1-26-2004

Antibiotics for acute otitis media in children [Review]

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Antibiotics for acute otitis media in children (Review)

Glasziou PP, Del Mar CB, Sanders SL, Hayem M

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ABSTRACT

Background
Acute otitis media is one of the most common diseases in early infancy and childhood. Antibiotic use for acute otitis media varies from 31% in the Netherlands to 98% in the USA and Australia.

Objectives
The objective of this review was to assess the effects of antibiotics for children with acute otitis media.

Search strategy
We searched the Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE, Index Medicus (pre 1965), Current Contents and reference lists of articles from 1958 to January 2000. The search was updated in 2003.

Selection criteria
Randomised trials comparing antimicrobial drugs with placebo in children with acute otitis media.

Data collection and analysis
Three reviewers independently assessed trial quality and extracted data.

Main results
Ten trials were eligible based on design, only eight of the trials, with a total of 2,287 children, included patient-relevant outcomes. The methodological quality of the included trials was generally high. All trials were from developed countries. The trials showed no reduction in pain at 24 hours, but a 30% relative reduction (95% confidence interval 19% to 40%) in pain at two to seven days. Since approximately 80% of patients will have settled spontaneously in this time, this means an absolute reduction of 7% or that about 15 children must be treated with antibiotics to prevent one child having some pain after two days. There was no effect of antibiotics on hearing problems of acute otitis media, as measured by subsequent tympanometry. However, audiometry was done in only two studies and incompletely reported. Nor did antibiotics influence other complications or recurrence. There were few serious complications seen in these trials: only one case of mastoiditis occurred in a penicillin treated group.

Authors’ conclusions
Antibiotics provide a small benefit for acute otitis media in children. As most cases will resolve spontaneously, this benefit must be weighed against the possible adverse reactions. Antibiotic treatment may play an important role in reducing the risk of mastoiditis in populations where it is more common.

[This abstract has been prepared centrally.]

PLAIN LANGUAGE SUMMARY

Antibiotics are not very useful for most children with acute otitis media
Acute otitis media (infection in the middle ear space) is common in children and causes pain and deafness. The review found that antibiotics did not alter pain within the first day, (when most children were better), only slightly reduced it in the few days following and did not reduce the deafness (that can last several weeks). There was not enough information to know if antibiotics reduced rare complications. Antibiotics caused unwanted effects such as diarrhoea, stomach pain, and rash, and may increase resistance to antibiotics in the community. It is difficult to balance the small benefits against the small harms of antibiotics for most children. However, they may be necessary in the very young or in severe or prolonged cases.

**BACKGROUND**

Acute otitis media 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 acute otitis media by three months of age. The peak age-specific incidence is between six and 15 months (Klein 1989). Despite a large number of published clinical trials, there is no consensus on the therapy of acute otitis media; for example, the rates of use of antibiotics for acute otitis media varies from 31% in the Netherlands to 98% in the USA and Australia (Froom 1990). A meta analysis (Rosenfeld 1994) emphasises that for most children acute otitis media is a disease which resolves spontaneously. However, one semi-randomised trial in Sweden of 1,365 subjects in 1954 (Rudberg 1954) reported a rate of mastoiditis of 17% in the untreated group versus none in the penicillin treated groups.

**OBJECTIVES**

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

We attempted to determine to what extent antibiotics therapy was more effective, and what, if any advantages it offered to children in terms of symptom relief, complications (such as mastoiditis), and longer term hearing problems from middle ear effusion (as measured by tympanometry or audiogram).

**SEARCH METHODS FOR IDENTIFICATION OF STUDIES**

See: Acute Respiratory Infections Group methods used in reviews.

Computer-based and manual literature searches were used to compile all relevant published randomised controlled trials of antibiotic treatment of otitis media 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. The Cochrane Central Register of Controlled Trials (CENTRAL) (issue 1, 2003); MEDLINE (January 2000 to March 2003); and EMBASE (January 1990 to March 2003) were searched. There were no language restrictions.

The following search strategy was run on MEDLINE and modified terms were used for the EMBASE database:
METHODS OF THE REVIEW

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, e.g., 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 each reviewer. Assessment was done “blind”, (i.e. without the knowledge of the study results, nor the names of the authors, institutions, journal of publication). The reviewers met after their study assessments in order to resolve any disagreements, still blinded to results.

