis is not a concern, primary medical carers could weigh the benefits against the risks of adverse effects from antibiotics with their patients. Adverse events such as diarrhoea, vomiting or rash were infrequently reported in the trials included in this review but were more common in children receiving antibiotics. In the individual patient data meta-analysis (Rovers 2006) the most commonly described adverse effect of antibiotic treatment was diarrhoea ranging from 2 to 14% in controls and from 4 to 21% in those given antibiotics. Occurence of rash ranged from 2 to 6% in the control groups and from 1 to 8% in the antibiotic groups. Bacterial resistance to antibiotics is also a consideration, with an association between antibiotic use and resistant bacteria demonstrated for many important pathogens (Arnold 2005).

Several trials (Little 2001; McCormick 2005; Neumark 2007; Spiro 2006) have evaluated a management approach for AOM in which an observational approach is used. In one of these (Little 2001) pain and malaise on day three were greater among those randomised to receive an antibiotic prescription with advice to fill it only if there was no improvement after 72 hours compared to those receiving immediate antibiotics. In a long term follow-up of this trial (Little 2006) no difference was found between delayed and immediate treatment groups in ear function and ear ache at 3 and 12 months. Another study using a similar prescribing approach and examining clinical outcomes on days four to six found no difference between immediate and delayed antibiotic groups (Spiro 2006). In the third study (McCormick 2005) immediate antibiotic treatment was associated with decreased numbers of treatment failures and improved symptom control at day 4 and 12 compared to those allocated to watchful waiting with no prescription. Neumark (Neumark 2007) in a similar comparison found that immediate antibiotics provided some symptomatic benefit; children who received antibiotics had less pain, used fewer analgesics and consulted less during the first seven days. Meta-

analysis of data from these four trials found no difference in pain between immediate antibiotics and observational approaches at three to seven days. Another review (Spurling 2007), which evaluated the effect of delayed versus immediate or no antibiotics for respiratory infections, and which included two studies on AOM (Little 2001; Spiro 2006) concluded that immediate antibiotics was the strategy most likely to provide the best clinical outcomes for AOM. A recent randomised study (Chao 2008) has found that observation therapy with or without a prescription in children with AOM was well accepted by parents. Antibiotic use was less in those randomised to observation without prescription and no complications were reported.

Of note, is a recent paper that has shown that doctors commonly over-diagnose AOM (Rothman 2003). What effect might this have on the efficacy of antibiotics (or any treatment)?One effect will be to apparently blunt any treatment effect by dilution (from the cases of non-AOM). On the other hand, if clinicians commonly use the same diagnostic methods (perhaps even less stringent), then the efficacy is a true reflection of actual clinical practice. However, if new and more accurate diagnostic procedures are employed, then the estimate of efficacy will have to be reconsidered.

AUTHORS' CONCLUSIONS

Implications for practice

Antibiotics produce a small reduction in the number of children with pain two to seven days from assessment. However in high-income countries, most cases spontaneously remit with no complications, and the NNT is about 16. Therefore management should emphasize advice about adequate analgesia and the limited role for antibiotics. Antibiotics seem to be most beneficial in children under two years of age with bilateral disease and in children with both AOM and otorrhoea. Cates has developed an appropriate handout and tested this together with an optional antibiotic prescription (Cates 1999). The handout is available at URL http://www.nntonline.net/.

Implications for research

Further research is needed to determine if it is possible to predict which children are more likely to suffer from the complications of AOM.

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Thankyou to Chris Cates for noticing and advising us of an error in the confidence intervals presented in the review.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Appelman 1991

Methods	R = computer generated list place in sealed envelopes - allocated by otolaryngologist Double blind (GP and patient blind) Baseline comparability documented
Participants	Netherlands 121 children in a general practice aged 6 months to 12 years with acute otitis media and a previous episode of otitis media within 1 to 12 months
Interventions	Rx: amoxycillin/clavulanate (weight tailored dose) Control: matching placebo Duration: 7 days All children were also given paracetamol and oxymetazoline nose drops
Outcomes	Assessment by (blinded) GP at (i) 3 days of fever (> 38 ^{o}C) and otalgia, and (ii) 14 days or otorrhoea, and (iii) 1 month otoscopy and tympanometry
Notes	"Failure" = either otalgia or fever > 38 ^{o}C or both at 3 days

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Burke 1991

Methods	R = identical number bottles; sealed randomisation code Double blind Intention to treat analysis
Participants	United Kingdom Children aged between 3 and 10 years Acute earache and at least one abnormal eardrum
Interventions	Rx: amoxicillin 250 mg tds Control: matching placebo tds Duration: 7 days
Outcomes	Symptom diary kept by parents Home visits by researcher: 24 hrs, 5 to 7 days
Notes	1. Fig 2 appears to show that, at baseline (0 hours), fewer children were crying in the amoxicillin arm, suggesting a failure of randomisation

Burke 1991 (*Continued*)

	2. It is not clear whether the "discharging ears" in Table I should be included as perforations

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Damoiseaux 2000

Methods	R = computerised two block randomisation
Participants	Netherlands. 240 children between 6 months and 2 years attending general practice. Diagnosis according to Dutch guidelines
Interventions	Rx: amoxicillin suspension 40 mg/kg/day in three divided doses for 10 days of placebo suspension
Outcomes	Persistent symptoms at day 4 assessed by GP. Defined as persistent earache, fever (> 38 ^{o}C), crying or irritability
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Halsted 1968

Methods	R = randomisation by predetermined code, unknown to physician Blinded using placebo
Participants	USA. Aged 2 to 66 months Clinical diagnosis of acute otitis media, excluded if rupture or recent antibiotics
Interventions	Rx: ampicillin 100 mg/kg/day or phenethicillin 30 mg/kg/day plus sulphisoxazole 150 mg/kg/day Control: placebo
Outcomes	Culture results and clinical improvement = decrease symptoms and defervescence
Notes	

Risk of bias

Item	Authors' judgement	Description

Halsted 1968 (*Continued*)

Allocation concealment?	Unclear	B - Unclear

Howie 1972

Methods	R = randomisation controlled by pharmacist Placebo controlled - all medications given 4 times daily
Participants	USA Age 2.5 years or less Clinical diagnosis of acute otitis media
Interventions	Rx: one of erythromycin, ampicillin, or triple sulphonamide plus erythromycin Control: placebo
Outcomes	Culture and randomisation compared with culture at 2 to 5 days. No patient-relevant outcomes
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Kaleida 1991

Methods	R = stratified randomisation, method not stated. Baseline comparability documented Double blind Intention-to-treat analysis
Participants	USA Children aged between 7 months and 12 years Acute otitis media: otoscopic middle ear effusion plus general symptoms or signs
Interventions	Rx: amoxicillin 40 mg/kg/day in 3 doses Control: Placebo in 3 divided doses Duration: 14 days
Outcomes	"Treatment failure" = high otalgia score or high fever
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**

Kaleida 1991 (*Continued*)

Allocation concealment?	Yes	A - Adequate

Laxdal 1970

Methods	R = randomisation claimed but no method stated Not blinded
Participants	Canada Children Clinical diagnosis of acute otitis media for at least one ear; excluded if rupture had occurred
Interventions	Rx: Penicillin 250 mg/sq.m./day qid or ampicillin 250 mg/sq.m./day qid Control: symptomatic therapy only
Outcomes	Poorly defined - "failure" was either deterioration or no improvement on 7th day based on middle ear inflammation
Notes	Unblinded assessment, and surveillance bias - control was more closely monitored

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	No	C - Inadequate

Le Saux 2005

Methods	R = Identical opaque sequentially numbered bottles Computer generated randomisation sequence accessible only to trial pharmacist Baseline comparability documented
Participants	Canada Children 6 months to 6 years attending ED, Urgent Care Center or Paediatric office
Interventions	Rx: amoxicillin 60 mg/kg daily Control: Placebo of similar appearance and taste
Outcomes	Primary outcome clinical resolution of symptoms defined as absence of receipt of an antimicrobial at any time during 14 day period Secondary outcomes include presence of fever and activity levels on days 1, 2 and 3 according to parent and measured on standardised interviewer administered questionnaire. Adverse effects in 14 days after randomisation Presence of middle ear effusion as assessed by tympanometry 1 and 3 months after diagnosis
Notes	

Risk of bias

Le Saux 2005 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Little 2001

Methods	R = sealed opaque numbered envelope
Participants	England Children aged 6 months to 10 years
Interventions	Rx: immediate amoxicillin syrup 125 mg in 5 ml three doses daily Control: same antibiotics prescribed and parents asked to fill prescription if substantial otalgia or fever present 72 hours after seeing doctor
Outcomes	Daily diary of symptoms, severity of pain, number of episodes of distress, spoonfuls of paracetamol used and temperature until children asymptomatic or medication finished
Notes	Trial comparing immediate versus delayed antibiotic prescription (prescription provided but advised to fill only if symptoms do not improve or worsen)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

McCormick 2005

Methods	R = computer generated list; documented baseline comparability
Participants	USA Children aged 6 months to 12 years
Interventions	Rx: immediate amoxicillin 90 mg/kg/day in 2 doses for 10 days Control: no script but same antibiotic provided if child returned with failure or recurrence within 30 days All received symptom medication
Outcomes	Parent satisfaction with care, resolution of symptoms as measured in diary by doses of symptom medication and ear treatment group symptom questionnaire, failure and recurrence
Notes	Trial comparing immediate versus watchful waiting approach (no prescription provided)

Risk of bias

Item	Authors' judgement	Description

McCormick 2005 (*Continued*)

Allocation concealment?	Yes	A - Adequate

Mygind 1981

Methods	R = coded bottles; documented baseline comparability Double blind Dropouts excluded (9 of 165)
Participants	Denmark Children between the ages of one and ten years Acute otitis media, who had had earache for I to 24 hours
Interventions	Rx: penicillin-V 55 mg/kg/day in three doses Control: placebo Duration: 7 days
Outcomes	Parents completed score cards for pain and fever each evening Otoscopy at follow-up Tympanometry classified blind
Notes	

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

Neumark 2007

Methods	R = Internet based random number generator
Participants	Sweden Children between 2 and 16 years attending general practice
Interventions	Rx: Phenoxymethylpenicillin 25mg/kg x 2 for 5 days Control: No antibiotic treatment. Advice on how to act if condition did not improve or became worse within 3 days after randomisation
Outcomes	Patient diary recording daily symptoms of pain, medication doses, fever, sleeping disturbance, rash, vomiting, diarrhoea, absence from school and recovery day. Follow-up at 3 months.
Notes	Trial comparing immediate antibiotic with watchful waiting (no prescription provided but advice on what to do if symptoms did not improve or worsened)

Risk of bias

Neumark 2007 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Spiro 2006

Methods	R = computer generated list; sealed opaque envelopes in randomly assigned numbered folders
Participants	USA Children between 6 months and 12 years attending Paediatric ED
Interventions	Rx: standard prescription for antibiotic type and dose determined by clinician Control: prescription for antibiotics with written and verbal instructions not to fill prescription unless child not better of worse 48 hours after visit
Outcomes	Blinded telephone interviews with parents at 4 to 6, 11 to 14 and 30 to 40 days after enrolment. Primary outcome was proportion of each group filling the antibiotic prescription
Notes	Trial comparing immediate versus delayed antibiotic prescription (prescription provided and advised to fill only if symptoms worsen or do not improve). All children received ibuprofen suspension and otic analgesic drops

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

Thalin 1985

Methods	R = block randomisation controlled by hospital pharmacy Double blind
Participants	Sweden Children aged 2 to 15 years Acute otitis media = clinical diagnosis
Interventions	Rx: penicillin 50 mg/kg/day in 3 doses Control: matching placebo Duration: 7 days
Outcomes	Examined on days 0, 3 to 4, 8 to 10, 30 Audiogram at days 30 (repeat at 2 months if abnormal)
Notes	

Risk of bias

Thalin 1985 (*Continued*)

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

vanBuchem 1981a

Methods	R = identical bottles; baseline comparability documented Double blind Not intention-to-treat (31 of 202 patients excluded)
Participants	Netherlands Children aged 2 to 12 years Acute otitis media - clinical diagnosis
Interventions	Rxs: amoxicillin 250 mg tds; (2 x 2 factorial design) Control: matching placebo; sham myringotomy Duration: 7 days
Outcomes	Parent report of pain Clinical assessment: day 2, 7, 14, 28, 56. Audiogram at > 2 weeks assessed blind
Notes	(a) Is the two arms without myringotomy