Treatment differences are analysed as odds ratios with 95% confidence intervals calculated by the Peto method using a fixed-effects model. Results of the meta-analyses are reported as relative risk or relative risk reductions. Heterogeneity was assessed using the chi-squared heterogeneity test as well as visual inspection of the forest plots. When heterogeneity was present (p<0.05) the data were 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).

DESCRIPTION OF STUDIES

Ten trials were eligible for the review of antibiotics against placebo, though only eight included patient-relevant outcomes. 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). One study (Howie 1972) did not report on patient-relevant outcomes such as symptoms or hearing problems; yet another study (Laxdal 1970) reported only recurrences. A recent trial (Little 2001) comparing immediate with delayed antibiotic therapy in which only 24% (36/150) of children in the delayed arm reported using antibiotics, has been included in a sensitivity analysis. Thus most analyses are based on at most eight studies.

METHODOLOGICAL QUALITY

The methodological quality of the ten eligible studies was generally high. Seven of the eight trials that reported patient-relevant outcomes used an adequately concealed allocation (blinded randomisation) and outcome assessment. Two studies failed to include all children in follow-up assessments, but exclusions were less than 10% (Halsted 1968; Howie 1972).

RESULTS

Pain: The combined results of the trials showed that by 24 hours from the start of treatment, two thirds of children had recovered whether or not they had placebo or antibiotics. At two to seven
days, approximately 80% of children had spontaneously recovered (pooled control groups). Antibiotics achieved a further 30% relative reduction in the risk of pain (95% CI: 19% to 40%). This means overall 7% fewer children had pain after two to seven days: about 15 (95%CI: 11 to 24) children needed to be treated to prevent one child experiencing pain after two to seven days (1/RRR*average risk). Results were similar when data from the trial (Little 2001) comparing immediate versus delayed antibiotics (only 24% of children in the delayed treatment arm used antibiotics) was included in a sensitivity analysis.

Hearing: There was 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, 1981, 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 vs placebo).”

Progression of symptoms: There appears to be reduced contralateral otitis media in the antibiotic group, though with the heterogeneous results, this was non-significant in the random effects model, but an increase in adverse effects, namely nausea, diarrhoea, and rash. This is largely based on the effects of amoxycillin seen in the Burke study, which was one of the few studies to report adverse effects. Relapse was common. Burke states “The mean number of recorded recurrences of otitis media or acute red ear was 0.70 (range 0-4) in the antibiotic group and 0.63 (range 0-7) in the placebo group and this difference was not significant (difference 0.06; 95% confidence interval -0.22 to 0.339).” Five other trials reported the proportions who relapsed; combined these give an odds ratio of 0.99, which is consistent with Burke’s findings.

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.

**DISCUSSION**

This review shows that antibiotics have no early impact, and a modest overall impact on the clinical course of acute otitis media. 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 sub-populations where mastoiditis is still judged a frequent problem, such as in some developing countries (Berman 1995), antibiotic treatment would be strongly advised.

Does the effect vary in different clinical groups? Our NNT of 15 is for the “average” case, and may vary in subgroups. Age, fever, and the presence of vomiting may all have implications. Though generally the clinical predictors of a delayed resolution or unfavourable course have been little explored, Burke (Burke 1991) and Appelman (Appelman 1991) both found higher rates of failure of placebo treatment among the young (less than two years), and those with bilateral acute otitis media, but the differences were modest. The more recent trial (Damoisaux 2000) in children under two confirms the longer duration, but same relative effect of antibiotics in this age group. A subgroup analysis of a trial by Little (Little 2001) suggested that most benefit was in the subgroup of children with high fevers or vomiting. Examination of the L’Abbé plot (Figure 01) for the presence of pain at 2-7 days suggests the absolute benefit of antibiotics increases with the severity of the disease (as measured by the control group event rate).

Does the impact vary by duration of antibiotics? Most trials use seven days of antibiotic treatment. A recent meta-analysis of five days of antibiotics compared with eight to ten days showed a further modest reduction, with an NNT of 44 at 20-30 days. However, it included signs of otitis as well as symptoms (Kozyrskyj 1998).

A previous meta-analysis had examined the question of whether antibiotics were indicated and concluded that the answer is a qualified “yes” (Rosenfeld 1994). It estimated a number needed to treat (NNT) of seven for “primary control”, 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. Children over 2 without high fever or vomiting could generally be treated with...
analgesia, and if thought necessary, a "delayed prescription" for antibiotics.

Of note, is a recent paper has shown that doctors commonly over-diagnose acute otitis media (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-acute otitis media). 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.

ASSHORS’ CONCLUSIONS

Implications for practice

Antibiotics shorten the course of acute otitis media. However in the West, most cases spontaneously remit with no complications, and the number-needed to treat is about 15. Therefore management should emphasize advice about adequate analgesia and the limited role for antibiotics. 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.cates.cwc.net/.

Implications for research

Further research is needed to identify which subgroups will have a prolonged or complicated course. Systematic reviews are needed on the role of different symptomatic treatments, such as paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs), and of preventive manoeuvres such as vaccines and xylitol.

FEEDBACK

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 treatment 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).

Author’s 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 antiobiotics. (see Johansen criticism 2 & 3).

Contributors
Helle Krogh Johansen

**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 amoxycillin 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.

Author’s 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

**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.

Contributors
Paul Corwin

POTENTIAL CONFLICT OF INTEREST

None noted.

ACKNOWLEDGEMENTS

We would like to thank Professor Charles Bridges-Webb for stimulating initial discussions and for constructive advice on the protocol for this review, and Professor Steve Berman for helpful comments on the draft review. We would also like to thank Bruce Arroll and Tom Fahey for peer refereeing the updated review.

SOURCES OF SUPPORT

External sources of support

- No sources of support supplied

Internal sources of support

- No sources of support supplied

REFERENCES

References to studies included in this review

Appelman 1991 (published data only)


Burke 1991 (published data only)

Damoiseaux 2000 (published data only)

Halsted 1968 (published data only)

Howie 1972 (published data only)
Kaleida 1991 [published data only]

Laxdal 1970 [published data only]

Mygind 1981 [published data only]

Thalin 1985 [published data only]

van Buchem 1981a [published data only]

van Buchem 1981b [published data only]