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Yes	A - Adequate

vanBuchem 1981b

Methods	R = identical bottles; baseline comparability documented
Participants	Netherlands Children aged 2 to 12 years Acute otitis media
Interventions	Rxs: amoxicillin 250 mg tds and myringotomy (2 x 2 factorial design) Control: matching placebo; myringotomy Duration: 7 days
Outcomes	Parent report of pain Clinical assessment: day 2, 7, 14, 28, 56 Audiogram at > 2 weeks assessed blind

vanBuchem 1981b (*Continued*)

Notes	(b) Is the two arms with myringotomy	
Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

R: randomisation
Rx: treatment
tds: three times a day
qid: four times daily
ED: Emergency Department

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

Chaput 1982	Short versus long course of therapy
Engelhard 1994	No comparison of antibiotic to placebo; the 3 arms were: Augmentin, myringotomy, or both
Ostfeld 1987	Non-randomised study
Rudberg 1954	Non-randomised study: assigned "randomly" based on case-number but then allowed to change groups
Ruohola 2003	Conducted in children with tympanostomy tubes
Sarrell 2003	No placebo control for antibiotic arm. Method of randomisation not provided and groups appear to be unbalanced at baseline
vanBuchem 1985	Non-randomised study

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

Hoberman NCT00377260

Trial name or title	Efficacy of antimicrobials in young children with acute otitis media
Methods	Randomised, double blind, placebo control
Participants	Children aged 6-23 months with acute otitis media
Interventions	Amoxicillin-Clavulanate
Outcomes	Time to resolution of symptoms
Starting date	Nov 2006
Contact information	
Notes	

Ruohola NCT00299455

Trial name or title	Phase 4 efficacy study of antimicrobials in the treatment of acute otitis media in young children
Methods	Randomised, double blind, placebo control
Participants	Children 6 to 35 months with acute otitis media
Interventions	Amoxicillin-Clavulanate
Outcomes	Time to treatment failure
Starting date	March 2006
Contact information	
Notes	

DATA AND ANALYSES

Comparison 1. Antibiotic versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain	10		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Pain at 24 hours	5	1229	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.78, 1.04]
1.2 Pain at 2 to 7 days	10	2791	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.62, 0.83]
2 Abnormal tympanometry	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 1 month	4	927	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.75, 1.07]
2.2 3 months	3	808	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.76, 1.24]
3 Perforation	2	381	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.24, 1.27]
4 Vomiting, diarrhoea, or rash	5	1401	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [1.09, 1.76]
5 Contralateral otitis (in unilateral cases)	3	579	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.17, 1.36]
6 Late recurrences	6	2153	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.79, 1.10]

Comparison 2. Immediate antibiotic versus delayed antibiotic

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Pain 3 to 7 days	4	959	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.50, 1.12]

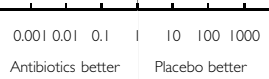
Analysis 1.1. Comparison 1 Antibiotic versus placebo, Outcome 1 Pain.

Review: Antibiotics for acute otitis media in children

Comparison: 1 Antibiotic versus placebo

Outcome: 1 Pain

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 Pain at 24 hours					
Burke 1991	53/112	56/117		22.5 %	0.99 [0.75, 1.30]
Le Saux 2005	82/258	106/254		43.9 %	0.76 [0.60, 0.96]
Thalin 1985	58/159	58/158		23.9 %	0.99 [0.74, 1.33]
vanBuchem 1981a	13/47	11/40		4.9 %	1.01 [0.51, 1.99]
vanBuchem 1981b	17/48	10/36		4.7 %	1.28 [0.67, 2.44]
Subtotal (95% CI)	**624**	**605**		**100.0 %**	**0.90 [0.78, 1.04]**
Total events: 223 (Antibiotics), 241 (Placebo)					
Heterogeneity: Chi^2 = 4.12, df = 4 (P = 0.39); I^2 =3%					
Test for overall effect: Z = 1.37 (P = 0.17)					
2 Pain at 2 to 7 days					
Appelman 1991	14/70	12/56		4.3 %	0.93 [0.47, 1.85]
Burke 1991	20/111	29/114		9.3 %	0.71 [0.43, 1.18]
Damoiseaux 2000	69/117	89/123		28.3 %	0.82 [0.68, 0.98]
Halsted 1968	17/62	7/27		3.2 %	1.06 [0.50, 2.25]
Kaleida 1991	19/488	38/492		12.3 %	0.50 [0.29, 0.86]
Le Saux 2005	43/253	53/246		17.5 %	0.79 [0.55, 1.13]
Mygind 1981	15/72	29/77		9.1 %	0.55 [0.32, 0.94]
Thalin 1985	15/158	25/158		8.1 %	0.60 [0.33, 1.09]
vanBuchem 1981a	6/46	10/38		3.6 %	0.50 [0.20, 1.24]
vanBuchem 1981b	10/48	11/35		4.1 %	0.66 [0.32, 1.39]
Subtotal (95% CI)	**1425**	**1366**		**100.0 %**	**0.72 [0.62, 0.83]**
Total events: 228 (Antibiotics), 303 (Placebo)					
Heterogeneity: Chi^2 = 7.27, df = 9 (P = 0.61); I^2 =0.0%					
Test for overall effect: Z = 4.59 (P < 0.00001)					