References to studies excluded from this review

Chaput 1982

Engelhard 1994

Little 2001

Ostfeld 1987

Rudberg 1954

Ruohola 2003

van Buchem 1985

Additional references

Berman 1995

Cates 1999

Chalmers 1990

Dickersin 1994

Froom 1990

Klein 1989

Kozyrskyj 1998

Rosenfeld 1994

Rothman 2003

Stool 1989
### Characteristics of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Appelman 1991</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>R= computer generated list place in sealed envelopes - allocated by otolaryngologist.</td>
</tr>
<tr>
<td></td>
<td>Double blind (GP and patient blind).</td>
</tr>
<tr>
<td></td>
<td>Baseline comparability documented.</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>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.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Rx: Amoxycillin/clavulanate (weight tailored dose)</td>
</tr>
<tr>
<td></td>
<td>Control: matching placebo.</td>
</tr>
<tr>
<td></td>
<td>Duration: 7 days.</td>
</tr>
<tr>
<td></td>
<td>All children were also given paracetamol and oxymetazoline nose drops.</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Assessment by (blinded) GP at (i) 3 days of fever (&gt;38°C) and otalgia, and (ii) 14 days or otorrhoea, and (iii) 1 month otoscopy and tympanometry.</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>“failure” = either otalgia or fever &gt; 38 or both at 3 days.</td>
</tr>
<tr>
<td><strong>Allocation concealment</strong></td>
<td>A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Burke 1991</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>R= identical number bottles; sealed randomisation code</td>
</tr>
<tr>
<td></td>
<td>double blind</td>
</tr>
<tr>
<td></td>
<td>Intention to treat analysis</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>United Kingdom. Children aged between 3 and 10 years</td>
</tr>
<tr>
<td></td>
<td>Acute earache and at least one abnormal eardrum.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Rx: Amoxycillin 250mg tds</td>
</tr>
<tr>
<td></td>
<td>Control: matching placebo tds</td>
</tr>
<tr>
<td></td>
<td>Duration: 7 days.</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Symptom diary kept by parents</td>
</tr>
<tr>
<td></td>
<td>Home visits by researcher: 24hrs, 5-7 days.</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>1. Fig 2 appears to show that, at baseline (0 hours), fewer children were crying in the amoxycillin arm, suggesting a failure of randomisation.</td>
</tr>
<tr>
<td></td>
<td>2. It is not clear whether the “discharging ears” in Table I should be included as perforations.</td>
</tr>
<tr>
<td><strong>Allocation concealment</strong></td>
<td>A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Damoiseaux 2000</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>R= computerised two block randomisation</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>Netherlands. 240 children between 6 mths and 2 years attending general practice. Diagnosis according to Dutch guidelines.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Rx: Amoxicillin suspension 40mg/kg/day in three divided doses for 10 days of placebo suspension</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Persistent symptoms at day 4 assessed by GP. Defined as persistent earache, fever (&gt;38°C), crying or irritability.</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Allocation concealment</strong></td>
<td>A</td>
</tr>
</tbody>
</table>
### Characteristics of included studies (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Methods</th>
<th>Participants</th>
<th>Interventions</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Halsted 1968</td>
<td>R=randomisation by predetermined code, unknown to physician Blinded using placebo</td>
<td>USA clinical diagnosis of acute otitis media, excluded if rupture or recent antibiotics</td>
<td>Rx: ampicillin 100mg/kg/day or phenethicillin 30mg/kg/day plus sulfoxazole 150mg/kg/day Control: placebo</td>
<td>Culture results and clinical improvement = decrease symptoms and defervescence.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Howie 1972</td>
<td>R= randomisation controlled by pharmacist Placebo controlled - all medications given 4 times daily</td>
<td>USA age 2.5 years or less clinical diagnosis of acute otitis media</td>
<td>Rx: One of erythromycin, ampicillin, or triple sulphonamide plus erythromycin Control: placebo</td>
<td>culture and randomisation compared with culture at 2-5 days. No patient-relevant outcomes.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kaleida 1991</td>
<td>R=stratified randomisation, method not stated. Baseline comparability documented. double blind Intention to treat analysis</td>
<td>USA Children aged between 7 months and 12 years Acute otitis media: otoscopic middle ear effusion plus general symptoms or signs</td>
<td>Rx: Amoxicillin 40mg/kg/day in 3 doses Control: Placebo in 3 divided doses Duration: 14 days.</td>
<td>“treatment failure” = high otalgia score or high fever</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laxdal 1970</td>
<td>R=randomisation claimed but no method stated Not blinded</td>
<td>Canada Children Clinical diagnosis of acute otitis media for at least one ear; excluded if rupture had occurred.</td>
<td>Rx: Penicillin 250mg/sq.m./day qid or ampicillin 250mg/sq.m./day qid</td>
<td></td>
</tr>
</tbody>
</table>
### Characteristics of included studies (Continued)

<table>
<thead>
<tr>
<th>Control</th>
<th>Symptomatic therapy only</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcomes</strong></td>
<td>Poorly defined - “failure” was either deterioration or no improvement on 7th day based on middle ear inflammation.</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td>Unblinded assessment, and surveillance bias - control was more closely monitored.</td>
</tr>
</tbody>
</table>

| Allocation concealment | C |

<table>
<thead>
<tr>
<th>Study</th>
<th>Mygind 1981</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>R= coded bottles; documented baseline comparability double blind dropouts excluded (9 of 165)</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>Denmark Children between the ages of one and ten years, Acute otitis media, who had had earache for 1-24 hours.</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Rx: Penicillin-V 55mg/kg/day in three doses Control: placebo Duration: 7 days</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Parents completed score cards for pain and fever each evening, Otoscopy at follow-up. Tympanometry classified blind.</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td></td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Thalin 1985</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>R= block randomization controlled by hospital pharmacy double blind</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>Sweden Children aged 2 to 15 years Acute otitis media = clinical diagnosis</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Rx: Penicillin 50mg/kg/day in 3 doses Control: matching placebo duration: 7 days</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Examined on days 0, 3-4, 8-10, 30, audiogram at days 30 (repeat at 2 months if abnormal)</td>
</tr>
<tr>
<td><strong>Notes</strong></td>
<td></td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>vanBuchem 1981a</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methods</strong></td>
<td>R= identical bottles; baseline comparability documented double blind not intention to treat (31 of 202 patients excluded)</td>
</tr>
<tr>
<td><strong>Participants</strong></td>
<td>Netherlands Children aged 2-12 years acute otitis media - clinical diagnosis</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td>Rx:s: Amoxycillin 250mg tds; (2x2 factorial design) Control: Matching placebo; sham myringotomy Duration: 7 days</td>
</tr>
<tr>
<td><strong>Outcomes</strong></td>
<td>Parent report of pain</td>
</tr>
</tbody>
</table>
Characteristics of included studies (Continued)

Clinical assessment: day 2, 7, 14, 28, 56.
Audiogram at > 2 weeks assessed blind

Notes
(a) is the two arms without myringotomy

Allocation concealment A

Study vanBuchem 1981b
Methods R=identical bottles; baseline comparability documented
Participants Netherlands
Children aged 2-12 years
acute otitis
Interventions Rx: Amoxycillin 250mg tds and myringotomy; (2x2 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
Notes (b) is the two arms with myringotomy
Allocation concealment A

Characteristics of excluded studies

Chaput 1982 short versus long course of therapy
Engelhard 1994 No comparison of antibiotic to placebo; the 3 arms were: augmentin, myringotomy, or both.
Little 2001 No placebo control. Immediate versus delayed therapy.
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.
vanBuchem 1985 Non-randomised study.

ANALYSES

Comparison 01. Antibiotic versus Placebo

<table>
<thead>
<tr>
<th>Outcome title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Pain</td>
<td></td>
<td></td>
<td>Peto Odds Ratio 95% CI</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>02 Abnormal Tympanometry</td>
<td></td>
<td></td>
<td>Peto Odds Ratio 95% CI</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>03 Perforation</td>
<td>2</td>
<td>381</td>
<td>Peto Odds Ratio 95% CI</td>
<td>0.51 [0.20, 1.26]</td>
</tr>
<tr>
<td>04 Vomiting, diarrhoea, or rash</td>
<td>4</td>
<td>938</td>
<td>Peto Odds Ratio 95% CI</td>
<td>1.94 [1.28, 2.94]</td>
</tr>
<tr>
<td>05 Contralateral Otitis (in unilateral cases)</td>
<td>3</td>
<td>666</td>
<td>Odds Ratio (Random) 95% CI</td>
<td>0.45 [0.16, 1.23]</td>
</tr>
<tr>
<td>06 Late Recurrences</td>
<td>5</td>
<td>1669</td>
<td>Peto Odds Ratio 95% CI</td>
<td>1.00 [0.78, 1.26]</td>
</tr>
</tbody>
</table>

INDEX TERMS

Medical Subject Headings (MeSH)
Acute Disease; Age Factors; Anti-Bacterial Agents [*therapeutic use]; Otitis Media [*drug therapy]; Randomized Controlled Trials
Antibiotics for acute otitis media in children (Review)

Copyright © 2006 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd
**Title**
Antibiotics for acute otitis media in children

**Authors**
Glasziou PP, Del Mar CB, Sanders SL, Hayem M

**Contribution of author(s)**
CDM, PG and MH prepared the original version of the review.
SLS has checked and updated the review.
PG and CDM reviewed and contributed to the review by re-extracting data and by providing expert interpretation of the findings.

**Issue protocol first published**
1996/1

**Review first published**
1997/1

**Date of most recent amendment**
17 February 2005

**Date of most recent SUBSTANTIVE amendment**
26 November 2003

**What's New**
The search was updated in March 2003. Two new trials were identified (Little01) (Ruohola03) but excluded from the review. One of the trials (Little01) did not include a placebo group and the other (Ruohola03) was conducted in children with tympanostomy tubes. In the Little (Little01) trial, immediate antibiotics were compared with delayed administration. As only 24% of children in the delayed arm actually received antibiotics, the results of the trial were included in a sensitivity analysis. For the outcome pain at 24 hours and 2-7 days, inclusion of this trial did not alter the overall conclusions of the primary analysis. A L'Abbé plot (graph of the proportion of participants with an outcome by the proportion of participants without an outcome) for pain at 2-7 days is now included. We have corrected some minor data abstraction errors. This results in small changes. The reduction in pain at 24 hours, (none), remains unchanged, but at 2-7 days it has fallen from 28% to 30% reduction in pain in the groups treated with antibiotics (and a consequent NNT of 15 rather than 17). There was no change in the absence of significant effect for hearing problems.