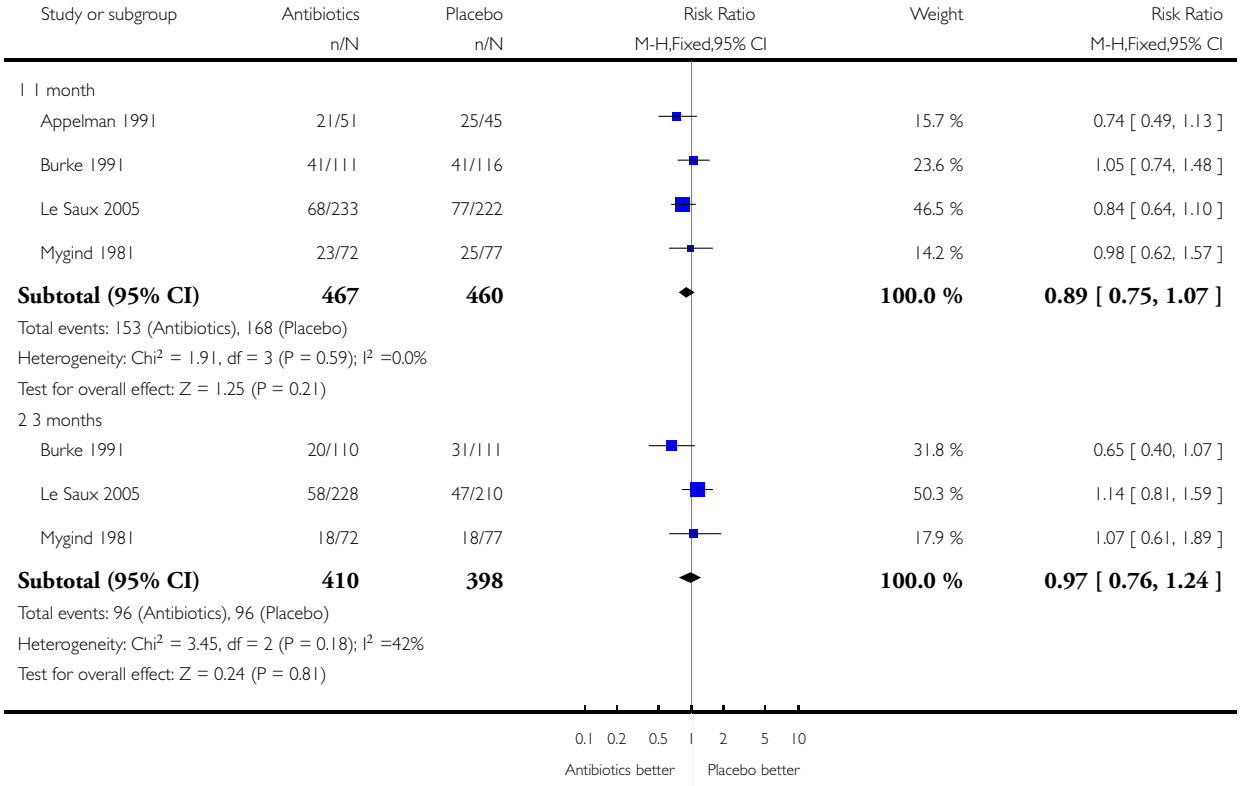


Analysis 1.2. Comparison 1 Antibiotic versus placebo, Outcome 2 Abnormal tympanometry.

Review: Antibiotics for acute otitis media in children

Comparison: 1 Antibiotic versus placebo

Outcome: 2 Abnormal tympanometry



Analysis 1.3. Comparison 1 Antibiotic versus placebo, Outcome 3 Perforation.

Review: Antibiotics for acute otitis media in children

Comparison: 1 Antibiotic versus placebo

Outcome: 3 Perforation

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Burke 1991	0/114	2/118		17.5 %	0.21 [0.01, 4.26]
Mygind 1981	7/72	12/77		82.5 %	0.62 [0.26, 1.50]
Total (95% CI)	**186**	**195**		**100.0 %**	**0.55 [0.24, 1.27]**

Total events: 7 (Antibiotics), 14 (Placebo)

Heterogeneity: Chi^2 = 0.48, df = 1 (P = 0.49); I^2 =0.0%

Test for overall effect: Z = 1.40 (P = 0.16)

Analysis 1.4. Comparison 1 Antibiotic versus placebo, Outcome 4 Vomiting, diarrhoea, or rash.

Review: Antibiotics for acute otitis media in children

Comparison: 1 Antibiotic versus placebo

Outcome: 4 Vomiting, diarrhoea, or rash

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Burke 1991	60/107	39/113		46.7 %	1.62 [1.20, 2.20]
Damoiseaux 2000	20/117	15/123		18.0 %	1.40 [0.75, 2.61]
Le Saux 2005	26/235	27/240		32.9 %	0.98 [0.59, 1.63]
Mygind 1981	3/72	1/77		1.2 %	3.21 [0.34, 30.14]
Thalin 1985	1/159	1/158		1.2 %	0.99 [0.06, 15.75]
Total (95% CI)	**690**	**711**		**100.0 %**	**1.38 [1.09, 1.76]**

Total events: 110 (Antibiotics), 83 (Placebo)

Heterogeneity: Chi^2 = 3.40, df = 4 (P = 0.49); I^2 =0.0%

Test for overall effect: Z = 2.64 (P = 0.0084)

Analysis 1.5. Comparison 1 Antibiotic versus placebo, Outcome 5 Contralateral otitis (in unilateral cases).

Review: Antibiotics for acute otitis media in children

Comparison: 1 Antibiotic versus placebo

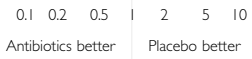
Outcome: 5 Contralateral otitis (in unilateral cases)

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Burke 1991	29/92	33/98		44.5 %	0.94 [0.62, 1.41]
Mygind 1981	2/64	6/65		23.3 %	0.34 [0.07, 1.62]
Thalin 1985	4/130	17/130		32.2 %	0.24 [0.08, 0.68]
Total (95% CI)	**286**	**293**		**100.0 %**	**0.47 [0.17, 1.36]**

Total events: 35 (Antibiotics), 56 (Placebo)

Heterogeneity: $Tau^2 = 0.60$; $Chi^2 = 7.18$, df = 2 (P = 0.03); $I^2 = 72\%$

Test for overall effect: Z = 1.39 (P = 0.16)



Analysis 1.6. Comparison 1 Antibiotic versus placebo, Outcome 6 Late recurrences.

Review: Antibiotics for acute otitis media in children

Comparison: 1 Antibiotic versus placebo

Outcome: 6 Late recurrences

Study or subgroup	Antibiotics n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Kaleida 1991	125/448	124/446		56.7 %	1.00 [0.81, 1.24]
Laxdal 1970	24/94	10/48		6.0 %	1.23 [0.64, 2.35]
Le Saux 2005	27/248	39/236		18.2 %	0.66 [0.42, 1.04]
Mygind 1981	19/72	21/77		9.3 %	0.97 [0.57, 1.65]
Thalin 1985	9/159	7/158		3.2 %	1.28 [0.49, 3.35]
vanBuchem 1981a	10/92	13/75		6.5 %	0.63 [0.29, 1.35]
Total (95% CI)	**1113**	**1040**		**100.0 %**	**0.93 [0.79, 1.10]**

Total events: 214 (Antibiotics), 214 (Placebo)

Heterogeneity: $Chi^2 = 4.81$, df = 5 (P = 0.44); $I^2 = 0.0\%$

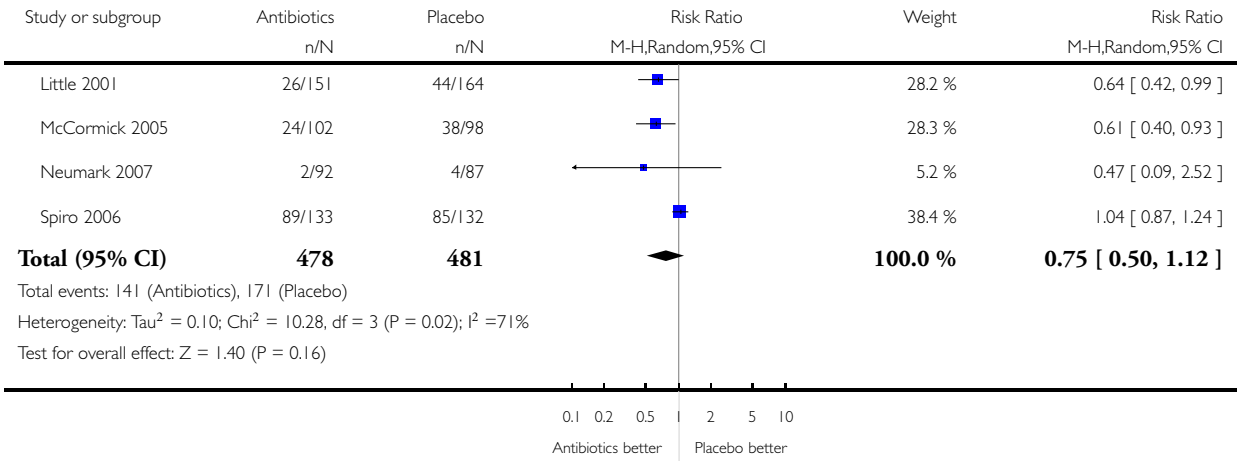
Test for overall effect: Z = 0.79 (P = 0.43)

Analysis 2.1. Comparison 2 Immediate antibiotic versus delayed antibiotic, Outcome 1 Pain 3 to 7 days.

Review: Antibiotics for acute otitis media in children

Comparison: 2 Immediate antibiotic versus delayed antibiotic

Outcome: 1 Pain 3 to 7 days



F E E D B A C K

Antibiotics for AOM

Summary

1. Types of interventions includes surgical procedures versus placebo which are not dealt with in this review and should therefore be deleted.
2. The authors included only six studies in the analysis but in 1994 another meta-analysis by Rosenfeld and colleagues to which the authors refer was published which included 33 randomized trials with 5400 children. Were any studies with a no-treatment control excluded and if so why?
3. The meta-analysis by Rosenfeld is only mentioned in the text; there is no reference to it. How many patients were included in the meta-analysis?
4. It is stated that trials analysed on an intention to treat basis were preferred. This indicates that other trials were excluded which does not seem reasonable?
5. The description of the factorial trial is unclear; I suppose the authors excluded all patients who were randomised to myringotomy?
6. In the trial by Laxdal the control group was more closely monitored. The trial therefore violates the principle that all other Traitement etc. should be the same in the two randomised groups and it should therefore be excluded.
7. The strategy described by Dickersin lacks a publication year and it is not cited in the references.
8. The search was done in August 1994 and the Cochrane review was published in April 1997. The search should therefore have been updated before publication since Cochrane reviews are meant to be up-to-date.
9. There is no information whether the original authors and the pharmaceutical industry were contacted about additional data including unpublished trials and trials not registered in Medline. Useful trial data might be expected to be available in books published in connection with symposia arranged by the drug industry for example.
10. What is quality methodology?
11. The term blinded randomisation should be avoided since it may be confused with blinded treatments; the term concealed allocation should be used.
12. The elaborated quality assessment scale for the trials does not appear under Results and should therefore be deleted.

13. The authors refer to Rosenfeld's meta-analysis when they state that 80% of the children have recovered spontaneously after 24 hours. Since such a percentage refers to untreated patients it raises the question why the authors did not use their own data? If these data are used in a meta-analysis of the risk difference the NNT will be 23 not 12 as stated in the Cochrane review.
14. For several of the excluded studies the authors gave no reason for the exclusion.
15. There should be a cross-reference to the authors' nearly identical review in the BMJ (24 May 1997).

Reply

The changes made were:
1. We updated the search. (see Johansen criticism 7 & 8). No recent trials were found, but we recognised that the Appelman trial qualifies (originally we had thought this was only prevention of recurrent otitis, rather than treatment of acute otitis in children with a recurrent episode).
2. We have corrected and updated the Relative Risk Reduction and consequent Number-Needed-to-Treat (see Johansen criticism 13).
3. We have separate the four arms of the Van Buchem factorial trial, and treated this as "two" trials (i.e., two separate strata): (a) without myringotomy - antibiotics versus placebo (b) with myringotomy - antibiotics versus placebo. (see Johansen criticism 5)
4. As suggested by Andrew Herxheimer, we have added several references including (a) Chris Cates BMJ, and (b) Kozrskyj's meta-analysis of short versus long duration of antibiotics (rather than just the de Saintonge paper).
5. We have made small text changes in response to Johansen's criticisms 5 (description added), 7 (dropped), 10 (- methodological quality), 11 (- allocation concealment), 13 (corrected in text), 14 (exclusions explained), and 15 (reference added).
6. As we have pointed out to Johansen in the BMJ correspondence, and point out in the discussion here, the Rosenfeld meta-analysis is largely concerned with comparison between antibiotics. (see Johansen criticism 2 & 3).

Contributors

Helle Krogh Johansen
Peter C. Gøtzsche
Posted 22/11/2000

Antibiotic versus placebo for acute otitis media

Summary

This excellent and important review was completed in 1996, and I hope it will soon be updated. It is especially worth noting and discussing the new study by Christopher Cates (BMJ 13 March 1999, p715-6), who has successfully tried a method in his general practice of substantially reducing the use of antibiotic in children with acute otitis media. This would considerably strengthen the 'implications for practice' in the conclusion.
I would like to suggest that in updating this review the objectives be amended and the trial by Chaput de Saintonge et al be added, because it contributes an important piece of evidence about the duration of amoxicillin therapy. The review concludes that some children will benefit from antibiotic treatment, and it would be valuable to say (as a result of the Chaput trial) that the evidence indicates that a 3-day course is no less effective than a 10-day course.