**Date new studies sought but none found**
01 March 2003

**Date new studies found but not yet included/excluded**
Information not supplied by author

**Date new studies found and included/excluded**
05 February 2000

**Date authors' conclusions section amended**
05 February 2000

**Contact address**
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Headington
Oxford
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UK
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Figure 01.
Analysis 01.01. Comparison 01 Antibiotic versus Placebo, Outcome 01 Pain

Review: Antibiotics for acute otitis media in children
Comparison: 01 Antibiotic versus Placebo
Outcome: 01 Pain

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Peto Odds Ratio 95% CI</th>
<th>Weight (%)</th>
<th>Peto Odds Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>01 Pain at 24 hours</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burke 1991</td>
<td>53/112</td>
<td>56/117</td>
<td>34.4</td>
<td>3.4</td>
<td>0.98 [0.58, 1.64]</td>
</tr>
<tr>
<td>Thalin 1985</td>
<td>58/159</td>
<td>58/158</td>
<td>44.2</td>
<td>4.2</td>
<td>0.99 [0.63, 1.56]</td>
</tr>
<tr>
<td>vanBuchem 1981a</td>
<td>13/47</td>
<td>11/40</td>
<td>10.5</td>
<td>1.0</td>
<td>1.01 [0.39, 2.57]</td>
</tr>
<tr>
<td>vanBuchem 1981b</td>
<td>17/48</td>
<td>10/36</td>
<td>10.9</td>
<td>1.0</td>
<td>1.41 [0.56, 3.55]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>366</td>
<td>351</td>
<td></td>
<td>100.0</td>
<td>1.03 [0.76, 1.39]</td>
</tr>
<tr>
<td>Total events: 141 (Treatment), 135 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity chi-square=0.52 df=3 p=0.91 I² =0.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect z=0.17 p=0.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Peto Odds Ratio 95% CI</th>
<th>Weight (%)</th>
<th>Peto Odds Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>02 Pain at 2-7 days</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appelman 1991</td>
<td>11/67</td>
<td>10/54</td>
<td>6.3</td>
<td>0.6</td>
<td>0.86 [0.34, 2.22]</td>
</tr>
<tr>
<td>Burke 1991</td>
<td>20/111</td>
<td>29/114</td>
<td>14.1</td>
<td>1.4</td>
<td>0.65 [0.34, 1.22]</td>
</tr>
<tr>
<td>Damoiseaux 2000</td>
<td>69/117</td>
<td>89/123</td>
<td>19.8</td>
<td>1.9</td>
<td>0.55 [0.32, 0.94]</td>
</tr>
<tr>
<td>Halsted 1968</td>
<td>17/62</td>
<td>7/27</td>
<td>5.5</td>
<td>0.5</td>
<td>1.08 [0.39, 2.97]</td>
</tr>
<tr>
<td>Kaleida 1991</td>
<td>19/488</td>
<td>38/492</td>
<td>19.7</td>
<td>1.9</td>
<td>0.50 [0.29, 0.85]</td>
</tr>
<tr>
<td>Mygind 1981</td>
<td>15/72</td>
<td>29/77</td>
<td>11.4</td>
<td>1.1</td>
<td>0.45 [0.22, 0.90]</td>
</tr>
<tr>
<td>Thalin 1985</td>
<td>15/158</td>
<td>25/158</td>
<td>12.8</td>
<td>1.2</td>
<td>0.57 [0.29, 1.10]</td>
</tr>
<tr>
<td>vanBuchem 1981a</td>
<td>6/46</td>
<td>10/38</td>
<td>4.8</td>
<td>0.5</td>
<td>0.43 [0.14, 1.27]</td>
</tr>
<tr>
<td>vanBuchem 1981b</td>
<td>10/48</td>
<td>11/35</td>
<td>5.7</td>
<td>0.6</td>
<td>0.57 [0.21, 1.56]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>1169</td>
<td>1118</td>
<td></td>
<td>100.0</td>
<td>0.57 [0.45, 0.73]</td>
</tr>
<tr>
<td>Total events: 182 (Treatment), 248 (Control)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity chi-square=3.42 df=8 p=0.91 I² =0.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect z=4.61 p&lt;0.000001</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Analysis 01.02. Comparison 01 Antibiotic versus Placebo, Outcome 02 Abnormal Tympanometry