Reply

Chris and I have revised the acute otitis media review. We have made a number of modest changes, though none of these change the conclusions. However, because a new trial is included we've called it a "substantive update".

Contributors

Andrew Herxheimer
Posted 22/11/2000

Antibiotic versus placebo for acute otitis media i

Summary

1. I am glad to see this has been updated, but the text does not explain what was updated, forcing the reader who wants to know to compare the previous version with the new one. Is it the sentence referring to Cates 99 [in implics for practice] or other points as well?
2. There are embarrassingly many typos in the refs to excluded and additional studies: Chaput de SaintoNGE, amoxyciillin, author not in bold in the first few additional refs, below that several authors' names begin in lower case when they should all begin with a capital.
3. It is implied that no comcrit was received before the final submission date for CL99 issue 3. Is this true? I think I sent one early this year.
CONFLICT OF INTEREST: None.

Reply

Excluded and additional references have been corrected and completed.

Contributors

Andrew Herxheimer
Posted 22/11/2000

Antibiotic versus placebo for acute otitis media

Summary

1. The new study also reported diarrhoea and rashes. Shouldn't it be included in this outcome (side effects) also?
2. I think the methods used for calculating the NNT should be made explicit.
3. The new trial is important because it looks at a sub-group who were believed to be a greater risk of poor outcomes. In EBM OM Rosenfeld and Bluestone review the study inclusion criteria and state that the meta-analysis 'most likely can be applied to children 2 years of age or older with non severe AOM, and most likely cannot be applied to infants with severe symptoms'. This study provides the best evidence that the conclusions of the meta-analysis do appear to apply to this group. Perhaps this point needs to be emphasised (the peak incidence of AOM is 9 months).
4. I think the comment that 80% resolve spontaneously within 2 to 7 days is now slightly misleading as about 70% of the control children were clinical failures in this new study.
5. The entry in the table 'characteristics of included studies' should be consistent with previous entries.
6. Some typographical errors and inconsistent spelling.

Reply

Thank you for your comments and suggestions.
The Absolute risk difference was used to calculate the NNT in this systematic review. This has now been stated in the Results section of the review. A comment regarding the application of the conclusions to infants with severe symptoms has been added to the discussion section. The 70% incidence of clinical failure in the Damoiseaux, 2000 study have been included and typographical errors and inconsistencies have been corrected.

Contributors

Peter Morris
Posted 22/11/2000

Antibiotics for acute otitis media

Summary

The second graph (comparison of outcome Abnormal Tympanometry) has wrong labels on the X-axis.
It says 'antibiotics better' (left) and 'placebo worse' (right). The second should probably be 'placebo better'.
The other graphs are correctly labelled.
I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my
criticisms.

Reply

The label on the x-axis has been corrected and now reads 'Placebo better'.

Contributors

Johannes C van der Wouden
Posted 19/02/2002

Antibiotics reduce the risk of mastoiditis?

Summary

I agree with other commentators that this is a very good and important review. However, I would like some more clarity concerning one statement in your conclusions: Antibiotic treatment may play an important role in reducing the risk of mastoiditis in populations where it is more common.
What is the basis for this statement?In the included studies with more than 2000 children only one mastoiditis case occurred in a patient in a penicillin treated group. In the review you mention two articles concerning the mastoiditis. Firstly, the study of Rudberg (1954), which was excluded since it was not properly randomised. Even if it were, the rate of 17 % of mastoiditis cases is in these times highly unlikely, as is shown in the included studies. The second article by Berman (1995) is a literature review, where only the available literature concerning developing countries were reviewed. The goal of this review was to determine the extent to which otitis media impacts mortality and morbidity in developing countries, not to study the effect of antibiotics on (acute) otitis media or mastoiditis.
In neither of these studies evidence is shown that antibiotic treatment reduces the risk of mastoiditis, certainly not in developed countries. Since I think the rest of the review is excellent, I wonder if you could explain to me the reasons for including this statement in the conclusions.
I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my criticisms.

Reply

Dear Markus,
We included the caveat about mastoiditis because we, and the reviewers, were concerned about misinterpretation of the results in situations with high rates of mastoiditis. We were mindful that "an absence of evidence is not equal to evidence of absence". Since the trials we analysed did not include high rates of mastoiditis, we can use them as the sole basis. Given that we have two weaker pieces of evidence:
1. The trials do show a modest reduction in other infective complications
2. The excluded Rudberg trial did show dramatic effects that we don't think explicable from the potential biases of that study.
Prudence would then suggest that antibiotics are advisable if there is a substantial risk of mastoiditis,
Regards,
Paul Glasziou

I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my criticisms.

Contributors

Markus Oei (ENT surgeon)
Posted 26/08/02

Incorrect NNT

Summary

I am a bit troubled by the way the conclusions of this review are written. By combining results of treatment at Days 2 to 7 in arriving at a NNT of 15 one is going to underestimate treatment benefit after 2 days. In your abstract though you say the ARR is 7% and NNT 15 for some pain after two days. This is simply not correct. If one carefully looks at trials that record pain at the end of day 2 the ARR is in fact 20% giving a NNT of 5. Clearly acute otitis media is an acute condition and the main benefit of antibiotics is pain control and symptom relief. If this is measured at the end of 2 days the benefits are greater than one would surmise just from reading the review. It would be absurd to do a review of pain relief for biliary colic treated with pethidine and measuring the outcome 7 days later. For acute conditions symptom control in the first few days should be the outcome of interest. NNT are meaningless unless giving a time period at which they apply. I think the review needs correcting. This is not just of academic interest but of direct relevance to parents and doctors faced with a child with AOM in pain. Unfortunately your review gets quoted uncritically and invariably the NNT of 15 is given for symptom control after 2 days. I am currently trying to correct a brochure produced here in New Zealand for GPs to give to parents of children with AOM and it uncritically repeats this misleading information. If you want to comment on symptom control after Day 2 DO NOT pool it with data from Day 7 or later!
I certify that I have no affiliations with or involvement in any organisation or entity with a direct financial interest in the subject matter of my criticisms.

Reply

Thankyou for your comment. We agree that we should be clearer about the time frame to which the ARR 7% and NNT 15 applies. With the availability of results of the individual patient data meta-analysis (Rovers 2006) we are able to obtain a clearer indication of the recovery pattern over time. We have reported this in the text and included an extra figure.

Contributors

Paul Corwin
Posted 19/02/05

Comment on two of the meta-analyses

Summary

Summary
Feedback: This is a comment on two of the meta-analyses in the Cochrane Review, Glasziou et al. (2004). These analyses are for the outcomes “Vomiting, Diarrhea or Rash” and “Contralateral AOM.”
1) Vomiting, Diarrhea or Rash
First we consider the meta-analysis relating possible adverse effects of treatment. In Glasziou et al. (2004), this is done using the composite outcome “Vomiting, Diarrhea or Rash.” The data used for this meta-analysis are reproduced in the table below.
Outcome: Vomiting, Diarrhea or Rash
Study Treatment Control

Thalin et al. (1985) 1/159 1/158
Burke et al. (1991) 53/114 36/116
Mygind et al. (1981) 3/72 1/77
Damoiseaux et al. (2000) 20 12
We noted five major problems with this meta-analysis. The first relates to clinical heterogeneity. This was manifested in variations in terms of the types of adverse effects recorded, who recorded them (parent or physician) and the time period over which they were recorded (from 3-4 days to 21 days). In Thalin et al. (1985), the effects were recorded by an ENT physician on days 3-4 or days 8-10. In Burke et al. (1991), they were recorded by a parent in a 21-day diary. In Mygind et al. (1981), it was done with 7 day parental score card. And in Damoiseaux et al. (2000), this was done by a physician on day 4 and day 11.
Another related problem is the use of the outcome "Vomiting, Diarrhea or Rash" as an entity. Vomiting is only reported in Burke et al. (1991). It is not clear whether it was not observed, or observed but not reported in the other studies. Also, in Burkeat al. (1991), as noted, such effects were recorded over a 21-day period while the maximum recording period for the other studies was 11 days. The totals then gave a much higher weight to Burke et al. (1991) than may be appropriate.
A third problem is possible double or triple counting with the use of the composite outcome. For Burke et al. (1991), the group numerator is the sum of the cases for each effect. A number of children may well have had two or three of these effects at the same time.
A fourth problem is also with the numbers used. Damoiseaux et al. (2000) gives two sets of numbers for "de novo diarrhoea," for day 4 and for day 11. Glasziou et al. (2004) uses the day 4 numbers only. The reason for this choice is not clear. It may be better to use the sums of the numbers for the two days (provided this does not involve double counting.)
Further, the group denominators used for Burke et al. (1991) are perhaps not what they should be. In this study, the adverse effects were recorded by parents. Only 220 (treatment = 107, control = 113) out of a total of 232 (treatment = 114, control = 118) diaries were collected. Using the total group size in the numerator (also done in Burke at al. (1991)) is thus not appropriate.
Finally, it is not clear if the numbers for adverse effects in Burke et al. (1991) and Damoiseaux et al. (2000) included the cases known or suspected to have dropped out of the study due to an adverse effect.
In our view, this meta-analysis should be modified as follows: First, do not use the data on vomiting until it is reported in at least one other study. Second, do not use a composite adverse effect outcome. Instead, perform separate meta-analyses for diarrhoea and rash. Third, for Damoiseaux et al. (2000), use the total numbers for day 4 and day 11, with the above noted qualification in mind. Fourth, for Burke et al. (1991) change the denominators as noted above. Finally, include drop outs due to side effects in the meta-analyses. The table below gives the possible numerators to be used for these meta-analysis.
Separated Data on Side Effects
Vomiting Diarrhea Rash
Study T C T C T C
Thalin et al. (1985) ? ? 0 0 1 1
Burke et al. (1991)+ 20 14 24 16 16 9
Mygind et al. (1981) ? ? 2 1 1/2? 0
Damoiseaux et al. (2000)*,+ ? ? 20 12 0 3
Damoiseaux et al. (2000)? ? ? 34 22 0 3
Note: ? Unclear if vomiting not observed or not reported.
Note: ? = 2 if a dropout was not counted; else = 1.
* Day 4; ? Day 4 and Day 11; + unclear if dropouts counted.
2) Contralateral AOM
The occurrence of contralateral AOM, as is made clear in Glasziou et al. (2004), is relevant for only the cases with unilateral AOM at the outset. This numbers in the table below are used for the meta-analysis of this outcome in Glasziou et al. (2004).
Outcome: Contralateral AOM
Study Treatment Control
Thalin et al. (1985) 4/159 17/158
Burke et al. (1991) 29/98 33/102
Mygind et al. (1981) 2/72 6/77
Overall 35/329 56/337
The first problem is clinical heterogeneity, as noted in the table below. The issues in that respect are similar to those stated for the meta-analysis of adverse effect.
Clinical Heterogeneity: Contralateral AOM
Study Time Period Evaluator(s)
Thalin et al. (1985) day 8-10 or day 30 ENT Physician