**Review:** Antibiotics for acute otitis media in children  
**Comparison:** 01 Antibiotic versus Placebo  
**Outcome:** 02 Abnormal Tympanometry

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>Peto Odds Ratio</th>
<th>Weight</th>
<th>Peto Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI (%)</td>
<td></td>
<td>95% CI</td>
</tr>
<tr>
<td>01 1 Month</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appelman 1991</td>
<td>21/51</td>
<td>25/45</td>
<td>22.0</td>
<td>0.57</td>
<td>[0.25, 1.26]</td>
</tr>
<tr>
<td>Burke 1991</td>
<td>41/111</td>
<td>41/116</td>
<td>48.1</td>
<td>1.07</td>
<td>[0.62, 1.84]</td>
</tr>
<tr>
<td>Mygind 1981</td>
<td>23/72</td>
<td>25/77</td>
<td>29.9</td>
<td>0.98</td>
<td>[0.49, 1.94]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>234</td>
<td>238</td>
<td>100.0</td>
<td>0.91</td>
<td>[0.62, 1.32]</td>
</tr>
<tr>
<td>Total events:</td>
<td>85 (Treatment), 91 (Control)</td>
<td>85 (Treatment), 91 (Control)</td>
<td>100.0</td>
<td>0.91 [0.62, 1.32]</td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity chi-square=1.75 df=2 p=0.42 I² =0.0%</td>
<td>Test for overall effect z=0.52 p=0.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>02 3 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burke 1991</td>
<td>20/110</td>
<td>31/111</td>
<td>58.9</td>
<td>0.58</td>
<td>[0.31, 1.08]</td>
</tr>
<tr>
<td>Mygind 1981</td>
<td>18/72</td>
<td>18/77</td>
<td>41.1</td>
<td>1.09</td>
<td>[0.52, 2.31]</td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>182</td>
<td>188</td>
<td>100.0</td>
<td>0.75</td>
<td>[0.47, 1.21]</td>
</tr>
<tr>
<td>Total events:</td>
<td>38 (Treatment), 49 (Control)</td>
<td>38 (Treatment), 49 (Control)</td>
<td>100.0</td>
<td>0.75 [0.47, 1.21]</td>
<td></td>
</tr>
<tr>
<td>Test for heterogeneity chi-square=1.63 df=1 p=0.20 I² =38.6%</td>
<td>Test for overall effect z=1.17 p=0.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Analysis 01.03. Comparison 01 Antibiotic versus Placebo, Outcome 03 Perforation

**Review:** Antibiotics for acute otitis media in children  
**Comparison:** 01 Antibiotic versus Placebo  
**Outcome:** 03 Perforation

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Peto Odds Ratio 95% CI</th>
<th>Weight %</th>
<th>Peto Odds Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burke 1991</td>
<td>0/114</td>
<td>2/118</td>
<td>0.14 [0.01, 2.23]</td>
<td>10.7</td>
<td></td>
</tr>
<tr>
<td>Mygind 1981</td>
<td>7/72</td>
<td>12/77</td>
<td>0.59 [0.23, 1.55]</td>
<td>89.3</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>186</td>
<td>195</td>
<td>0.51 [0.20, 1.26]</td>
<td>100.0</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 7 (Treatment), 14 (Control)  
Test for heterogeneity chi-square=0.94 df=1 p=0.33 I² =0.0%  
Test for overall effect z=1.46 p=0.1
### Analysis 01.04. Comparison 01 Antibiotic versus Placebo, Outcome 04 Vomiting, diarrhoea, or rash

**Review:** Antibiotics for acute otitis media in children  
**Comparison:** 01 Antibiotic versus Placebo  
**Outcome:** 04 Vomiting, diarrhoea, or rash

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Control</th>
<th>Peto Odds Ratio</th>
<th>Weight</th>
<th>Peto Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>95% CI</td>
<td>(%)</td>
<td>95% CI</td>
</tr>
<tr>
<td>Burke 1991</td>
<td>53/114</td>
<td>36/118</td>
<td>62.0</td>
<td>1.96</td>
<td>[ 1.16, 3.32 ]</td>
</tr>
<tr>
<td>Damoiseaux 2000</td>
<td>20/117</td>
<td>12/123</td>
<td>31.3</td>
<td>1.88</td>
<td>[ 0.90, 3.96 ]</td>
</tr>
<tr>
<td>Mygind 1981</td>
<td>3/72</td>
<td>1/77</td>
<td>4.4</td>
<td>2.98</td>
<td>[ 0.41, 21.58 ]</td>
</tr>
<tr>
<td>Thalin 1985</td>
<td>1/159</td>
<td>1/158</td>
<td>2.2</td>
<td>0.99</td>
<td>[ 0.06, 15.96 ]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>462</td>
<td>476</td>
<td>100.0</td>
<td>1.94</td>
<td>[ 1.28, 2.94 ]</td>
</tr>
</tbody>
</table>

Total events: 77 (Treatment), 50 (Control)  
Test for heterogeneity chi-square=0.41 df=3 p=0.94 I² =0.0%  
Test for overall effect z=3.13 p=0.002
### Analysis 01.05. Comparison 01 Antibiotic versus Placebo, Outcome 05 Contralateral Otitis (in unilateral cases)

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Odds Ratio (Random) 95% CI (%)</th>
<th>Weight</th>
<th>Odds Ratio (Random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burke 1991</td>
<td>29/98</td>
<td>33/102</td>
<td>45.3 [0.88, 1.60]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mygind 1981</td>
<td>2/72</td>
<td>6/77</td>
<td>22.2 [0.34, 1.73]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thalin 1985</td>
<td>4/159</td>
<td>17/158</td>
<td>32.5 [0.21, 0.65]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>329</td>
<td>337</td>
<td>100.0 [0.45, 1.23]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 35 (Treatment), 56 (Control)
Test for heterogeneity: chi-square = 5.38 df = 2 p = 0.07 I² = 62.8%
Test for overall effect: z = 1.56 p = 0.1

Antibiotics for acute otitis media in children (Review)
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### Analysis 01.06. Comparison 01 Antibiotic versus Placebo, Outcome 06 Late Recurrences

**Review:** Antibiotics for acute otitis media in children  
**Comparison:** 01 Antibiotic versus Placebo  
**Outcome:** 06 Late Recurrences

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Peto Odds Ratio</th>
<th>Weight (%)</th>
<th>Peto Odds Ratio 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaleida 1991</td>
<td>125/448</td>
<td>124/446</td>
<td>67.2</td>
<td>1.00</td>
<td>[0.75, 1.35]</td>
</tr>
<tr>
<td>Laxdal 1970</td>
<td>24/94</td>
<td>10/48</td>
<td>8.7</td>
<td>1.29</td>
<td>[0.57, 2.91]</td>
</tr>
<tr>
<td>Mygind 1981</td>
<td>19/72</td>
<td>21/77</td>
<td>11.0</td>
<td>0.96</td>
<td>[0.46, 1.97]</td>
</tr>
<tr>
<td>Thalin 1985</td>
<td>9/159</td>
<td>7/158</td>
<td>5.7</td>
<td>1.29</td>
<td>[0.47, 3.53]</td>
</tr>
<tr>
<td>vanBuchem 1981a</td>
<td>10/92</td>
<td>13/75</td>
<td>7.4</td>
<td>0.58</td>
<td>[0.24, 1.41]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>865</strong></td>
<td><strong>804</strong></td>
<td><strong>100.0</strong></td>
<td><strong>1.00</strong></td>
<td><strong>[0.78, 1.26]</strong></td>
</tr>
</tbody>
</table>

Total events: 187 (Treatment), 175 (Control)  
Test for heterogeneity chi-square=2.09 df=4 p=0.72 I² =0.0%  
Test for overall effect z=0.04 p=1

- Antibiotics better
- Placebo better