Burke et al. (1991) 21 days Parent
Mygind et al. (1981) 1 week Physician
A further problem with this meta-analysis is the denominators used. Consider this issue for each study.
Thalin et al. (1985): The denominators in Glasziou et al. (2004) include unilateral and bilateral cases. Only 82% of the episodes were unilateral at the start, but the breakdown by group is not given in the paper. We obtained adjusted denominators as follows. Treatment: 0.82?159 = 130; Control: 0.82?158 = 130. The bias now remains the same but the precision level is now corrected.
Burke et al. (1991): The denominators represent the total unilateral cases for each group. The study authors used these denominators. Completed 21-day diaries, the source of data on contralateral otitis, were, however, available only for 107 (of 114) in the treatment group and 113 (of 118) in the control group. So either one assumes that only the bilateral cases had missing diaries (which is unlikely) or that the rate of missingness in each group was not affected by laterality. In the latter case, the adjusted denominators are: Treatment: (98?107)/114 = 92; Control: (102?113)/118 = 98. The level of bias remains unknown but the precision level is possibly better.
Mygind et al. (1991): The denominators used include unilateral and bilateral cases. But there were 8 bilateral cases in the placebo group and 14 in the control group. So the appropriate denominators are Treatment: 72 - 8 = 64; Control: 77 - 14 = 65. The bias and precision levels are now corrected.
The appropriately adjusted data for this meta analysis are given below.
Contralateral AOM: Adjusted Data
Study Treatment Control
Thalin et al. (1985) 4/130 17/130
Burke et al. (1991) 29/92 33/98
Mygind et al. (1981) 2/64 6/65
Overall 35/286 56/294
References
1. Burke P, Bain J, Robinson D and Dunleavey J (1991) Acute red ear in children: Controlled trial of non-antibiotic treatment in general practice, British Medical Journal, 303, 558?562.
2. Damoiseaux RAMJ, van Balen FAM, Hoes AW, Verheij TJM and de Melker RA (2000) Primary care based randomised, double blind trial of amoxicillin versus placebo for acute otitis media in children aged under 2 years, British Medical Journal, 320: 330?334.
3. Glasziou PP, Del Mar CB, HayemMand Sanders SL (2004) Antibiotics for acute otitis media in children, Cochrane Database of Systematic Reviews, 2004; (1): CD000219. Art. No: CD000219, DOI: 10.1002/14651858.CD000219.pub2 (21pages)
4. Mygind N, Meistrup-Larsen K-I, Thomsen J, Thomsen VF, Josefsson K and Sorenson H (1981) Penicillin in acute otitis media: a double-blind placebo-controlled trial, Clinical Otolaryngology, 6: 5?13.
5. Thalin A, Densert O, Larsson A, Lyden E and Ripa T (1986) Is penicillin necessary in the treatment of acute otitis media? In: Proceedings of the International Conference on Acute and Secretory Otitis Media, Amsterdam, The Netherlands, Kegler Publications, pages 441?446.
Submitter agrees with default conflict of interest statement:
I certify that I have no affiliations with or involvement in any organization or entity with a financial interest in the subject matter of my feedback.

Reply

1) We acknowledge the variation in methods of collecting and recording information on adverse events and in the types of adverse events reported in the included trials. We contend however, that considering vomiting, diarrhoea or rash as an entity is justified by the easier interpretation it provides . Though the events are biologically very different, they are of similar seriousness; irritating and difficult to manage but minor in nature. Also, as pointed out in the above comments, dividing the adverse events into each type would not be helpful as they are infrequently reported (i.e. vomiting is only reported in one study). We recognise that 'lumping' the adverse events together is a crude approach but believe the benefits in continuing to do so outweigh the drawbacks. In the discussion section of this update we have made reference to the results of the individual patient data meta analysis (Rovers 2006) (which included a subset [n=6] of the trials included in this review [n=10]) which reports separately on the frequency of diarrhoea and rash in the treatment and control groups. We appreciate your consideration and suggestions related to the inclusion of drop outs due to side effects in the Burke and Damoiseaux studies. Corrections to the data have been incorporated.
2) Thankyou for pointing out the numerical errors in the meta analysis of contralateral AOM. We have corrected the analysis as suggested. This results in a minor changed to the pooled random effects OR (OR 0.44 95% CI 0.16, 1.26 versus 0.45 95% CI 0.16, 1.23) with antibiotics appearing to reduce contralateral AOM though the effect was not significant with the random effects model.

Contributors

Karim F. Hirji, D.Sc
Peter C. Gøtzsche
Posted 06/09/07

WHAT'S NEW

Last assessed as up-to-date: 8 November 2008.

2 September 2009	Amended	95% confidence intervals for the outcome pain at 2-7 days and adverse events stated in the abstract and body of the review corrected.

HISTORY

Protocol first published: Issue 1, 1995

Review first published: Issue 3, 1996

2 July 2008	New search has been performed	The search was updated in July 2008. Four new trials were identified and included in the review (Le Saux 2005, Spiro 2006, Neumark 2007 and McCormick 2005). One of these trials (Le Saux 2005) compared antibiotics with placebo. For the outcome pain at 24 hours and 2 to 7 days, inclusion of this trial did not alter the overall conclusions of the primary analysis. The three other new trials (Spiro 2006, Neumark 2007, McCormick 2005) compared immediate antibiotics with various observational approaches. One of the new trials compared immediate antibiotics with delayed prescribing (Spiro 2006). The other trials (McCormick 2005 and Neumark 2007) compared immediate antibiotics with 'watchful waiting', in which no prescription was supplied but advise on when to seek treatment was provided. Outcome data on pain at 3 to 7 days from these trials were analysed with data from another trial of immediate versus delayed prescription (Little 2001). In earlier versions of the review data from the Little (Little 2001) trial had been included in a sensitivity analysis. In this update, data from the four trials comparing immediate versus observational management strategies have been included in the main analysis. Information on subgroups of children who are most likely to benefit from treatment with antibiotics, obtained from a meta-analysis of individual patient data has been included in this review (Rovers 2006). Methods of the IPD meta-analysis, conducted by two authors on this review (and others) are also included. Survival curves from the IPD meta-analysis showing the pattern of recovery from acute otitis media over time has been included as an extra figure. Two ongoing trials comparing antibiotics with placebo in children < 35 months have been identified.
17 January 2008	Amended	Converted to new review format.
4 September 2007	Feedback has been incorporated	Feedback added.
18 February 2005	Feedback has been incorporated	Feedback and reply added.
24 March 2003	New search has been performed	Searches conducted.
24 August 2002	Feedback has been incorporated	Feedback added.
17 February 2002	Feedback has been incorporated	Feedback added.
20 November 2000	Feedback has been incorporated	Feedback comments and replies added.

(*Continued*)

3 February 2000	New citation required and conclusions have changed	Conclusions changed.
3 February 2000	New search has been performed	Searches conducted.
30 December 1998	New search has been performed	Searches conducted.
30 July 1994	New search has been performed	Searches conducted.

CONTRIBUTIONS OF AUTHORS

Chris Del Mar (CDM) and Paul Glasziou (PG) prepared the original version of the review.

Sharon Sanders (SLS) conducted searches, identified studies, extracted data and prepared manuscript for the updated the reviews in 2003, 2007 and 2008.

Maroeska Rovers (MMR) participated in the 2007 update providing data and information from the individual patient data meta-analysis that has been included in this update.

PG, CDM, MMR and SLS have reviewed and provided comment on the updated version of the review.

DECLARATIONS OF INTEREST

None noted.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Age Factors; Anti-Bacterial Agents [*therapeutic use]; Otitis Media [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Child; Humans